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Supplementary Materials for Guidelines of care for the management of acne vulgaris

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Detailed Methods

Expert Work Group Composition and Disclosures of Interest

The co-chairs of the Work Group (J.B. and R.R.) were reviewed for potential disclosures of interest (DOIs) and approved by the AAD's Clinical Guidelines Committee (CGC). Additional Work Group members were nominated by the co-chairs based on their expertise related to the clinical questions. All Work Group nominees were reviewed for potential DOIs by the CGC. The majority (at least 51%) of the Work Group was required to be free of financial DOIs relevant to the topic of the guideline, and those found to have no relevant financial DOIs were required to stay free of financial DOIs during the guideline development process and until online publication of the clinical guideline. Nominees found to have no relevant financial DOIs were approved, whereas nominees found to have potentially relevant financial DOIs were approved with management. Work Group members approved with management were prohibited from discussions on and voting for recommendations in which they had relevant DOIs. Work Group members completed a DOI form that was periodically updated and reviewed for potential relevant DOIs throughout guideline development and used to ensure management terms were observed. The multidisciplinary Work Group consisted of the co-chairs, 11 members, a methodologist, a measure representative, and a patient representative. The Work Group was supported by an AAD guidelines staff member with health research methodology expertise.

Formulation of Clinical Questions and Study/PICO Eligibility Criteria Development

Based on the scope and objectives of this guideline, the expert Work Group identified nine clinical questions (CQs) (**Table 1**). Next, the Work Group developed the study eligibility criteria and PICO eligibility criteria using the CQs. During the PICO eligibility criteria development, the Work Group identified outcomes considered important for making clinical decisions in acne management and ranked the importance of each outcome for CQs 3-9 via anonymous online voting using a 9-point scale (a ranking of 7-9 was assigned to outcomes critical for decision-making, 4-6 for outcomes important for decision-making, and 1-3 for outcomes of limited importance for decision-making).¹ Results of voting were used to categorize outcomes as "critical", "important", or "not important" (**e-Table 1**). The pre-defined study eligibility/PICO criteria for the update guidelines for all 9 CQs are outlined in **e-Table 2**.

e-Table 1. Outcome importance rating

Outcome	Average Rating	Importance
CQ3. Topical Agents		
Physicians' global/local evaluation (e.g., Investigator global assessment scale/score, Global acne grading system, Global Acne Severity Score, etc.)	7.9	Critical
Participants' global self-assessment of acne improvement (e.g., patient's improvement assessment in treatment area appearance, patient's improvement assessment measured by a 4-point scale, etc.)	6.8	Important
Change in lesion counts (e.g., total Inflammatory and non-inflammatory lesions, inflammatory lesions, non-inflammatory lesions, mean % change or mean absolute change in total/inflammatory lesion count, etc.)	7.5	Critical
Quality of Life (e.g., Dermatology Life Quality Index, Dermatology-Specific Quality of Life, Skindex, Assessment of Quality of Life, Acne Disability Index, The Cardiff Acne Disability Index, etc.)	6.0	Important
Withdrawal due to adverse events	6.4	Important
Any adverse events (assessed as the total number of participants who experienced at least adverse event)	5.2	Important
Skin irritation (e.g., Burning, tingling, dryness, swelling, redness, peeling, etc.)	6.1	Important
[Topical retinoid only] Photosensitivity	5.2	Important
CQ4. Oral Antibiotics		

Physicians' global/local evaluation (e.g., Investigator global assessment scale/score, Global acne grading system, Global Acne Severity Score, etc.)	7.7	Critical
Participants' global self-assessment of acne improvement (e.g., patient's improvement assessment in treatment area appearance, patient's improvement assessment measured by a 4-point scale, etc.)	6.5	Important
Change in lesion counts (e.g., total Inflammatory and non-inflammatory lesions, inflammatory lesions, non-inflammatory lesions, mean % change or mean absolute change in total/inflammatory lesion count, etc.)	7.6	Critical
Acne reoccurrence	5.5	Important
Quality of Life (e.g., Dermatology Life Quality Index, Dermatology-Specific Quality of Life, Skindex, Assessment of Quality of Life, Acne Disability Index, The Cardiff Acne Disability Index, etc.)	6.4	Important
Withdrawal due to adverse events	6.4	Important
Any adverse events (assessed as the total number of participants who experienced at least adverse event)	5.4	Important
Serious adverse events (e.g., life threatening event, death, etc.)	7.1	Critical
Gastrointestinal side effects	5.5	Important
Candidiasis	4.4	Important
Photosensitivity	5.1	Important
Inflammatory bowel disease	5.5	Important
Change in microbiome (cutaneous and gastrointestinal)	4.4	Important
Colon polyps/cancer	4.3	Important
CQ5. Hormonal Agents		
Physicians' global/local evaluation (e.g., Investigator global assessment scale/score, Global acne grading system, Global Acne Severity Score, etc.)	7.9	Critical
Change in lesion counts (e.g., total Inflammatory and non-inflammatory lesions, inflammatory lesions, non-inflammatory lesions, mean % change or mean absolute change in total/inflammatory lesion count, etc.)	7.4	Critical
Serious adverse events (e.g., life threatening event, death, etc.)	7.1	Critical
[For COC] thromboembolic events	7	Critical
Participants' global self-assessment of acne improvement (e.g., patient's improvement assessment in treatment area appearance, patient's improvement assessment measured by a 4-point scale, etc.)	6.9	Important
Withdrawal due to adverse events	6.7	Important
Quality of Life (e.g., Dermatology Life Quality Index, Dermatology-Specific Quality of Life, Skindex, Assessment of Quality of Life, Acne Disability Index, The Cardiff Acne Disability Index, etc.)	6.6	Important
[For SPIRONOLACTONE] hyperkalemia	6	Important
[For SPIRONOLACTONE] cancer (e.g. breast cancer)	5.6	Important
[For SPIRONOLACTONE] teratogenicity	5.6	Important
Acne reoccurrence	5.4	Important
Any adverse events (assessed as the total number of participants who experienced at least adverse event)	5.4	Important
[For COC] mood disturbance	5.4	Important
[For SPIRONOLACTONE] menstrual irregularities	5.3	Important
CQ6. Isotretinoin		
Physicians' global/local evaluation (e.g., Investigator global assessment scale/score, Global acne grading system, Global Acne Severity Score, etc.)	8.1	Critical

Participants' global self-assessment of acne improvement (e.g., patient's improvement assessment in treatment area appearance, patient's improvement assessment measured by a 4-point scale, etc.)	6.9	Important
Change in lesion counts (e.g., total Inflammatory and non-inflammatory lesions, inflammatory lesions, non-inflammatory lesions, mean % change or mean absolute change in total/inflammatory lesion count, etc.)	7.6	Critical
Acne reoccurrence	6.4	Important
Quality of Life (e.g., Dermatology Life Quality Index, Dermatology-Specific Quality of Life, Skindex, Assessment of Quality of Life, Acne Disability Index, The Cardiff Acne Disability Index, etc.)	6.7	Important
Withdrawal due to adverse events	6.6	Important
Any adverse events (assessed as the total number of participants who experienced at least adverse event)	5.2	Important
Serious adverse events (e.g., life threatening event, death, etc.)	7.4	Critical
Chelitis	3.6	Not Important
Visual disturbance/impaired night vision	4.5	Important
Photosensitivity	4.3	Important
Joint or muscle pain	4.6	Important
Teratogenicity	6.5	Important
Abnormal levels of lipids	5.7	Important
Abnormal levels of liver enzymes	5.9	Important
Abnormal level of creatine kinase	5.6	Important
Abnormal complete blood counts	5.0	Important
Inflammatory Bowel Disease	5.8	Important
Mood change	6.6	Important
CQ 7. Physical Modalities		
Physicians' global/local evaluation (e.g., Investigator global assessment scale/score, Global acne grading system, Global Acne Severity Score, etc.)	8.0	Critical
Participants' global self-assessment of acne improvement (e.g., patient's improvement assessment in treatment area appearance, patient's improvement assessment measured by a 4-point scale, etc.)	7.0	Critical
Change in lesion counts (e.g., total Inflammatory and non-inflammatory lesions, inflammatory lesions, non-inflammatory lesions, mean % change or mean absolute change in total/inflammatory lesion count, etc.)	7.6	Critical
Acne reoccurrence	6.4	Important
Quality of Life (e.g., Dermatology Life Quality Index, Dermatology-Specific Quality of Life, Skindex, Assessment of Quality of Life, Acne Disability Index, The Cardiff Acne Disability Index, etc.)	6.2	Important
Withdrawal due to adverse events	6.8	Important
Any adverse events (assessed as the total number of participants who experienced at least adverse event)	5.4	Important
Skin irritation (e.g., burning, tingling, dryness, swelling, redness, peeling, etc.)	5.8	Important
Serious skin reaction (e.g., blistering, scarring following the therapy)	7.9	Critical
Hyperpigmentation	6.5	Important
CQs 8 & 9. Complementary/Alternative Medicine & Diet		
Physicians' global/local evaluation (e.g., Investigator global assessment scale/score, Global acne grading system, Global Acne Severity Score, etc.)	8.1	Critical

Participants' global self-assessment of acne improvement (e.g., patient's improvement assessment in treatment area appearance, patient's improvement assessment measured by a 4-point scale, etc.)	6.9	Important
Change in lesion counts (e.g., total Inflammatory and non-inflammatory lesions, inflammatory lesions, non-inflammatory lesions, mean % change or mean absolute change in total/inflammatory lesion count, etc.)	7.6	Critical
Acne reoccurrence	5.7	Important
Quality of Life (e.g., Dermatology Life Quality Index, Dermatology-Specific Quality of Life, Skindex, Assessment of Quality of Life, Acne Disability Index, The Cardiff Acne Disability Index, etc.)	6.1	Important
Withdrawal due to adverse events	7.0	Critical
Any adverse events (assessed as the total number of participants who experienced at least adverse event)	5.7	Important
Serious adverse events (e.g., life threatening event, death, etc.)	7.8	Critical

e-Table 2. Study eligibility criteria for the Grading and Classification and Microbiologic and Endocrinologic Testing for Acne (CQs 1 and 2)

	Inclusion Criteria	Exclusion Criteria
Grading and Classification	- Primary diagnostic studies reporting disease severity outcome measures in acne - Studies reporting the relevant clinical characteristics with which acne patients would present (number of lesions, anatomical location, extent of acne, etc.) and their association/correlation with acne severity	- Acneiform skin eruptions - Children aged younger than 9 years
Microbiologic Testing	- Studies evaluating microbiologic tests in acne P. acnes (C. acnes) - Gram negative bacteria S. aureus - Studies reporting the relevant clinical characteristics that warrant microbiologic tests	- Acneiform skin eruptions - Children aged younger than 9 years
Endocrinologic Testing	- Studies evaluating endocrinologic tests in acne - Studies reporting the relevant clinical characteristics or current or a history of disease states that warrant endocrinologic tests - Hyperandrogenism 21-hydroxylase deficiency - Use of hormone-based therapies (e.g., anti-androgen medication) - Polycystic ovarian syndrome	- Acneiform skin eruptions - Children aged younger than 9 years

e-Table 3. PICO eligibility criteria for the treatments available for acne (CQs 3-4, 5b, 6b, and 7)

PICO	Inclusion Criteria	Exclusion Criteria
Population	Adults, adolescents, and preadolescents (≥ 9 years) with acne vulgaris	- Acneiform skin eruptions - Children aged younger than 9 years
	Sub-groups or special populations considered separately if data are available: - Mild acne - Moderate acne	

	- Severe acne - Moderate to severe acne - Pediatric patients - Adolescents (9 to 18) - Adults - Females	
Intervention	Topical agents - Retinoids: adapalene, tazarotene, tretinoin, and trifarotene - Benzoyl peroxide - Topical antibiotics: clindamycin, dapsone, erythromycin, and minocycline - Alpha hydroxy acid: glycolic acid - Beta hydroxy acid: salicylic acid - Azelaic acid - Topical antiandrogen: clascoterone - Others: sulfur/Sulfacetamide sodium, resorcinol - Combinations of topical agents Systemic Antibiotics - Tetracyclines: doxycycline, minocycline, and sarecycline - Macrolides: azithromycin, clarithromycin, and erythromycin - Penicillins: amoxicillin and ampicillin - Cephalosporin: cephalexin - Trimethoprim/sulfamethoxazole - Others: dapsone Hormonal agents - Combined oral contraceptives: estrogen and progestins - Aldosterone receptor antagonist: spironolactone - Intralesional steroids: triamcinolone - Oral corticosteroids: prednisolone and prednisone Retinoid: isotretinoin Physical modalities - Chemical peels: alpha hydroxy acid (glycolic acid, lactic acid, malic acid) and beta hydroxy acid (salicylic acid) - Comedo extraction - Lasers - Photodynamic/Light therapies: blue light therapy, red light therapy, ALA, and IPL Any combination therapy of the above	Therapies not available or approved for use in the US
Comparator	- Any listed above - Control/Placebo/No treatment	N/A
Outcome	Outcomes rated as critical or important	Outcomes that are not rated as critical or important
Timing	≥ 4 weeks follow up	N/A
Setting	Any	N/A
Study Design	- RCTs - Pooled analyses - Systematic reviews of RCTs	- Pre-clinical/animal - Case reports/series - Non-randomized clinical trials

		• Observational studies • Narrative reviews
Language	• English	
Publication date restriction	• Database: PubMed ○ Interventions included in the previous guidelines: 2014 to current ○ Interventions not included in the previous guideline: Inception to Current	

e-Table 4. PICO eligibility criteria for long term safety outcomes (CQ 4-6)

PICO	Inclusion Criteria	Exclusion Criteria
Population	• Adults, adolescents, and preadolescents (≥ 9 years) with acne vulgaris	• Acneiform skin eruptions • Children aged younger than 9 years
Intervention	Systemic Antibiotics • Tetracyclines: doxycycline, minocycline, and sarecycline • Trimethoprim/sulfamethoxazole • Macrolides: azithromycin, clarithromycin, and erythromycin • Penicillins: amoxicillin and ampicillin • Cephalosporin: cephalexin • Others: dapsone Hormonal agents • Combined oral contraceptives: estrogen and progestins • Aldosterone receptor antagonist: spironolactone • Oral corticosteroids: prednisolone and prednisone Retinoid • Isotretinoin	• Therapies that are not listed.
Comparator	• Control/Placebo/No treatment	• N/A
Outcome	• Oral antibiotics: change in microbiome, inflammatory bowel disease, bacterial resistance, breast cancer, colon polyps/cancer • Combined contraceptive agents: any thromboembolic events • Spironolactone: breast cancer • Isotretinoin: inflammatory bowel disease, depression, suicidality	• N/A
Timing	• ≥ 6 months follow up	• N/A
Setting	• Any	• N/A
Study Design	• Cohort studies • Case control studies • Systematic reviews of observational studies	• Pre-clinical/animal • Case reports/series • Narrative reviews
Language	• English	• N/A
Others	• Study size: at least 50 participants in each group	• N/A

Publication date restriction	• Database: PubMed ○ Interventions included in the previous guidelines: 2014 to current ○ Interventions not included in the previous guideline: Inception to Current	

32 **e-Table 5. PICO eligibility criteria for lab monitoring questions (CQ 5b and 6b)**

PICO	Inclusion Criteria	Exclusion Criteria
Population	• Adults, adolescents, and preadolescents (≥ 9 years) with acne vulgaris	• Acneiform skin eruptions • Children aged younger than 9 years
Intervention	Hormonal agents • Aldosterone receptor antagonist: spironolactone Retinoid • Isotretinoin	• Therapies that are not listed.
Comparator	• Control/Placebo/No treatment	• N/A
Outcome	• Spironolactone: hyperkalemia • Isotretinoin: abnormal levels of lipids, liver enzymes, creatine kinase, and complete blood count abnormalities (threshold to be determined by the section leads)	• N/A
Timing	• ≥ 6 months for single-arm cohort studies, cohort, and case-control studies • ≥ 4 weeks for RCTs	• N/A
Setting	• Any	• N/A
Study Design	• RCTs • Cohort studies • Case control studies • Single-arm cohort studies assessing safety outcomes in patients receiving an intervention of interest • Systematic reviews of RCTs and/or observational studies	• Pre-clinical/animal • Case reports/series • Narrative reviews
Language	• English	• N/A
Others	• Study size: ○ No size limit for RCTs ○ At least 50 participants in each group for non-randomized comparative studies ○ At least 100 participants for single-arm cohort studies	• N/A
Publication date restriction	• Database: PubMed ○ 2014 to current	

33 **e-Table 6. PICO eligibility criteria for metformin studies (CQ 5c)**

PICO	Inclusion Criteria	Exclusion Criteria
Population	Any population	N/A
Intervention	Metformin	Therapies that are not listed
Comparator	- Control/Placebo/No treatment - Any acne treatments	N/A
Outcome	Acne outcomes (Presence of acne, lesion count, physician global assessment, patient global assessment, quality of life)	N/A
Timing	≥ 4 weeks	N/A
Setting	Any	N/A
Study Design	RCTs	- Observational studies - Pre-clinical/animal - Case reports/series - Narrative reviews
Language	English	N/A
Publication date restriction	- Database: PubMed - Inception to current	

e-Table 7. PICO eligibility criteria for complementary and alternative medicine and diet interventions for acne (CQ 8 and 9)

PICO	Inclusion Criteria	Exclusion Criteria
Population	Adults, adolescents, and preadolescents (≥ 9 years) with acne vulgaris	- Acneiform skin eruptions - Children aged younger than 9 years
	Sub-groups or special populations considered separately if data are available: - Mild acne - Moderate acne - Severe acne - Moderate to severe acne - Pediatric patients - Adolescents (9 to 18) - Adults - Females	
Intervention	Complementary/alternative therapies - botanicals/plant-derived agents (tea tree oil, green tea, and witch hazel) - vitamin oral formulation (zinc, niacinamide, pantothenic acid) - vitamin topical formulation (zinc and niacinamide) Diet - Low glycemic diet - Low dairy diet - Low whey protein diet	N/A

	• Omega-3 and chocolate	
Comparator	• Any listed above • Control/Placebo/No treatment	• N/A
Outcome	Outcomes rated as critical or important	• Outcomes that are not rated as critical or important
Timing	• ≥ 4 weeks follow up	• N/A
Setting	• Any	• N/A
Study Design	• RCTs • Pooled analyses • Systematic reviews of RCTs	• Pre-clinical/animal • Case reports/series • Non-randomized clinical trials • Observational studies • Narrative reviews
Language	• English	
Publication date restriction	• Database: PubMed ○ Interventions included in the previous guidelines: 2014 to current ○ Interventions not included in the previous guideline: Inception to Current	

For Grading and Classification and Microbiologic and Endocrinologic Testing (CQs 1 and 2) sections, we conducted focused literature reviews to search for all relevant studies. The findings are narratively discussed in the text and there are no recommendations provided for these two sections.

Literature Searches

AAD partnered with Evidinno, Inc. to conduct components of the systematic review process, including literature searches, study selection, risk of bias assessment, data extraction, and analysis. AAD and Evidinno conducted a series of literature searches on MEDLINE (all sections) and Embase (Topical agents and Physical modalities sections only) based on the predefined study and PICO eligibility criteria (**e-Table 2**). The searches were limited from 2014 to the date of each search (June - December 2021; updated periodically through May 2022; **e-Table 8**) except for those the previous guidelines did not cover (inception - search date). The references of relevant systematic reviews were also screened.

e-Table 8. Search strategies

CQ 1. Grading and Classification	
Database	MEDLINE via PubMed
Search date	June 5, 2021
#1	"Acne Vulgaris"[Mesh] OR acne[tiab]
#2	Severity[tiab] OR grade[tiab] OR grading[tiab] OR assess[tiab] OR assessment[tiab] OR score[tiab] OR scoring[tiab] OR "lesion count"[tiab] OR scale[tiab] OR tool[tiab] OR "severity of illness index"[tiab]
#3	#1 AND #2
#4	#3 AND 2014:2021[dp]
CQ 2. Microbiology and endocrinology testing	
Database	MEDLINE via PubMed
Search date	June 5, 2021
#1	"Acne Vulgaris"[Mesh] OR acne[tiab]
#2	"Microbiologic test*"[tiab] OR "microbiology test*"[tiab] OR "Gram-negative folliculitis"[tiab] OR "Gram negative"[tiab] OR "Escherichia coli"[tiab] OR "E. coli"[tiab] OR "Pseudomonas

	aeruginosa"[tiab] OR "P. aeruginosa"[tiab] OR "Serratia marcescens"[tiab] OR "S. marcescens"[tiab] OR "Klebsiella"[tiab] OR "Proteus"[tiab] OR "Propionibacterium acnes"[Mesh] OR "Propionibacterium acnes"[tiab] OR "P. acnes"[tiab] OR "Cutibacterium acnes"[tiab] OR "C. acnes"[tiab] OR "Staphylococcus aureus"[Mesh] OR "Staphylococcus aureus"[tiab] OR "S. aureus"[tiab] OR "staphylococ*" [tiab] OR "microbial aetiology"[tiab] OR "micro-organism"[tiab] OR "susceptibility"[tiab] OR "Microbial Sensitivity Tests"[Mesh]
#3	"hormonal test*" [tiab] OR "hormonal panel"[tiab] OR "hormone test"[tiab] OR "hormone panel"[tiab] OR "hormonal assessment"[tiab] OR "hormone assessment"[tiab] OR "Hyperandrogenism"[Mesh] OR "androgen excess"[tiab] OR hyperandrogen*[tiab] OR "polycystic ovarian syndrome"[tiab] OR PCOS[tiab] OR "Polycystic Ovary Syndrome"[Mesh] OR "21-hydroxylase deficiency"[tiab] OR "21 hydroxylase"[tiab] OR "Insulin"[Mesh] OR "insulin"[tiab] OR "Dehydroepiandrosterone Sulfate"[Mesh] OR "Dehydroepiandrosterone Sulfate"[tiab] OR DHEA*[tiab] OR "Luteinizing Hormone"[Mesh] OR "Follicle Stimulating Hormone"[Mesh] OR "Growth Hormone"[Mesh] OR "growth hormone"[tiab] OR "Insulin-Like Growth Factor I"[Mesh] OR "insulin growth factor"[tiab] OR "Sex Hormone-Binding Globulin"[Mesh] OR SHBG[tiab] OR "total testosterone"[tiab] OR "free testosterone" [tiab] OR "thyroid stimulating hormone"[tiab] OR "TSH"[tiab] OR prolactin[tiab]
#4	#2 OR #3
#5	#1 AND #4
#6	#5 AND 2014:2021[dp]
CQ3. Topical agents	
Database	MEDLINE (via Ovid)
Search date	December 15, 2021
1	exp acne vulgaris/
2	acne.ti,ab.
3	or/1-2
4	exp Retinoid/
5	retinoid*.ti,ab.
6	exp adapalene/
7	(adapalene or "6 [3 (1 adamantyl) 4 methoxyphenyl] 2 naphthoic acid" or acnelec or adaferin or "cd 271" or "cd271" or differin or differine or neopalen or redap).ti,ab.
8	exp Adapalene, Benzoyl Peroxide Drug Combination/
9	(effezel or epiduo or tactuo or tactuoben).ti,ab.
10	(tazarotene or "6 [(3,4 dihydro 4,4 dimethyl 2h 1 benzothiopyran 6 yl)ethynyl] 3 pyridinecarboxylic acid ethyl ester" or "6 [2 (4,4 dimethylthiochroman 6 yl)ethynyl]nicotinic acid ethyl ester" or "agn 190168" or "agn190168" or arazlo or avage or "ethyl 6 [2 (4,4 dimethylthiochroman 6 yl)ethynyl]nicotinate" or fabior or tazaroten or tazorac or tazoral or zorac).ti,ab.
11	exp Tretinoin/
12	("retinoic acid" or "1 (8 carboxy 3,7 dimethyl 1,3,5,7 octatetraen 1 yl) 2,6,6 trimethyl 1 cyclohexene" or "11,13 dicis tretinoin" or "3,7 dimethyl 9 (2,6,6 trimethyl 1 cyclohexen 1 yl) 2,4,6,8 nonatetraenoic acid" or "3,7 dimethyl 9 (2,6,6 trimethyl 1 cyclohexen 1 yl)nona 2,4,6,8 tetraen 1 oic acid" or a-acido or aberel or aberela or "acid a vit" or "acne free" or acnederm or airol or alquingel or alten or altinac or altreno or "anhydroretinoic acid" or "ar 623" or "ar623" or atra or atragen or atralin or avita or avitcid or "beta retinoic acid" or betarretin or "cordes vas" or "derm a" or dermairol or "dermik a" or effederm or "epi aberel" or epiaberel or eudyna or facenol or ilotycin-a or ketrel or locacid or neocare or "nsc 122758" or "nsc122758" or "prosome a cream" or reacel-a or renova or retacnyl or retavit or retiderma or "retin a" or retinova or retirides or "retrieve cream" or "ro 01 5488" or "ro 1 5488" or "ro 15488" or "ro015488" or "ro15488" or "stieva a" or "stieva-a forte" or stievaa or tracne or trentin or tretinoin or vesanoid or "vitamin A acid" or vitinoin).ti,ab.
13	exp benzoyl peroxide/

14	(((benzoyl or dibenzoyl or diphenylglyoxal) adj (peroxide* or superoxide*)) or benzoylperoxide or acetoxyl or acnacyl or "acne dermat" or "acne mask" or "acne-clear" or acneclear or acnecide or acnegel or acnetick-10 or acnexyl or acnie or akneroxid or aldoacne or basiron or benoxid or benoxyl or benzac* or benzagel* or benzashave or benzeperox or benzihex or benzolac or benzoperoxide or benzperox or brevoxyl or "clear by design" or clearplex or clearskin or "clinac bpo" or cordes or cutacnyl or debroxide or del-aqua or desquam* or diafen or "dry and clear" or eclaran or ecuaderm or effacne or eloxyl or "epi clear" or "fostex bpo" or inoxitan or klinoxid or "lisagel 5" or lucidol or mytolac or "nsc 676" or oxiderma or "oxy 10" or "oxy 5" or "oxy lotion" or "oxy preps" or "oxy sensitive vanishing gel" or "oxy wash" or oxyderm or pannogel or panoxyl or pansulfox or peroxiben or persadox or "persol gel" or pimplex or sanoxit or scherogel or seba-gel or theraderm or tinagel or topexac or triaz or tritaze or "ultra clearasil" or uvacnyl or vixiderm or xerac).ti,ab.
15	exp clindamycin/
16	(clind?mycin* or "7 chlor 7 desoxylincomycin" or "7 chloro 7 deoxylincomycin" or "7 chloro 7 desoxylincomycin" or "7 chlorolincomycin" or "7(s) chloro 7 deoxylincomycin" or "7s chloro 7 deoxylincomycin" or antirobe or aquadrops or (cleocin adj (hcl or hydrochloride)) or cleocine or clinda-ipp or clinda-saar or "clindamycin in sodium chloride 0.9%" or clindasol or clinimycin or dalacin or "lincomycin,7 chloro" or sobelin or sobeline or "u 21251" or "u 21251f" or "u21251" or "u21251f" or zindaclin).ti,ab.
17	(acanya or "beclometasone dipropionate/formoterol fumarate" or benzaclin or clindoxyl or duac or "formoterol fumarate/beclometasone dipropionate" or "gsk 2585823" or "gsk2585823" or indoxyl or onexton or septigel).ti,ab.
18	exp dapsone/
19	(d?pson* or "4,4 bis(aminophenyl)sulfone" or "4,4 diaminodiphenylsulfone" or "4,4 sulfonyldianiline" or "4,4' diaminodiphenyl sulfone" or "4,4' sulfonylbisbenzamine" or aczone or atrisone or avlosulf?n* or "bis (4 aminophenyl)sulfone" or "bn 2405" or "bn2405" or crosulfone or dapsoderm-x or dds or "diamino diphenyl sulfone" or "diaminodiphenyl sulfone" or diaminodiphenylosulfone or diaminodiphenylsulfon* or diaminodiphenylsulfone or diammodiphenylsulfone or "diaphenyl sulfone" or diaphenylsulfon* or diaphenylsulphone or diphenason* or diphone or disulone or dunitone or eporal or "f 1358" or "f1358" or lennon-dapsone or lepravir or novasulfon or novophone or "nsc 6091" or "nsc6091" or "para,para' sulfodaniline" or servidapson* or sulfadione or sulfadoine or sulfona or "sulfone mere" or udolac).ti,ab.
20	exp erythromycin/
21	(erythromycin* or "a/t/s" or abomacetin or acneryne or acnesol or "akne mycin" or "aknederm ery gel" or aknemycin or anamycin or bonac gel or "c-solve-2" or cliniderm or deripil or duraerythromycin or "e mycin" or e-base or e-glades or "e-solve 2" or emgel or "emu v" or "emu-ve" or emuvin or emycin or eriecu or erimycin-t or eriprodin or eritimix or eritrex or eritrocina or eritromicina or erixyl or ermy?in or "ery maxin" or ery-b or ery-diolan or ery-tab or eryacne* or eryc or erycen or erycette or erycin or erycinum or eryderm or erydermec or erydermer or eryfluid or erygel or eryhexal or erymax or erymaxin or erymed or erysafe or erystrat or erytab or "eryth mycin" or erythelan or erythmycin or erythomycin or erythra-derm or erythran or "erythro 200" or "erythro teva" or erythro-statin or erythrogan or erythrogel or erythrogran or erythroguent or erythromid or erythroteva or erytop or erytrarco or erytroiclin or etinycine or etrolate or etromycin or ilocap* or ilotocina or ilotycin or "inderm gel" or labocne or latotryd or lederpax or mepharmycin or ("oftalmolosa cusi" adj (eritromicina or erythromycin)) or oftamolets or pantodrin or pantomycin or pce or pharyngocin or primacine or "r-p mycin" or robimycin or romycin or roymicin or "rp mycin" or rythocin or sans-acne or sansac or "skid gel e" or staticin or stiemycin or stimycine or "t stat" or theramycin).ti,ab.
22	exp minocycline/
23	(minocyclin* or "4,7 bis(dimethylamino) 1,10,11,12a tetrahydroxy 3,12 dioxo 4a,5,5a,6 tetrahydro 4h tetracene 2 carboxamide" or "4,7 bis(dimethylamino) 1,4,4a,5,5a,6,11,12a octahydro 3,10,12,12a tetrahydroxy 1,11 dioxo 2 naphthacenecarboxamide" or "7 dimethylamino 6 demethyl 6 deoxytetracycline" or akamin or aknemin or aknosan or amzeeq

	or arestin or borymycin or cyclimycin or cynomycin or dynacin or klinomycin or klinotab or lederderm or logryx or menocycline or mestacine or micromycin or minaxen or "mino-50" or mino-wolff or minocin or minocli\$ or minocyn or minogalen or minoline or minolira or minomax or minomycin or minotab or mirosin or mynocine or romin or skinocyclin or solodyn or spicline or vectran or vectrin or ximino or zilxi).ti,ab.
24	("2 hydroxyacid" or ("alpha" adj ("hydroxyacid" or "hydroxy acid" or "hydroxyacids" or "hydroxy acids"))).ti,ab.
25	("glycolic acid" or "2 hydroxyacetic acid" or glycolate or glycollate or "glycollic acid" or "hydroxyacetic acid" or "hydroxyethanoic acid").ti,ab.
26	((("beta hydroxy" adj acid*) or bha).ti,ab.
27	exp salicylic acid/
28	("salicylic acid" or "2 hydroxybenzoic acid" or catox or cerosal or cornina or dobagen or domerine or fomac or getreed or gordofilm or hydrisalic or ionil or keralyt or monphyto or occlusal or "ortho hydroxybenzoic acid" or "oxy clean" or phytodermine or pragmatar or psorimed or reipar or salac or salicresin or "salicyclic acid" or salicyl or salicylate or salikaren or salisol-2 or sanitos or sebucare or squamasol).ti,ab.
29	exp Hydroxybenzoates/
30	((hydroxybenzoic adj acid*) or hydroxybenzoate).ti,ab.
31	exp Dicarboxylic Acids/
32	((dicarboxylic adj acid*) or dicarboxylate).ti,ab.
33	((az?leic adj acid*) or "1,7 heptanedicarboxylic acid" or "anchoic acid" or azelate or azelea or azelex or "bay 39 6251" or "bay39 6251" or "bay396251" or cutacelan or finacea or finevin or "lepargylic acid" or nonanedioic or "sh c 441 f" or skinoderm or skinore\$ or zeliris or "zk 62498" or "zk62498").ti,ab.
34	(topical adj2 antiandrogen*).ti,ab.
35	exp sulfur/
36	(sulphur or sulfur or bensulfoid or fostril).ti,ab.
37	(sulfacetamide adj sodium).ti,ab.
38	exp Resorcinols/
39	(re?orcinol or "1,3 benzenediol" or "1,3 dihydroxybenzene" or "3 hydroxyphenol" or dihydroxybenzol or "durafur developer g" or "meta dihydroxybenzene" or "meta dihydroxybenzol" or recorcone or resorchine or resorcin* or rezamid).ti,ab.
40	or/4-39
41	(trifarotene or akief or "cd 5789" or "cd5789").ti,ab.
42	(clascoterone or "11 deoxycortisol 17alfa propionate" or "11 deoxycortisol 17alpha propionate" or "21 hydroxy 17 (1 oxopropoxy) 4 pregnene 3,20 dione" or "21 hydroxy 17 (1 oxopropoxy)pregn 4 ene 3,20 dione" or "21 hydroxy 3,20 dioxopregn 4 en 17 yl propanoate" or "[17 (2 hydroxyacetyl) 10,13 dimethyl 3 oxo 2,6,7,8,9,11,12,14,15,16 decahydro 1h cyclopenta[a]phenanthren 17 yl] propanoate" or "cb 03 01" or "cb0301" or "cortexolone 17alfa propionate" or "cortexolone 17alpha propionate" or winlevi).ti,ab.
43	or/41-42
44	Randomized Controlled Trials as Topic/
45	randomized controlled trial/
46	Random Allocation/
47	Double Blind Method/
48	Single Blind Method/
49	clinical trial/
50	clinical trial, phase i.pt.
51	clinical trial, phase ii.pt.
52	clinical trial, phase iii.pt.
53	clinical trial, phase iv.pt.
54	controlled clinical trial.pt.
55	randomized controlled trial.pt.

56	multicenter study.pt.
57	clinical trial.pt.
58	exp Clinical Trials as topic/
59	(clinical adj trial\$.tw.
60	((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.
61	PLACEBOS/
62	placebo\$.tw.
63	randomly allocated.tw.
64	(allocated adj2 random\$.tw.
65	or/44-64
66	Meta-Analysis as Topic/
67	meta analy\$.tw.
68	metaanaly\$.tw.
69	Meta-Analysis/
70	(systematic adj (review\$1 or overview\$1)).tw.
71	exp Review Literature as Topic/
72	cochrane.ab.
73	embase.ab.
74	(psychlit or psyclit).ab.
75	(psychinfo or psycinfo).ab.
76	(cinahl or cinhal).ab.
77	science citation index.ab.
78	bids.ab.
79	cancerlit.ab.
80	reference list\$.ab.
81	bibliograph\$.ab.
82	hand-search\$.ab.
83	relevant journals.ab.
84	manual search\$.ab.
85	or/66-84
86	selection criteria.ab.
87	data extraction.ab.
88	or/86-87
89	Review/
90	88 and 89
91	or/85,90
92	(pooled adj analys*).ti,ab.
93	or/65,91-92
94	and/3,40,93
95	limit 94 to yr="2014-current"
96	and/3,43,93
97	or/95-96
98	Case Study/
99	case report.tw.
100	letter/
101	(book or chapter or editorial or erratum or letter or note or short survey or tombstone or comment).pt.
102	(exp animal/ or nonhuman/) not exp human/
103	or/98-102
104	97 not 103
105	limit 104 to english
Database	Embase (via Ovid)

Search date	December 15, 2021
1	exp acne vulgaris/
2	acne.ti,ab.
3	or/1-2
4	exp retinoid/
5	retinoid*.ti,ab.
6	exp adapalene/
7	(adapalene or "6 [3 (1 adamantyl) 4 methoxyphenyl] 2 naphthoic acid" or acneclear or adaferin or "cd 271" or "cd271" or differin or differine or neopalen or redap).ti,ab.
8	exp adapalene plus benzoyl peroxide/
9	(effezel or epiduo or tactuo or tactuoben).ti,ab.
10	exp tazarotene/
11	(tazarotene or "6 [(3,4 dihydro 4,4 dimethyl 2h 1 benzothiopyran 6 yl)ethynyl] 3 pyridinecarboxylic acid ethyl ester" or "6 [2 (4,4 dimethylthiochroman 6 yl)ethynyl]nicotinic acid ethyl ester" or "agn 190168" or "agn190168" or arazlo or avage or "ethyl 6 [2 (4,4 dimethylthiochroman 6 yl)ethynyl]nicotinate" or fabior or tazaroten or tazorac or tazoral or zorac).ti,ab.
12	exp retinoic acid/
13	("retinoic acid" or "1 (8 carboxy 3,7 dimethyl 1,3,5,7 octatetraen 1 yl) 2,6,6 trimethyl 1 cyclohexene" or "11,13 dicis tretinoin" or "3,7 dimethyl 9 (2,6,6 trimethyl 1 cyclohexen 1 yl) 2,4,6,8 nonatetraenoic acid" or "3,7 dimethyl 9 (2,6,6 trimethyl 1 cyclohexen 1 yl)nona 2,4,6,8 tetraen 1 oic acid" or a-acido or aberel or aberela or "acid a vit" or "acne free" or acnederma or airol or alquingel or alten or altinac or altreno or "anhydroretinoic acid" or "ar 623" or "ar623" or atra or atragen or atralin or avita or avitcid or "beta retinoic acid" or betarretin or "cordes vas" or "derm a" or dermaol or "dermik a" or effederma or "epi aberel" or epiabderel or eudyna or facenol or ilotycin-a or ketrel or locacid or neocare or "nsc 122758" or "nsc122758" or "prosome a cream" or reacer-a or renova or retacnyl or retavit or retiderma or "retin a" or retinova or retirides or "retrieve cream" or "ro 01 5488" or "ro 1 5488" or "ro 15488" or "ro015488" or "ro15488" or "stieva a" or "stieva-a forte" or stievaa or trane or tretinoin or tretinoin or vesanoid or "vitamin A acid" or vitinoin).ti,ab.
14	exp benzoyl peroxide/
15	((benzoyl or dibenzoyl or diphenylglyoxal) adj (peroxide* or superoxide*)) or benzoylperoxide or acetoxyl or acnacyl or "acne derm" or "acne mask" or "acne-clear" or acneclear or acnecide or acnegel or acnetick-10 or acnexyl or acnie or akneroxid or aldoacne or basiron or benoxid or benoxyl or benzac* or benzagel* or benzashave or benzeperox or benzihex or benzolac or benzoperoxide or benzperox or brevoxyl or "clear by design" or clearplex or clearskin or "clinac bpo" or cordes or cutacnyl or debroxide or del-aqua or desquam* or diafen or "dry and clear" or eclaran or ecuaderm or effacne or eloxyl or "epi clear" or "fostex bpo" or inoxitan or klinoxid or "lisagel 5" or lucidol or mytolac or "nsc 676" or oxiderma or "oxy 10" or "oxy 5" or "oxy lotion" or "oxy preps" or "oxy sensitive vanishing gel" or "oxy wash" or oxyderm or pannogel or panoxyl or pansulfox or peroxiben or persadox or "persol gel" or pimplex or sanoxit or scherogel or seba-gel or theraderm or tinagel or topexac or triaz or tritaze or "ultra clearasil" or uvacnyl or vixiderm or xerac).ti,ab.
16	exp clindamycin/
17	(clind?mycin* or "7 chlor 7 desoxylincomycin" or "7 chloro 7 deoxylincomycin" or "7 chloro 7 desoxylincomycin" or "7 chlorolincomycin" or "7(s) chloro 7 deoxylincomycin" or "7s chloro 7 deoxylincomycin" or antirope or aquadrops or (cleocin adj (hcl or hydrochloride)) or cleocine or clinda-ipp or clinda-saar or "clindamycin in sodium chloride 0.9%" or clindasol or clinimycin or dalacin or "lincomycin,7 chloro" or sobelin or sobeline or "u 21251" or "u 21251f" or "u21251" or "u21251f" or zindaclin).ti,ab.
18	exp benzoyl peroxide plus clindamycin/

19	(acanya or "beclometasone dipropionate/formoterol fumarate" or benzaclin or clindoxyl or duac or "formoterol fumarate/beclometasone dipropionate" or "gsk 2585823" or "gsk2585823" or indoxyl or onexton or septigel).ti,ab.
20	exp dapsone/
21	(d?pson* or "4,4 bis(aminophenyl)sulfone" or "4,4 diaminodiphenylsulfone" or "4,4 sulfonyldianiline" or "4,4' diaminodiphenyl sulfone" or "4,4' sulfonylbisbenzamine" or aczone or atrisone or avlosulf?n* or "bis (4 aminophenyl)sulfone" or "bn 2405" or "bn2405" or croysulfone or dapsoderm-x or dds or "diamino diphenyl sulfone" or "diaminodiphenyl sulfone" or diaminodiphenylosulfone or diaminodiphenylsulfon* or diaminodiphenylsulfone or diammodiphenylsulfone or "diaphenyl sulfone" or diaphenylsulfon* or diaphenylsulphone or diphenason* or diphone or disulone or dunitone or eporal or "f 1358" or "f1358" or lennon-dapsone or lepravir or novasulfon or novophone or "nsc 6091" or "nsc6091" or "para,para' sulfodaniline" or servidapson* or sulfadione or sulfadoine or sulfona or "sulfone mere" or udolac).ti,ab.
22	exp erythromycin/
23	(erythromycin* or "a/t/s" or abomacetin or acneryne or acnesol or "akne mycin" or "aknederm ery gel" or aknemycin or anamycin or bonac gel or "c-solve-2" or cliniderm or deripil or duraerythromycin or "e mycin" or e-base or e-glades or "e-solve 2" or emgel or "emu v" or "emu-ve" or emuvin or emycin or eriecu or erimycin-t or eriprodin or eritimix or eritrex or eritrocina or eritromicina or erixyl or ermy?in or "ery maxin" or ery-b or ery-diolan or ery-tab or eryacne* or eryc or erycen or erycette or erycin or erycinum or eryderm or erydermec or erydermer or eryfluid or erygel or eryhexal or erymax or erymaxin or erymed or erysafe or erystrat or erytab or "eryth mycin" or erythelan or erythmycin or erythomycin or erythra-derm or erythran or "erythro 200" or "erythro teva" or erythro-statin or erythrogan or erythrogel or erythrogran or erythroguent or erythromid or erythroteva or erytop or erytrarco or erytrocinlin or etinycine or etolate or etromycin or ilocap* or ilotocina or ilotycin or "inderm gel" or labocne or latotryd or lederpax or mepharmycin or ("oftalmolosa cusi" adj (eritromicina or erythromycin)) or oftamolets or pantodrin or pantomycin or pce or pharyngocin or primacine or "r-p mycin" or robimycin or romycin or roymicin or "rp mycin" or rythocin or sans-acne or sansac or "skid gel e" or staticin or stiemycin or stimycine or "t stat" or theramycin).ti,ab.
24	exp minocycline/
25	(minocyclin* or "4,7 bis(dimethylamino) 1,10,11,12a tetrahydroxy 3,12 dioxo 4a,5,5a,6 tetrahydro 4h tetracene 2 carboxamide" or "4,7 bis(dimethylamino) 1,4,4a,5,5a,6,11,12a octahydro 3,10,12,12a tetrahydroxy 1,11 dioxo 2 naphthacenecarboxamide" or "7 dimethylamino 6 demethyl 6 deoxytetracycline" or akamin or aknemin or aknosan or amzeeq or arestin or borymycin or cyclimycin or cynomycin or dynacin or klinomycin or klinotab or lederderm or logryx or menocycline or mestacine or micromycin or minaxen or "mino-50" or mino-wolff or minocin or minocli\$1 or minocyn or minogalen or minoline or minolira or minomax or minomycin or minotab or mirosin or mynocine or romin or skinocyclin or solodyn or spicline or vectran or vectrin or ximino or zilxi).ti,ab.
26	exp 2 hydroxyacid/
27	("2 hydroxyacid" or ("alpha" adj ("hydroxyacid" or "hydroxy acid" or "hydroxyacids" or "hydroxy acids"))).ti,ab.
28	exp glycolic acid/
29	("glycolic acid" or "2 hydroxyacetic acid" or glycolate or glycollate or "glycollic acid" or "hydroxyacetic acid" or "hydroxyethanoic acid").ti,ab.
30	((("beta hydroxy" adj acid*) or bha).ti,ab.
31	exp salicylic acid/
32	("salicylic acid" or "2 hydroxybenzoic acid" or catox or cerosal or cornina or dobagen or domerine or fomac or getreed or gordofilm or hydrisalic or ionil or keralyt or monphyto or occlusal or "ortho hydroxybenzoic acid" or "oxy clean" or phytodermine or pragmatar or psorimed or reipar or salac or salicresin or "salicyclic acid" or salicyl or salicylate or salikaren or salisol-2 or sanitos or sebucare or squamasol).ti,ab.
33	exp hydroxybenzoic acid/

34	((hydroxybenzoic adj acid*) or hydroxybenzoate).ti,ab.
35	exp dicarboxylic acid/
36	((dicarboxylic adj acid*) or dicarboxylate).ti,ab.
37	exp azelaic acid/
38	((az?leic adj acid*) or "1,7 heptanedicarboxylic acid" or "anchoic acid" or azelate or azelea or azelex or "bay 39 6251" or "bay39 6251" or "bay396251" or cutacelan or finacea or finevin or "lepargylic acid" or nonanedioic or "sh c 441 f" or skinoderm or skinore\$ or zeliris or "zk 62498" or "zk62498").ti,ab.
39	(topical adj2 antiandrogen*).ti,ab.
40	exp sulfur/
41	(sulphur or sulfur or bensulfoid or fostril).ti,ab.
42	(sulfacetamide adj sodium).ti,ab.
43	exp resorcinol/
44	(re?orcinol or "1,3 benzenediol" or "1,3 dihydroxybenzene" or "3 hydroxyphenol" or dihydroxybenzol or "durafur developer g" or "meta dihydroxybenzene" or "meta dihydroxybenzol" or recorcone or resorchine or resorcin* or rezamid).ti,ab.
45	or/4-44
46	exp trifarotene/
47	(trifarotene or aklief or "cd 5789" or "cd5789").ti,ab.
48	exp clascoterone/
49	(clascoterone or "11 deoxycortisol 17alfa propionate" or "11 deoxycortisol 17alpha propionate" or "21 hydroxy 17 (1 oxopropoxy) 4 pregnene 3,20 dione" or "21 hydroxy 17 (1 oxopropoxy)pregn 4 ene 3,20 dione" or "21 hydroxy 3,20 dioxopregn 4 en 17 yl propanoate" or "[17 (2 hydroxyacetyl) 10,13 dimethyl 3 oxo 2,6,7,8,9,11,12,14,15,16 decahydro 1h cyclopenta[a]phenanthren 17 yl] propanoate" or "cb 03 01" or "cb0301" or "cortexolone 17alfa propionate" or "cortexolone 17alpha propionate" or winlevi).ti,ab.
50	or/46-49
51	Clinical Trial/
52	Randomized Controlled Trial/
53	controlled clinical trial/
54	multicenter study/
55	Phase 3 clinical trial/
56	Phase 4 clinical trial/
57	exp RANDOMIZATION/
58	Single Blind Procedure/
59	Double Blind Procedure/
60	Crossover Procedure/
61	PLACEBO/
62	randomi?ed controlled trial\$.tw.
63	rct.tw.
64	(random\$ adj2 allocat\$).tw.
65	single blind\$.tw.
66	double blind\$.tw.
67	((treble or triple) adj blind\$).tw.
68	placebo\$.tw.
69	Prospective Study/
70	or/51-69
71	exp Meta Analysis/
72	((meta adj analy\$) or metaanalys\$).tw.
73	(systematic adj (review\$1 or overview\$1)).tw.
74	cancerlit.ab.
75	cochrane.ab.
76	embase.ab.

77	(psychlit or psyclit).ab.
78	(psychinfo or psycinfo).ab.
79	(cinahl or cinhal).ab.
80	science citation index.ab.
81	bids.ab.
82	reference lists.ab.
83	bibliograph\$.ab.
84	hand-search\$.ab.
85	manual search\$.ab.
86	relevant journals.ab.
87	data extraction.ab.
88	selection criteria.ab.
89	review.pt.
90	or/71-89
91	(pooled adj analys*).ti,ab.
92	or/70,90-91
93	and/3,45,92
94	limit 93 to yr="2014-current"
95	and/3,50,92
96	or/94-95
97	Case Study/
98	case report.tw.
99	abstract report/ or letter/
100	(book or chapter or editorial or erratum or letter or note or short survey or tombstone or comment or conference proceeding or conference abstract).pt.
101	(exp animal/ or nonhuman/) not exp human/
102	or/97-101
103	96 not 102
104	limit 103 to english
CQs 4-9. Systemic antibiotics, Hormonal agents, Isotretinoin, Complementary and alternative medicine, and Diet (RCT search)	
Database	MEDLINE via PubMed
Search date	June 5, 2021 (Updated periodically through May 10, 2022)
#1	"Acne Vulgaris"[Mesh] OR acne[tiab]
#2	randomized controlled trial[pt] OR randomized controlled trials as topic[mh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR random*[tw] OR "Placebos"[Mesh] OR placebo[tiab] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw] OR dumm*[tw]))
#3	#1 AND #2
#4	#3 AND 2014:9999[dp]
CQ 4. Systemic antibiotics (non-RCT search)	
Database	MEDLINE via PubMed
Search date	June 5, 2021
#1	"Acne Vulgaris"[Mesh] OR acne[tiab]
#2	"Anti-Bacterial Agents"[Mesh] OR anti-bacterial*[tiab] OR antibiotic*[tiab] OR "Tetracycline"[Mesh] OR tetracycline[tiab] OR minocycline[tiab] OR doxycycline[tiab] OR Sarecycline[tiab] OR "Macrolides"[Mesh] OR macrolide[tiab] OR erythromycin[tiab] OR clarithromycin[tiab] OR azithromycin[tiab] OR "Penicillins"[Mesh] OR penicillin[tiab] OR ampicillin[tiab] OR amoxicillin[tiab] OR "Cephalosporins"[Mesh] OR cephalosporin[tiab] OR cephalixin[tiab] OR "Dapsone"[Mesh] OR dapsone[tiab] OR "Trimethoprim"[Mesh] OR "Trimethoprim, Sulfamethoxazole Drug Combination"[Mesh] OR trimethoprim*[tiab] OR "Antimicrobial Stewardship"[Mesh]
#3	#1 AND #2

#4	"Observational Study"[pt] OR observation*[tiab] OR cohort[tiab] OR (case-control[tiab] OR "case control"[tiab]) OR (prospective[tiab] OR "Prospective Studies"[Mesh] OR "Retrospective Studies"[Mesh] OR retrospective[tiab])
#5	#3 AND #4
#6	#5 AND 2014:2021[dp]
CQ 5. Hormonal agents (non-RCT search)	
Database	MEDLINE via PubMed
Search date	August 18, 2021
#1	"Acne Vulgaris"[Mesh] OR acne[tiab]
#2	"Contraceptives, Oral, Combined"[Mesh] OR contraceptive[tiab] OR hormon*[tiab] OR "Ethinyl Estradiol"[Mesh] OR ethinyl[tiab] OR estinyl[tiab] OR "Norethindrone"[Mesh] OR norethindrone[tiab] OR norgestimate[tiab] OR drospirenone[tiab] OR "Spironolactone"[Mesh] OR spironolactone[tiab] OR "Prednisone"[Mesh] OR prednisone[tiab] OR "Prednisolone"[Mesh] OR prednisolone[tiab]
#3	#1 AND #2
#4	"Observational Study"[pt] OR observation*[tiab] OR cohort[tiab] OR (case-control[tiab] OR "case control"[tiab]) OR (prospective[tiab] OR "Prospective Studies"[Mesh] OR "Retrospective Studies"[Mesh] OR retrospective[tiab])
#5	#3 AND #4
#6	#5 AND 2014:2021[dp]
CQ5. Hormonal agents (Metformin RCTs)	
Database	MEDLINE via PubMed
Search Date	November 11, 2021
#1	"Acne Vulgaris"[Mesh] OR acne[tiab]
#2	"Metformin"[Mesh] OR metformin[tiab]
#3	#1 AND #2
#4	randomized controlled trial[pt] OR randomized controlled trials as topic[mh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR random*[tw] OR "Placebos"[Mesh] OR placebo[tiab] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw] OR dumm*[tw]))
#5	#3 AND #4
CQ 6. Isotretinoin (non-RCT search)	
Database	MEDLINE via PubMed
Search date	December 3, 2021
#1	"Acne Vulgaris"[Mesh] OR acne[tiab]
#2	"Isotretinoin"[Mesh] or isotretinoin[tiab]
#3	#1 AND #2
#4	"Observational Study"[pt] OR observation*[tiab] OR cohort[tiab] OR (case-control[tiab] OR "case control"[tiab]) OR (prospective[tiab] OR "Prospective Studies"[Mesh] OR "Retrospective Studies"[Mesh] OR retrospective[tiab])
#5	#3 AND #4
#6	#5 AND 2014:2021[dp]
CQ 7. Physical Modalities	
Database	MEDLINE (via Ovid)
Search date	December 15, 2021
1	exp acne vulgaris/
2	acne.ti,ab.
3	or/1-2
4	exp Triamcinolone/
5	exp Triamcinolone Acetonide/

6	(tria?cinolon* or tria?cinolonacetoni* or (chemical adj peel*)).ti,ab.
7	(Intralesional adj steroid*).ti,ab.
8	("2 hydroxyacid" or (alpha adj ("hydroxyacid" or "hydroxy acid" or "hydroxyacids" or "hydroxy acids"))).ti,ab.
9	("glycolic acid" or "2 hydroxyacetic acid" or glycolate or glycollate or "glycollic acid" or "hydroxyacetic acid" or "hydroxyethanoic acid").ti,ab.
10	exp Lactic Acid/
11	((lactic adj acid*) or "2 hydroxypropanoic acid" or "2 hydroxypropionic acid" or "alpha hydroxypropionic acid").ti,ab.
12	((("beta hydroxy" adj acid*) or bha).ti,ab.
13	exp Salicylic Acid/
14	("salicylic acid" or "2 hydroxybenzoic acid" or catox or cerosal or cornina or dobagen or domerine or fomac or getreed or gordofilm or hydralisic or ionil or keralyt or monphyto or occlusal or "ortho hydroxybenzoic acid" or "oxy clean" or phytodermine or pragmatar or psorimed or reipar or salac or salicresin or "salicyclic acid" or salicyl or salicylate or salikaren or "salisol-2" or sanitos or sebucare or squamasol).ti,ab.
15	exp Hydroxybenzoates/
16	((hydroxybenzoic adj acid*) or hydroxybenzoate).ti,ab.
17	(Comedo adj2 extraction*).ti,ab.
18	exp Lasers/
19	(laser* or "light amplification by stimulated emission of radiation").ti,ab.
20	exp Phototherapy/
21	(phototherapy or photo-therapy or (light adj therap*)).ti,ab.
22	(photodynamic adj (therap* or treatment*)).ti,ab.
23	exp Photochemotherapy/
24	(photochemotherap* or phototherap*).ti,ab.
25	exp Photosensitizing Agents/
26	(photosensiti?ing adj agent*).ti,ab.
27	exp Ultraviolet Therapy/
28	(ultraviolet adj2 therap*).ti,ab.
29	exp Photolysis/
30	photolysis.ti,ab.
31	exp Aminolevulinic Acid/
32	((((aminol?vulinic or aminolaevulinic or "amino levulinic" or "amino laevulinic" or "amino lavulinic") adj acid*) or "5 amino 4 oxopentanoic acid" or aminolaevulinate or aminolevulinate).ti,ab.
33	or/4-32
34	Randomized Controlled Trials as Topic/
35	randomized controlled trial/
36	Random Allocation/
37	Double Blind Method/
38	Single Blind Method/
39	clinical trial/
40	clinical trial, phase i.pt.
41	clinical trial, phase ii.pt.
42	clinical trial, phase iii.pt.
43	clinical trial, phase iv.pt.
44	controlled clinical trial.pt.
45	randomized controlled trial.pt.
46	multicenter study.pt.
47	clinical trial.pt.
48	exp Clinical Trials as topic/
49	(clinical adj trial\$).tw.

50	((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.
51	PLACEBOS/
52	placebo\$.tw.
53	randomly allocated.tw.
54	(allocated adj2 random\$).tw.
55	or/34-54
56	Meta-Analysis as Topic/
57	meta analy\$.tw.
58	metaanaly\$.tw.
59	Meta-Analysis/
60	(systematic adj (review\$1 or overview\$1)).tw.
61	exp Review Literature as Topic/
62	cochrane.ab.
63	embase.ab.
64	(psychlit or psyclit).ab.
65	(psychinfo or psycinfo).ab.
66	(cinahl or cinhal).ab.
67	science citation index.ab.
68	bids.ab.
69	cancerlit.ab.
70	reference list\$.ab.
71	bibliograph\$.ab.
72	hand-search\$.ab.
73	relevant journals.ab.
74	manual search\$.ab.
75	or/56-74
76	selection criteria.ab.
77	data extraction.ab.
78	or/76-77
79	Review/
80	78 and 79
81	or/75,80
82	(pooled adj analys*).ti,ab.
83	or/55,81-82
84	and/3,33,83
85	Case Study/
86	case report.tw.
87	letter/
88	(book or chapter or editorial or erratum or letter or note or short survey or tombstone or comment).pt.
89	(exp animal/ or nonhuman/) not exp human/
90	or/85-89
91	84 not 90
92	limit 91 to english
93	limit 92 to yr="2014-current"
Database	Embase (via Ovid)
Search date	December 15, 2021
1	exp acne vulgaris/
2	acne.ti,ab.
3	or/1-2
4	exp triamcinolone/
5	exp triamcinolone acetone/

6	(Intralesional adj steroid*).ti,ab.
7	(tria?cinolon* or tria?cinolonacetone* or (chemical adj peel*)).ti,ab.
8	exp 2 hydroxyacid/
9	("2 hydroxyacid" or ("alpha" adj ("hydroxyacid" or "hydroxy acid" or "hydroxyacids" or "hydroxy acids"))).ti,ab.
10	exp glycolic acid/
11	("glycolic acid" or "2 hydroxyacetic acid" or glycolate or glycollate or "glycollic acid" or "hydroxyacetic acid" or "hydroxyethanoic acid").ti,ab.
12	exp lactic acid/
13	((lactic adj acid*) or "2 hydroxypropanoic acid" or "2 hydroxypropionic acid" or "alpha hydroxypropionic acid").ti,ab.
14	((("beta hydroxy" adj acid*) or bha).ti,ab.
15	exp Salicylic Acid/
16	("salicylic acid" or "2 hydroxybenzoic acid" or catox or cerosal or cornina or dobagen or domerine or fomac or getreed or gordofilm or hydrisalic or ionil or keralyt or monphyto or occlusal or "ortho hydroxybenzoic acid" or "oxy clean" or phytodermine or pragmatar or psorimed or reipar or salac or salicresin or "salicyclic acid" or salicyl or salicylate or salikaren or salisol-2 or sanitos or sebucare or squamasol).ti,ab.
17	exp hydroxybenzoic acid/
18	((hydroxybenzoic adj acid*) or hydroxybenzoate).ti,ab.
19	(Comedo adj2 extraction*).ti,ab.
20	exp laser/
21	(laser* or "light amplification by stimulated emission of radiation").ti,ab.
22	exp phototherapy/
23	(phototherapy or photo-therapy or (light adj therap*)).ti,ab.
24	exp photodynamic therapy/
25	(photodynamic adj (therap* or treatment*)).ti,ab.
26	exp photochemotherapy/
27	(photochemotherap* or phototherap*).ti,ab.
28	exp photosensitizing agent/
29	(photosensiti?ing adj agent*).ti,ab.
30	(ultraviolet adj2 therap*).ti,ab.
31	exp photolysis/
32	photolysis.ti,ab.
33	((((aminol?vulnic or aminolaevulinic or "amino levulinic" or "amino laevulinic" or "amino lavulinic") adj acid*) or "5 amino 4 oxopentanoic acid" or aminolaevulinate or aminolevulinate).ti,ab.
34	or/4-33
35	Clinical Trial/
36	Randomized Controlled Trial/
37	controlled clinical trial/
38	multicenter study/
39	Phase 3 clinical trial/
40	Phase 4 clinical trial/
41	exp RANDOMIZATION/
42	Single Blind Procedure/
43	Double Blind Procedure/
44	Crossover Procedure/
45	PLACEBO/
46	randomi?ed controlled trial\$.tw.
47	rct.tw.
48	(random\$ adj2 allocat\$).tw.
49	single blind\$.tw.

50	double blind\$.tw.
51	((treble or triple) adj blind\$.tw.
52	placebo\$.tw.
53	Prospective Study/
54	or/35-53
55	exp Meta Analysis/
56	((meta adj analy\$) or metaanalys\$.tw.
57	(systematic adj (review\$1 or overview\$1)).tw.
58	cancerlit.ab.
59	cochrane.ab.
60	embase.ab.
61	(psychlit or psyclit).ab.
62	(psychinfo or psycinfo).ab.
63	(cinahl or cinhal).ab.
64	science citation index.ab.
65	bids.ab.
66	reference lists.ab.
67	bibliograph\$.ab.
68	hand-search\$.ab.
69	manual search\$.ab.
70	relevant journals.ab.
71	data extraction.ab.
72	selection criteria.ab.
73	review.pt.
74	or/55-73
75	(pooled adj analys*).ti,ab.
76	or/54,74-75
77	and/3,34,76
78	Case Study/
79	case report.tw.
80	abstract report/ or letter/
81	(book or chapter or editorial or erratum or letter or note or short survey or tombstone or comment or conference proceeding or conference abstract).pt.
82	(exp animal/ or nonhuman/) not exp human/
83	or/78-82
84	77 not 83
85	limit 84 to english
86	limit 85 to yr="2014-current"

Study Selection

A reviewer was responsible for reviewing abstracts according to the pre-defined selection criteria (**e-Table 2**). All eligible studies identified during title/abstract screening, as well as 54 studies from the 2016 acne guidelines were proceeded to the full-text screening phase, where they were assessed for eligibility by the same reviewer. Studies that matched the PICO criteria following the full-text screening were included for data extraction.

Data Extraction

Using structured data abstraction forms, data extraction was initially performed by an independent reviewer with subsequent quality control performed by a second reviewer.

Risk of Bias Assessment and Evidence Synthesis

Study quality was assessed using Cochrane's Risk of Bias Tool.² Following risk of bias assessment, the Cochrane Collaboration Review Manager, version 5.3³ was used to conduct meta-analyses when data were

homogenous and poolable. Individual estimates were pooled using a random-effects model and the method of DerSimonian and Laird.^{4, 5} For dichotomous and continuous outcomes risk ratios and mean differences with accompanying 95% CIs were reported, respectively. Statistical heterogeneity was assessed using the Higgins I² value and the χ^2 test. A Higgins' I² value $\geq 75\%$ were considered to represent significant heterogeneity. Narrative synthesis was conducted when meta-analysis was not possible due to insufficient data reporting, differences in study designs, interventions, or comparators, or statistical heterogeneity suggesting that an average effect across studies is not useful.

Assessing the Overall Certainty of the Body of Evidence

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach was used to assess the overall certainty of the evidence for each critical or important outcome.⁶ The GRADEPro Guideline Development Tool (online software) was used to create evidence profiles that categorized the overall certainty of the body of evidence for each outcome into one of four categories: high, moderate, low, or very low. Each category represents the confidence in the estimate of effect for an outcome (**e-Table 9**).

e-Table 9. Certainty of evidence ratings

Certainty of the Evidence	Confidence in the Estimate of Effect
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very Low	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Formulating and Grading Recommendations

The Work Group drafted recommendations using the evidence profiles and considering the following: desirable effects, undesirable effects, certainty of the evidence, values & preferences, balance of effects, resources (costs) and certainty around the resources, equity, acceptability, and feasibility (**e-Table 10**).⁷ In accordance with the GRADE approach, recommendations were either “strong” or “conditional”.⁸ The implications of each strength of recommendation are summarized in **e-Table 11**. Recommendations were also graded according to the GRADE approach.⁸ In situations in which the supporting evidence for a recommendation was indirect only or not available, but the certainty surrounding an intervention’s impact was high and the benefits of the intervention clearly outweigh the harms (or vice versa), a Good Practice Statement was developed.⁹ Good Practice Statements are strong recommendations as the certainty surrounding the impact of the recommended intervention is high.

e-Table 10. GRADE Evidence to recommendation framework⁷

Criterion	Question
Problem	Is the problem a priority?
Desirable effects	How substantial are the desirable anticipated effects?
Undesirable effects	How substantial are the undesirable anticipated effects?
Certainty of the evidence	What is the overall certainty of the evidence of effects?
Values and preferences	Is there important uncertainty about or variability in how much people value the main outcomes?
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison?
Resource use	How large are the resource requirements (costs)?

Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)?
Cost effectiveness	Does the cost effectiveness of the intervention favour the intervention or the comparison?
Equity	What would be the impact on health equity?
Acceptability	Is the intervention acceptable to key stakeholders?
Feasibility	Is the intervention feasible to implement?

e-Table 11. Strength of recommendation implications

Strength	Implication
Strong	Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh the benefits
Conditional	Benefits finely balanced with risks and burden

Manuscript Review and Currency Statement

This guideline was developed in accordance with the AAD/AAD Association Administrative Regulations for Evidence-Based Clinical Practice Guidelines (March 2021), which includes the opportunity for review and comment by the entire AAD membership and final review and comment by the AAD Board of Directors.¹⁰ This guideline will be considered current for a period of 5 years from the date of publication unless reaffirmed, updated, or retired before that time.

Search Results

Acne Grading and Classification

The titles and abstracts of a total of 1,898 references identified from the search conducted in June 2021 were screened, 59 of which were included for full-text screening. Following the full-text screening, 10 of the 59 studies were included along with 8 and 6 studies from the 2016 and 2007 guidelines^{11, 12}, respectively, totaling 24 studies included for this section.

Microbiological and Endocrine Testing

The titles and abstracts of a total of 1,239 references identified from the search conducted in June 2021 were screened, 90 of which were included for full-text screening. Following the full-text screening, 50 of the 90 studies were included along with 11 and 1 studies from the 2016 and 2007 guidelines^{11, 12}, respectively, totaling 52 studies included for this section.

Topical Therapies

The titles and abstracts of a total of 1,389 references (1,262 references identified from the search conducted in December 2021 and 127 from the two previous guidelines) were screened, 103 of which were included for full-text screening. Following the full-text screening, 156 publications were included, pertaining to 137 unique studies. Of the included studies, 65 publications pertaining to 57 unique studies were included in the evidence synthesis.

Systemic Antibiotics

The titles and abstracts of a total of 1,194 references identified from the search conducted in June 2021 were screened, 52 were included for full-text screening. We have identified 14 additional studies from a systematic review that meets our PICO eligibility criteria. Following the full-text screening, 10 of the 52 studies were included along with 5 and 11 studies from the 2016 and 2007 guidelines^{11, 12}, respectively, and 12 studies from manual search, totaling 38 studies (40 trials) included for this section.

Hormonal Agents

The titles and abstracts of a total of 883 references identified from the searches conducted in June 2021, August 21, and November 2021 were screened, 40 of which were included for full-text screening. Following the full-text screening, 27 of the 40 studies were included along with 4 and 8 studies from the 2016 and 2007 guidelines^{11, 12}, respectively, totaling 39 studies (40 trials) included for this section.

Isotretinoin

The titles and abstracts of a total of 973 references identified from the searches conducted in December 2021 were screened, 58 of which were included for full-text screening. Following the full-text screening, 15 of the 58 studies were included along with 9 and 5 studies from the 2016 and 2007 guidelines^{11, 12}, respectively, and 5 from manual search, totaling 34 studies included for this section.

Physical Modalities

The titles and abstracts of a total of 803 references (745 references identified from the search conducted in December 2021 and 58 from the two previous guidelines^{11, 12} and manual search) were screened, 107 of which were included for full-text screening. Following the full-text screening, 74 publications were included for this section.

Complementary / Alternative Therapies

The titles and abstracts of a total of 935 references identified from the search conducted in May 2022 were screened, 16 of which were included for full-text screening. Following the full-text screening, 9 of the 16 studies were included along with 2 and 1 studies from the 2016 and 2007 guidelines^{11, 12}, respectively, and 2 studies from manual search, totaling 14 studies included for this section.

Dietary Interventions

The titles and abstracts of a total of 935 references identified from the search conducted in May 2022 were screened, 16 of which were included for full-text screening. Following the full-text screening, 3 of the 16 studies were included along with 5 studies from the 2016 guideline¹¹, totaling 7 studies (5 trials) included for this section.

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GRADE Evidence Profiles

Topical Therapies

1. Topical retinoid vs. vehicle

e-Table 12. GRADE Evidence Profile for topical retinoid vs. vehicle

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		

Investigator Global Assessment, Grade 0-1 at 12 weeks

4 ^{1,2,3,4}	randomised trials	not serious	not serious	not serious	not serious	none	337/1258 (26.8%)	156/909 (17.2%)	RR 1.57 (1.21 to 2.04)	98 more per 1,000 (from 36 more to 178 more)	⊕⊕⊕⊕ High	CRITICAL

Investigator Global Assessment, Grade 0-1 and ≥2-grade reduction at 12 weeks

3 ^{5,6}	randomised trials	not serious	not serious	not serious	not serious	none	676/2013 (33.6%)	418/2021 (20.7%)	RR 1.63 (1.46 to 1.80)	130 more per 1,000 (from 95 more to 165 more)	⊕⊕⊕⊕ High	CRITICAL

Acne severity index at 8 weeks (mean percent change from baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ⁷	randomised trials	not serious	not serious	not serious	serious ^a	none	32	15	-	MD 13.55 lower (33.32 lower to 6.22 higher)	⊕⊕⊕ ○ Moderate	CRITICAL

Acne severity, Evaluator Global Severity Score, Grade 0-1 and ≥2-grade reduction at 12 weeks (Sex: females)

2 ^{8,9}	randomised trials	not serious	not serious	not serious	not serious	none	111/470 (23.6%)	69/514 (13.4%)	RR 1.75 (1.33 to 2.31)	101 more per 1,000 (from 44 more to 176 more)	⊕⊕⊕⊕ High	CRITICAL

Acne severity, Evaluator Global Severity Score, Grade 0-1 and ≥2-grade reduction at 12 weeks (Sex: females; pediatric to adolescent)

2 ^{10,11}	randomised trials	not serious	not serious	not serious	not serious	none	90/365 (24.7%)	53/383 (13.8%)	RR 1.78 (1.31 to 2.42)	108 more per 1,000 (from 43 more to 197 more)	⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Any, 21-40% reduction at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹²	randomised trials	not serious	not serious	not serious	serious ^b	none	0/30 (0.0%)	0/30 (0.0%)	not estimable		⊕⊕⊕ ○ Moderate	CRITICAL

Number of lesions, Any, <50% reduction at 12 weeks

1 ¹²	randomised trials	not serious	not serious	not serious	serious ^c	none	0/30 (0.0%)	30/30 (100.0%)	RR 0.02 (0.00 to 0.26)	980 fewer per 1,000 (from 740 fewer to --)	⊕⊕⊕ ○ Moderate	CRITICAL

Number of lesions, Any, ≥50% reduction at 8 weeks

1 ¹³	randomised trials	not serious	not serious	not serious	serious ^a	none	53/124 (42.7%)	40/129 (31.0%)	RR 1.38 (0.99 to 1.91)	118 more per 1,000 (from 3 fewer to 282 more)	⊕⊕⊕ ○ Moderate	CRITICAL

Number of lesions, Any, ≥50% reduction at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		
3 ^{12,13,14}	randomised trials	not serious	serious ^d	not serious	serious ^e	none	155/227 (68.3%)	91/222 (41.0%)	RR 1.54 (0.86 to 2.75)	221 more per 1,000 (from 57 fewer to 717 more)	⊕⊕○ ○ Low	CRITICAL

Number of lesions, Any, 41-60% reduction at 12 weeks

1 ¹²	randomised trials	not serious	not serious	not serious	serious ^b	none	0/30 (0.0%)	0/30 (0.0%)	not estimable		⊕⊕⊕ ○ Moderate	CRITICAL

Number of lesions, Any, 61-95% reduction at 12 weeks

1 ¹²	randomised trials	not serious	not serious	not serious	serious ^c	none	19/30 (63.3%)	0/30 (0.0%)	RR 39.00 (2.46 to 617.81)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕ ○ Moderate	CRITICAL

Number of lesions, Any, 100% reduction at 12 weeks

1 ¹²	randomised trials	not serious	not serious	not serious	serious ^c	none	11/30 (36.7%)	0/30 (0.0%)	RR 23.00 (1.42 to 373.46)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕ ○ Moderate	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Inflammatory, ≥50% reduction at 12 weeks

1 ¹⁴	randomised trials	not serious	not serious	not serious	serious ^a	none	55/73 (75.3%)	42/63 (66.7%)	RR 1.13 (0.91 to 1.41)	87 more per 1,000 (from 60 fewer to 273 more)	⊕⊕⊕ ○ Moderate	CRITICAL

Number of lesions, Any at 8 weeks (mean percent change from baseline)

1 ⁷	randomised trials	not serious	not serious	not serious	serious ^a	none	32	15	-	MD 15.51 lower (34.57 lower to 3.55 higher)	⊕⊕⊕ ○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, ≥50% reduction at 12 weeks

1 ¹⁴	randomised trials	not serious	not serious	not serious	serious ^c	none	62/73 (84.9%)	35/63 (55.6%)	RR 1.53 (1.20 to 1.95)	294 more per 1,000 (from 111 more to 528 more)	⊕⊕⊕ ○ Moderate	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Any at 12 weeks (mean percent change from baseline)

2 ^{13,15}	randomised trials	not serious	not serious	not serious	serious ^f	none	Lucky 1998 At week 12, patients receiving commercially-available tretinoin and tretinoin with polyolprepolymer-2 had significantly lower total lesion counts than those receiving vehicle. The mean percent decrease in total lesion count was significantly higher for patients receiving commercially-available tretinoin and tretinoin with polyolprepolymer-2 as compared with vehicle at week 12 (p<0.05). Shalita 1999 Mean percent decreases from baseline in total lesion counts were statistically significant at week 12 (p<0.001) in both tazarotene 0.05% gel and 0.1% gel groups. Both concentrations were significantly more effective than vehicle (p<0.05) at week 12			⊕⊕⊕ ○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (PERFECT 1 study; face; mean absolute change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ⁵	randomised trials	not serious	not serious	not serious	not serious	none	612 and 596 patients were randomized to receive topical retinoid or vehicle, respectively. The mean absolute changes from baseline for topical retinoid and vehicle groups were -19 and -15.4, respectively. The difference between the two groups was statistically significant ($p < 0.001$).				⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Inflammatory at 12 weeks (PERFECT 2 study; face; mean absolute change from baseline)

1 ⁵	randomised trials	not serious	not serious	not serious	not serious	none	602 and 610 patients were randomized to receive topical retinoid or vehicle, respectively. The mean absolute changes from baseline for topical retinoid and vehicle groups were -24.2 and -18.7, respectively. The difference between the two groups was statistically significant ($p < 0.001$).				⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Inflammatory at 12 weeks (PERFECT 1 study; face; mean percent change from baseline)

1 ⁵	randomised trials	not serious	not serious	not serious	not serious	none	612 and 596 patients were randomized to receive topical retinoid or vehicle, respectively. The mean percentage changes from baseline for topical retinoid and vehicle groups were -54.4% and -44.8%, respectively. The difference between the two groups was statistically significant ($p < 0.001$).				⊕⊕⊕⊕ High	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Inflammatory at 12 weeks (PERFECT 2 study; face; mean percent change from baseline)

1 ⁵	randomised trials	not serious	not serious	not serious	not serious	none	602 and 610 patients were randomized to receive topical retinoid or vehicle, respectively. The mean percentage changes from baseline for topical retinoid and vehicle groups were -66.2% and -51.2%, respectively. The difference between the two groups was statistically significant ($p < 0.001$).			⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Inflammatory at 8 weeks (mean percent change from baseline)

1 ⁷	randomised trials	not serious	not serious	not serious	serious ^a	none	32	15	-	MD 11.73 lower (32.35 lower to 8.89 higher)	⊕⊕⊕ ○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline)

5 ^{4,6,13,15,16}	randomised trials	not serious	not serious	not serious	serious ^{a,g}	none	Lucky 1998: At week 12, patients receiving commercially-available tretinoin and tretinoin with polyolprepolymer-2 had significantly lower inflammatory lesion counts than those receiving vehicle. The mean percent decrease in inflammatory lesion count was significantly higher for patients receiving commercially-available tretinoin and tretinoin with polyolprepolymer-2 as compared with vehicle at week 12 ($p<0.05$). Shalita 1999: Mean percent decreases from baseline in inflammatory lesion counts were statistically significant at week 12 ($p<0.001$) in both tazarotene 0.05% gel and 0.1% gel groups. Both concentrations were significantly more effective than vehicle ($p<0.05$) at week 12. Tanghetti 2019: Mean percentage change from baseline at week 12 in inflammatory lesion count was -63.8% and -51.4% in tazarotene 0.045% and vehicle, respectively ($p=0.006$) Webster 2020 Mean percentage change from baseline at week 12 in noninflammatory lesion count was -55.8% and -30.7% in encapsulated all-trans-retinoic acid 0.1% and vehicle groups, respectively ($p<0.001$) Tanghetti 2020: Mean inflammatory lesion counts were reduced 57.9% and 47.8% in the tazarotene and vehicle arms, respectively ($p<0.001$) at week 12	⊕⊕⊕ ○ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Inflammatory at 12 weeks (Sex: females; mean percent change from baseline)

1 ⁸	randomised trials	not serious	not serious	not serious	serious ^h	none	The mean percentage changes from baseline for topical retinoid and vehicle groups were -65.4% (n: 41) and -53.6% (n: 38), respectively.		⊕⊕⊕ ○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (Sex: females; pediatric to adolescent; mean percent change from baseline)

1 ¹⁷	randomised trials	not serious	not serious	not serious	serious ^h	none	The mean percentage changes from baseline for topical retinoid and vehicle groups were -55.3% (n: 173) and -45.2% (n: 184), respectively. The difference between the two groups was statistically significant (p = 0.019).		⊕⊕⊕ ○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean percent change from baseline)

5 ^{4,6,13,15,16}	randomised trials	not serious	not serious	not serious	serious ^f	none	Lucky 1998: At week 12, patients receiving commercially-available tretinoin and tretinoin with polyolprepolymer-2 had significantly lower noninflammatory lesion counts than those receiving vehicle. The mean percent decrease in noninflammatory lesion count was significantly higher for patients receiving commercially-available tretinoin and tretinoin with polyolprepolymer-2 as compared with vehicle at week 12 ($p<0.05$). Shalita 1999: Mean percent decreases from baseline in noninflammatory lesion counts were statistically significant at week 12 ($p<0.001$) in both tazarotene 0.05% gel and 0.1% gel groups. Both concentrations were significantly more effective than vehicle ($p<0.05$) at week 12. Tanghetti 2019: Mean percentage change from baseline at week 12 in noninflammatory lesion count was -56.9% and -35.2% in tazarotene 0.045% and vehicle, respectively ($p<0.001$) Webster 2020: Mean percentage change from baseline at week 12 in noninflammatory lesion count was -58.6% and -32.4% in encapsulated all-trans-retinoic acid 0.1% and vehicle groups, respectively ($p<0.001$) Tanghetti 2020: Mean inflammatory lesion counts were reduced 56.0% and 42.0% in the tazarotene and vehicle arms, respectively ($p<0.001$) at week 12	⊕⊕⊕ ○ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Non-inflammatory at 12 weeks (Sex: females; mean percent change from baseline)

1 ⁸	randomised trials	not serious	not serious	not serious	serious ^h	none	The mean percentage changes from baseline for topical retinoid and vehicle groups were -57.2% (n: 41) and -40.9% (n: 38), respectively.		⊕⊕⊕ ○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (Sex: females; pediatric to adolescent; mean percent change from baseline)

1 ¹⁷	randomised trials	not serious	not serious	not serious	serious ^h	none	The mean percentage changes from baseline for topical retinoid and vehicle groups were -47.1% (n: 173) and -27.6% (n: 184), respectively. The difference between the two groups was statistically significant (p < 0.001).		⊕⊕⊕ ○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (PERFECT 1 study; face; mean absolute change from baseline)

1 ⁵	randomised trials	not serious	not serious	not serious	not serious	none	612 and 596 patients were randomized to receive topical retinoid or vehicle, respectively. The mean absolute changes from baseline for topical retinoid and vehicle groups were -25 and -17.9, respectively. The difference between the two groups was statistically significant (p < 0.001).		⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (PERFECT 2 study; face; mean absolute change from baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ⁵	randomised trials	not serious	not serious	not serious	not serious	none	602 and 610 patients were randomized to receive topical retinoid or vehicle, respectively. The mean absolute changes from baseline for topical retinoid and vehicle groups were -30.1 and -21.6, respectively. The difference between the two groups was statistically significant ($p < 0.001$).				⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (PERFECT 1 study; face; mean percent change from baseline)

1 ⁵	randomised trials	not serious	not serious	not serious	not serious	none	612 and 596 patients were randomized to receive topical retinoid or vehicle, respectively. The mean percentage changes from baseline for topical retinoid and vehicle groups were -49.7% and -35.7%, respectively. The difference between the two groups was statistically significant ($p < 0.001$).				⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (PERFECT 2 study; face; mean percent change from baseline)

1 ⁵	randomised trials	not serious	not serious	not serious	not serious	none	602 and 610 patients were randomized to receive topical retinoid or vehicle, respectively. The mean percentage changes from baseline for topical retinoid and vehicle groups were -57.7% and -43.9%, respectively. The difference between the two groups was statistically significant ($p < 0.001$).				⊕⊕⊕⊕ High	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Non-inflammatory at 12 weeks (PERFECT 2 study; trunk; mean percent change from baseline)

1 ⁵	randomised trials	not serious	not serious	not serious	not serious	none	The mean percentage changes from baseline for topical retinoid and vehicle groups were -55.2% (n: 598) and -45.1% (n: 609), respectively. The difference between the two groups was statistically significant (p < 0.001).				⊕⊕⊕⊕ High	CRITICAL

Acne-Specific QoL at 12 weeks

1 ⁶	randomised trials	not serious	not serious	not serious	not serious	none	Improvements in Acne-Specific QoL scores at 12 weeks were numerically greater for the tazarotene 0.045% cohort versus vehicle in all 4 domains (self-perception: 7.5 vs. 6.7; role emotional: 6.0 vs. 5.5; role-social: 4.7 vs. 4.1; acne symptoms: 6.4 vs. 5.3)				⊕⊕⊕⊕ High	IMPORTANT

Acne severity, Patient assessment of improvement, Clear/Almost clear at 12 weeks

1 ¹⁶	randomised trials	not serious	not serious	not serious	serious ^a	none	25/72 (34.7%)	16/69 (23.2%)	RR 1.50 (0.88 to 2.55)	116 more per 1,000 (from 28 fewer to 359 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

Acne severity, Patient assessment of improvement, Grade 0-1 at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	308/464 (66.4%)	128/242 (52.9%)	RR 1.25 (1.10 to 1.44)	132 more per 1,000 (from 53 more to 233 more)	⊕⊕⊕⊕ High	IMPORTANT

AE, Any, Leading to discontinuation at 12 weeks

2 ^{2,3}	randomised trials	not serious	not serious	not serious	serious ^e	none	6/676 (0.9%)	5/552 (0.9%)	RR 0.82 (0.08 to 8.08)	2 fewer per 1,000 (from 8 fewer to 64 more)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Any, Leading to discontinuation at 12 weeks

4 ^{4,6,16,18}	randomised trials	not serious	not serious	not serious	not serious	none	25/1455 (1.7%)	9/1343 (0.7%)	RR 1.75 (0.31 to 9.80)	5 more per 1,000 (from 5 fewer to 59 more)	⊕⊕⊕⊕ High	IMPORTANT

AE, Any, Leading to discontinuation at 12 weeks (Females)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹⁹	randomised trials	not serious	not serious	not serious	serious ^j	none	4/433 (0.9%)	0/476 (0.0%)	RR 9.89 (0.53 to 183.20)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Burning at 4 weeks

2 ^{13,15}	randomised trials	not serious	not serious	not serious	serious ^c	none	20/198 (10.1%)	5/199 (2.5%)	RR 3.87 (1.48 to 10.10)	72 more per 1,000 (from 12 more to 229 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Burning at 8 weeks

1 ¹³	randomised trials	not serious	not serious	not serious	serious ^a	none	4/124 (3.2%)	3/129 (2.3%)	RR 1.39 (0.32 to 6.07)	9 more per 1,000 (from 16 fewer to 118 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Burning at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		
3 ^{12,13,15}	randomised trials	not serious	not serious	not serious	serious ^e	none	21/228 (9.2%)	12/229 (5.2%)	RR 1.76 (0.66 to 4.72)	40 more per 1,000 (from 18 fewer to 195 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Burning, Mild at 12 weeks

1 ⁴	randomised trials	not serious	not serious	not serious	serious ^c	none	32/118 (27.1%)	12/115 (10.4%)	RR 2.60 (1.41 to 4.79)	167 more per 1,000 (from 43 more to 395 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Burning, Moderate at 12 weeks

1 ⁴	randomised trials	not serious	not serious	not serious	serious ^c	none	12/118 (10.2%)	2/115 (1.7%)	RR 5.85 (1.34 to 25.55)	84 more per 1,000 (from 6 more to 427 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Burning, Severe at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ⁴	randomised trials	not serious	not serious	not serious	serious ^k	none	1/118 (0.8%)	0/115 (0.0%)	RR 2.92 (0.12 to 71.06)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Dryness at 4 weeks

2 ^{13,15}	randomised trials	not serious	serious ^l	not serious	serious ^k	none	34/198 (17.2%)	11/199 (5.5%)	RR 4.42 (0.46 to 42.68)	189 more per 1,000 (from 30 fewer to 1,000 more)	⊕⊕○ ○ Low	IMPORTANT

AE, Dryness at 8 weeks

1 ¹³	randomised trials	not serious	not serious	not serious	serious ^k	none	6/124 (4.8%)	1/129 (0.8%)	RR 6.24 (0.76 to 51.11)	41 more per 1,000 (from 2 fewer to 388 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Dryness at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		
4 ^{4,13,15,16}	randomised trials	not serious	not serious	not serious	not serious	none	26/384 (6.8%)	9/381 (2.4%)	RR 2.81 (1.35 to 5.83)	43 more per 1,000 (from 8 more to 114 more)	⊕⊕⊕⊕ High	IMPORTANT

TEAE, Dryness at 12 weeks

1 ¹⁸	randomised trials	not serious	not serious	not serious	not serious	none	28/767 (3.7%)	1/783 (0.1%)	RR 28.58 (3.90 to 209.57)	35 more per 1,000 (from 4 more to 266 more)	⊕⊕⊕⊕ High	IMPORTANT

AE, Dryness at 12 weeks (Female & Pediatric to adolescent)

1 ¹⁷	randomised trials	not serious	not serious	not serious	serious ^c	none	9/163 (5.5%)	0/178 (0.0%)	RR 20.74 (1.22 to 353.51)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Erythema at 4 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		
2 ^{13,15}	randomised trials	not serious	not serious	not serious	serious ^a	none	32/198 (16.2%)	15/199 (7.5%)	RR 2.22 (0.70 to 7.04)	92 more per 1,000 (from 23 fewer to 455 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Erythema at 8 weeks

1 ¹³	randomised trials	not serious	not serious	not serious	serious ^k	none	4/124 (3.2%)	1/129 (0.8%)	RR 4.16 (0.47 to 36.72)	24 more per 1,000 (from 4 fewer to 277 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Erythema at 12 weeks

4 ^{12,13,15,16}	randomised trials	not serious	not serious	not serious	not serious	none	32/296 (10.8%)	18/296 (6.1%)	RR 1.75 (1.05 to 2.90)	46 more per 1,000 (from 3 more to 116 more)	⊕⊕⊕⊕ High	IMPORTANT

TEAE, Erythema at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹⁸	randomised trials	not serious	not serious	not serious	not serious	none	11/767 (1.4%)	1/783 (0.1%)	RR 11.23 (1.45 to 86.77)	13 more per 1,000 (from 1 more to 110 more)	⊕⊕⊕⊕ High	IMPORTANT

AE, Erythema at 12 weeks (Female & Pediatric to adolescent)

1 ¹⁷	randomised trials	not serious	not serious	not serious	serious ^k	none	4/163 (2.5%)	0/178 (0.0%)	RR 9.82 (0.53 to 181.06)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Application site erythema at 12 weeks

1 ¹⁶	randomised trials	not serious	not serious	not serious	serious ^k	none	1/71 (1.4%)	0/67 (0.0%)	RR 2.83 (0.12 to 68.37)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Erythema, Mild at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		
14	randomised trials	not serious	not serious	not serious	serious ^a	none	15/118 (12.7%)	21/115 (18.3%)	RR 0.70 (0.38 to 1.28)	55 fewer per 1,000 (from 113 fewer to 51 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Erythema, Moderate at 12 weeks

14	randomised trials	not serious	not serious	not serious	serious ^a	none	10/118 (8.5%)	7/115 (6.1%)	RR 1.39 (0.55 to 3.53)	24 more per 1,000 (from 27 fewer to 154 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Erythema, Severe at 12 weeks

14	randomised trials	not serious	not serious	not serious	serious ^b	none	0/118 (0.0%)	0/115 (0.0%)	not estimable		⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Exfoliation at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		
24,16	randomised trials	not serious	not serious	not serious	serious ^k	none	5/186 (2.7%)	0/182 (0.0%)	RR 10.72 (0.60 to 191.73)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Exfoliation at 12 weeks (Female & Pediatric to adolescent)

1 ¹⁷	randomised trials	not serious	not serious	not serious	serious ^k	none	2/163 (1.2%)	1/178 (0.6%)	RR 2.18 (0.20 to 23.86)	7 more per 1,000 (from 4 fewer to 128 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Pain at 12 weeks

24,16	randomised trials	not serious	not serious	not serious	serious ^c	none	12/186 (6.5%)	3/182 (1.6%)	RR 3.46 (1.08 to 11.10)	41 more per 1,000 (from 1 more to 166 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Pain at 12 weeks (Female & Pediatric to adolescent)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹⁷	randomised trials	not serious	not serious	not serious	serious ^k	none	7/163 (4.3%)	0/178 (0.0%)	RR 16.37 (0.94 to 284.43)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕ ○ Moderate	IMPORTANT

TEAE, Pain at 12 weeks

1 ¹⁸	randomised trials	not serious	not serious	not serious	not serious	none	24/767 (3.1%)	3/783 (0.4%)	RR 8.17 (2.47 to 27.01)	27 more per 1,000 (from 6 more to 100 more)	⊕⊕⊕⊕ High	IMPORTANT

AE, Peeling at 8 weeks

1 ¹³	randomised trials	not serious	not serious	not serious	serious ^k	none	6/124 (4.8%)	0/129 (0.0%)	RR 13.52 (0.77 to 237.50)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Peeling at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		
3 ^{12,13,15}	randomised trials	not serious	not serious	not serious	serious ^j	none	25/228 (11.0%)	9/229 (3.9%)	RR 2.67 (0.38 to 18.70)	66 more per 1,000 (from 24 fewer to 696 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Dermatitis at 12 weeks (Female & Pediatric to adolescent)

1 ¹⁷	randomised trials	not serious	not serious	not serious	serious ^b	none	0/163 (0.0%)	0/178 (0.0%)	not estimable		⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Irritation at 12 weeks (Female & Pediatric to adolescent)

1 ¹⁷	randomised trials	not serious	not serious	not serious	serious ^k	none	2/163 (1.2%)	0/178 (0.0%)	RR 5.46 (0.26 to 112.84)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Swelling at 12 weeks (Female & Pediatric to adolescent)

1 ¹⁷	randomised trials	not serious	not serious	not serious	serious ^k	none	2/163 (1.2%)	0/178 (0.0%)	RR 5.46 (0.26 to 112.84)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕ ○ Moderate	IMPORTANT

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		

AE, Pruritus, Mild at 12 weeks

14	randomised trials	not serious	not serious	not serious	serious ^a	none	34/118 (28.8%)	22/115 (19.1%)	RR 1.51 (0.94 to 2.41)	98 more per 1,000 (from 11 fewer to 270 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Pruritus, Moderate at 12 weeks

14	randomised trials	not serious	not serious	not serious	serious ^c	none	11/118 (9.3%)	3/115 (2.6%)	RR 3.57 (1.02 to 12.48)	67 more per 1,000 (from 1 more to 299 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Pruritus, Severe at 12 weeks

14	randomised trials	not serious	not serious	not serious	serious ^b	none	0/118 (0.0%)	0/115 (0.0%)	not estimable		⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Pruritus at 12 weeks (Female & Pediatric to adolescent)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹⁷	randomised trials	not serious	not serious	not serious	serious ^k	none	1/163 (0.6%)	0/178 (0.0%)	RR 3.27 (0.13 to 79.82)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Scaling, Mild at 12 weeks

1 ⁴	randomised trials	not serious	not serious	not serious	serious ^a	none	11/118 (9.3%)	11/115 (9.6%)	RR 0.97 (0.44 to 2.16)	3 fewer per 1,000 (from 54 fewer to 111 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Scaling, Moderate at 12 weeks

1 ⁴	randomised trials	not serious	not serious	not serious	serious ^a	none	3/118 (2.5%)	8/115 (7.0%)	RR 0.37 (0.10 to 1.34)	44 fewer per 1,000 (from 63 fewer to 24 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Scaling, Severe at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		
14	randomised trials	not serious	not serious	not serious	serious ^b	none	0/118 (0.0%)	0/115 (0.0%)	not estimable		⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Stinging, Mild at 12 weeks

14	randomised trials	not serious	not serious	not serious	serious ^a	none	27/118 (22.9%)	16/115 (13.9%)	RR 1.64 (0.94 to 2.89)	89 more per 1,000 (from 8 fewer to 263 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Stinging, Moderate at 12 weeks

14	randomised trials	not serious	not serious	not serious	serious ^c	none	11/118 (9.3%)	0/115 (0.0%)	RR 22.42 (1.34 to 376.10)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Stinging, Severe at 12 weeks

14	randomised trials	not serious	not serious	not serious	serious ^k	none	2/118 (1.7%)	0/115 (0.0%)	RR 4.87 (0.24 to 100.44)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕ ○ Moderate	IMPORTANT

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		

AE, Tightness of the skin at 12 weeks

1 ¹⁵	randomised trials	not serious	not serious	not serious	serious ^a	none	8/71 (11.3%)	8/70 (11.4%)	RR 0.99 (0.39 to 2.48)	1 fewer per 1,000 (from 70 fewer to 169 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

TEAE, Any at 12 weeks

5 ^{3,4,6,16,18}	randomised trials	not serious	not serious ^m	not serious	serious ^e	none	487/1990 (24.5%)	345/1890 (18.3%)	RR 1.40 (1.06 to 1.84)	73 more per 1,000 (from 11 more to 153 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Any at 12 weeks

3 ^{2,12,15}	randomised trials	not serious	not serious	not serious	serious ^e	none	177/522 (33.9%)	121/518 (23.4%)	RR 1.81 (0.60 to 5.47)	189 more per 1,000 (from 93 fewer to 1,000 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

AE, Any, Serious at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[2023 update] Topical retinoid	Vehicle	Relative (95% CI)	Absolute (95% CI)		
3 ^{4,6,16,18}	randomised trials	not serious	not serious	not serious	serious ^e	none	12/1732 (0.7%)	8/1756 (0.5%)	RR 1.47 (0.61 to 3.56)	2 more per 1,000 (from 2 fewer to 12 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

- a. CI included both appreciable benefits and harm. Small sample size.
- b. Double zero study.
- c. Small sample size.
- d. $I^2 = 84\%$
- e. CI included both appreciable benefits and harm.
- f. The studies did not report standard deviation values. Therefore, data could not be pooled.
- g. Studies did not report standard deviation values.
- h. SDs were not reported. Small sample size.
- i. n: number of patients
- j. Wide CI included both appreciable benefits and harm.
- k. Wide CI included both appreciable benefits and harm. Small sample size.
- l. $I^2 = 79\%$
- m. $I^2 = 74\%$

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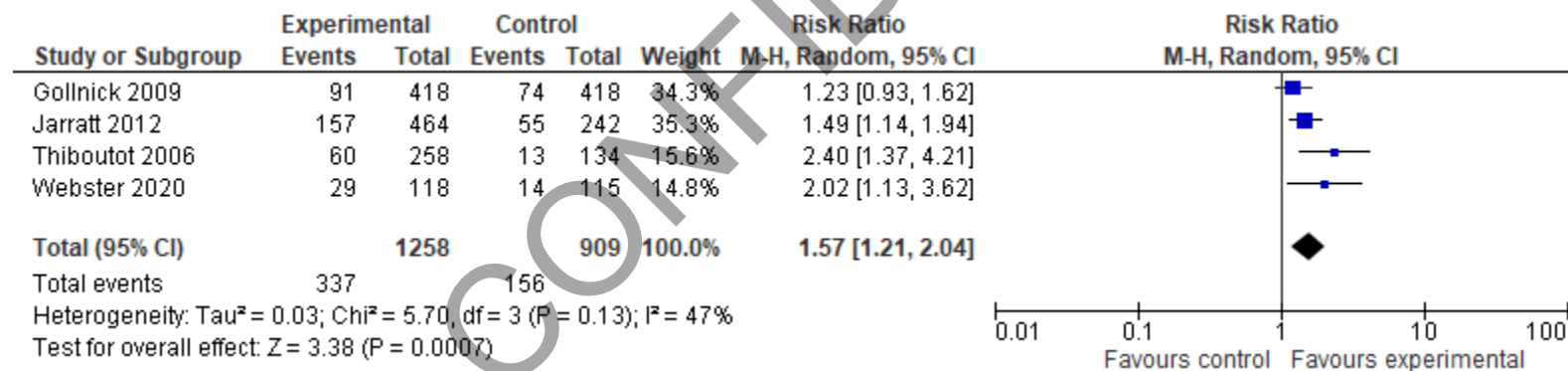
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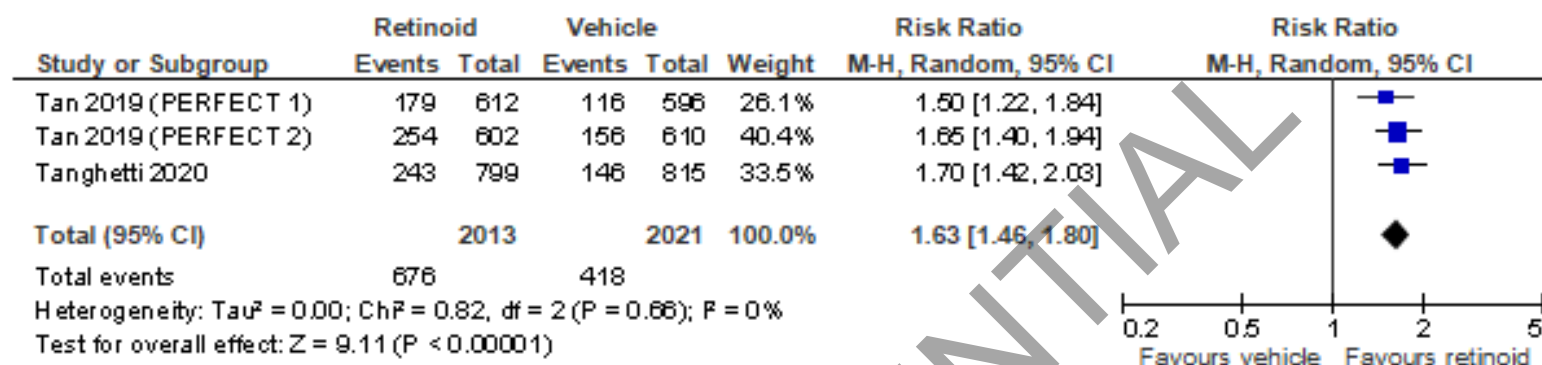
Forest plots

e-Figure 1. Investigator Global Assessment, Grade 0-1 at 12 weeks, topical retinoid vs. vehicle

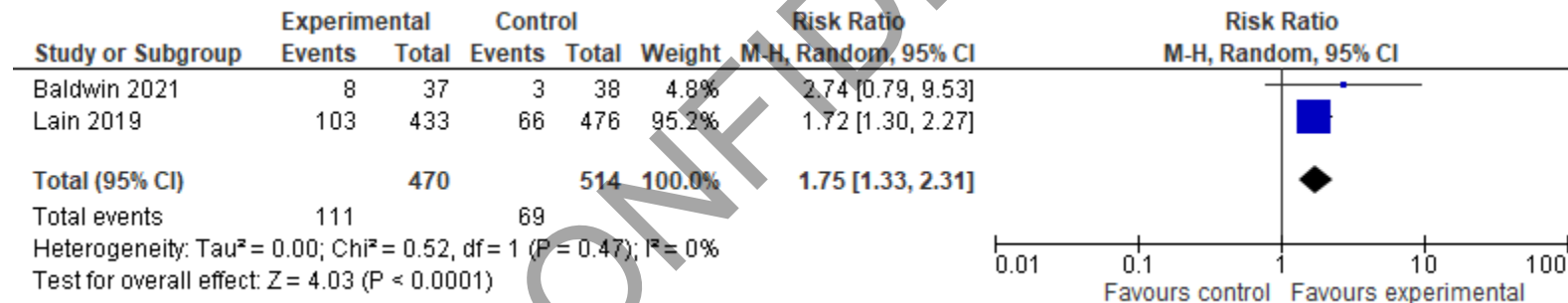


e-Figure 2. Investigator Global Assessment, Grade 0-1 and ≥ 2 -grade reduction at 12 weeks, topical retinoid vs. vehicle

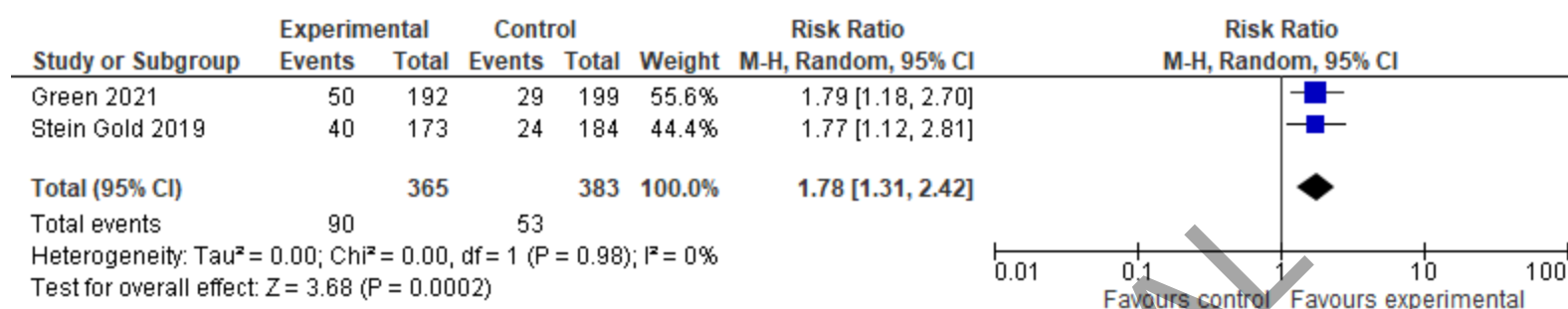
11.22 Acne severity, Evaluator Global Severity Score, Grade 0-1 and ≥ 2 -grade reduction at 12 weeks



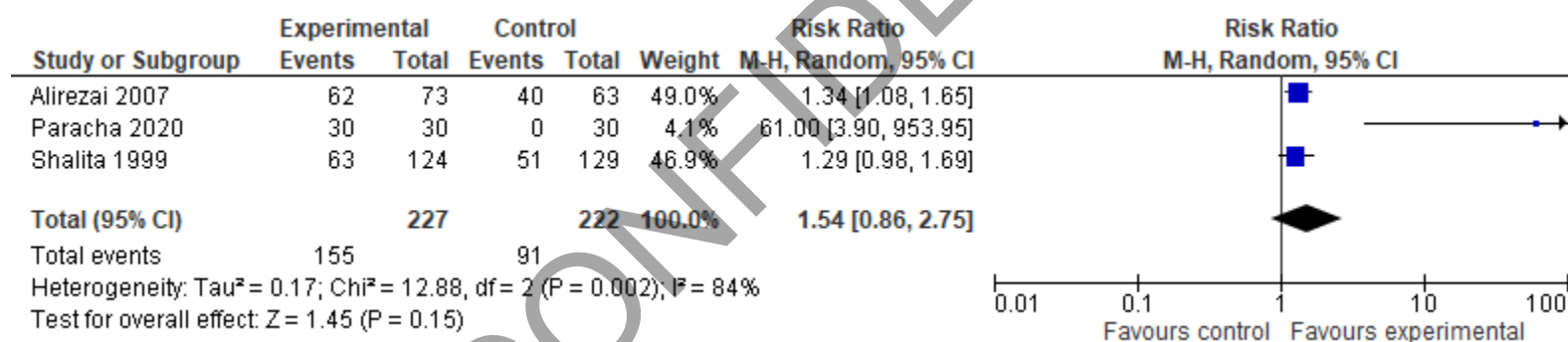
e-Figure 3. Acne severity, Evaluator Global Severity Score, Grade 0-1 and ≥ 2 -grade reduction (female subgroup) at 12 weeks, topical retinoid vs. vehicle



e-Figure 4. Acne severity, Evaluator Global Severity Score, Grade 0-1 and ≥ 2 -grade reduction (female & pediatric to adolescent subgroup) at 12 weeks, topical retinoid vs. vehicle

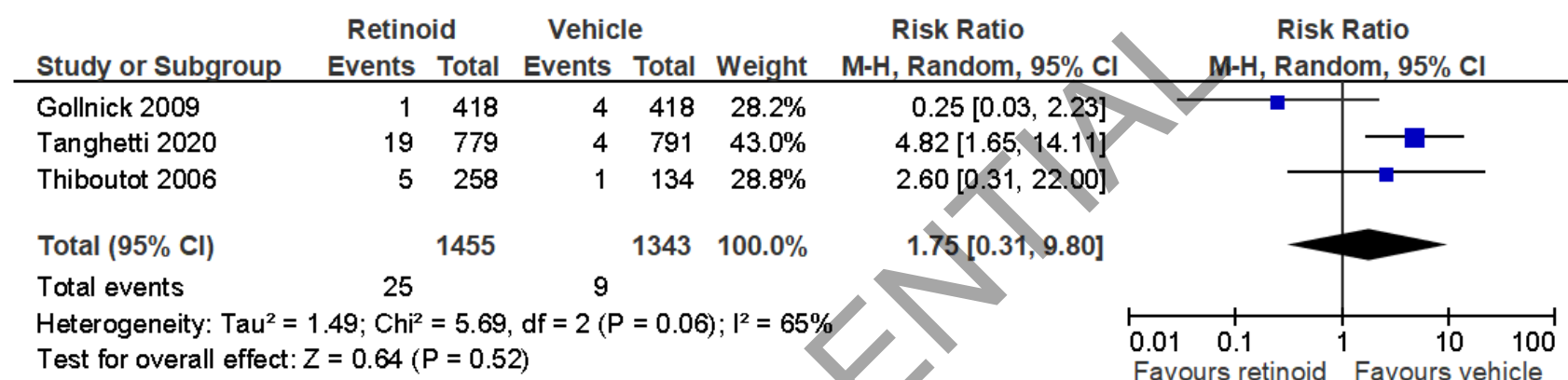


e-Figure 5. Number of lesions, Any, $\geq 50\%$ reduction at 12 weeks, topical retinoid vs. vehicle

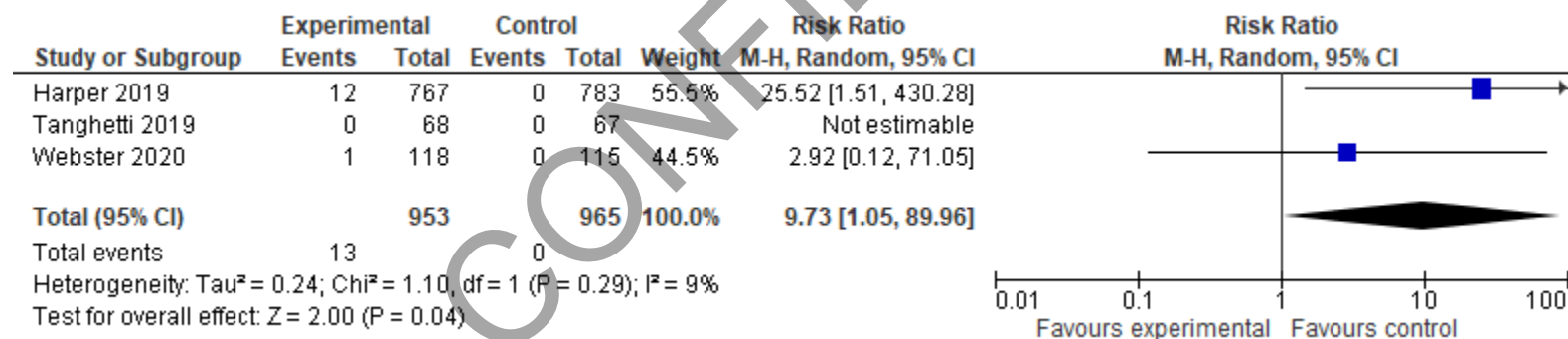


e-Figure 6. AE, Any, Leading to discontinuation at 12 weeks, topical retinoid vs. vehicle

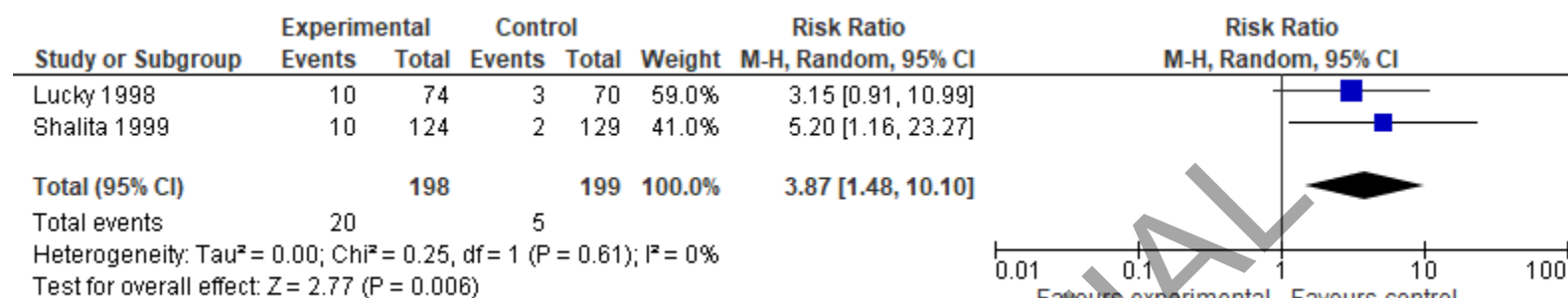
11.4 AE, Any, Leading to discontinuation at 12 weeks



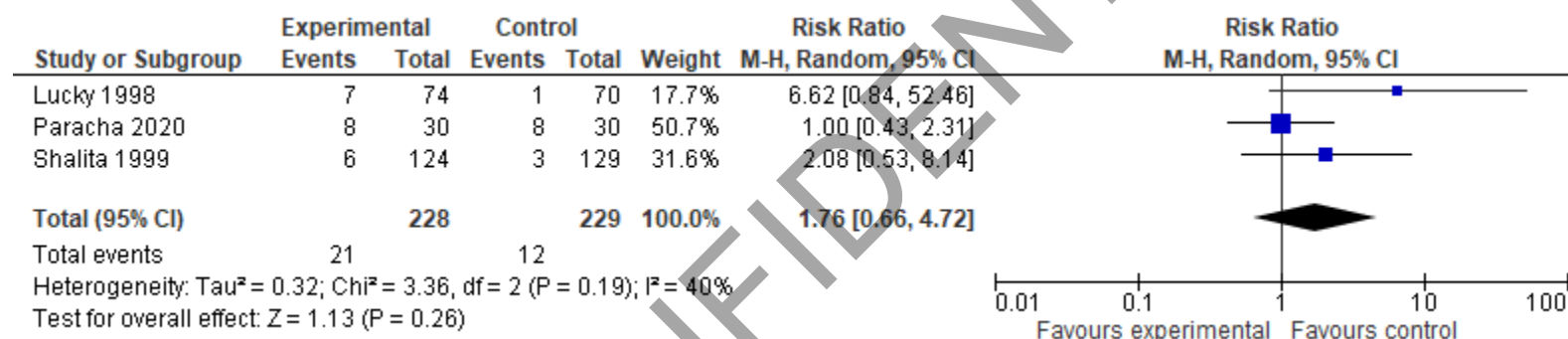
e-Figure 7. TEAE, Any, Leading to discontinuation at 12 weeks, topical retinoid vs. vehicle



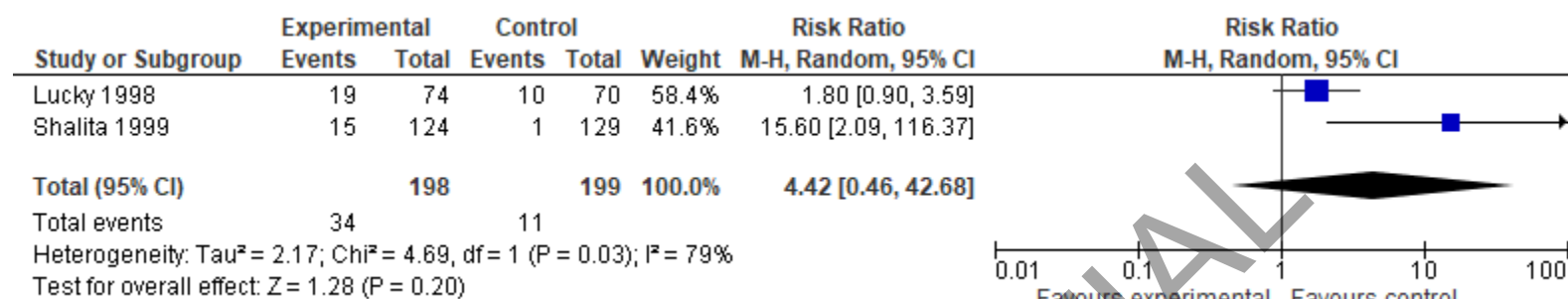
e-Figure 8. AE, Burning at 4 weeks, topical retinoid vs. vehicle



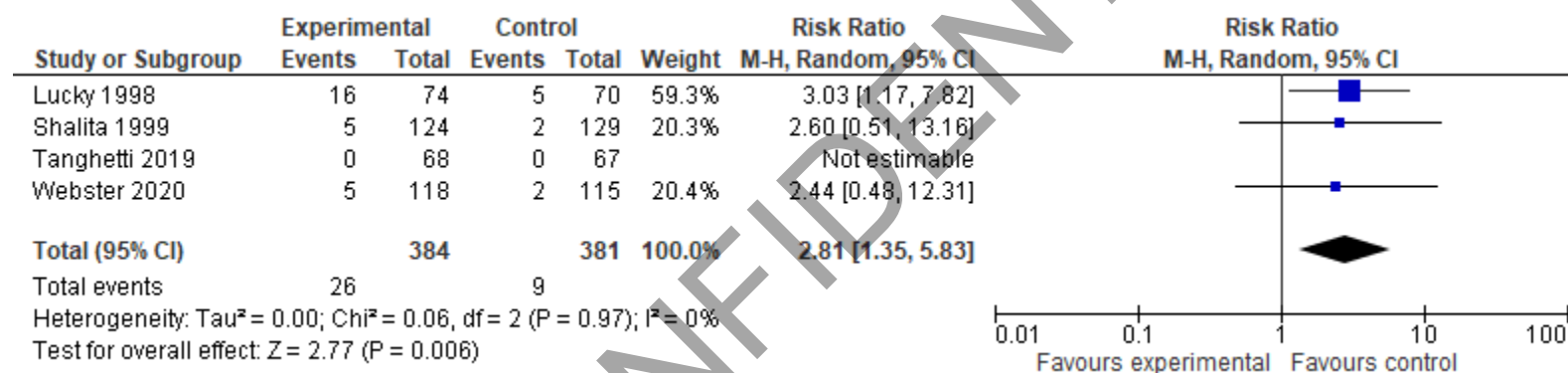
e-Figure 9. AE, Burning at 12 weeks, topical retinoid vs. vehicle



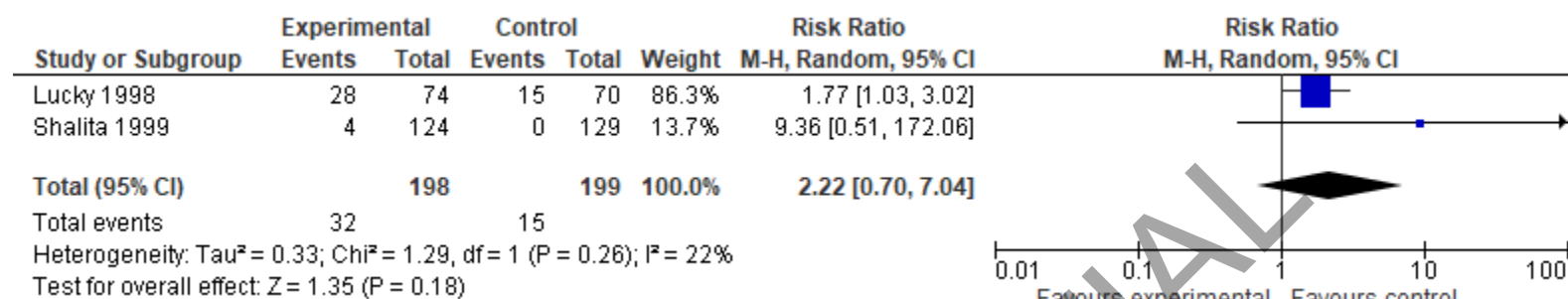
e-Figure 10. AE, Dryness at 4 weeks, topical retinoid vs. vehicle



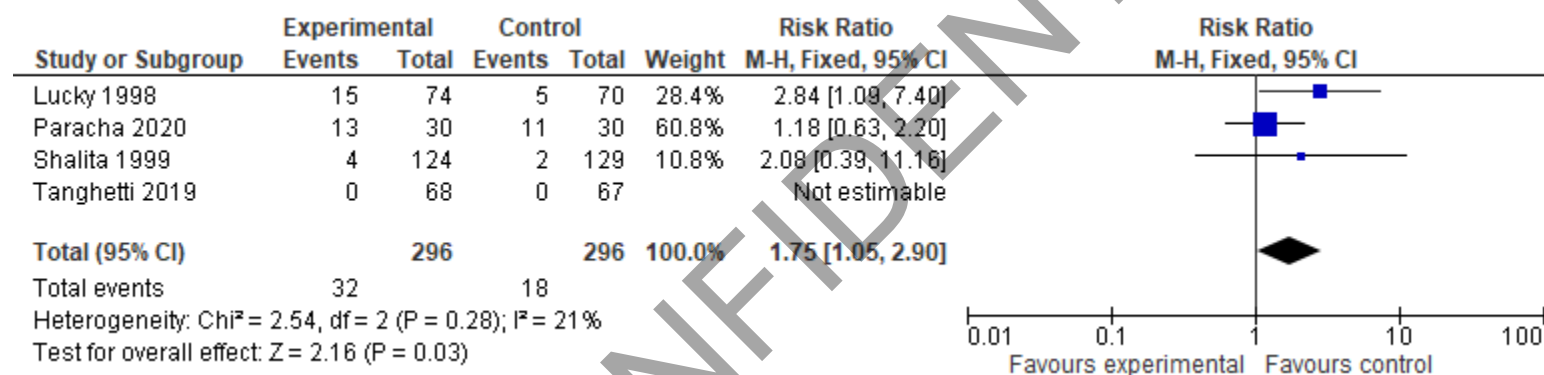
e-Figure 11. AE, Dryness at 12 weeks, topical retinoid vs. vehicle



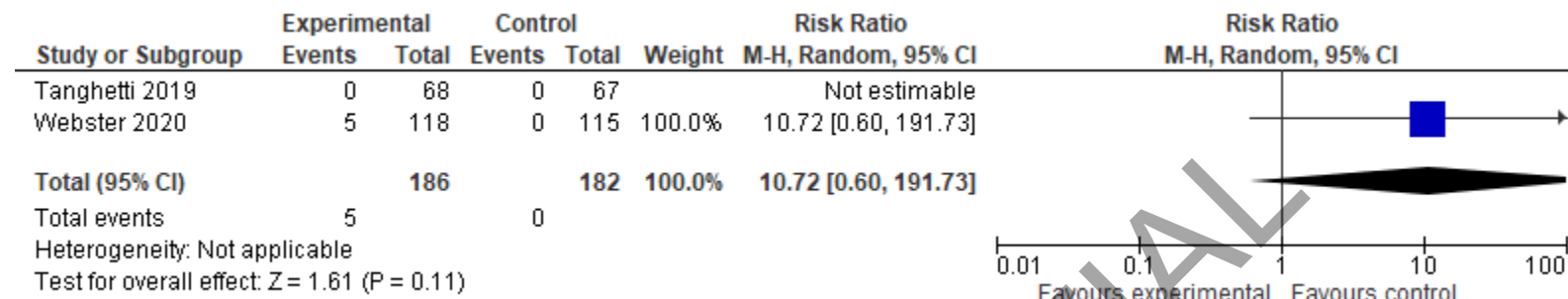
e-Figure 12. AE, Erythema at 4 weeks, topical retinoid vs. vehicle



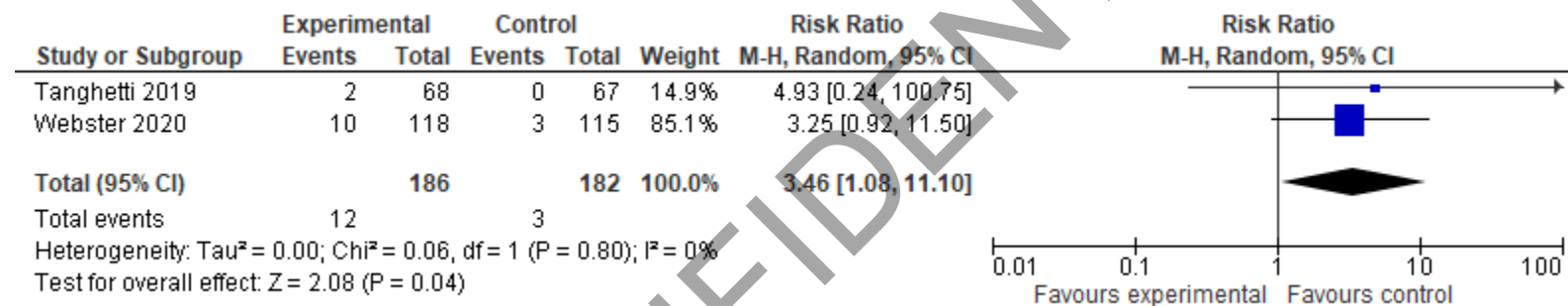
e-Figure 13. AE, Erythema at 12 weeks, topical retinoid vs. vehicle



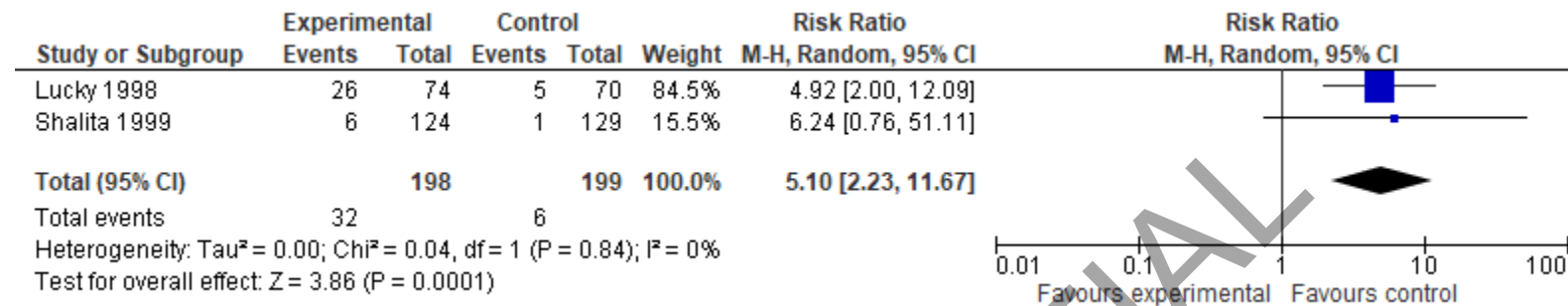
e-Figure 14. AE, Exfoliation at 12 weeks, topical retinoid vs. vehicle



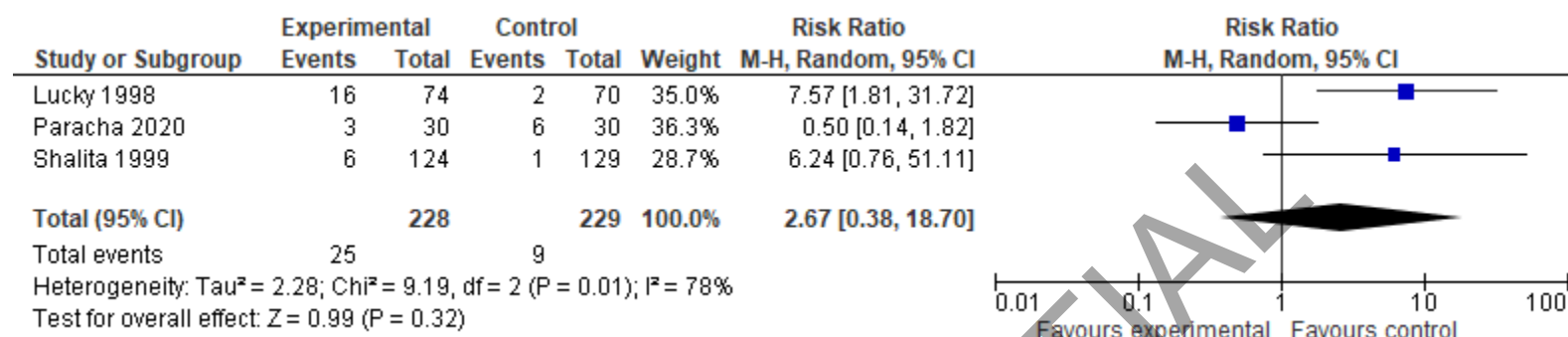
e-Figure 15. AE, Pain at 12 weeks, topical retinoid vs. vehicle



e-Figure 16. AE, Peeling at 4 weeks, topical retinoid vs. vehicle



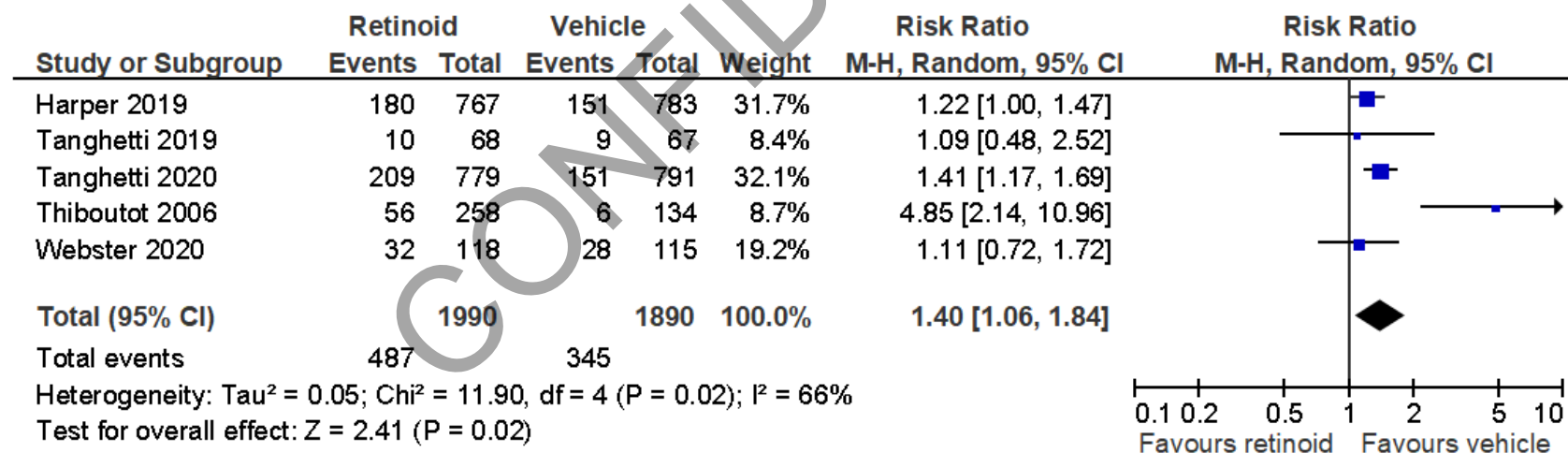
e-Figure 17. AE, Peeling at 12 weeks, topical retinoid vs. vehicle



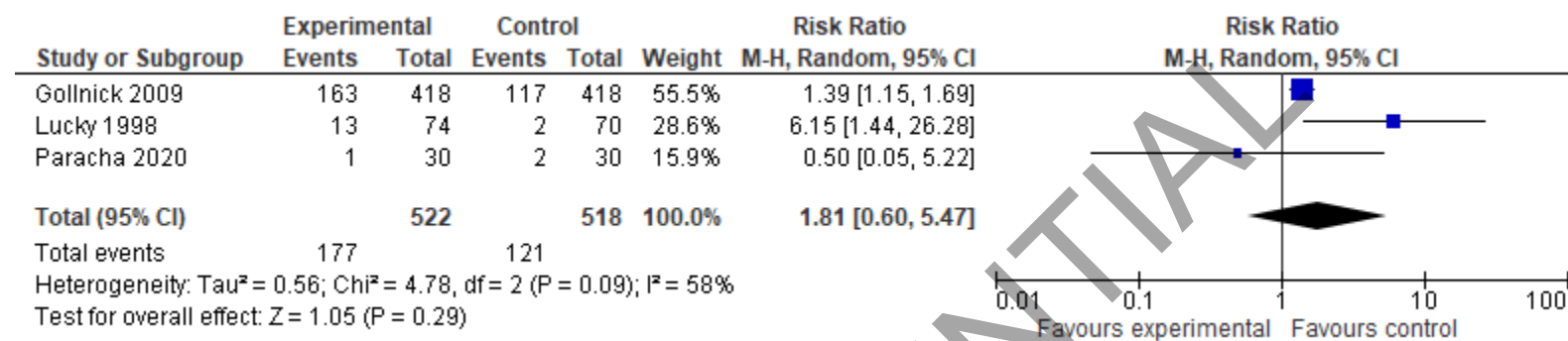
e-Figure 18. TEAE, Any at 12 weeks, topical retinoid vs. vehicle

11 Topical retinoid vs. Vehicle

11.15 TEAE, Any at 12 weeks



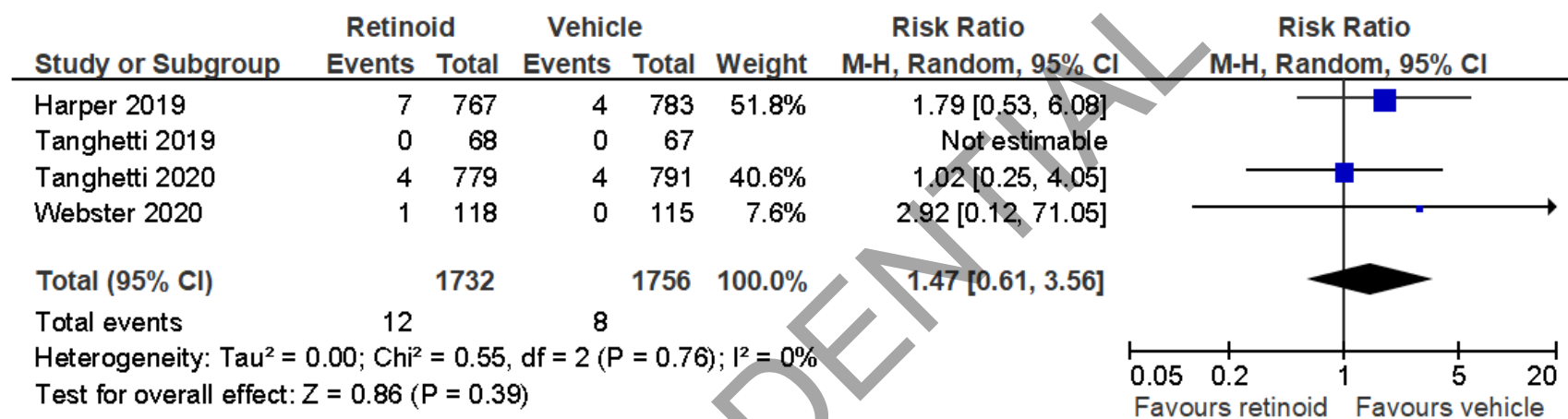
e-Figure 19.AE, Any at 12 weeks, topical retinoid vs. vehicle



e-Figure 20. AE, Any, Serious at 12 weeks, topical retinoid vs. vehicle

11 Topical retinoid vs. Vehicle

11.5 AE, Any, Serious at 12 weeks



2. Benzoyl peroxide vs. vehicle

e-Table 13. GRADE Evidence Profile for benzoyl peroxide vs. vehicle

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
Investigator Global Assessment, Grade 0-1 at 4 weeks												
3 ^{1,2,3}	randomised trials	not serious	not serious	not serious	serious ^a	none	43/711 (6.0%)	12/715 (1.7%)	RR 3.12 (0.87 to 11.18)	36 more per 1,000 (from 2 fewer to 171 more)	⊕⊕⊕○ Moderate	CRITICAL
Investigator Global Assessment, Grade 0-1 at 12 weeks												
3 ^{1,2,3}	randomised trials	not serious	serious ^b	not serious	not serious	none	173/711 (24.3%)	91/715 (12.7%)	RR 2.70 (1.10 to 6.65)	216 more per 1,000 (from 13 more to 719 more)	⊕⊕⊕○ Moderate	CRITICAL
Investigator Global Assessment, ≥2-grade reduction at 12 weeks												
2 ^{2,4}	randomised trials	not serious	serious ^c	not serious	serious ^d	none	133/501 (26.5%)	60/511 (11.7%)	RR 6.67 (0.26 to 171.74)	666 more per 1,000 (from 87 fewer to 1,000 more)	⊕⊕○○ Low	CRITICAL
Number of lesions, Any at 12 weeks (mean absolute change from baseline)												
1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	178	182	-	MD 12.8 lesions lower (28.66 lower to 14.94 lower)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any at 12 weeks (mean percent change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
2 ^{4,5}	randomised trials	not serious	not serious	not serious	not serious ^f	none	323	329	-	MD 15.1 % lower (20.23 lower to 9.97 lower)	⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Inflammatory at 4 weeks (mean percent change from baseline)

1 ³	randomised trials	not serious	not serious	not serious	serious ^g	none	The mean percentage changes from baseline for benzoyl peroxide and vehicle were -28.8% (n: 118) and -25.5% (n: 115), respectively. h			⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 10 weeks (mean percent change from baseline)

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^g	none	44 and 44 patients were randomized to receive benzoyl peroxide or vehicle, respectively. The mean percentage changes from baseline for benzoyl peroxide and vehicle were -56.24% and -25.23%, respectively.			⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Papules at 10 weeks (mean percent change from baseline)

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^e	none	44 and 44 patients were randomized to receive benzoyl peroxide and vehicle, respectively. The mean percentage changes from baseline for benzoyl peroxide and vehicle were -53.44% and -29.49%, respectively. The difference between the two treatment groups was statistically significant. i			⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Pustules at 10 weeks (mean percent change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ⁶	randomised trials	not serious	not serious	not serious	serious ^e	none	44 and 44 patients were randomized to receive benzoyl peroxide and vehicle, respectively. The mean percentage changes from baseline for benzoyl peroxide and vehicle were -68.46% and -24.33%, respectively. The difference between the two treatment groups was statistically significant.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (mean absolute change from baseline)

1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	178	182	-	MD 8.7 lesions lower (11.2 lower to 6.17 lower)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline)

3 ^{3,4,7}	randomised trials	not serious	serious ^j	not serious	not serious ^k	none	415	387	-	MD 22.13 % lower (42.53 lower to 1.72 lower)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks (mean percent change from baseline)

1 ³	randomised trials	not serious	not serious	not serious	serious ^g	none	The mean percentage changes from baseline for benzoyl peroxide and vehicle were -18.4% (n: 118) and -18.4% (n: 115), respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 5 weeks (mean percent change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ⁷	randomised trials	not serious	not serious	not serious	serious ^g	none	92 and 58 patients were randomized to receive benzoyl peroxide or vehicle, respectively. The mean percentage changes from baseline for benzoyl peroxide and vehicle were -16.3% and -3.37%, respectively. The difference between the two treatment groups was statistically significant (p <= 0.005).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, Open and closed comedones at 10 weeks (mean percent change from baseline)

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^g	none	44 and 44 patients were randomized to receive benzoyl peroxide and vehicle, respectively. The mean percentage changes from baseline for benzoyl peroxide and vehicle were -31.37% and -3.15%, respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean percent change from baseline)

3 ^{3,4,7}	randomised trials	not serious	not serious	not serious	not serious ^k	none	415	387	-	MD 17.05 % lower (22.96 lower to 11.14 lower)	⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Any, <25% reduction at 12 weeks

1 ⁵	randomised trials	not serious	not serious	not serious	serious ^l	none	4/26 (15.4%)	10/25 (40.0%)	RR 0.38 (0.14 to 1.07)	248 fewer per 1,000 (from 344 fewer to 28 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, 26-50% reduction at 12 weeks

1 ⁵	randomised trials	not serious	not serious	not serious	serious ^l	none	3/26 (11.5%)	5/25 (20.0%)	RR 0.58 (0.15 to 2.16)	84 fewer per 1,000 (from 170 fewer to 232 more)	⊕⊕⊕○ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Any, ≥50% reduction at 12 weeks

1 ⁴	randomised trials	not serious	not serious	not serious	not serious	none	228/323 (70.6%)	175/329 (53.2%)	RR 1.33 (1.17 to 1.50)	176 more per 1,000 (from 90 more to 266 more)	⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Any, 51-75% reduction at 12 weeks

1 ⁵	randomised trials	not serious	not serious	not serious	serious ^l	none	9/26 (34.6%)	7/25 (28.0%)	RR 1.24 (0.54 to 2.81)	67 more per 1,000 (from 129 fewer to 507 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, >75% reduction at 12 weeks

1 ⁵	randomised trials	not serious	not serious	not serious	serious ^e	none	10/26 (38.5%)	3/25 (12.0%)	RR 3.21 (1.00 to 10.30)	265 more per 1,000 (from 0 fewer to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL

Acne severity, Patient assessment of improvement, ≥2-grade reduction at 12 weeks

1 ⁴	randomised trials	not serious	not serious	not serious	not serious	none	189/323 (58.5%)	154/329 (46.8%)	RR 1.25 (1.08 to 1.45)	117 more per 1,000 (from 37 more to 211 more)	⊕⊕⊕⊕ High	IMPORTANT

AE, Any, Leading to discontinuation at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	6/415 (1.4%)	4/418 (1.0%)	RR 1.51 (0.43 to 5.31)	5 more per 1,000 (from 5 fewer to 41 more)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Any, Leading to discontinuation at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ³	randomised trials	not serious	not serious	not serious	serious ^m	none	4/118 (3.4%)	0/115 (0.0%)	RR 8.77 (0.48 to 161.14)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT
AE, Burning, Mild at 8 weeks												
1 ²	randomised trials	not serious	not serious	not serious	serious ⁿ	none	0/178 (0.0%)	0/182 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT
AE, Burning, Moderate at 8 weeks												
1 ²	randomised trials	not serious	not serious	not serious	serious ^m	none	1/178 (0.6%)	1/182 (0.5%)	RR 1.02 (0.06 to 16.22)	0 fewer per 1,000 (from 5 fewer to 84 more)	⊕⊕⊕○ Moderate	IMPORTANT
AE, Burning at 12 weeks												
2 ^{7,8}	randomised trials	not serious	not serious	not serious	serious ^m	none	3/118 (2.5%)	0/84 (0.0%)	RR 7.00 (0.38 to 129.11)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT
AE, Burning, Slight at 12 weeks												
1 ²	randomised trials	not serious	not serious	not serious	serious ^l	none	11/178 (6.2%)	4/182 (2.2%)	RR 2.81 (0.91 to 8.67)	40 more per 1,000 (from 2 fewer to 169 more)	⊕⊕⊕○ Moderate	IMPORTANT
AE, Burning, Mild at 12 weeks												
2 ^{2,3}	randomised trials	not serious	not serious	not serious	serious ^a	none	17/296 (5.7%)	13/297 (4.4%)	RR 1.30 (0.66 to 2.55)	13 more per 1,000 (from 15 fewer to 68 more)	⊕⊕⊕○ Moderate	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		

AE, Burning, Moderate at 12 weeks

2 ^{2,3}	randomised trials	not serious	not serious	not serious	serious ^a	none	4/296 (1.4%)	2/297 (0.7%)	RR 1.58 (0.31 to 8.11)	4 more per 1,000 (from 5 fewer to 48 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Burning, Severe at 12 weeks

1 ³	randomised trials	not serious	not serious	not serious	serious ⁿ	none	0/118 (0.0%)	0/115 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Dryness at 12 weeks

4 ^{3,4,7,8}	randomised trials	not serious	not serious	not serious	serious ^a	none	14/559 (2.5%)	4/528 (0.8%)	RR 2.22 (0.70 to 7.05)	9 more per 1,000 (from 2 fewer to 46 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Dryness, Slight at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^l	none	9/178 (5.1%)	8/182 (4.4%)	RR 1.15 (0.45 to 2.91)	7 more per 1,000 (from 24 fewer to 84 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Dryness, Mild at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^l	none	0/178 (0.0%)	3/182 (1.6%)	RR 0.15 (0.01 to 2.81)	14 fewer per 1,000 (from 16 fewer to 30 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Dryness, Moderate at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	serious ^m	none	3/178 (1.7%)	0/182 (0.0%)	RR 7.16 (0.37 to 137.56)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema, Mild at 8 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^l	none	4/178 (2.2%)	4/182 (2.2%)	RR 1.02 (0.26 to 4.03)	0 fewer per 1,000 (from 16 fewer to 67 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema, Moderate at 8 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^m	none	1/178 (0.6%)	0/182 (0.0%)	RR 3.07 (0.13 to 74.79)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema at 12 weeks

3 ^{4,7,8}	randomised trials	not serious	not serious	not serious	serious ^d	none	23/441 (5.2%)	7/413 (1.7%)	RR 2.73 (0.63 to 11.83)	29 more per 1,000 (from 6 fewer to 184 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema, Slight at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^l	none	23/178 (12.9%)	34/182 (18.7%)	RR 0.69 (0.42 to 1.13)	58 fewer per 1,000 (from 108 fewer to 24 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema, Mild at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
2 ^{2,3}	randomised trials	not serious	not serious	not serious	serious ^d	none	24/296 (8.1%)	21/297 (7.1%)	RR 2.16 (0.18 to 25.97)	82 more per 1,000 (from 58 fewer to 1,000 more)	⊕⊕⊕○ Moderate	IMPORTANT
AE, Erythema, Moderate at 12 weeks												
2 ^{2,3}	randomised trials	not serious	not serious	not serious	serious ^a	none	11/296 (3.7%)	9/297 (3.0%)	RR 1.20 (0.51 to 2.84)	6 more per 1,000 (from 15 fewer to 56 more)	⊕⊕⊕○ Moderate	IMPORTANT
AE, Erythema, Severe at 12 weeks												
1 ³	randomised trials	not serious	not serious	not serious	serious ⁿ	none	0/118 (0.0%)	0/115 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT
AE, Erythema/Peeling												
1 ⁵	randomised trials	not serious	not serious	not serious	serious ^l	none	21/26 (80.8%)	17/25 (68.0%)	RR 1.19 (0.86 to 1.65)	129 more per 1,000 (from 95 fewer to 442 more)	⊕⊕⊕○ Moderate	IMPORTANT
AE, Pain at 12 weeks												
3 ^{3,4,8}	randomised trials	not serious	not serious	not serious	serious ^d	none	6/467 (1.3%)	3/470 (0.6%)	RR 1.79 (0.29 to 11.12)	5 more per 1,000 (from 5 fewer to 65 more)	⊕⊕⊕○ Moderate	IMPORTANT
AE, Peeling at 12 weeks												
2 ^{7,8}	randomised trials	not serious	not serious	not serious	serious ^l	none	20/118 (16.9%)	11/84 (13.1%)	RR 1.25 (0.62 to 2.51)	33 more per 1,000 (from 50 fewer to 198 more)	⊕⊕⊕○ Moderate	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		

AE, Peeling, Slight at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^l	none	7/178 (3.9%)	3/182 (1.6%)	RR 2.39 (0.63 to 9.08)	23 more per 1,000 (from 6 fewer to 133 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Peeling, Mild at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ⁿ	none	0/178 (0.0%)	0/182 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Peeling, Moderate at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^m	none	3/178 (1.7%)	0/182 (0.0%)	RR 7.16 (0.37 to 137.56)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus, Mild at 8 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^l	none	0/178 (0.0%)	1/182 (0.5%)	RR 0.34 (0.01 to 8.31)	4 fewer per 1,000 (from 5 fewer to 40 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus, Moderate at 8 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^m	none	3/178 (1.7%)	0/182 (0.0%)	RR 7.16 (0.37 to 137.56)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
3 ^{4,7,8}	randomised trials	not serious	not serious	not serious	serious ^a	none	5/441 (1.1%)	3/413 (0.7%)	RR 1.13 (0.19 to 6.75)	1 more per 1,000 (from 6 fewer to 42 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus, Slight at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^l	none	8/178 (4.5%)	9/182 (4.9%)	RR 0.91 (0.36 to 2.30)	4 fewer per 1,000 (from 32 fewer to 64 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus, Mild at 12 weeks

2 ^{2,3}	randomised trials	not serious	not serious	not serious	serious ^a	none	22/296 (7.4%)	23/297 (7.7%)	RR 0.95 (0.56 to 1.60)	4 fewer per 1,000 (from 34 fewer to 46 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus, Moderate at 12 weeks

2 ^{2,3}	randomised trials	not serious	not serious	not serious	serious ^a	none	5/296 (1.7%)	3/297 (1.0%)	RR 1.39 (0.34 to 5.64)	4 more per 1,000 (from 7 fewer to 47 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus, Severe at 12 weeks

1 ³	randomised trials	not serious	not serious	not serious	serious ⁿ	none	0/118 (0.0%)	0/115 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Dermatitis at 12 weeks

1 ⁴	randomised trials	not serious	not serious	not serious	serious ⁿ	none	0/323 (0.0%)	0/329 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Dermatitis, Contact, Allergic at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ⁵	randomised trials	not serious	not serious	not serious	serious ⁿ	none	0/26 (0.0%)	0/25 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Eczema at 12 weeks

1 ⁴	randomised trials	not serious	not serious	not serious	serious ^d	none	1/323 (0.3%)	0/329 (0.0%)	RR 3.06 (0.12 to 74.74)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Scaling at 12 weeks

1 ⁸	randomised trials	not serious	not serious	not serious	serious ^l	none	7/26 (26.9%)	3/26 (11.5%)	RR 2.33 (0.68 to 8.05)	153 more per 1,000 (from 37 fewer to 813 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Scaling, Mild at 12 weeks

1 ³	randomised trials	not serious	not serious	not serious	serious ^l	none	10/118 (8.5%)	11/115 (9.6%)	RR 0.89 (0.39 to 2.01)	11 fewer per 1,000 (from 58 fewer to 97 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Scaling, Moderate at 12 weeks

1 ³	randomised trials	not serious	not serious	not serious	serious ^l	none	3/118 (2.5%)	8/115 (7.0%)	RR 0.37 (0.10 to 1.34)	44 fewer per 1,000 (from 63 fewer to 24 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Scaling, Severe at 12 weeks

1 ³	randomised trials	not serious	not serious	not serious	serious ⁿ	none	0/118 (0.0%)	0/115 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Stinging at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ⁸	randomised trials	not serious	not serious	not serious	serious ^l	none	1/26 (3.8%)	2/26 (7.7%)	RR 0.50 (0.05 to 5.18)	38 fewer per 1,000 (from 73 fewer to 322 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Stinging, Mild at 12 weeks

1 ³	randomised trials	not serious	not serious	not serious	serious ^l	none	15/118 (12.7%)	16/115 (13.9%)	RR 0.91 (0.47 to 1.76)	13 fewer per 1,000 (from 74 fewer to 106 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Stinging, Moderate at 12 weeks

1 ³	randomised trials	not serious	not serious	not serious	serious ^m	none	7/118 (5.9%)	0/115 (0.0%)	RR 14.62 (0.84 to 253.11)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Stinging, Severe at 12 weeks

1 ³	randomised trials	not serious	not serious	not serious	serious ⁿ	none	0/118 (0.0%)	0/115 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Exfoliation at 12 weeks

1 ³	randomised trials	not serious	not serious	not serious	serious ⁿ	none	0/118 (0.0%)	0/115 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Hypersensitivity at 12 weeks

1 ⁴	randomised trials	not serious	not serious	not serious	serious ^d	none	1/323 (0.3%)	0/329 (0.0%)	RR 3.06 (0.12 to 74.74)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Irritation at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ⁴	randomised trials	not serious	not serious	not serious	serious ^d	none	2/323 (0.6%)	0/329 (0.0%)	RR 5.09 (0.25 to 105.67)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Photosensitivity at 12 weeks

1 ⁴	randomised trials	not serious	not serious	not serious	serious ^a	none	1/323 (0.3%)	2/329 (0.6%)	RR 0.51 (0.05 to 5.59)	3 fewer per 1,000 (from 6 fewer to 28 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Roughness at 12 weeks

1 ⁸	randomised trials	not serious	not serious	not serious	serious ^m	none	1/26 (3.8%)	0/26 (0.0%)	RR 3.00 (0.13 to 70.42)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Any at 12 weeks

2 ^{1,4}	randomised trials	not serious	not serious	not serious	serious ^a	none	144/738 (19.5%)	122/747 (16.3%)	RR 1.18 (0.97 to 1.45)	29 more per 1,000 (from 5 fewer to 73 more)	⊕⊕⊕○ Moderate	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

a. CI included both appreciable benefits and harm.

b. $I^2 = 85\%$

c. $I^2 = 91\%$

d. Wide CI included both appreciable benefits and harm.

e. Small sample size.

f. One study (Smith 1980) did not report standard deviation values. Therefore, data could not be pooled.

g. Standard deviation values were not reported. Small sample size.

h. n: number of patients

i. P value not reported.

j. $I^2 = 84\%$

k. One study (Webster 2020) did not report standard deviation values. Therefore, data could not be pooled.

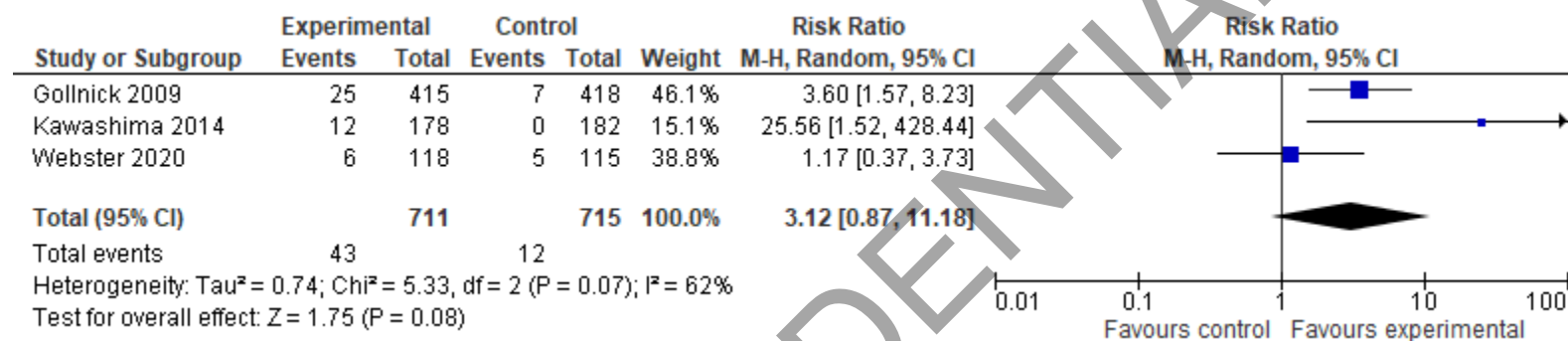
l. CI included both appreciable benefits and harm. Small sample size.

m. Wide CI included both appreciable benefits and harm. Small sample size.

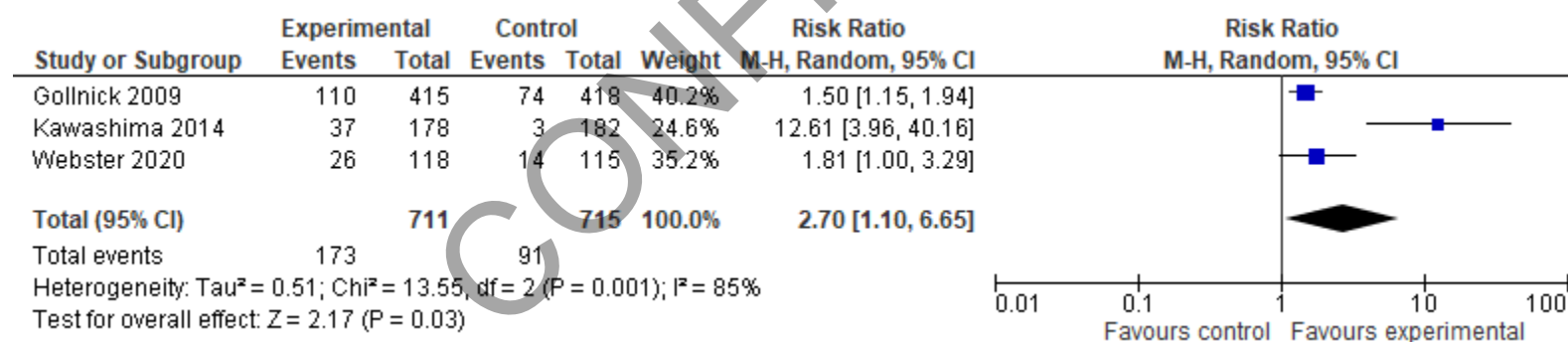
n. Double zero study.

Forest plots

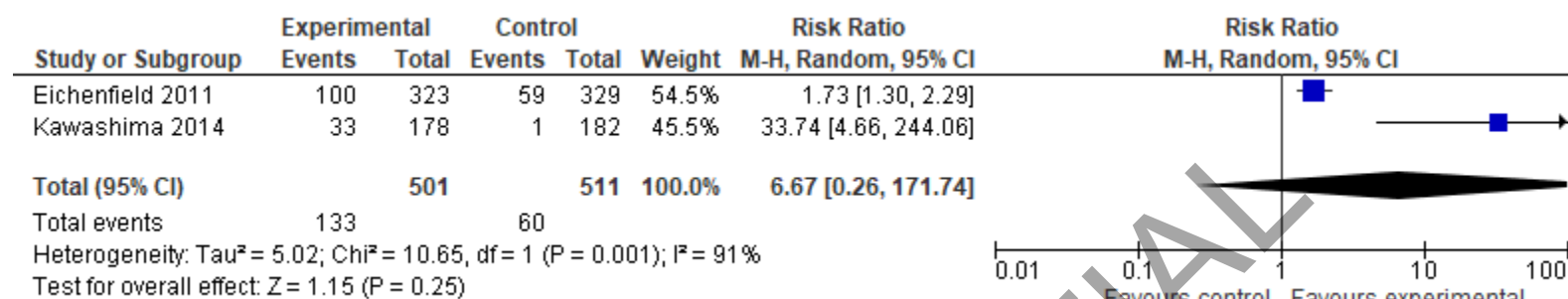
e-Figure 21. Investigator Global Assessment, Grade 0-1 at 4 weeks, benzoyl peroxide vs. vehicle



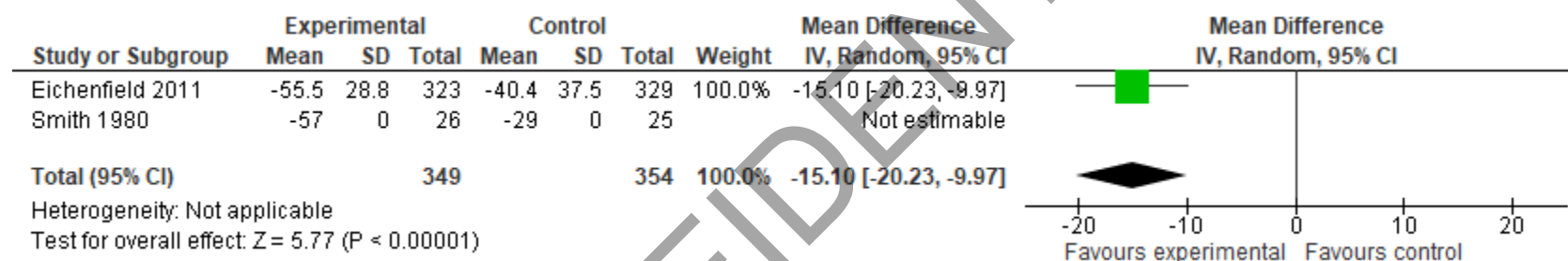
e-Figure 22. Investigator Global Assessment, Grade 0-1 at 12 weeks, benzoyl peroxide vs. vehicle



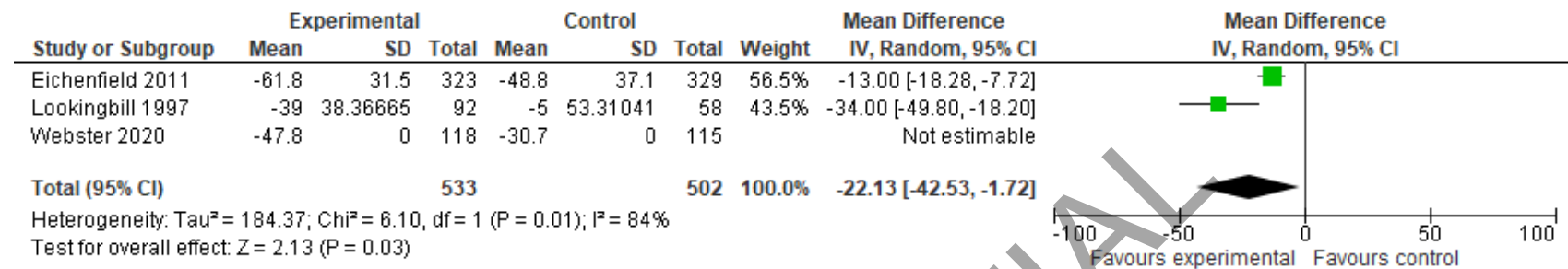
e-Figure 23. Investigator Global Assessment, ≥ 2 -grade reduction at 12 weeks, benzoyl peroxide vs. vehicle



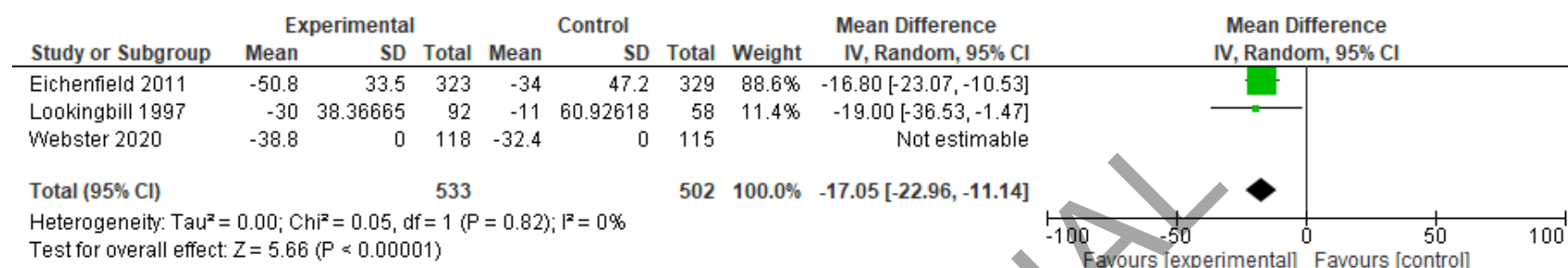
e-Figure 24. Number of lesions, Any at 12 weeks (mean percent change from baseline), benzoyl peroxide vs. vehicle



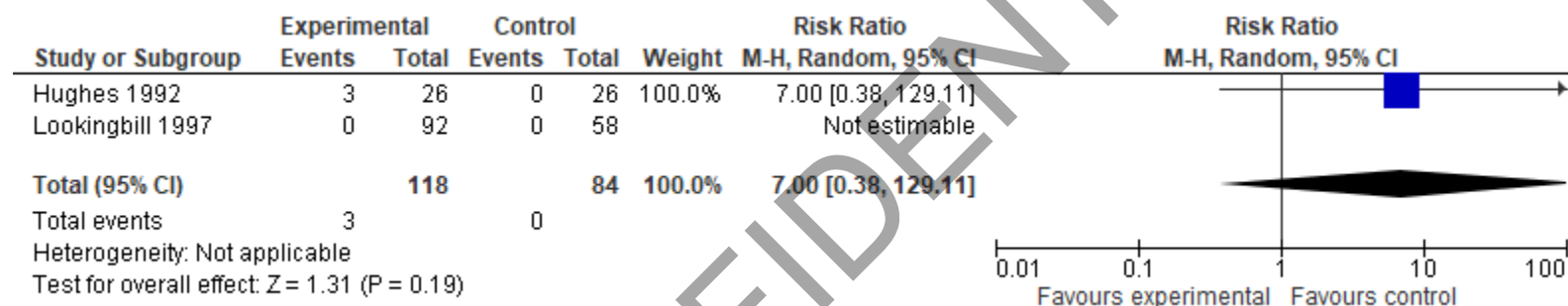
e-Figure 25. Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline), benzoyl peroxide vs. vehicle



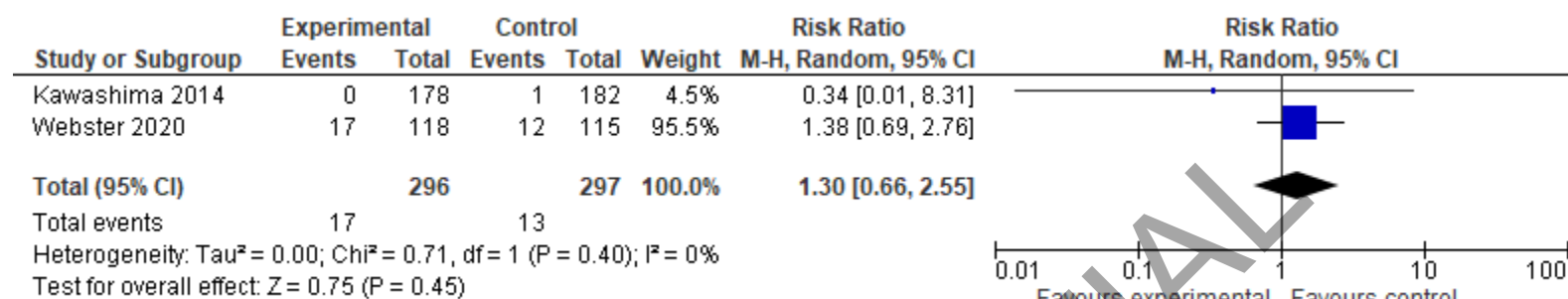
e-Figure 26. Number of lesions, Non-inflammatory at 12 weeks (mean percent change from baseline), benzoyl peroxide vs. vehicle



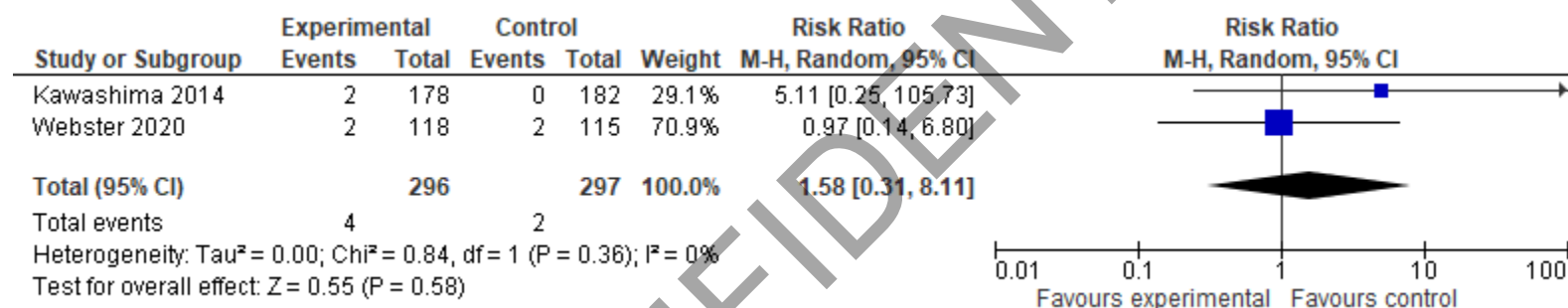
e-Figure 27. AE, Burning at 12 weeks, benzoyl peroxide vs. vehicle



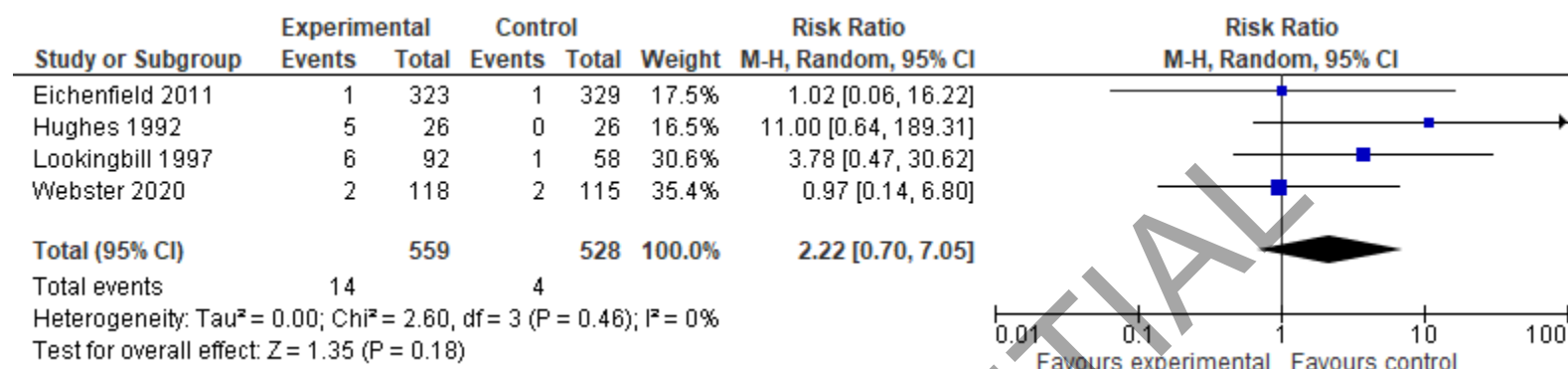
e-Figure 28. AE, Burning, Mild at 12 weeks, benzoyl peroxide vs. vehicle



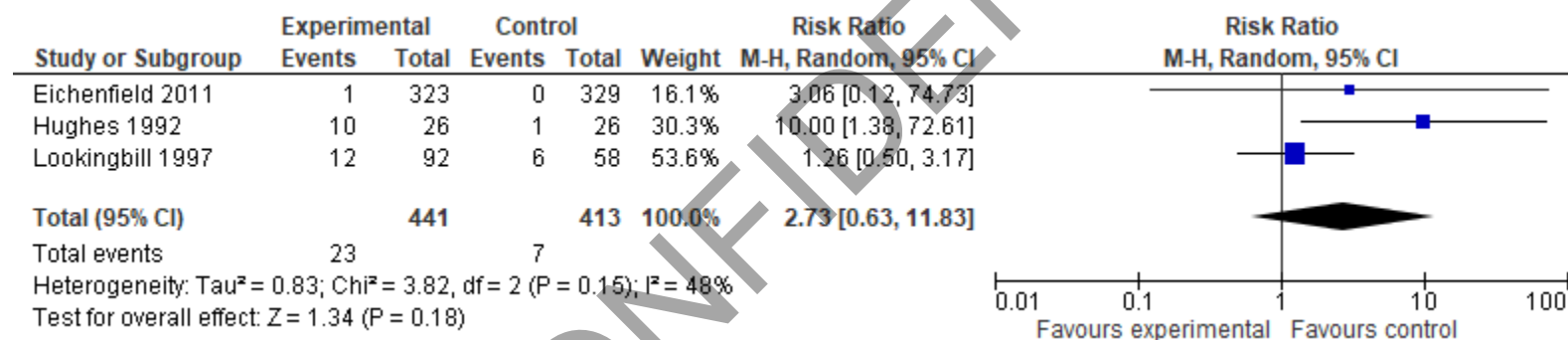
e-Figure 29. AE, Burning, Moderate at 12 weeks, benzoyl peroxide vs. vehicle



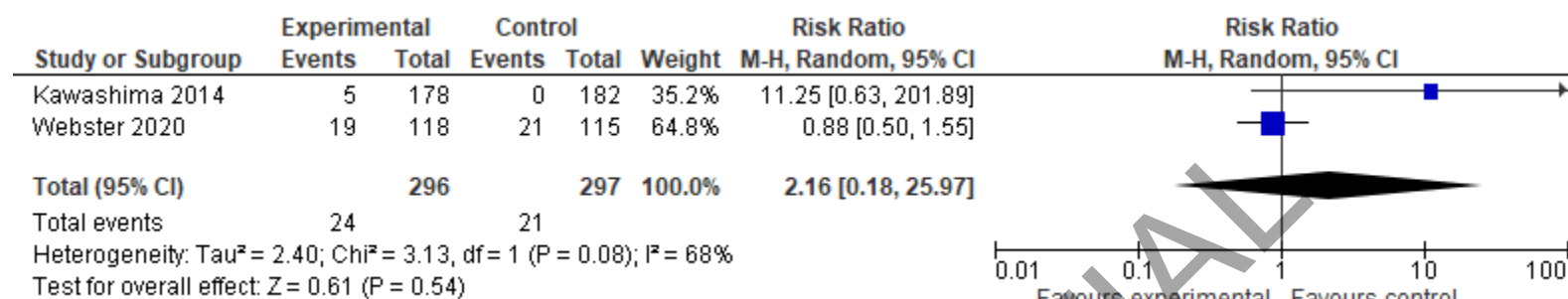
e-Figure 30. AE, Dryness at 12 weeks, benzoyl peroxide vs. vehicle



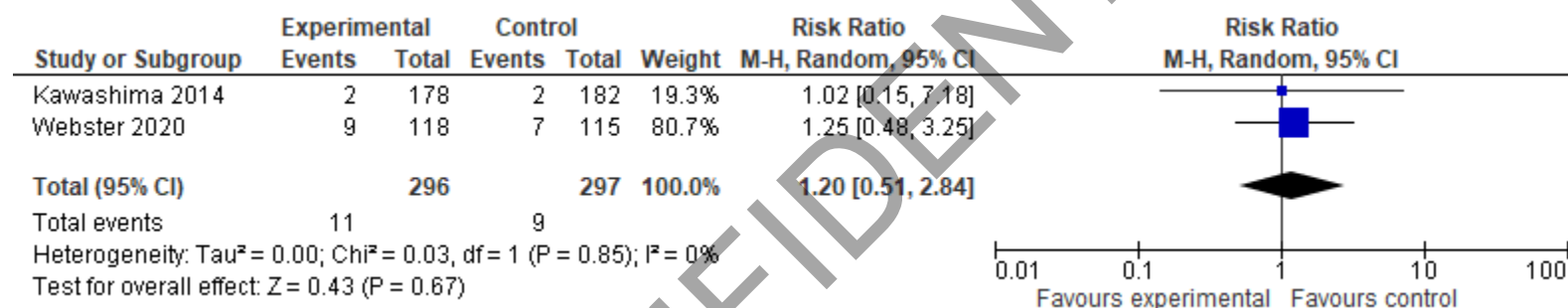
e-Figure 31. AE, Erythema at 12 weeks, benzoyl peroxide vs. vehicle



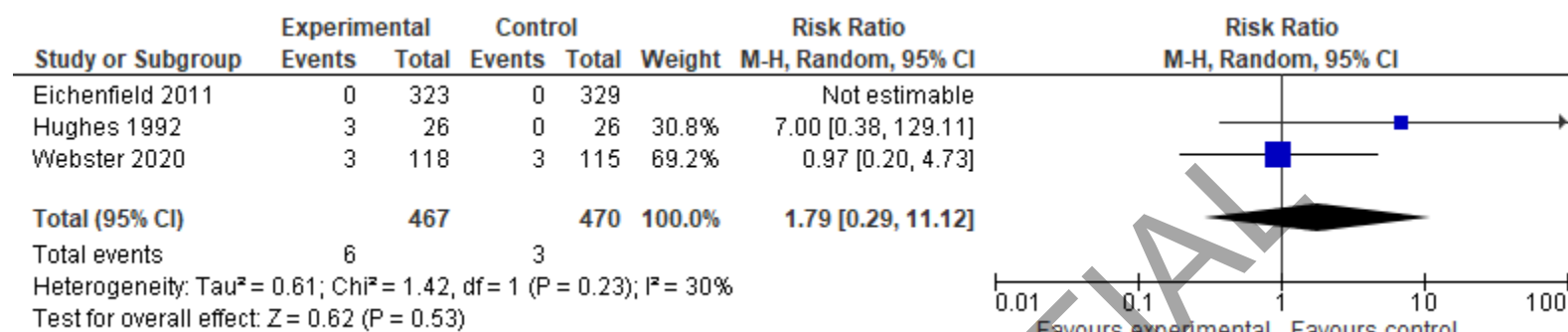
e-Figure 32. AE, Erythema, Mild at 12 weeks, benzoyl peroxide vs. vehicle



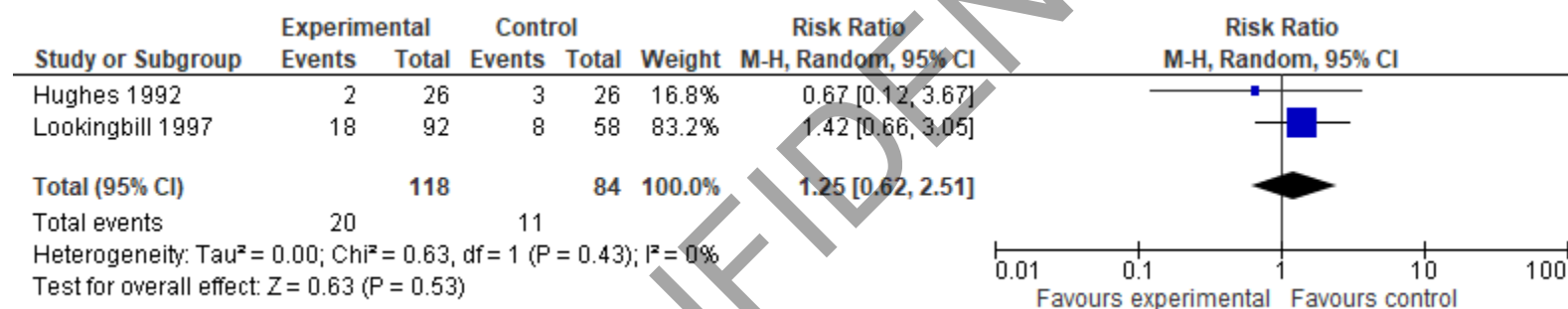
e-Figure 33. AE, Erythema, Moderate at 12 weeks, benzoyl peroxide vs. vehicle



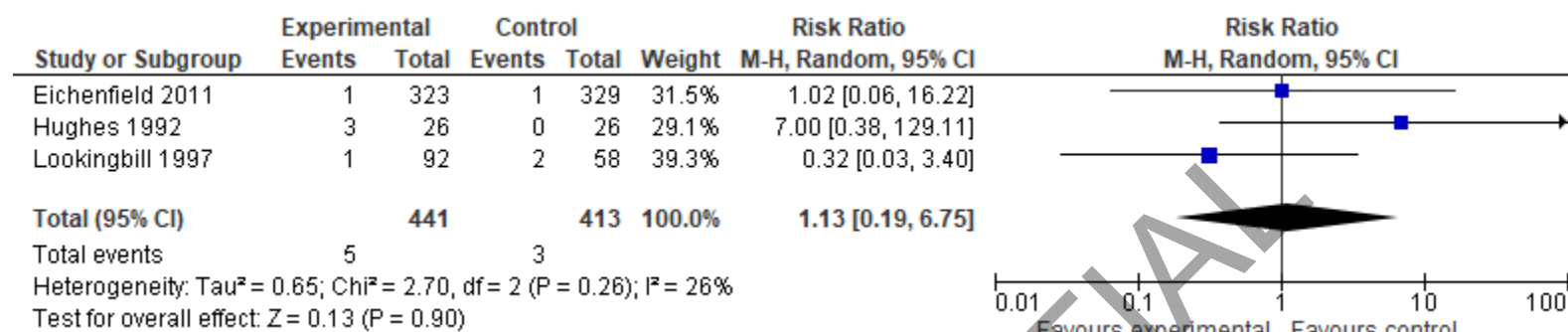
e-Figure 34. AE, Pain at 12 weeks, benzoyl peroxide vs. vehicle



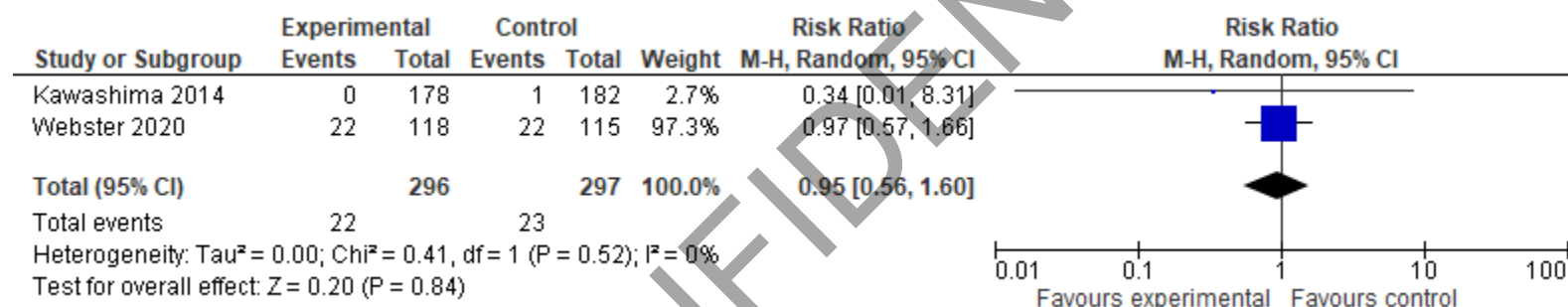
e-Figure 35. AE, Peeling at 12 weeks, benzoyl peroxide vs. vehicle



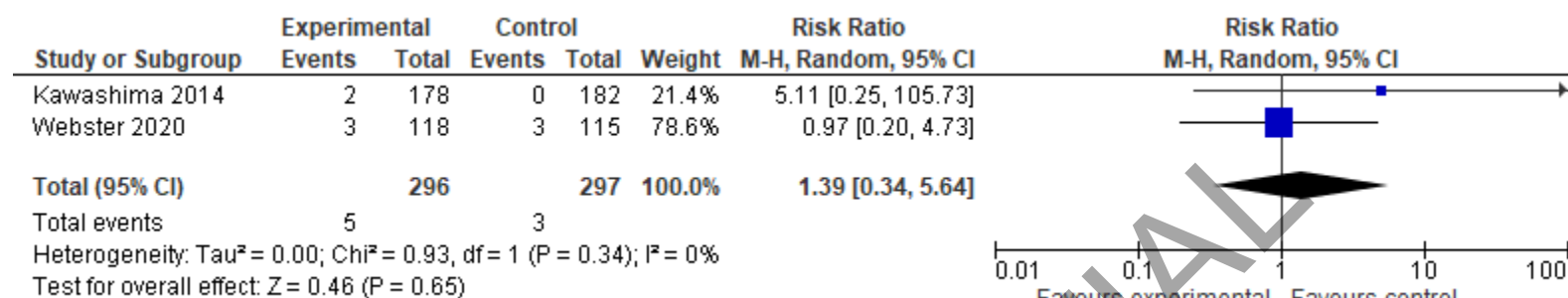
e-Figure 36. AE, Pruritus at 12 weeks, benzoyl peroxide vs. vehicle



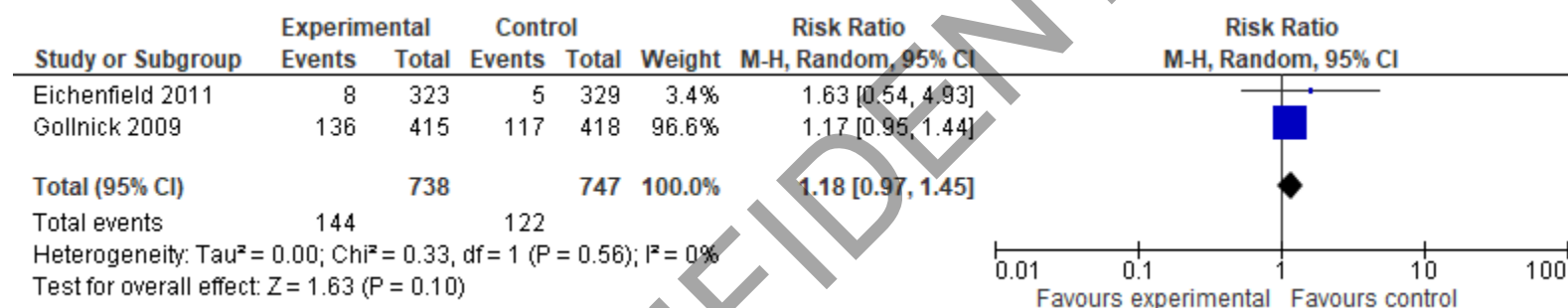
e-Figure 37. AE, Pruritus, Mild at 12 weeks, benzoyl peroxide vs. vehicle



e-Figure 38. AE, Pruritus, Moderate at 12 weeks, benzoyl peroxide vs. vehicle



e-Figure 39. AE, Any at 12 weeks, benzoyl peroxide vs. vehicle



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CONFIDENTIAL

3. Topical antibiotic vs. vehicle

e-Table 14. GRADE evidence profile for topical antibiotic vs. vehicle

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Global Acne Assessment Score, Grade 0-1 at 4 weeks												
2 ^{1,2}	randomised trials	not serious	serious ^a	not serious	serious ^b	none	136/2162 (6.3%)	107/2178 (4.9%)	RR 1.27 (0.69 to 2.35)	13 more per 1,000 (from 15 fewer to 66 more)	⊕⊕○○ Low	CRITICAL
Investigator Global Assessment, ≥2-grade reduction at 12 weeks												
2 ^{3,4}	randomised trials	not serious	not serious	not serious	not serious	none	206/785 (26.2%)	107/571 (18.7%)	RR 1.39 (1.13 to 1.71)	73 more per 1,000 (from 24 more to 133 more)	⊕⊕⊕⊕ High	CRITICAL
Investigator Global Assessment, Grade 0-1 and ≥2-grade reduction at 12 weeks												
3 ^{3,5,6}	randomised trials	not serious ^c	not serious	not serious	not serious	none	353/1278 (27.6%)	203/1066 (19.0%)	RR 1.49 (1.28 to 1.73)	93 more per 1,000 (from 53 more to 139 more)	⊕⊕⊕⊕ High	CRITICAL
Number of lesions, Inflammatory, Papules at 4 weeks (mean absolute change from baseline)												
2 ^{7,8}	randomised trials	not serious	not serious	not serious	not serious	none	216	204	-	MD 2.2 lesions lower (3.83 lower to 0.57 lower)	⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Inflammatory, Papules at 8 weeks (mean absolute change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
2 ^{7,8}	randomised trials	not serious	not serious	not serious	not serious	none	215	204	-	MD 2.45 lesions lower (4.16 lower to 0.74 lower)	⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Inflammatory, Papules at 10 weeks (mean percent change from baseline)

1 ⁹	randomised trials	not serious	not serious	not serious	serious ^d	none	The mean percentage changes from baseline for topical antibiotic and vehicle groups were -57.17% (n: 41) and -29.49% (n: 40), respectively. The difference between the two groups was statistically significant. ^e				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Papules at 12 weeks (Mean percent change from baseline)

1 ¹⁰	randomised trials	not serious	not serious	not serious	serious ^d	none	The mean percentage changes from baseline for topical antibiotic and vehicle groups were -56.9% (n: 109) and -43.6% (n: 90), respectively. The difference between the two groups was statistically significant (p < 0.025). ^e				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Pustules at 4 weeks (mean absolute change from baseline)

2 ^{7,8}	randomised trials	not serious	not serious	not serious	serious ^b	none	216	203	-	MD 0.77 lesions higher (0.15 lower to 1.69 higher)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Pustules at 8 weeks (mean absolute change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
2 ^{7,8}	randomised trials	not serious	not serious	not serious	not serious	none	215	203	-	MD 0.81 lesions lower (1.54 lower to 0.08 lower)	⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Inflammatory, Pustules at 10 weeks (mean percent change from baseline)

1 ⁹	randomised trials	not serious	not serious	not serious	serious ^d	none	The mean percentage changes from baseline for topical antibiotic and vehicle groups were -68.20% (n: 41) and -24.33% (n: 40), respectively. The difference between the two groups was statistically significant. ^e				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Papules and pustules at 4 weeks (mean percent change from baseline)

1 ¹¹	randomised trials	not serious	not serious	not serious	serious ^d	none	178 and 170 patients were randomized to receive topical antibiotic or vehicle, respectively. The mean percentage changes from baseline for topical antibiotic and vehicle groups were 41% and 27.3%, respectively. The difference between the two groups was statistically significant.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 4 weeks (mean percent change from baseline)

7 ^{1,2,5,6,9,12,13}	randomised trials	not serious ^c	not serious	not serious	serious ^{f,g}	none	112	115	-	MD 20.4 % lower (34.81 lower to 5.99 lower)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
8 ^{1,2,4,5,6,12,13,14}	randomised trials	not serious ^c	serious ^h	not serious	not serious ⁱ	none	1637	1622	-	MD 10.86 % lower (18.81 lower to 2.91 lower)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks (mean percent change from baseline)

5 ^{1,2,6,12,14}	randomised trials	not serious	not serious	not serious	serious ^{j,k}	none	39	41	-	MD 7.78 higher (13.92 lower to 29.48 higher)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, Open and closed comedones at 4 weeks (mean percent change from baseline)

1 ⁹	randomised trials	not serious	not serious	not serious	serious ^d	none	The mean percentage changes from baseline for topical antibiotic and vehicle groups were -1.14% (n: 41) and -1.15% (n: 40), respectively. The difference between the two groups was not statistically significant. ^e				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, Closed comedones at 12 weeks (Mean percent change from baseline)

1 ¹⁰	randomised trials	not serious	not serious	not serious	serious ^d	none	The mean percentage changes from baseline for topical antibiotic and vehicle groups were -23.6% (n: 109) and -18.5% (n: 90), respectively. The difference between the two groups was not statistically significant. ^e				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, Open comedones at 12 weeks (Mean percent change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹⁰	randomised trials	not serious	not serious	not serious	serious ^d	none	The mean percentage changes from baseline for topical antibiotic and vehicle groups were -30.8% (n: 109) and -22.4% (n: 90), respectively. The difference between the two groups was not statistically significant. ^e				⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Non-inflammatory at 12 weeks (mean percent change from baseline)												
7 ^{1,2,4,5,6,12,14}	randomised trials	not serious ^c	not serious	not serious	serious ^{b,l}	none	1637	1622	-	MD 3.33 % lower (7.9 lower to 1.24 higher)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any at 4 weeks (mean percent change from baseline)												
4 ^{1,2,11,12}	randomised trials	not serious	not serious	not serious	serious ^{i,m}	none	39	41	-	MD 6.97 lower (22.17 lower to 8.23 higher)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any at 12 weeks (mean percent change from baseline)												
4 ^{1,2,4,12}	randomised trials	not serious	not serious	not serious	not serious ⁿ	none	357	370	-	MD 9.28 % lower (14.55 lower to 4 lower)	⊕⊕⊕⊕ High	CRITICAL
Number of lesions, Any, <=25% reduction at 12 weeks												
1 ¹⁰	randomised trials	not serious ^o	not serious	not serious	serious ^f	none	12/109 (11.0%)	27/90 (30.0%)	RR 0.37 (0.20 to 0.68)	189 fewer per 1,000 (from 240 fewer to 96 fewer)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, 26-50% reduction at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹⁰	randomised trials	not serious ^o	not serious	not serious	serious ^f	none	19/109 (17.4%)	27/90 (30.0%)	RR 0.58 (0.35 to 0.97)	126 fewer per 1,000 (from 195 fewer to 9 fewer)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, ≥50% reduction at 8 weeks

1 ⁸	randomised trials	not serious	not serious	not serious	serious ^f	none	55/92 (59.8%)	32/91 (35.2%)	RR 1.70 (1.23 to 2.35)	246 more per 1,000 (from 81 more to 475 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, >50% reduction at 12 weeks

1 ¹⁰	randomised trials	not serious ^o	not serious	not serious	serious ^f	none	109/109 (100.0%)	90/90 (100.0%)	RR 1.00 (0.98 to 1.02)	0 fewer per 1,000 (from 20 fewer to 20 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, ≥50% reduction at 12 weeks

1 ⁴	randomised trials	not serious	not serious	not serious	not serious	none	195/318 (61.3%)	175/329 (53.2%)	RR 1.15 (1.01 to 1.32)	80 more per 1,000 (from 5 more to 170 more)	⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Any, 51-75% reduction at 12 weeks

1 ¹⁰	randomised trials	not serious ^o	not serious	not serious	serious ^j	none	39/109 (35.8%)	22/90 (24.4%)	RR 1.46 (0.94 to 2.28)	112 more per 1,000 (from 15 fewer to 313 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, >75% reduction at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹⁰	randomised trials	not serious ^o	not serious	not serious	serious ^f	none	39/109 (35.8%)	14/90 (15.6%)	RR 2.30 (1.34 to 3.96)	202 more per 1,000 (from 53 more to 460 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Papules, >50% reduction at 12 weeks

1 ¹⁰	randomised trials	not serious ^o	not serious	not serious	serious ^j	none	108/108 (100.0%)	90/90 (100.0%)	RR 1.00 (0.98 to 1.02)	0 fewer per 1,000 (from 20 fewer to 20 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Pustules, >50% reduction at 12 weeks

1 ¹⁰	randomised trials	not serious ^o	not serious	not serious	serious ^j	none	104/104 (100.0%)	87/87 (100.0%)	RR 1.00 (0.98 to 1.02)	0 fewer per 1,000 (from 20 fewer to 20 more)	⊕⊕⊕○ Moderate	CRITICAL

Patient assessment of improvement, Global, Improvement/Notable improvement at 8 weeks

1 ⁷	randomised trials	not serious	not serious	not serious	serious ^f	none	94/123 (76.4%)	62/112 (55.4%)	RR 1.38 (1.14 to 1.67)	210 more per 1,000 (from 77 more to 371 more)	⊕⊕⊕○ Moderate	IMPORTANT

Patient assessment of improvement, Global, Worse/Unchanged at 8 weeks

1 ⁷	randomised trials	not serious	not serious	not serious	serious ^f	none	28/123 (22.8%)	48/112 (42.9%)	RR 0.53 (0.36 to 0.78)	201 fewer per 1,000 (from 274 fewer to 94 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

Acne severity, Patient assessment of improvement, Grade 0-1 at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ³	randomised trials	not serious	not serious	not serious	not serious	none	297/467 (63.6%)	128/242 (52.9%)	RR 1.20 (1.05 to 1.38)	106 more per 1,000 (from 26 more to 201 more)	⊕⊕⊕⊕ High	IMPORTANT

Patient assessment of improvement, Global, Improvement at 12 weeks

1 ¹²	randomised trials	not serious	not serious	not serious	serious ^j	none	22/39 (56.4%)	21/41 (51.2%)	RR 1.10 (0.73 to 1.65)	51 more per 1,000 (from 138 fewer to 333 more)	⊕⊕⊕○ Moderate	IMPORTANT

Acne severity, Patient assessment of improvement, ≥2-grade reduction at 12 weeks

1 ⁴	randomised trials	not serious	not serious	not serious	serious ^b	none	171/318 (53.8%)	154/329 (46.8%)	RR 1.15 (0.99 to 1.34)	70 more per 1,000 (from 5 fewer to 159 more)	⊕⊕⊕○ Moderate	IMPORTANT

Patient assessment of improvement, Global, No change at 12 weeks

1 ¹²	randomised trials	not serious	not serious	not serious	serious ^j	none	10/39 (25.6%)	16/41 (39.0%)	RR 0.66 (0.34 to 1.27)	133 fewer per 1,000 (from 258 fewer to 105 more)	⊕⊕⊕○ Moderate	IMPORTANT

Patient assessment of improvement, Global, Worse at 12 weeks

1 ¹²	randomised trials	not serious	not serious	not serious	serious ^p	none	5/39 (12.8%)	2/41 (4.9%)	RR 2.63 (0.54 to 12.76)	80 more per 1,000 (from 22 fewer to 574 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Any, Leading to discontinuation at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
3 ^{2,6,10}	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	10/1895 (0.5%)	13/1916 (0.7%)	RR 0.77 (0.33 to 1.79)	2 fewer per 1,000 (from 5 fewer to 5 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Dryness at 12 weeks

3 ^{2,4,14}	randomised trials	not serious	not serious	not serious	serious ^b	none	12/1451 (0.8%)	13/1445 (0.9%)	RR 0.82 (0.32 to 2.12)	2 fewer per 1,000 (from 6 fewer to 10 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Dryness, Mild at 12 weeks

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^b	none	53/737 (7.2%)	68/747 (9.1%)	RR 0.79 (0.56 to 1.11)	19 fewer per 1,000 (from 40 fewer to 10 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Dryness, Moderate at 12 weeks

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^b	none	5/737 (0.7%)	4/747 (0.5%)	RR 1.27 (0.34 to 4.70)	1 more per 1,000 (from 4 fewer to 20 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Dryness, Severe at 12 weeks

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^b	none	0/737 (0.0%)	1/747 (0.1%)	RR 0.34 (0.01 to 8.28)	1 fewer per 1,000 (from 1 fewer to 10 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Dryness, None at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ⁶	randomised trials	not serious	not serious	not serious	serious ^b	none	568/737 (77.1%)	550/747 (73.6%)	RR 1.05 (0.99 to 1.11)	37 more per 1,000 (from 7 fewer to 81 more)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Dryness at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	19/1117 (1.7%)	11/1118 (1.0%)	RR 1.73 (0.83 to 3.62)	7 more per 1,000 (from 2 fewer to 26 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema at 12 weeks

3 ^{2,4,14}	randomised trials	not serious	not serious	not serious	serious ^b	none	12/1451 (0.8%)	17/1445 (1.2%)	RR 0.60 (0.29 to 1.24)	5 fewer per 1,000 (from 8 fewer to 3 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema, Mild at 12 weeks

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^b	none	100/737 (13.6%)	98/747 (13.1%)	RR 1.03 (0.80 to 1.34)	4 more per 1,000 (from 26 fewer to 45 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema, Moderate at 12 weeks

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^b	none	11/737 (1.5%)	11/747 (1.5%)	RR 1.01 (0.44 to 2.32)	0 fewer per 1,000 (from 8 fewer to 19 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema, None at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ⁶	randomised trials	not serious	not serious	not serious	serious ^b	none	515/737 (69.9%)	514/747 (68.8%)	RR 1.02 (0.95 to 1.09)	14 more per 1,000 (from 34 fewer to 62 more)	⊕⊕⊕○ Moderate	IMPORTANT

Erythema score, 0 at 12 weeks

1 ¹³	randomised trials	not serious	not serious	not serious	serious ^j	none	84/105 (80.0%)	82/103 (79.6%)	RR 1.00 (0.88 to 1.15)	0 fewer per 1,000 (from 96 fewer to 119 more)	⊕⊕⊕○ Moderate	IMPORTANT

Erythema score, 1 at 12 weeks

1 ¹³	randomised trials	not serious	not serious	not serious	serious ^j	none	18/105 (17.1%)	18/103 (17.5%)	RR 0.98 (0.54 to 1.78)	3 fewer per 1,000 (from 80 fewer to 136 more)	⊕⊕⊕○ Moderate	IMPORTANT

Erythema score, 2 at 12 weeks

1 ¹³	randomised trials	not serious	not serious	not serious	serious ^j	none	2/105 (1.9%)	2/103 (1.9%)	RR 0.98 (0.14 to 6.83)	0 fewer per 1,000 (from 17 fewer to 113 more)	⊕⊕⊕○ Moderate	IMPORTANT

Erythema score, 3 at 12 weeks

1 ¹³	randomised trials	not serious	not serious	not serious	serious ^p	none	1/105 (1.0%)	1/103 (1.0%)	RR 0.98 (0.06 to 15.48)	0 fewer per 1,000 (from 9 fewer to 141 more)	⊕⊕⊕○ Moderate	IMPORTANT

Erythema score, 4 at 12 weeks

1 ¹³	randomised trials	not serious	not serious	not serious	serious ^r	none	0/105 (0.0%)	0/103 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Pain at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
2 ^{2,4}	randomised trials	not serious	not serious	not serious	serious ^b	none	3/1362 (0.2%)	14/1387 (1.0%)	RR 0.48 (0.03 to 8.91)	5 fewer per 1,000 (from 10 fewer to 80 more)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Pain at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	9/1117 (0.8%)	19/1118 (1.7%)	RR 0.47 (0.22 to 1.04)	9 fewer per 1,000 (from 13 fewer to 1 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Peeling, Mild at 12 weeks

2 ^{6,13}	randomised trials	not serious	not serious	not serious	serious ^b	none	26/842 (3.1%)	38/850 (4.5%)	RR 0.84 (0.31 to 2.28)	7 fewer per 1,000 (from 31 fewer to 57 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Peeling, Moderate at 12 weeks

2 ^{6,13}	randomised trials	not serious	not serious	not serious	serious ^b	none	1/842 (0.1%)	2/850 (0.2%)	RR 0.51 (0.05 to 5.58)	1 fewer per 1,000 (from 2 fewer to 11 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Peeling, Severe at 12 weeks

2 ^{6,13}	randomised trials	not serious	not serious	not serious	serious ^b	none	0/842 (0.0%)	1/850 (0.1%)	RR 0.34 (0.01 to 8.28)	1 fewer per 1,000 (from 1 fewer to 9 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Peeling, None at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
2 ^{6,13}	randomised trials	not serious	not serious	not serious	serious ^b	none	702/842 (83.4%)	683/850 (80.4%)	RR 1.02 (0.94 to 1.10)	16 more per 1,000 (from 48 fewer to 80 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Peeling at 12 weeks

1 ¹⁴	randomised trials	not serious	not serious	not serious	serious ^j	none	6/89 (6.7%)	8/58 (13.8%)	RR 0.49 (0.18 to 1.34)	70 fewer per 1,000 (from 113 fewer to 47 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Peeling, Moderate-to-severe at 12 weeks

1 ¹³	randomised trials	not serious	not serious	not serious	serious ^j	none	2/105 (1.9%)	2/103 (1.9%)	RR 0.98 (0.14 to 6.83)	0 fewer per 1,000 (from 17 fewer to 113 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Burning at 12 weeks

1 ¹⁴	randomised trials	not serious	not serious	not serious	serious ^r	none	0/89 (0.0%)	0/58 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Dermatitis at 12 weeks

1 ⁴	randomised trials	not serious	not serious	not serious	serious ^r	none	0/318 (0.0%)	0/329 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Eczema at 12 weeks

1 ⁴	randomised trials	not serious	not serious	not serious	serious ^r	none	0/318 (0.0%)	0/329 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Exfoliation at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^b	none	7/1044 (0.7%)	11/1058 (1.0%)	RR 0.64 (0.25 to 1.66)	4 fewer per 1,000 (from 8 fewer to 7 more)	⊕⊕⊕○ Moderate	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
AE, Hyperpigmentation, Mild at 12 weeks												
1 ⁶	randomised trials	not serious	not serious	not serious	serious ^b	none	75/737 (10.2%)	90/747 (12.0%)	RR 0.84 (0.63 to 1.13)	19 fewer per 1,000 (from 45 fewer to 16 more)	⊕⊕⊕○ Moderate	IMPORTANT
AE, Hyperpigmentation, Moderate at 12 weeks												
1 ⁶	randomised trials	not serious	not serious	not serious	serious ^b	none	14/737 (1.9%)	17/747 (2.3%)	RR 0.83 (0.41 to 1.68)	4 fewer per 1,000 (from 13 fewer to 15 more)	⊕⊕⊕○ Moderate	IMPORTANT
AE, Hyperpigmentation, Severe at 12 weeks												
1 ⁶	randomised trials	not serious	not serious	not serious	serious ^s	none	1/737 (0.1%)	1/747 (0.1%)	RR 1.01 (0.06 to 16.18)	0 fewer per 1,000 (from 1 fewer to 20 more)	⊕⊕⊕○ Moderate	IMPORTANT
AE, Hyperpigmentation, None at 12 weeks												
1 ⁶	randomised trials	not serious	not serious	not serious	serious ^b	none	536/737 (72.7%)	515/747 (68.9%)	RR 1.05 (0.99 to 1.13)	34 more per 1,000 (from 7 fewer to 90 more)	⊕⊕⊕○ Moderate	IMPORTANT
AE, Irritation at 12 weeks												
1 ⁴	randomised trials	not serious	not serious	not serious	serious ^r	none	0/318 (0.0%)	0/329 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT
AE, Photosensitivity at 12 weeks												
1 ⁴	randomised trials	not serious	not serious	not serious	serious ^b	none	1/318 (0.3%)	2/329 (0.6%)	RR 0.52 (0.05 to 5.68)	3 fewer per 1,000 (from 6 fewer to 28 more)	⊕⊕⊕○ Moderate	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		

AE, Pruritus, Mild at 12 weeks

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^b	none	30/737 (4.1%)	40/747 (5.4%)	RR 0.76 (0.48 to 1.21)	13 fewer per 1,000 (from 28 fewer to 11 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus at 12 weeks

3 ^{2,4,14}	randomised trials	not serious	not serious	not serious	serious ^b	none	12/1451 (0.8%)	11/1445 (0.8%)	RR 1.05 (0.38 to 2.86)	0 fewer per 1,000 (from 5 fewer to 14 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus, Moderate at 12 weeks

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^b	none	7/737 (0.9%)	6/747 (0.8%)	RR 1.18 (0.40 to 3.50)	1 more per 1,000 (from 5 fewer to 20 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus, Severe at 12 weeks

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^s	none	1/737 (0.1%)	0/747 (0.0%)	RR 3.04 (0.12 to 74.52)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus, None at 12 weeks

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^b	none	588/737 (79.8%)	577/747 (77.2%)	RR 1.03 (0.98 to 1.09)	23 more per 1,000 (from 15 fewer to 70 more)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Pruritus at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	12/1117 (1.1%)	6/1118 (0.5%)	RR 2.00 (0.75 to 5.31)	5 more per 1,000 (from 1 fewer to 23 more)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Any at 12 weeks

2 ^{2,6}	randomised trials	not serious	not serious	not serious	serious ^b	none	223/1778 (12.5%)	218/1807 (12.1%)	RR 1.05 (0.89 to 1.24)	6 more per 1,000 (from 13 fewer to 29 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Any at 12 weeks

3 ^{2,4,6}	randomised trials	not serious	not serious	not serious	serious ^b	none	408/2096 (19.5%)	415/2137 (19.4%)	RR 1.00 (0.89 to 1.13)	0 fewer per 1,000 (from 21 fewer to 25 more)	⊕⊕⊕○ Moderate	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

a. $I^2 = 84\%$

b. CI included both appreciable benefits and harm.

c. One study (Alexis 2018) had a high dropout rate of 24.3%.

d. Standard deviation values were not reported. Small sample size.

e. n: number of patients

f. Small sample size.

g. Five studies (Chalker 1983, Eichenfield 2016, Leshner 1985, Raoof 2020, and Stein Gold2016) did not report the standard deviation values. Therefore, data could not be pooled.

h. $I^2 = 82\%$

i. Three studies (Leshner 1985, Raoof 2020, and Stein Gold2016) did not report the standard deviation values. Therefore, data could not be pooled.

j. CI included both appreciable benefits and harm. Small sample size.

k. Four studies (Eichenfield 2016, Lookingbill 1997, Raoof 2020, and Stein Gold 2016) did not report the standard deviation values. Therefore, data could not be pooled.

l. Two studies (Raoof 2020 and Stein Gold2016) did not report the standard deviation values. Therefore, data could not be pooled.

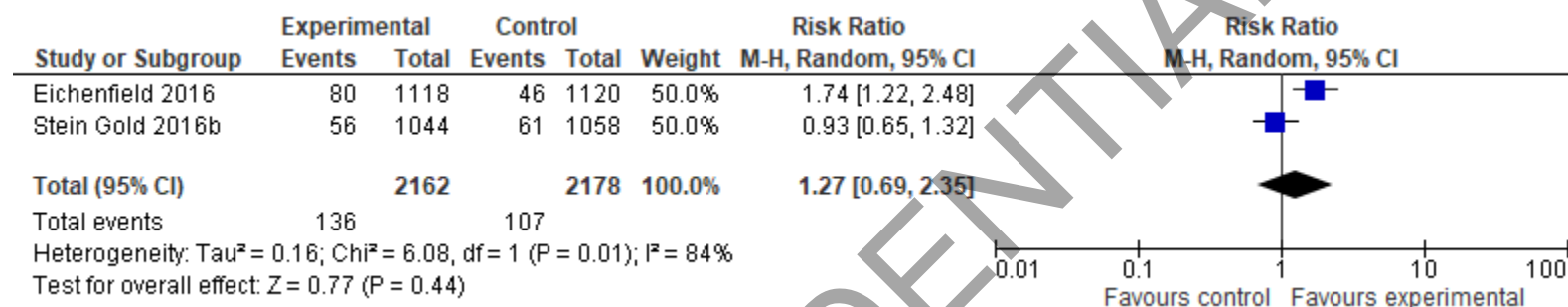
m. Three studies (Eichenfield 2016, Bernstein 1980, and Stein Gold 2016) did not report the standard deviation values. Therefore, data could not be pooled.

n. Two studies (Eichenfield 2016 and Stein Gold2016) did not report the standard deviation values. Therefore, data could not be pooled.

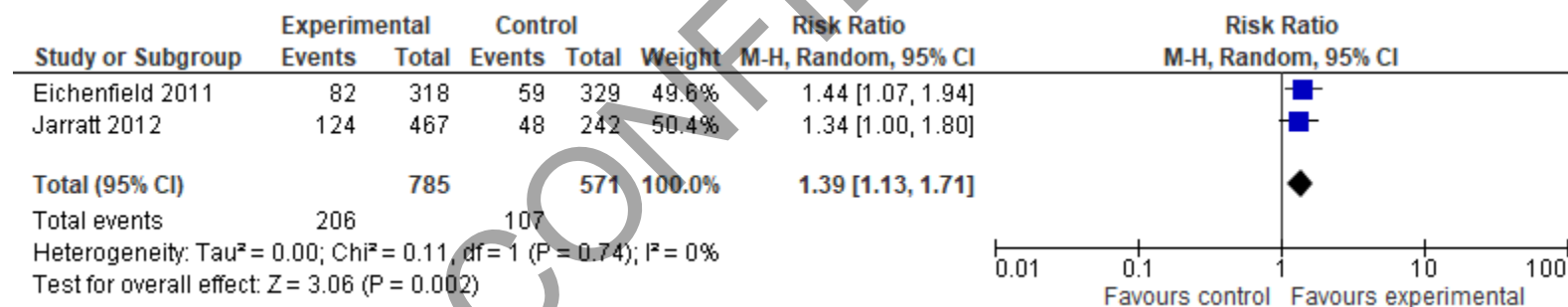
- o. The study had a high dropout rate of 21.3%.
- p. Wide CI included both appreciable benefits and harm. Small sample size.
- q. One study (Dobson 1980) had a high dropout rate of 21.3%.
- r. Double zero study.
- s. Wide CI included both appreciable benefits and harm.

Forest plots

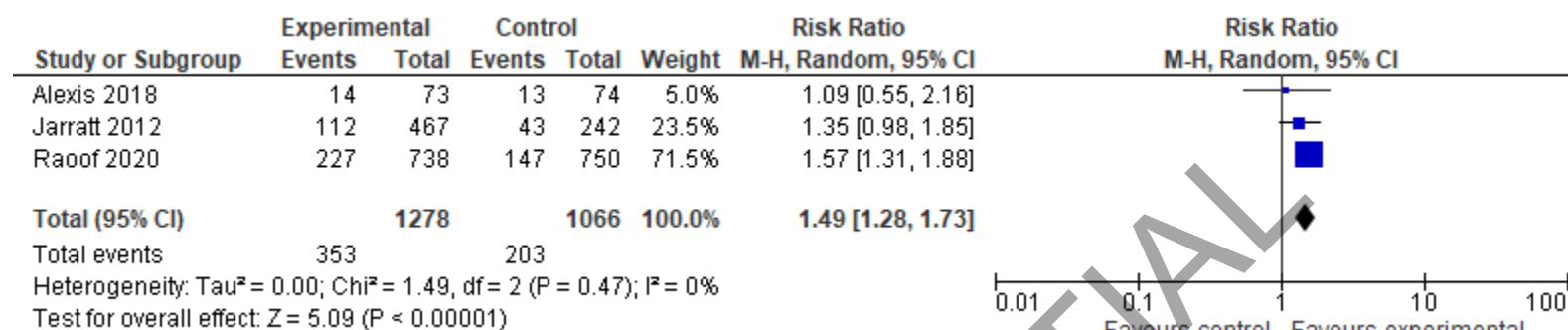
e-Figure 40. Acne severity, Global Acne Assessment Score, Grade 0-1 at 4 weeks, topical antibiotic vs. vehicle



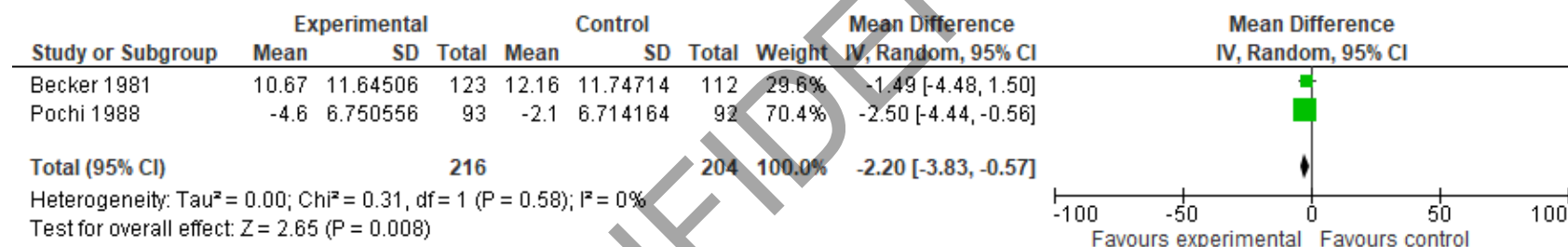
e-Figure 41. Investigator Global Assessment, ≥ 2 -grade reduction at 12 weeks, topical antibiotic vs. vehicle



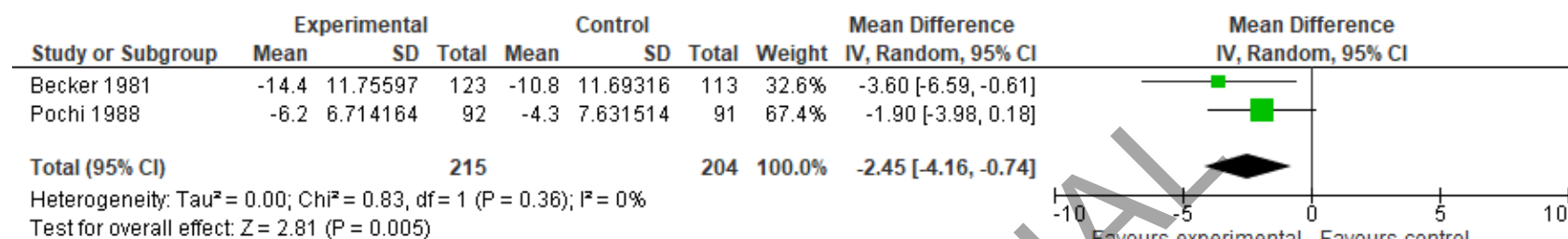
e-Figure 42. Investigator Global Assessment, Grade 0-1 and ≥ 2 -grade reduction at 12 weeks, topical antibiotic vs. vehicle



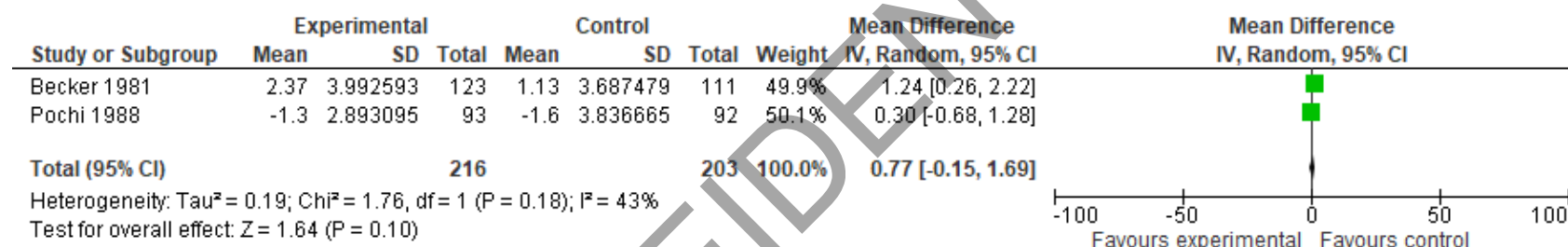
e-Figure 43. Number of lesions, Inflammatory, Papules at 4 weeks (mean absolute change from baseline), topical antibiotic vs. vehicle



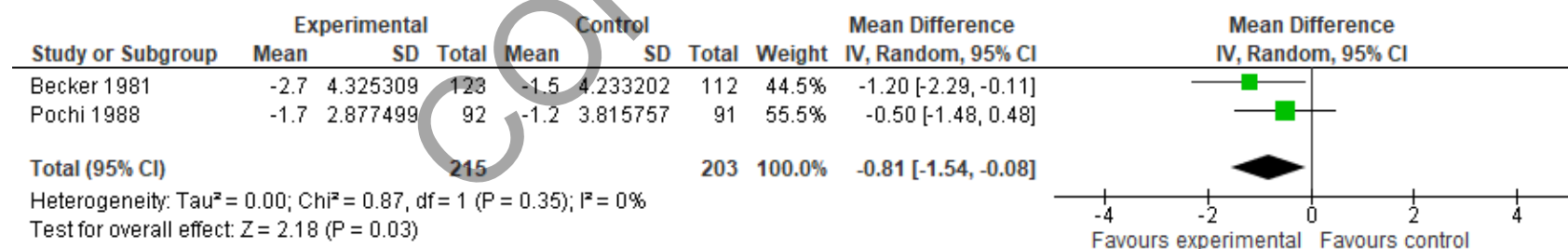
e-Figure 44. Number of lesions, Inflammatory, Papules at 8 weeks (mean absolute change from baseline), topical antibiotic vs. vehicle



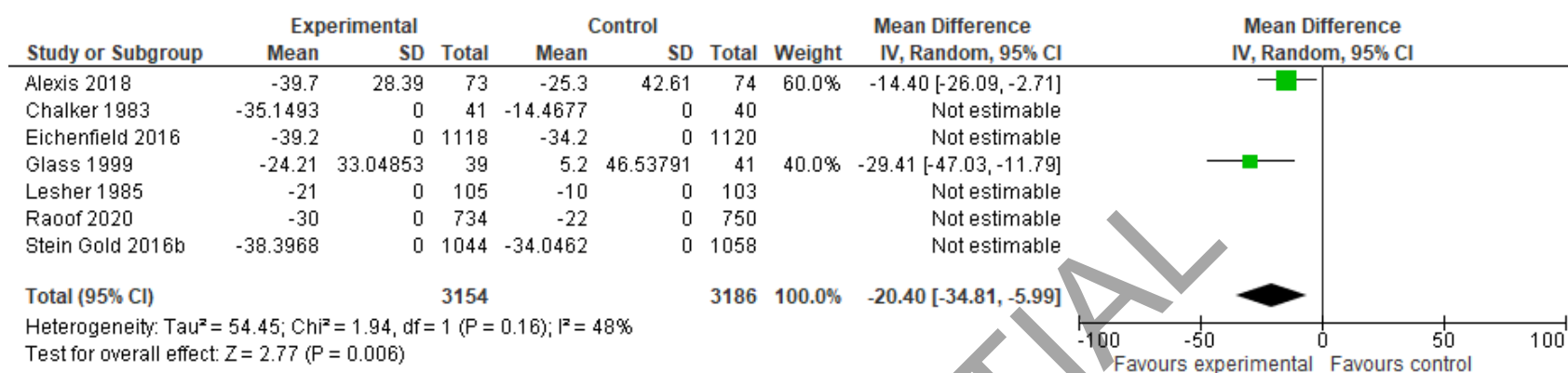
e-Figure 45. Number of lesions, Inflammatory, Pustules at 4 weeks (mean absolute change from baseline), topical antibiotic vs. vehicle



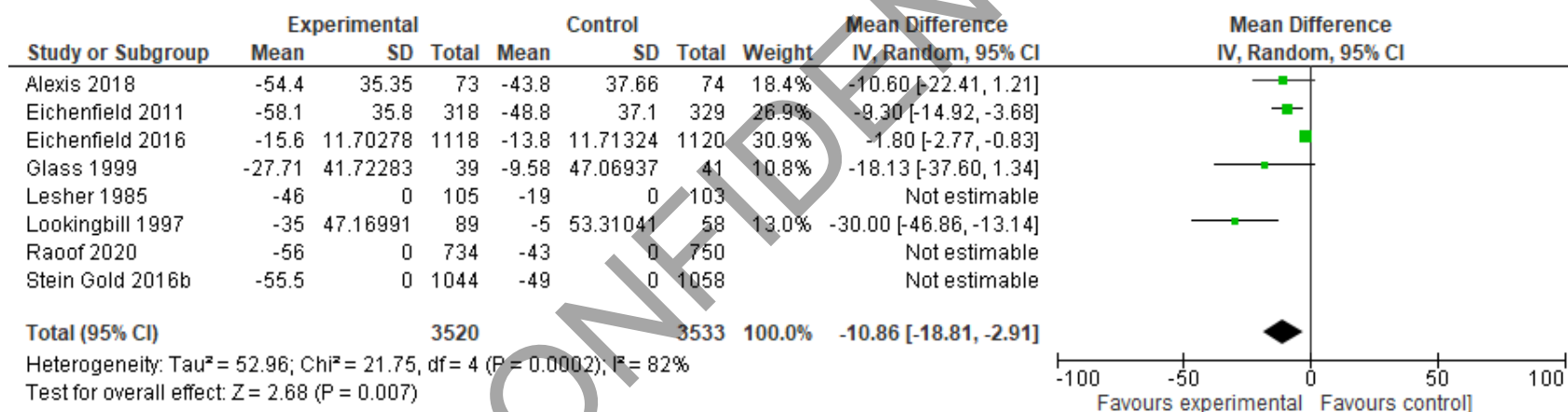
e-Figure 46. Number of lesions, Inflammatory, Pustules at 8 weeks (mean absolute change from baseline), topical antibiotic vs. vehicle



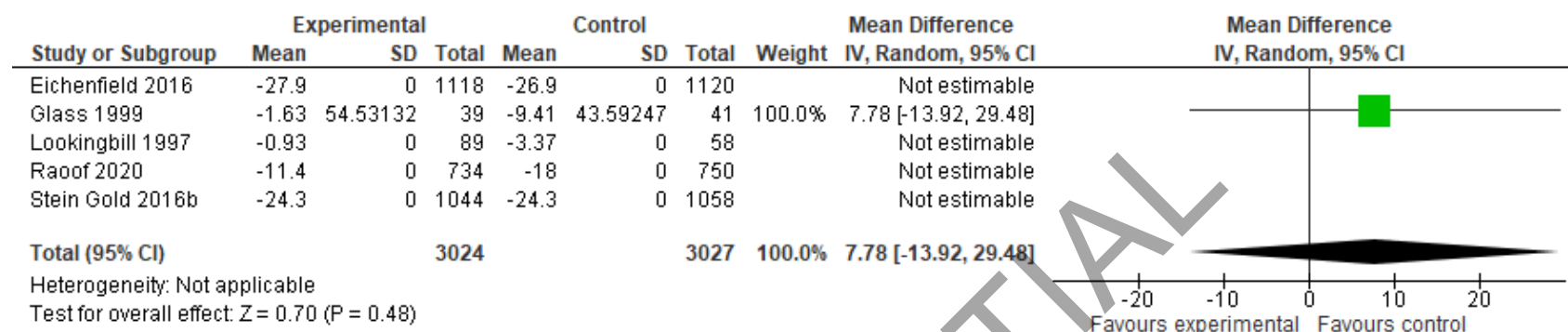
e-Figure 47. Number of lesions, Inflammatory at 4 weeks (mean percent change from baseline), topical antibiotic vs. vehicle



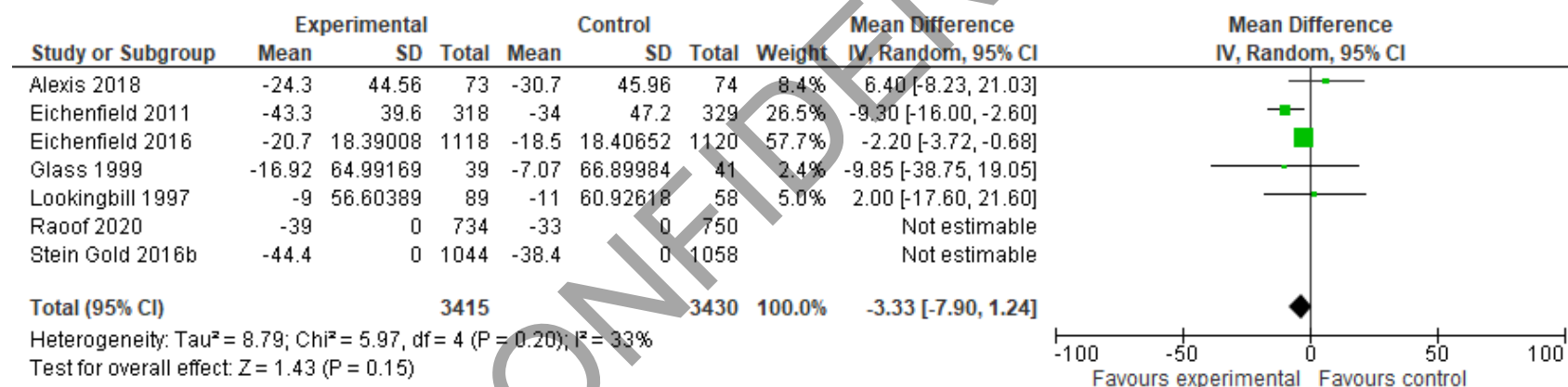
e-Figure 48. Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline), topical antibiotic vs. vehicle



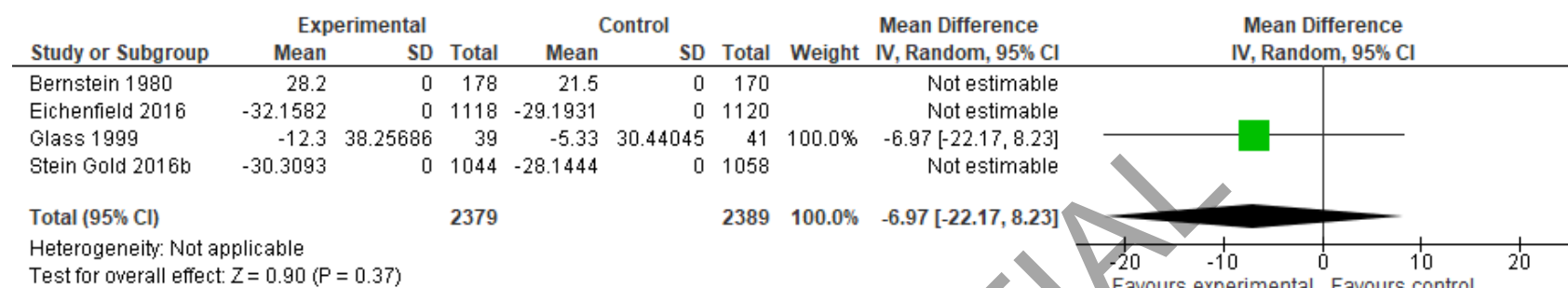
e-Figure 49. Number of lesions, Non-inflammatory at 4 weeks (mean percent change from baseline), topical antibiotic vs. vehicle



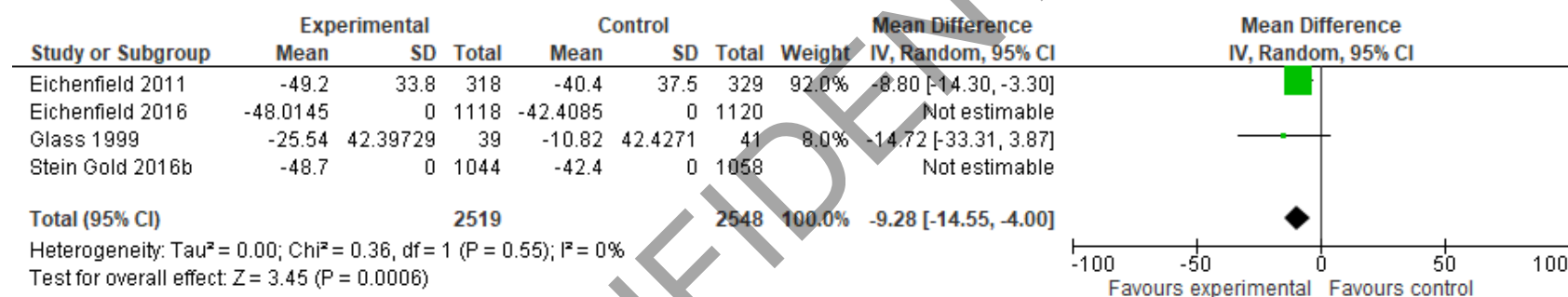
e-Figure 50. Number of lesions, Non-inflammatory at 12 weeks (mean percent change from baseline), topical antibiotic vs. vehicle



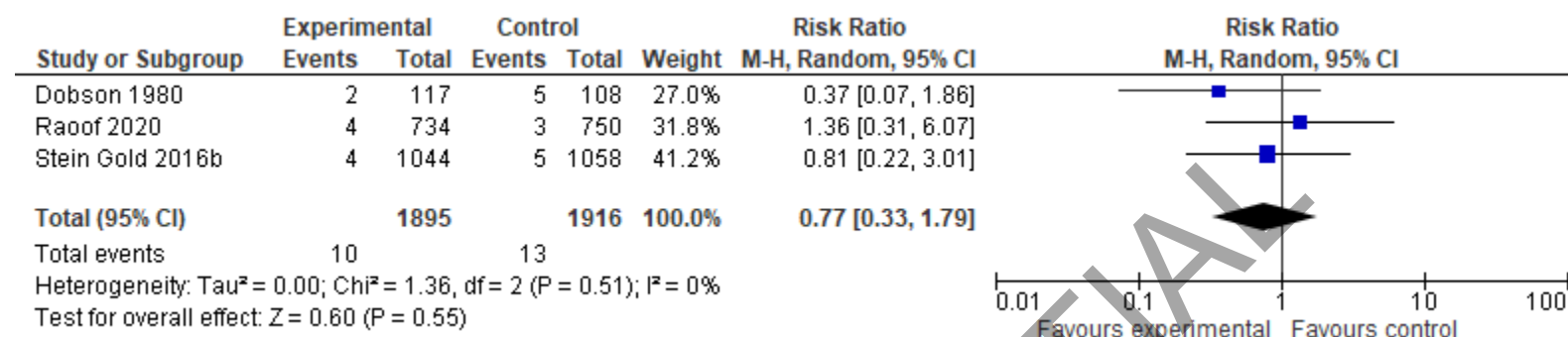
e-Figure 51. Number of lesions, Any at 4 weeks (mean percent change from baseline), topical antibiotic vs. vehicle



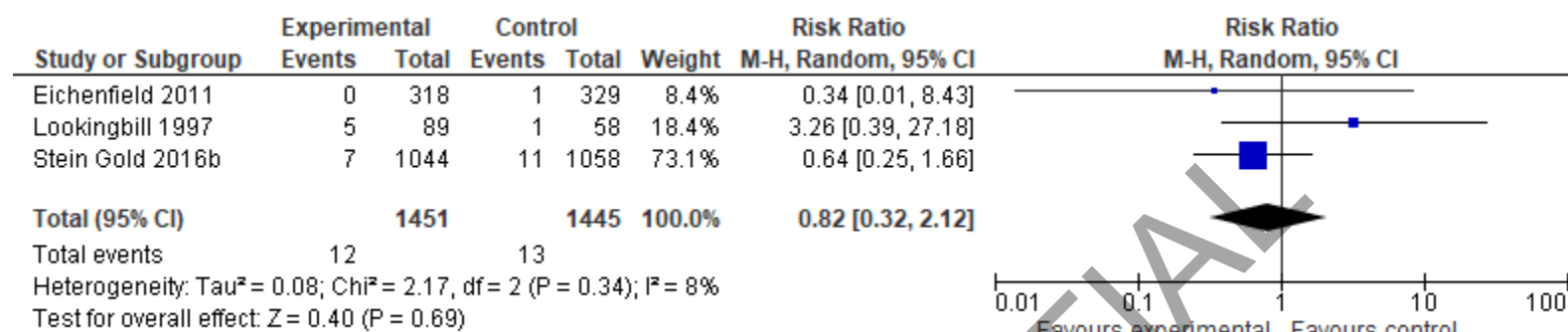
e-Figure 52. Number of lesions, Any at 12 weeks (mean percent change from baseline), topical antibiotic vs. vehicle



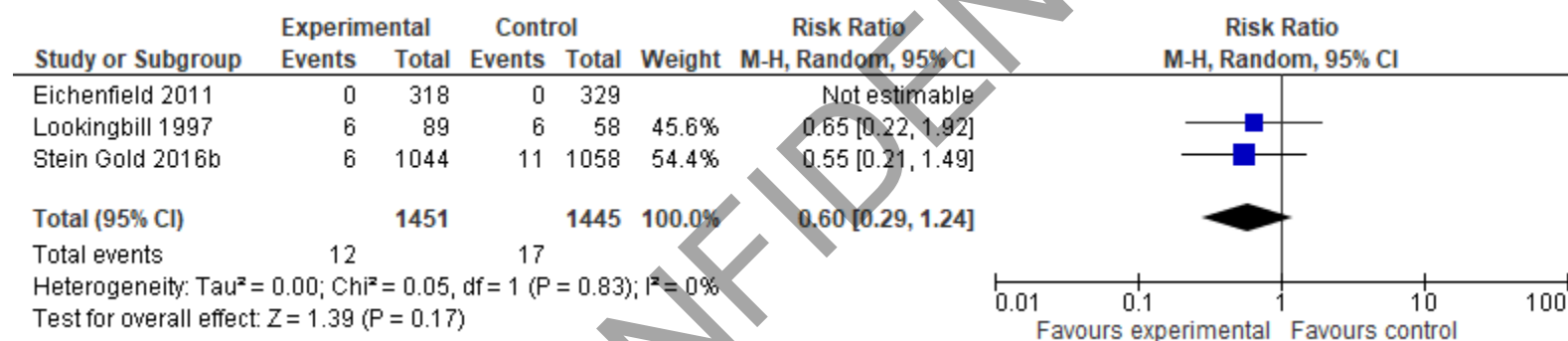
e-Figure 53. AE, Any, Leading to discontinuation at 12 weeks, topical antibiotic vs. vehicle



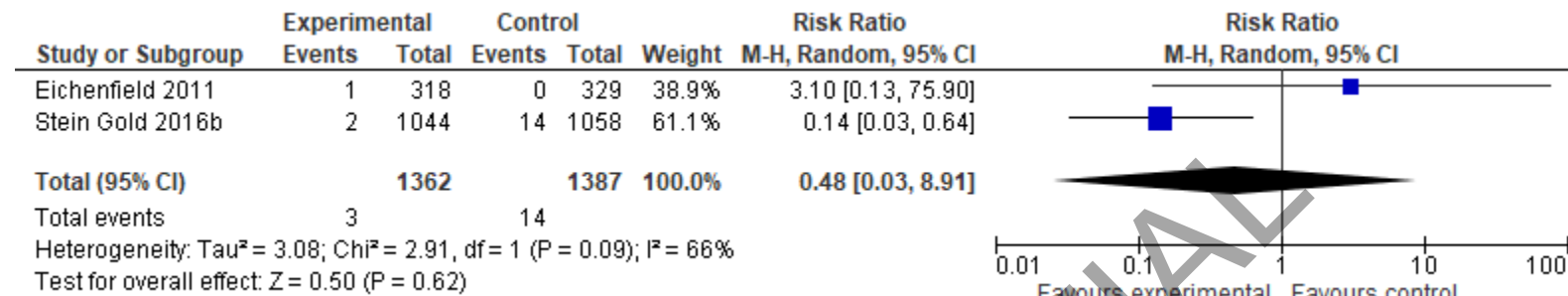
e-Figure 54. AE, Dryness at 12 weeks, topical antibiotic vs. vehicle



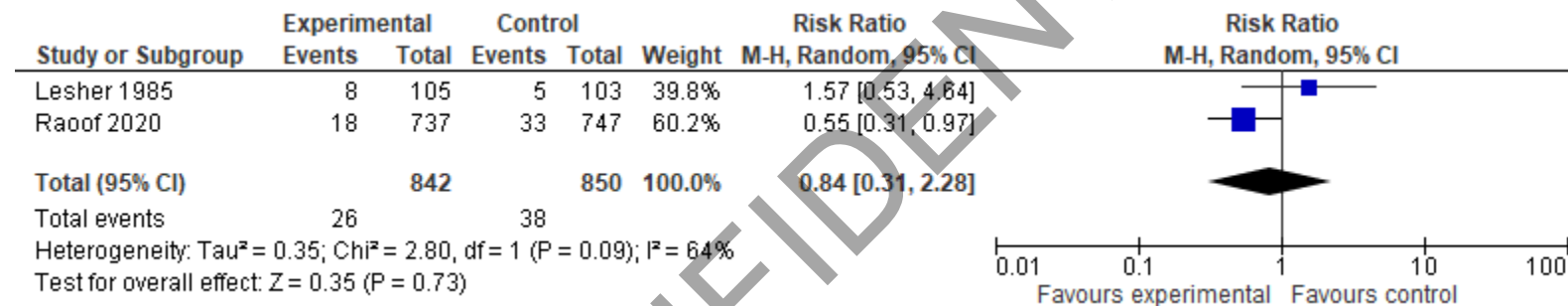
e-Figure 55. AE, Erythema at 12 weeks, topical antibiotic vs. vehicle



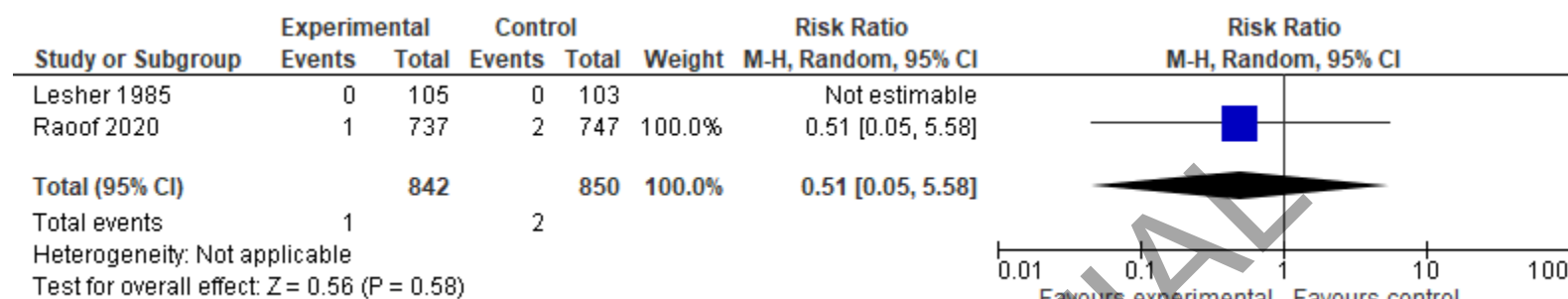
e-Figure 56. AE, Pain at 12 weeks, topical antibiotic vs. vehicle



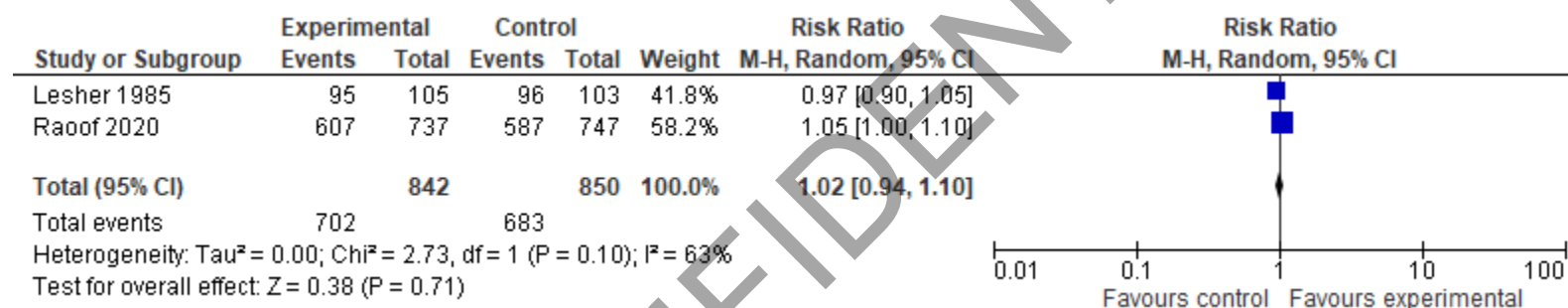
e-Figure 57. AE, Peeling, Mild at 12 weeks, topical antibiotic vs. vehicle



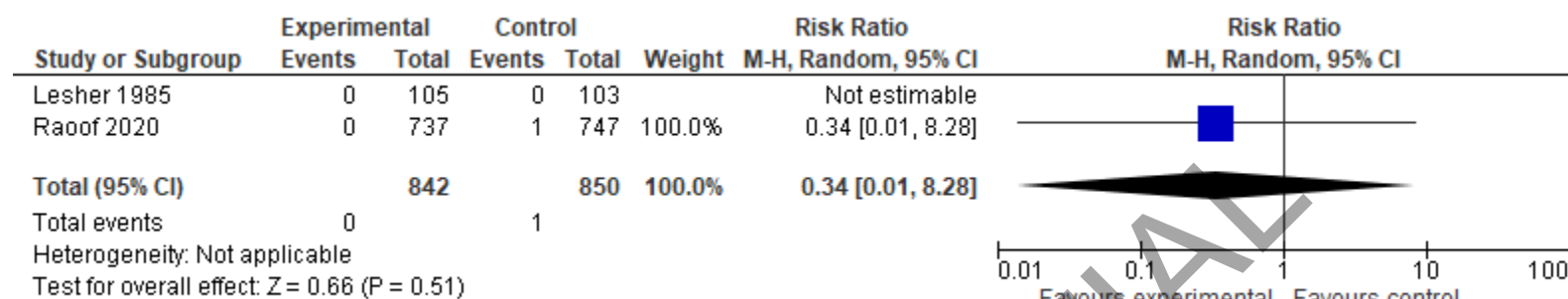
e-Figure 58. AE, Peeling, Moderate at 12 weeks, topical antibiotic vs. vehicle



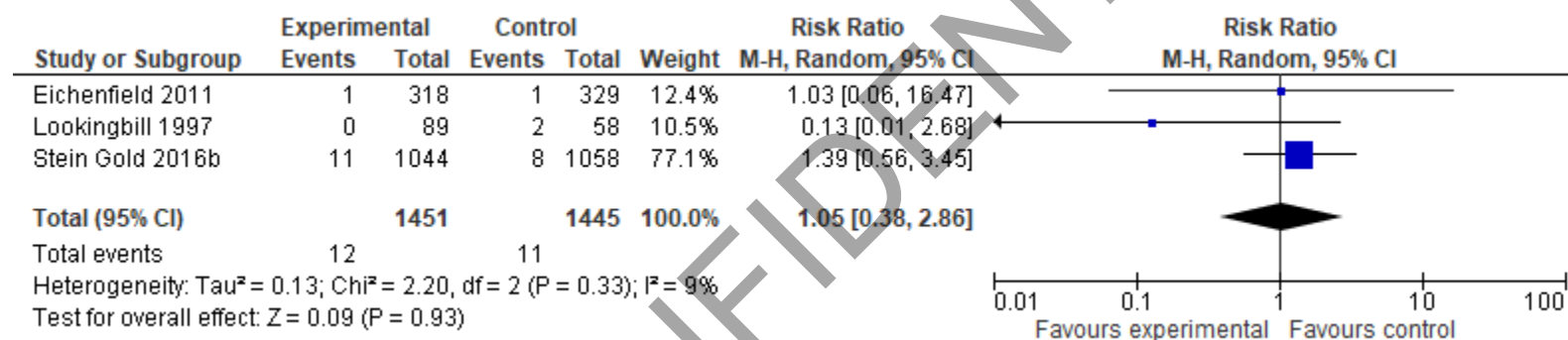
e-Figure 59. AE, Peeling, None at 12 weeks, topical antibiotic vs. vehicle



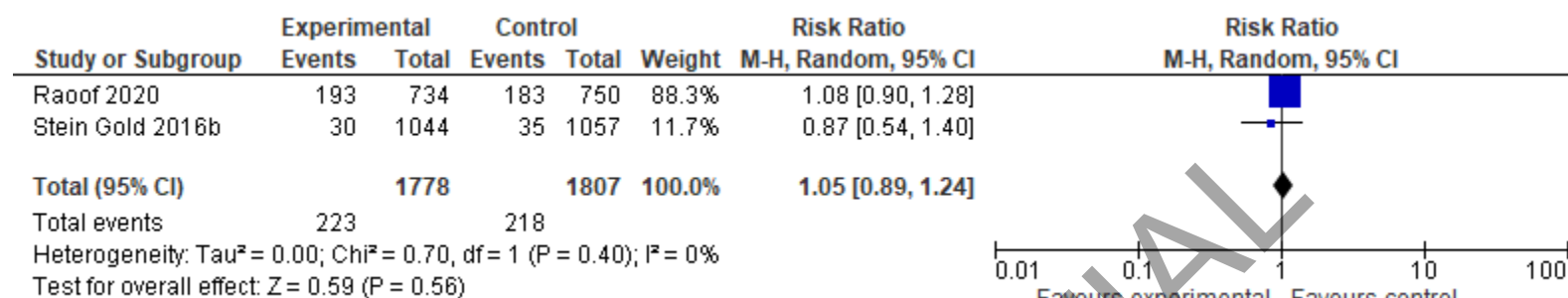
e-Figure 60. AE, Peeling, Severe at 12 weeks, topical antibiotic vs. vehicle



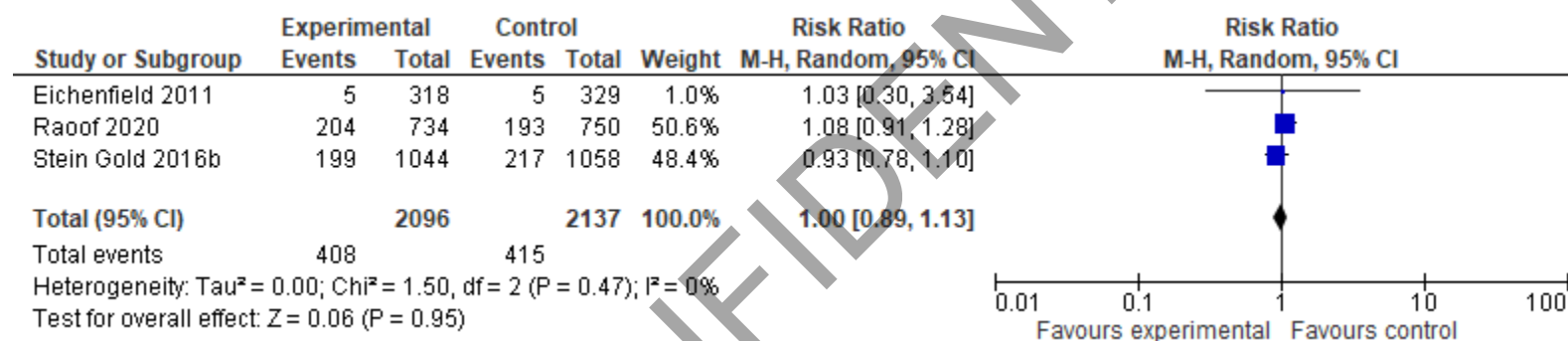
e-Figure 61. AE, Pruritus at 12 weeks, topical antibiotic vs. vehicle



e-Figure 62. TEAE, Any at 12 weeks, topical antibiotic vs. vehicle



e-Figure 63. AE, Any at 12 weeks, topical antibiotic vs. vehicle



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4. Topical antibiotic + benzoyl peroxide vs. vehicle

e-Table 15. GRADE Evidence Profile for topical antibiotic + benzoyl peroxide vs. vehicle

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Inflammatory at 10 weeks (mean percent change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for topical antibiotic + benzoyl peroxide and vehicle groups were -74.85% (n: 41) and -25.23% (n: 40), respectively. The difference between the two groups was statistically significant. _{b,c}				⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Inflammatory, Papules at 10 weeks (mean percent change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for topical antibiotic + benzoyl peroxide and vehicle groups were -69.5% (n: 41) and -29.49% (n: 40), respectively. _b				⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Inflammatory, Pustules at 10 weeks (mean percent change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for topical antibiotic + benzoyl peroxide and vehicle groups were -75% (n: 41) and -23.15% (n: 40), respectively. The difference between the two groups was statistically significant. _{b,c}				⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Inflammatory at 12 weeks (mean absolute change from baseline)												
1 ²	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean absolute changes from baseline for topical antibiotic + benzoyl peroxide and vehicle groups were -24.8 (n: 146) and -19.6 (n: 148), respectively. _b				⊕⊕⊕○ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline)

4 ^{2,3,4,5}	randomised trials	not serious	serious ^d	not serious	not serious ^e	none	417	387	-	MD 37.34 lower (72.49 lower to 2.18 lower)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (Sex: females; mean percent change from baseline)

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^f	none	The mean percentage changes from baseline for topical antibiotic + benzoyl peroxide and vehicle groups were -65.3% (n: 123) and -30% (n: 119), respectively. The difference between the two groups was statistically significant (p < 0.001). _b				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (Acne severity: moderate; mean percent change from baseline)

1 ⁷	randomised trials	not serious	not serious	not serious	serious ^f	none	The mean percentage changes from baseline for topical antibiotic + benzoyl peroxide and vehicle groups were -61.9% (n: 212) and -34.3% (n: 200), respectively. The difference between the two groups was statistically significant (p < 0.001). _b				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (Acne severity: severe; mean percent change from baseline)

1 ⁷	randomised trials	not serious	not serious	not serious	serious ^f	none	The mean percentage changes from baseline for topical antibiotic + benzoyl peroxide and vehicle groups were -52.6% (n: 41) and -18% (n: 45), respectively. The difference between the two groups was statistically significant (p < 0.001). _b				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (Pediatric to adolescent; mean percent change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ⁸	randomised trials	not serious	not serious	not serious	serious ^f	none	The mean percentage changes from baseline for topical antibiotic + benzoyl peroxide and vehicle groups were -59.9% (n: 155) and -22.6% (n: 134), respectively. The difference between the two groups was statistically significant (p < 0.001). ^b				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, Open and closed comedones at 10 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for topical antibiotic + benzoyl peroxide and vehicle groups were -31.37% (n: 41) and -3.15% (n: 40), respectively. The difference between the two groups was statistically significant. ^{b,c}				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean absolute change from baseline)

1 ²	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean absolute changes from baseline for topical antibiotic + benzoyl peroxide and vehicle groups were -27.8 (n: 146) and -21.8 (n: 148), respectively. ^b				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean percent change from baseline)

4 ^{2,3,4,5}	randomised trials	not serious	not serious	not serious	not serious ^e	none	417	387	-	MD 20.47 lower (26.31 lower to 14.62 lower)	⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (Sex: females; mean percent change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ⁶	randomised trials	not serious	not serious	not serious	serious ^f	none	The mean percentage changes from baseline for topical antibiotic + benzoyl peroxide and vehicle groups were -55.7% (n: 123) and -30% (n: 119), respectively. The difference between the two groups was statistically significant (p < 0.001). _b				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (Acne severity: moderate; mean percent change from baseline)

1 ⁷	randomised trials	not serious	not serious	not serious	serious ^f	none	The mean percentage changes from baseline for topical antibiotic + benzoyl peroxide and vehicle groups were -52.1% (n: 212) and -28.3% (n: 200), respectively. The difference between the two groups was statistically significant (p < 0.001). _b				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (Acne severity: severe; mean percent change from baseline)

1 ⁷	randomised trials	not serious	not serious	not serious	serious ^f	none	The mean percentage changes from baseline for topical antibiotic + benzoyl peroxide and vehicle groups were -50.5% (n: 41) and -24.8% (n: 45), respectively. The difference between the two groups was statistically significant (p = 0.001). _b				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (Pediatric to adolescent; mean percent change from baseline)

1 ⁸	randomised trials	not serious	not serious	not serious	serious ^f	none	The mean percentage changes from baseline for topical antibiotic + benzoyl peroxide and vehicle groups were -50.5% (n: 155) and -21.3% (n: 134), respectively. The difference between the two groups was statistically significant (p < 0.001). _b				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, ≥50% reduction at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ⁵	randomised trials	not serious	not serious	not serious	not serious	none	245/322 (76.1%)	175/329 (53.2%)	RR 1.43 (1.27 to 1.61)	229 more per 1,000 (from 144 more to 324 more)	⊕⊕⊕⊕ High	CRITICAL

Acne severity, Patient assessment of improvement, Clear/Almost clear at 12 weeks

1 ³	randomised trials	not serious	not serious	not serious	not serious	none	88/253 (34.8%)	42/245 (17.1%)	RR 2.03 (1.47 to 2.80)	177 more per 1,000 (from 81 more to 309 more)	⊕⊕⊕⊕ High	IMPORTANT

Acne severity, Patient assessment of improvement, Clear/Almost clear at 12 weeks (Moderate acne)

1 ⁷	randomised trials	not serious	not serious	not serious	serious ^f	none	75/212 (35.4%)	38/200 (19.0%)	RR 1.86 (1.33 to 2.61)	163 more per 1,000 (from 63 more to 306 more)	⊕⊕⊕○ Moderate	IMPORTANT

Acne severity, Patient assessment of improvement, Clear/Almost clear at 12 weeks (Severe acne)

1 ⁷	randomised trials	not serious	not serious	not serious	serious ^f	none	12/41 (29.3%)	3/45 (6.7%)	RR 4.39 (1.33 to 14.46)	226 more per 1,000 (from 22 more to 897 more)	⊕⊕⊕○ Moderate	IMPORTANT

Acne severity, Patient assessment of improvement, Clear/Almost clear at 12 weeks (Pediatric to adolescent)

1 ⁸	randomised trials	not serious	not serious	not serious	serious ^f	none	53/155 (34.2%)	17/134 (12.7%)	RR 2.70 (1.64 to 4.42)	216 more per 1,000 (from 81 more to 434 more)	⊕⊕⊕○ Moderate	IMPORTANT

Acne severity, Patient assessment of improvement, ≥2-grade reduction at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ⁵	randomised trials	not serious	not serious	not serious	not serious	none	209/322 (64.9%)	154/329 (46.8%)	RR 1.39 (1.20 to 1.60)	183 more per 1,000 (from 94 more to 281 more)	⊕⊕⊕⊕ High	IMPORTANT

AE, Any, Leading to discontinuation at 12 weeks (Moderate acne)

1 ⁹	randomised trials	not serious	not serious	not serious	serious ^g	none	0/212 (0.0%)	3/200 (1.5%)	RR 0.13 (0.01 to 2.59)	13 fewer per 1,000 (from 15 fewer to 24 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Any, Leading to discontinuation at 12 weeks (Severe acne)

1 ⁹	randomised trials	not serious	not serious	not serious	serious ^h	none	0/41 (0.0%)	0/45 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Any, Leading to discontinuation at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^g	none	0/144 (0.0%)	2/146 (1.4%)	RR 0.20 (0.01 to 4.19)	11 fewer per 1,000 (from 14 fewer to 44 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Dermatitis, Leading to study withdrawal at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^h	none	0/144 (0.0%)	0/146 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Pain, Leading to withdrawal at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^h	none	0/144 (0.0%)	0/146 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Burning at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
2 ^{2,4}	randomised trials	not serious	not serious	not serious	serious ⁱ	none	1/239 (0.4%)	0/204 (0.0%)	RR 1.84 (0.08 to 44.52)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Dermatitis at 12 weeks

2 ^{2,5}	randomised trials	not serious	not serious	not serious	serious ⁱ	none	2/466 (0.4%)	0/475 (0.0%)	RR 5.11 (0.25 to 105.99)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Dryness at 12 weeks

3 ^{2,4,5}	randomised trials	not serious	not serious	not serious	serious ⁱ	none	9/561 (1.6%)	2/533 (0.4%)	RR 2.54 (0.56 to 11.47)	6 more per 1,000 (from 2 fewer to 39 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema at 12 weeks

3 ^{2,4,5}	randomised trials	not serious	not serious	not serious	serious ^j	none	8/561 (1.4%)	6/533 (1.1%)	RR 0.82 (0.30 to 2.20)	2 fewer per 1,000 (from 8 fewer to 14 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema, Severe at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^h	none	0/144 (0.0%)	0/146 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Irritation at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
2 ^{2,5}	randomised trials	not serious	not serious	not serious	serious ⁱ	none	1/466 (0.2%)	0/475 (0.0%)	RR 3.04 (0.12 to 74.05)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pain at 12 weeks

2 ^{2,5}	randomised trials	not serious	not serious	not serious	serious ⁱ	none	1/466 (0.2%)	1/475 (0.2%)	RR 1.01 (0.06 to 16.06)	0 fewer per 1,000 (from 2 fewer to 32 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus at 12 weeks

3 ^{2,4,5}	randomised trials	not serious	not serious	not serious	serious ^j	none	2/561 (0.4%)	3/533 (0.6%)	RR 0.58 (0.11 to 2.96)	2 fewer per 1,000 (from 5 fewer to 11 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Eczema at 12 weeks

1 ⁵	randomised trials	not serious	not serious	not serious	serious ^h	none	0/322 (0.0%)	0/329 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Exfoliation at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^g	none	0/144 (0.0%)	1/146 (0.7%)	RR 0.34 (0.01 to 8.23)	5 fewer per 1,000 (from 7 fewer to 50 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Hyperpigmentation at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	serious ^k	none	2/144 (1.4%)	1/146 (0.7%)	RR 2.03 (0.19 to 22.12)	7 more per 1,000 (from 6 fewer to 145 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Hypersensitivity at 12 weeks

1 ⁵	randomised trials	not serious	not serious	not serious	serious ^h	none	0/322 (0.0%)	0/329 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Peeling at 12 weeks

1 ⁴	randomised trials	not serious	not serious	not serious	serious ^g	none	21/95 (22.1%)	8/58 (13.8%)	RR 1.60 (0.76 to 3.38)	83 more per 1,000 (from 33 fewer to 328 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Photosensitivity at 12 weeks

1 ⁵	randomised trials	not serious	not serious	not serious	serious ^l	none	2/322 (0.6%)	2/329 (0.6%)	RR 1.02 (0.14 to 7.21)	0 fewer per 1,000 (from 5 fewer to 38 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Scaling at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^h	none	0/144 (0.0%)	0/146 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Stinging at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^h	none	0/144 (0.0%)	0/146 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio

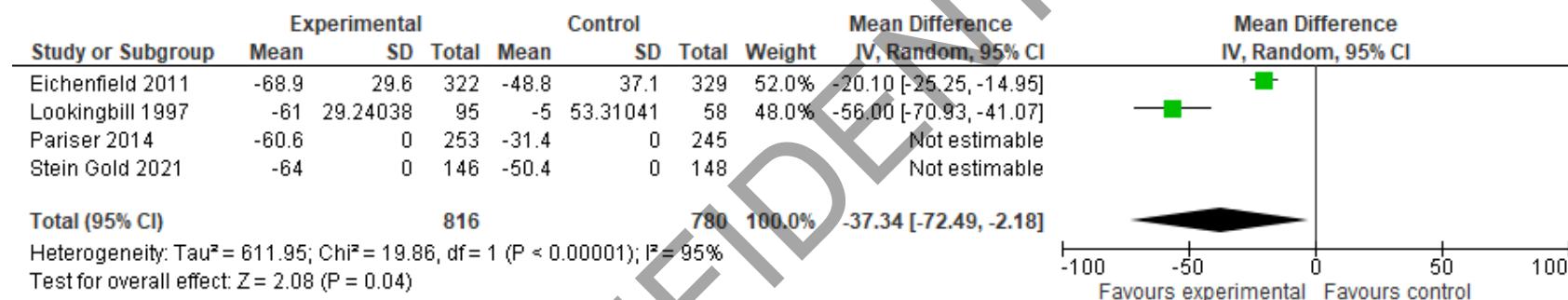
Explanations

a. Standard deviation values were not reported. Small sample size.

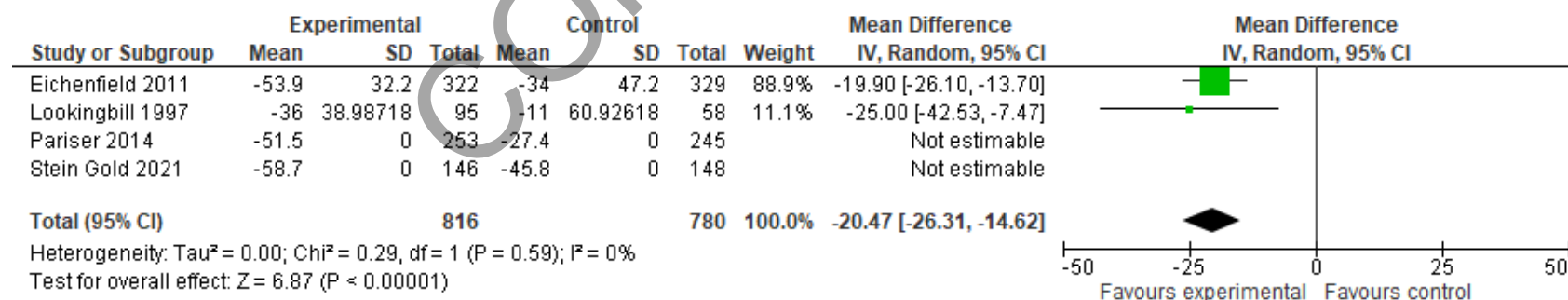
- b. n: number of patients
c. P value was not provided.
d. $I^2 = 95\%$
e. Two studies (Pariser 2014 and Stein Gold 2021) did not report standard deviation values. Therefore, data could not be pooled.
f. Small sample size.
g. CI included both appreciable benefits and harm. Small sample size.
h. Double zero study.
i. Wide CI included both appreciable benefits and harm.
j. CI included both appreciable benefits and harm.
k. Wide CI included both appreciable benefits and harm. Small sample size.

Forest plots

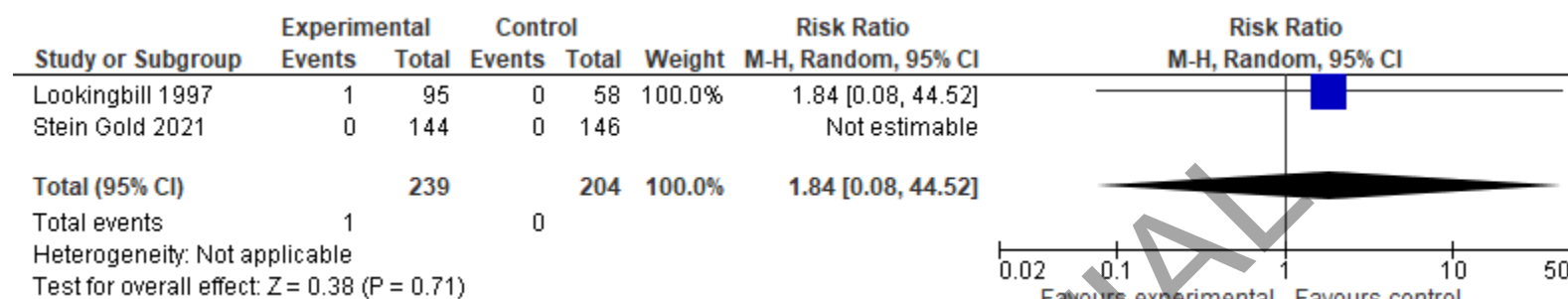
e-Figure 64. Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline), topical antibiotic + benzoyl peroxide vs. vehicle



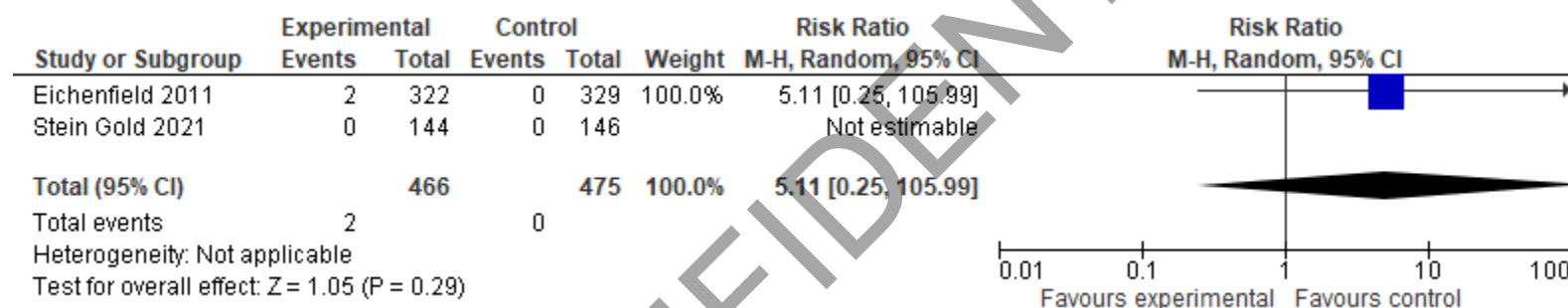
e-Figure 65. Number of lesions, Non-inflammatory at 12 weeks (mean percent change from baseline), topical antibiotic + benzoyl peroxide vs. vehicle



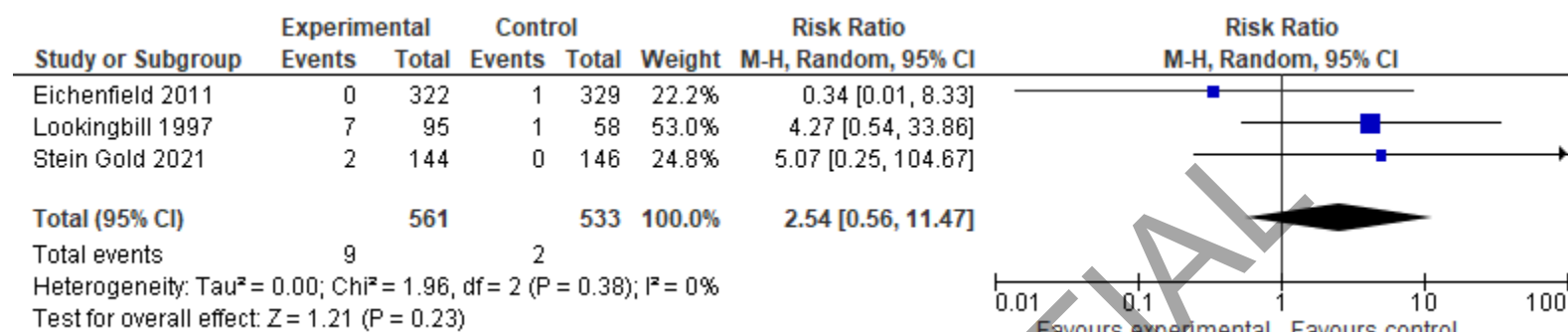
e-Figure 66. AE, Burning at 12 weeks, topical antibiotic + benzoyl peroxide vs. vehicle



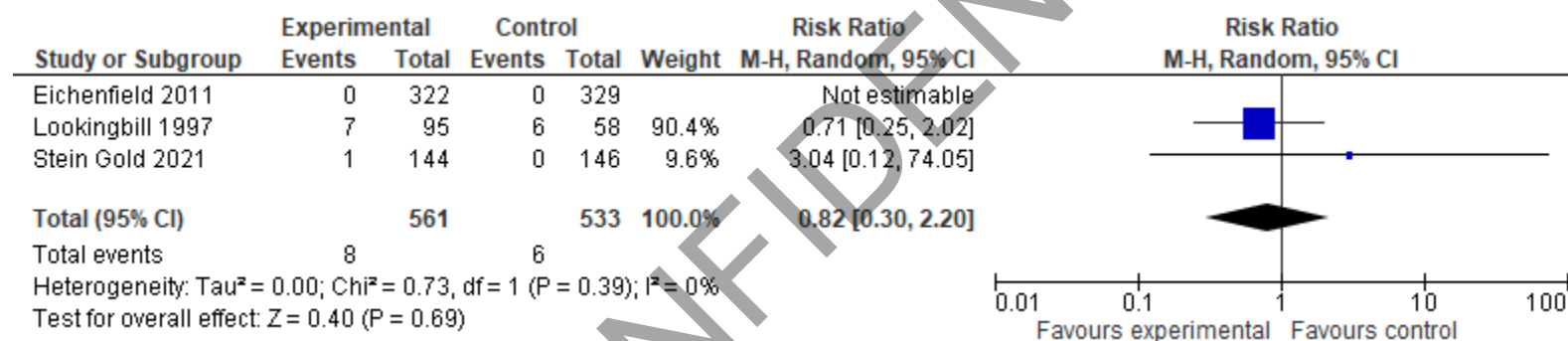
e-Figure 67. AE, Dermatitis at 12 weeks, topical antibiotic + benzoyl peroxide vs. vehicle



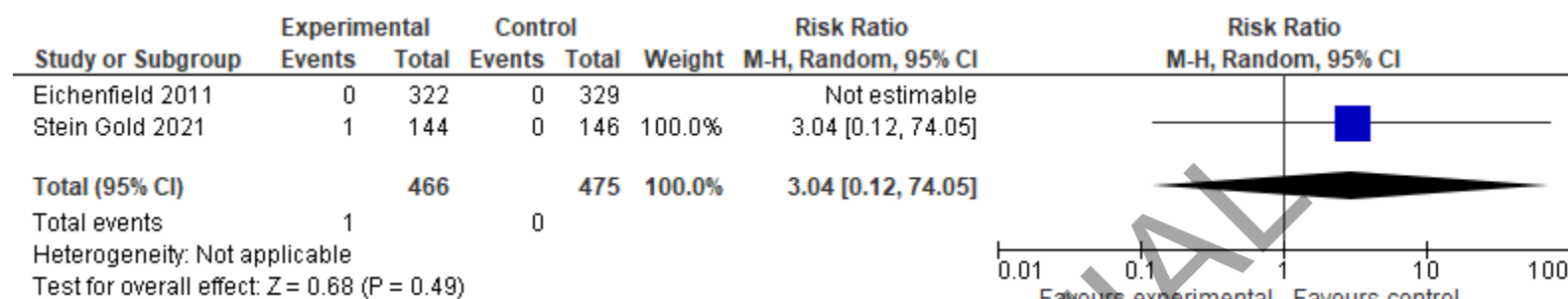
e-Figure 68. AE, Dryness at 12 weeks, topical antibiotic + benzoyl peroxide vs. vehicle



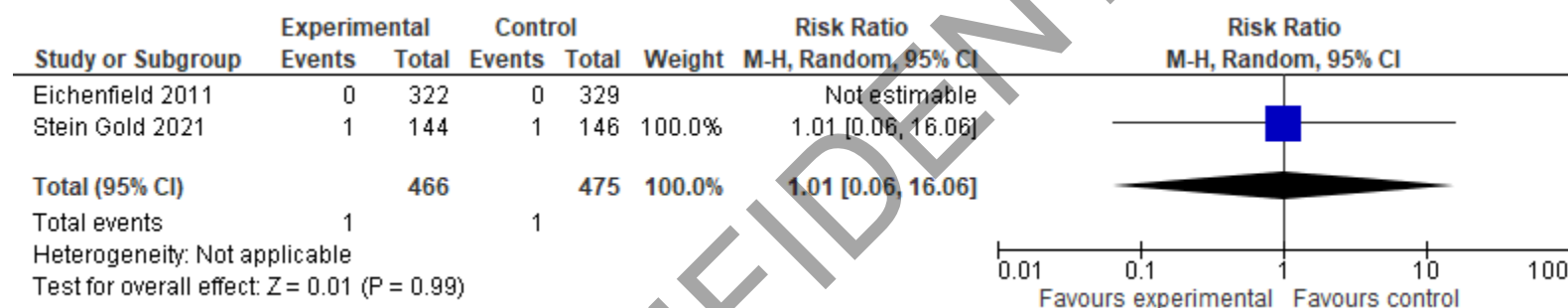
e-Figure 69. AE, Erythema at 12 weeks, topical antibiotic + benzoyl peroxide vs. vehicle



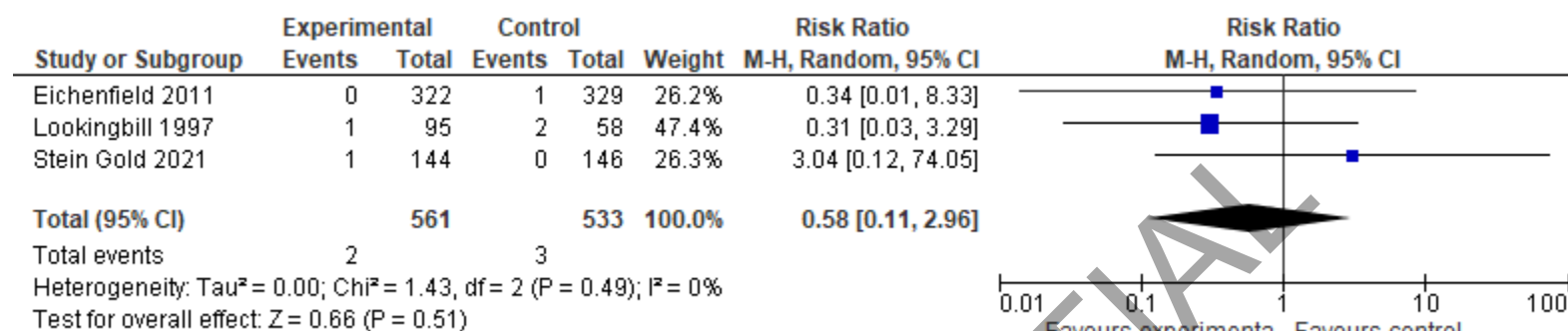
e-Figure 70. AE, Irritation at 12 weeks, topical antibiotic + benzoyl peroxide vs. vehicle



e-Figure 71. AE, Pain at 12 weeks, topical antibiotic + benzoyl peroxide vs. vehicle



e-Figure 72. AE, Pruritus at 12 weeks, topical antibiotic + benzoyl peroxide vs. vehicle



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5. Topical antibiotic + benzoyl peroxide vs. benzoyl peroxide

e-Table 16. GRADE Evidence Profile for topical antibiotic + benzoyl peroxide vs. benzoyl peroxide

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic + Benzoyl peroxide	Benzoyl peroxide	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline)												
2 ^{1,2}	randomised trials	not serious	serious ^a	not serious	serious ^b	none	417	415	-	MD 13.91 lower (28.45 lower to 0.64 higher)	⊕⊕○○ Low	CRITICAL
Number of lesions, Non-inflammatory at 12 weeks (meant percent change from baseline)												
2 ^{1,2}	randomised trials	not serious	not serious	not serious	serious ^b	none	417	415	-	MD 3.6 lower (8.21 lower to 1.01 higher)	⊕⊕⊕○ Moderate	CRITICAL
AE, Dryness at 12 weeks												
2 ^{1,2}	randomised trials	not serious	not serious	not serious	serious ^b	none	7/417 (1.7%)	7/415 (1.7%)	RR 1.00 (0.37 to 2.72)	0 fewer per 1,000 (from 11 fewer to 29 more)	⊕⊕⊕○ Moderate	IMPORTANT
AE, Erythema at 12 weeks												
2 ^{1,2}	randomised trials	not serious	not serious	not serious	serious ^b	none	7/417 (1.7%)	13/415 (3.1%)	RR 0.54 (0.23 to 1.28)	14 fewer per 1,000 (from 24 fewer to 9 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic + Benzoyl peroxide	Benzoyl peroxide	Relative (95% CI)	Absolute (95% CI)		
2 ^{1,2}	randomised trials	not serious	not serious	not serious	serious ^b	none	1/417 (0.2%)	2/415 (0.5%)	RR 0.62 (0.08 to 4.96)	2 fewer per 1,000 (from 4 fewer to 19 more)	⊕⊕⊕○ Moderate	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio

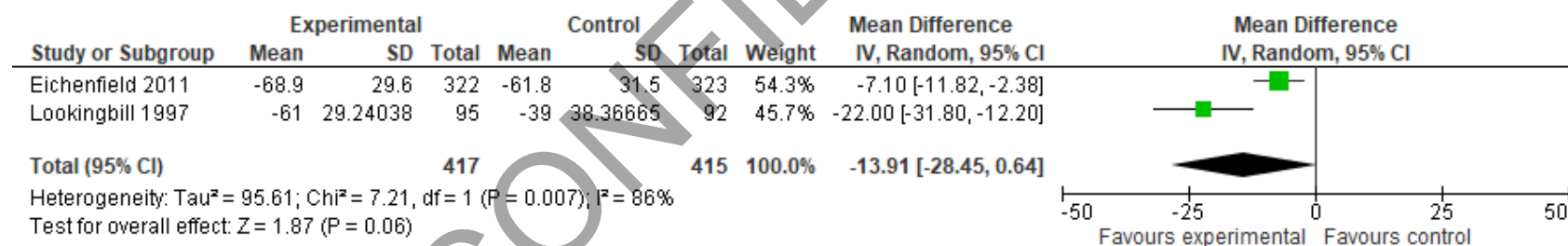
Explanations

a. $I^2 = 86\%$

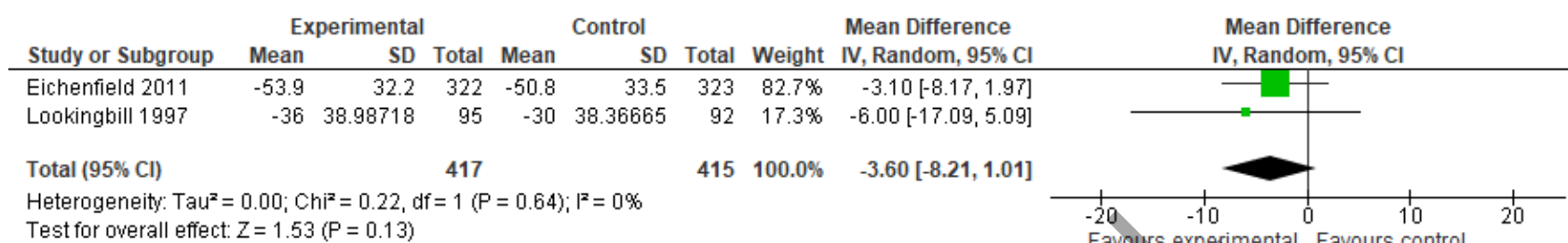
b. CI included both appreciable benefits and harm.

Forest plots

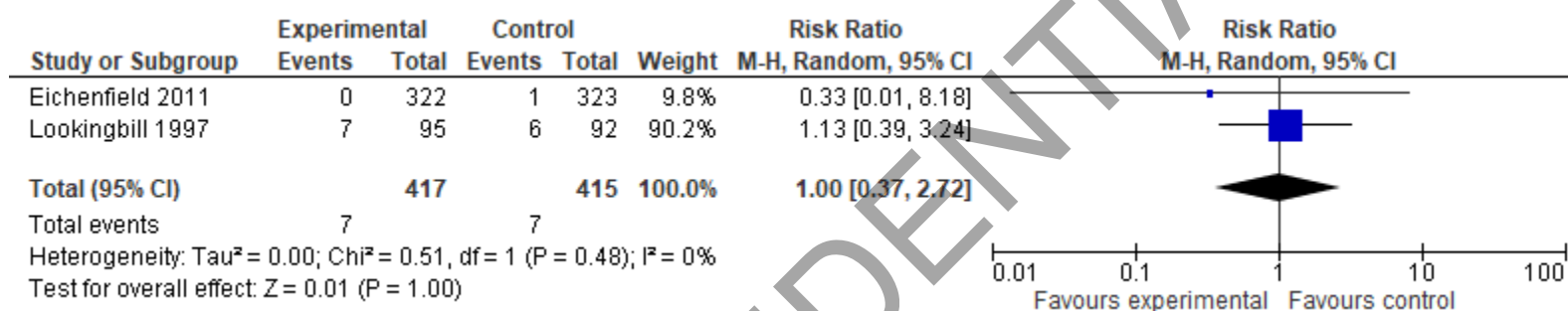
e-Figure 73. Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline), topical antibiotic + benzoyl peroxide vs. benzoyl peroxide



e-Figure 74. Number of lesions, Non-inflammatory at 12 weeks (meant percent change from baseline), topical antibiotic + benzoyl peroxide vs. benzoyl peroxide



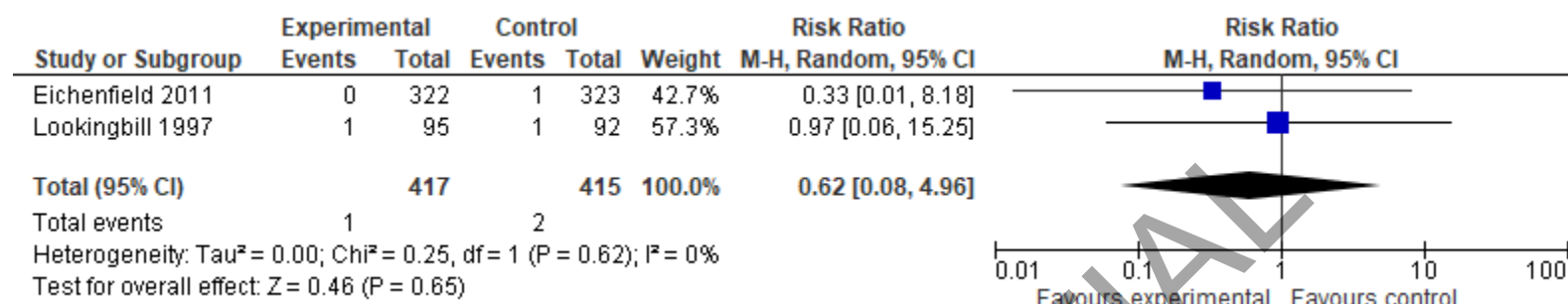
e-Figure 75.AE, Dryness at 12 weeks, topical antibiotic + benzoyl peroxide vs. benzoyl peroxide



e-Figure 76.AE, Erythema at 12 weeks, topical antibiotic + benzoyl peroxide vs. benzoyl peroxide



e-Figure 77. AE, Pruritus at 12 weeks, topical antibiotic + benzoyl peroxide vs. benzoyl peroxide



References

1. Eichenfield LF, Alio Saenz AB. Safety and efficacy of clindamycin phosphate 1.2%-benzoyl peroxide 3% fixed-dose combination gel for the treatment of acne vulgaris: a phase 3, multicenter, randomized, double-blind, active- and vehicle-controlled study. *J Drugs Dermatol.* 2011;10(12):1382-1396.
2. Lookingbill DP, Chalker DK, Lindholm JS, et al. Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: Combined results of two double-blind investigations. *Journal of the American Academy of Dermatology.* 1997;37(4):590-595.

6. Topical antibiotic + benzoyl peroxide vs. topical antibiotic

e-Table 17. GRADE Evidence Profile for topical antibiotic + benzoyl peroxide vs. topical antibiotic

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic + Benzoyl peroxide	Topical antibiotic	Relative (95% CI)	Absolute (95% CI)		
Investigator Global Assessment, ≥2-grade reduction at 4 weeks												
2 ^{1,2}	randomised trials	not serious	not serious ^a	not serious	serious ^b	none	64/704 (9.1%)	51/815 (6.3%)	RR 1.57 (0.80 to 3.08)	36 more per 1,000 (from 13 fewer to 130 more)	⊕⊕⊕○ Moderate	CRITICAL
Investigator Global Assessment, ≥2-grade reduction at 12 weeks												
3 ^{1,2,3}	randomised trials	not serious	not serious ^c	not serious	not serious	none	341/1026 (33.2%)	241/1133 (21.3%)	RR 1.58 (1.25 to 2.00)	123 more per 1,000 (from 53 more to 213 more)	⊕⊕⊕⊕ High	CRITICAL
Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline)												
3 ^{2,3,4}	randomised trials	not serious	serious ^d	not serious	not serious ^e	none	417	407	-	MD 17.5 lower (32.3 lower to 2.71 lower)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Non-inflammatory at 12 weeks (mean percent change from baseline)												
3 ^{2,3,4}	randomised trials	not serious	serious ^f	not serious	not serious ^e	none	417	407	-	MD 17.46 lower (33.32 lower to 1.61 lower)	⊕⊕⊕○ Moderate	CRITICAL

Acne severity, Patient assessment of improvement, ≥2-grade reduction at week 12

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic + Benzoyl peroxide	Topical antibiotic	Relative (95% CI)	Absolute (95% CI)		
2 ^{2,3}	randomised trials	not serious	not serious	not serious	not serious	none	375/822 (45.6%)	317/834 (38.0%)	RR 1.20 (1.08 to 1.33)	76 more per 1,000 (from 30 more to 125 more)	⊕⊕⊕⊕ High	IMPORTANT

AE, Burning at 12 weeks

2 ^{1,4}	randomised trials	not serious	not serious	not serious	serious ^g	none	5/299 (1.7%)	2/388 (0.5%)	RR 2.90 (0.65 to 12.91)	10 more per 1,000 (from 2 fewer to 61 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Dryness at 12 weeks

3 ^{1,3,4}	randomised trials	not serious	not serious	not serious	serious ^b	none	26/621 (4.2%)	30/706 (4.2%)	RR 1.15 (0.69 to 1.91)	6 more per 1,000 (from 13 fewer to 39 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema, Mild at 4 weeks

2 ^{5,6}	randomised trials	not serious	not serious	not serious	serious ^h	none	8/130 (6.2%)	6/130 (4.6%)	RR 1.33 (0.50 to 3.56)	15 more per 1,000 (from 23 fewer to 118 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema at 12 weeks

4 ^{1,2,3,4}	randomised trials	not serious	serious ⁱ	not serious	serious ^b	none	68/1121 (6.1%)	66/1222 (5.4%)	RR 1.98 (0.55 to 7.11)	53 more per 1,000 (from 24 fewer to 330 more)	⊕⊕○○ Low	IMPORTANT

AE, Pain at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic + Benzoyl peroxide	Topical antibiotic	Relative (95% CI)	Absolute (95% CI)		
2 ^{2,3}	randomised trials	not serious	not serious	not serious	serious ^g	none	6/822 (0.7%)	3/834 (0.4%)	RR 1.57 (0.21 to 11.85)	2 more per 1,000 (from 3 fewer to 39 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Peeling at 12 weeks

2 ^{1,4}	randomised trials	not serious	serious ^j	not serious	serious ^b	none	34/299 (11.4%)	25/388 (6.4%)	RR 1.76 (0.55 to 5.63)	49 more per 1,000 (from 29 fewer to 298 more)	⊕⊕○○ Low	IMPORTANT

AE, Pruritus, Mild at 4 weeks

2 ^{5,6}	randomised trials	not serious	not serious	not serious	serious ^h	none	16/130 (12.3%)	12/130 (9.2%)	RR 1.61 (0.34 to 7.49)	56 more per 1,000 (from 61 fewer to 599 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus, Moderate at 4 weeks

2 ^{5,6}	randomised trials	not serious	not serious	not serious	serious ^h	none	0/130 (0.0%)	1/130 (0.8%)	RR 0.33 (0.01 to 7.99)	5 fewer per 1,000 (from 8 fewer to 54 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus at 12 weeks

4 ^{1,2,3,4}	randomised trials	not serious	not serious	not serious	serious ^b	none	23/1121 (2.1%)	15/1222 (1.2%)	RR 1.83 (0.47 to 7.10)	10 more per 1,000 (from 7 fewer to 75 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Any at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic + Benzoyl peroxide	Topical antibiotic	Relative (95% CI)	Absolute (95% CI)		
2 ^{2,3}	randomised trials	not serious	not serious	not serious	serious ^b	none	76/822 (9.2%)	46/834 (5.5%)	RR 1.53 (0.80 to 2.95)	29 more per 1,000 (from 11 fewer to 108 more)	⊕⊕⊕○ Moderate	IMPORTANT

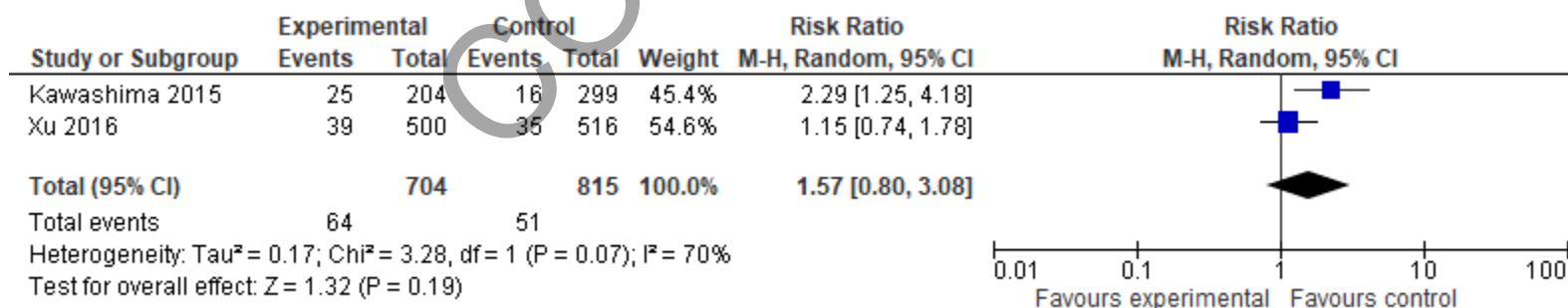
CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

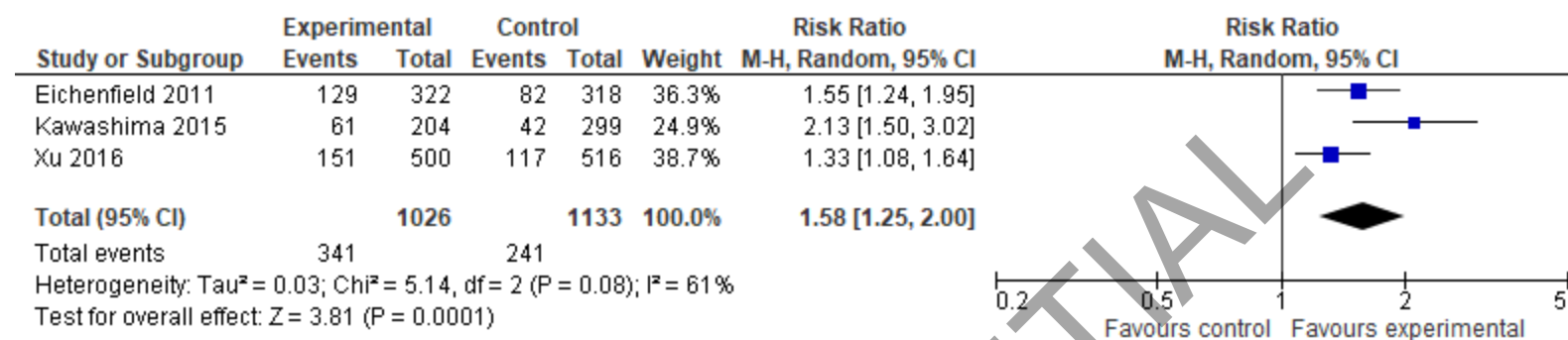
- a. $I^2 = 70\%$
- b. CI included both appreciable benefits and harm.
- c. $I^2 = 61\%$
- d. $I^2 = 82\%$
- e. One study (Xu 2016) did not report standard deviation values. Therefore, its data could not be pooled.
- f. $I^2 = 78\%$
- g. Wide CI included both appreciable benefits and harm.
- h. CI included both appreciable benefits and harm. Small sample size.
- i. $I^2 = 83\%$
- j. $I^2 = 78\%$

Forest plots

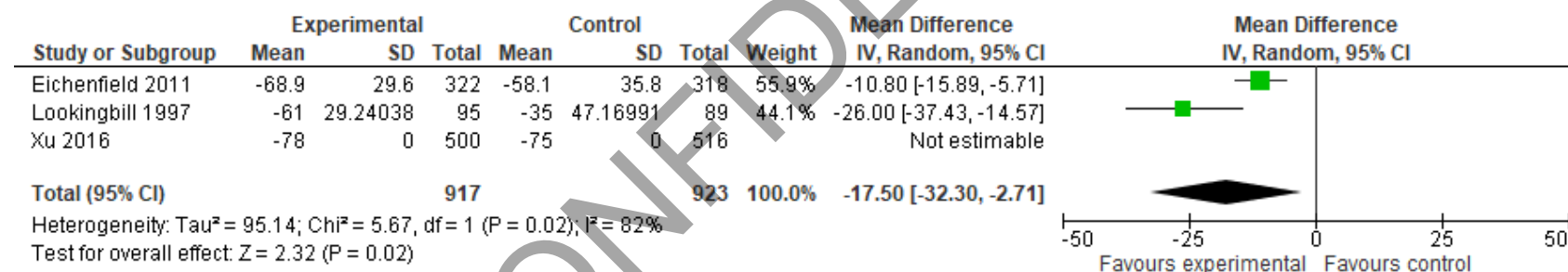
e-Figure 78. Investigator Global Assessment, ≥2-grade reduction at 4 weeks, topical antibiotic + benzoyl peroxide vs. topical antibiotic



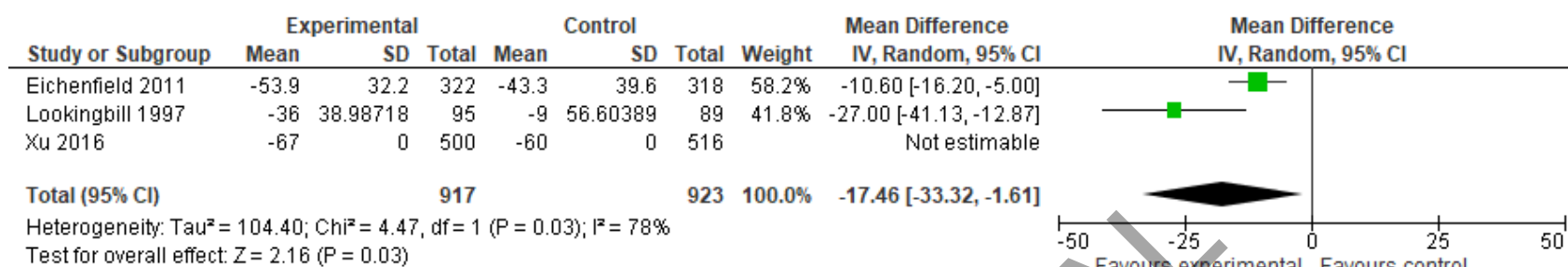
e-Figure 79. Investigator Global Assessment, ≥ 2 -grade reduction at 12 weeks, topical antibiotic + benzoyl peroxide vs. topical antibiotic



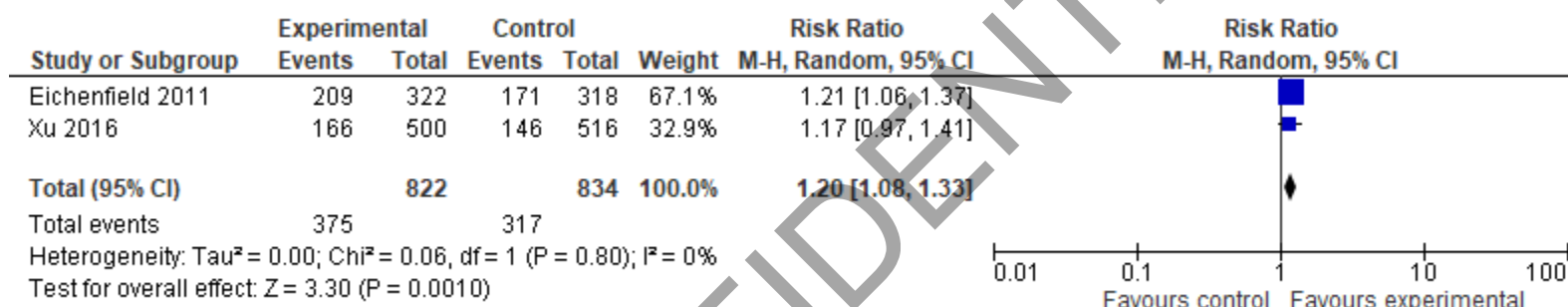
e-Figure 80. Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline), topical antibiotic + benzoyl peroxide vs. topical antibiotic



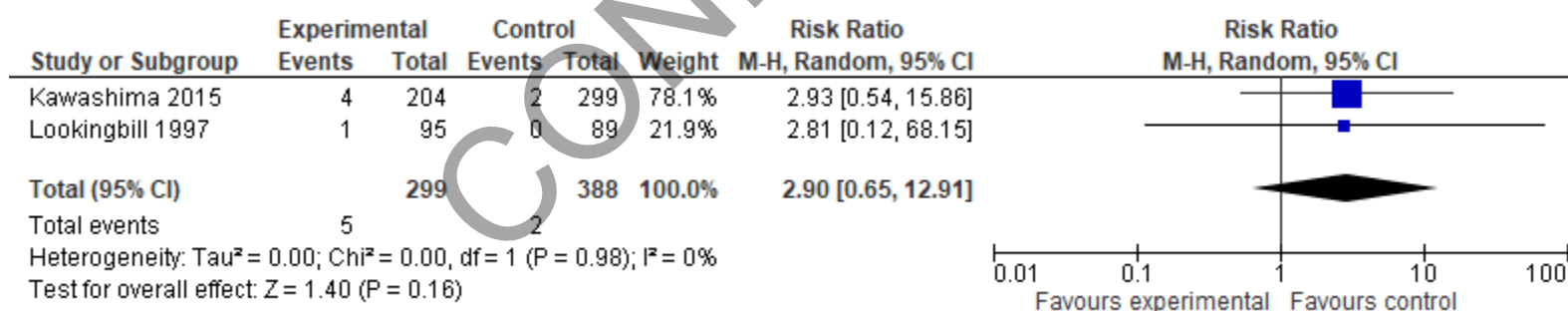
e-Figure 81. Number of lesions, Non-inflammatory at 12 weeks (mean percent change from baseline), topical antibiotic + benzoyl peroxide vs. topical antibiotic



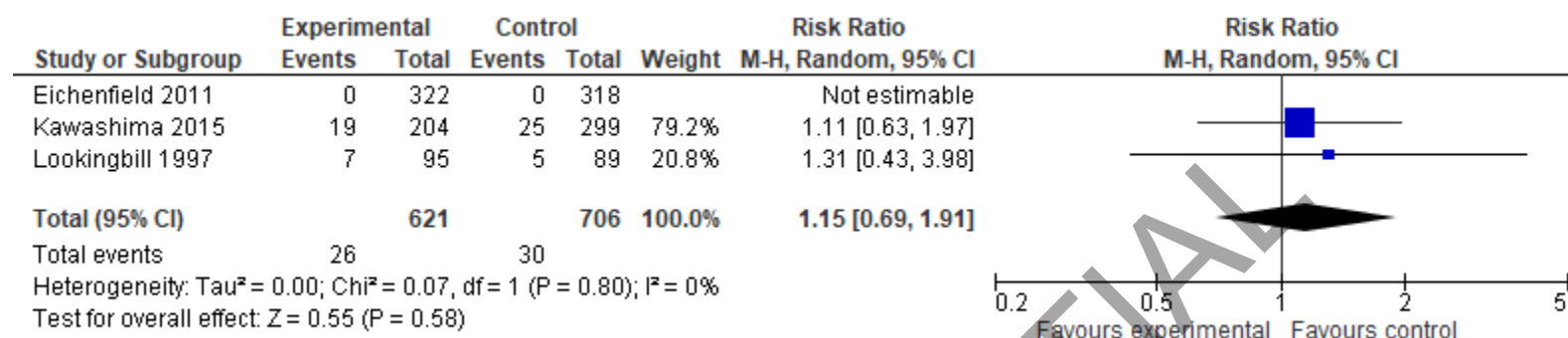
e-Figure 82. Acne severity, Patient assessment of improvement, ≥ 2 -grade reduction at week 12, topical antibiotic + benzoyl peroxide vs. topical antibiotic



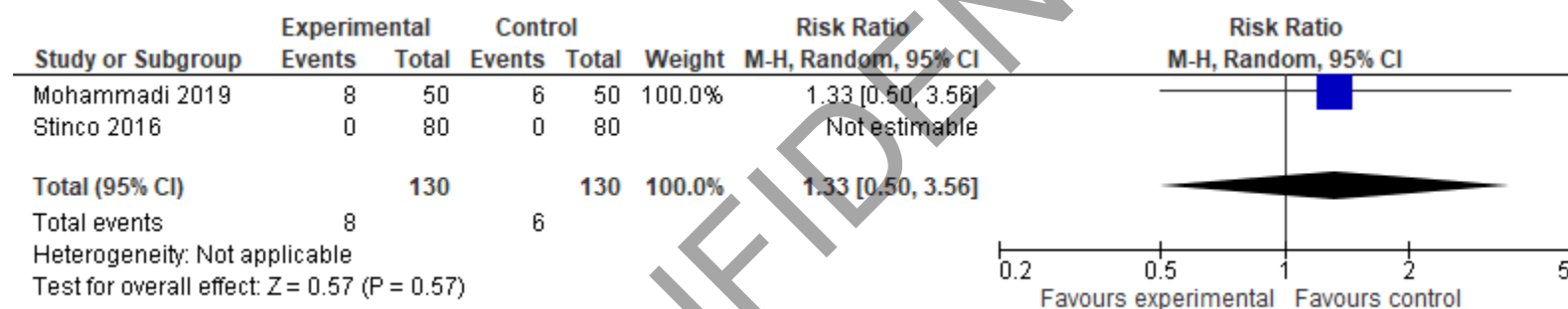
e-Figure 83. AE, Burning at 12 weeks, topical antibiotic + benzoyl peroxide vs. topical antibiotic



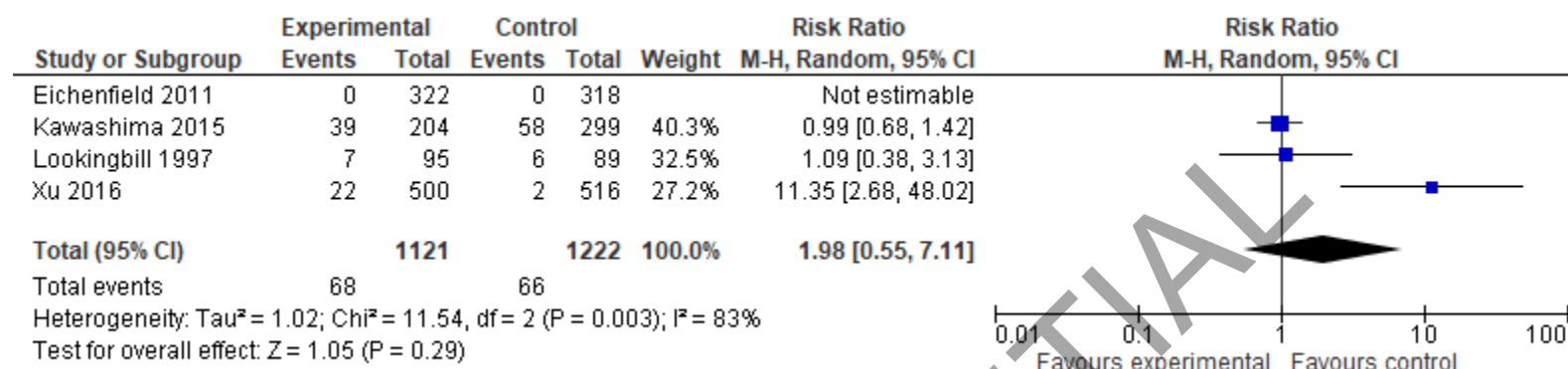
e-Figure 84. AE, Dryness at 12 weeks, topical antibiotic + benzoyl peroxide vs. topical antibiotic



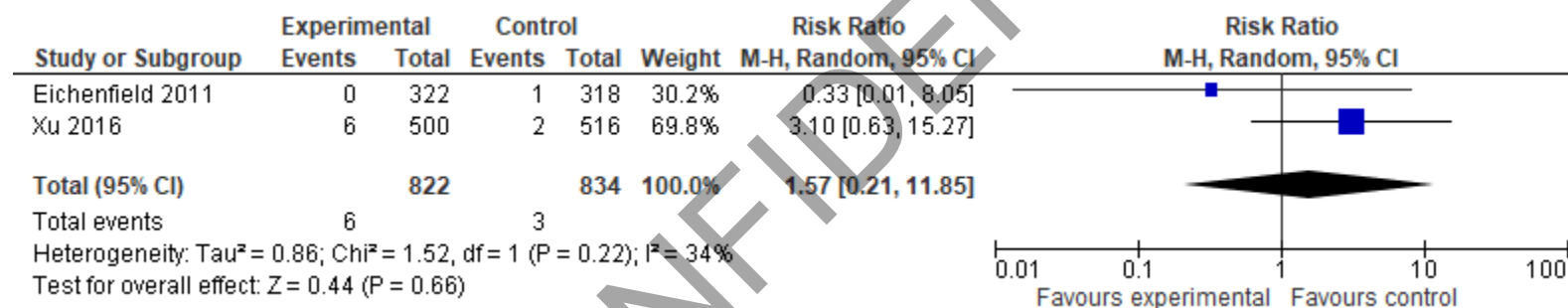
e-Figure 85. AE, Erythema, Mild at 4 weeks, topical antibiotic + benzoyl peroxide vs. topical antibiotic



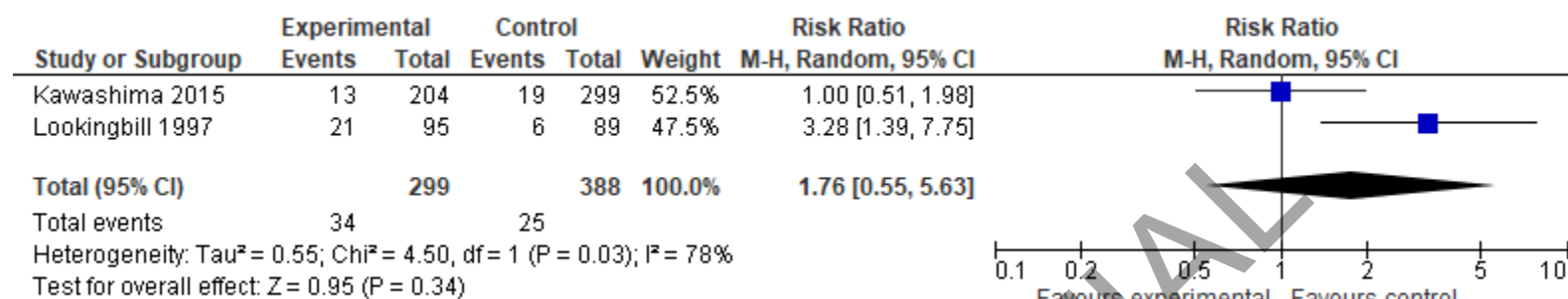
e-Figure 86. AE, Erythema at 12 weeks, topical antibiotic + benzoyl peroxide vs. topical antibiotic



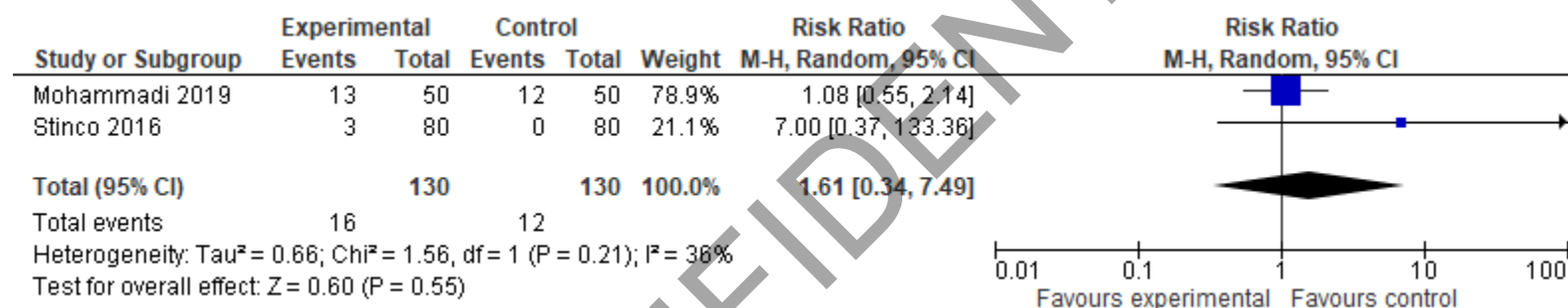
e-Figure 87. AE, Pain at 12 weeks, topical antibiotic + benzoyl peroxide vs. topical antibiotic



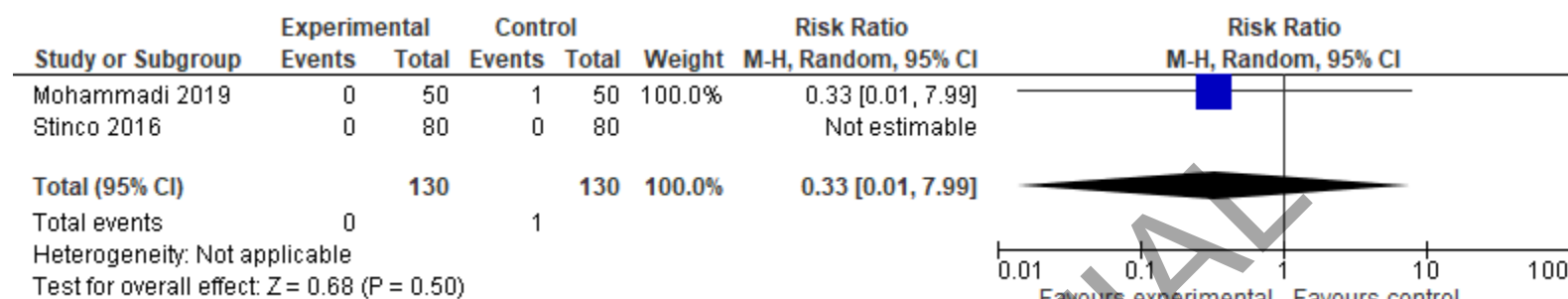
e-Figure 88. AE, Peeling at 12 weeks, topical antibiotic + benzoyl peroxide vs. topical antibiotic



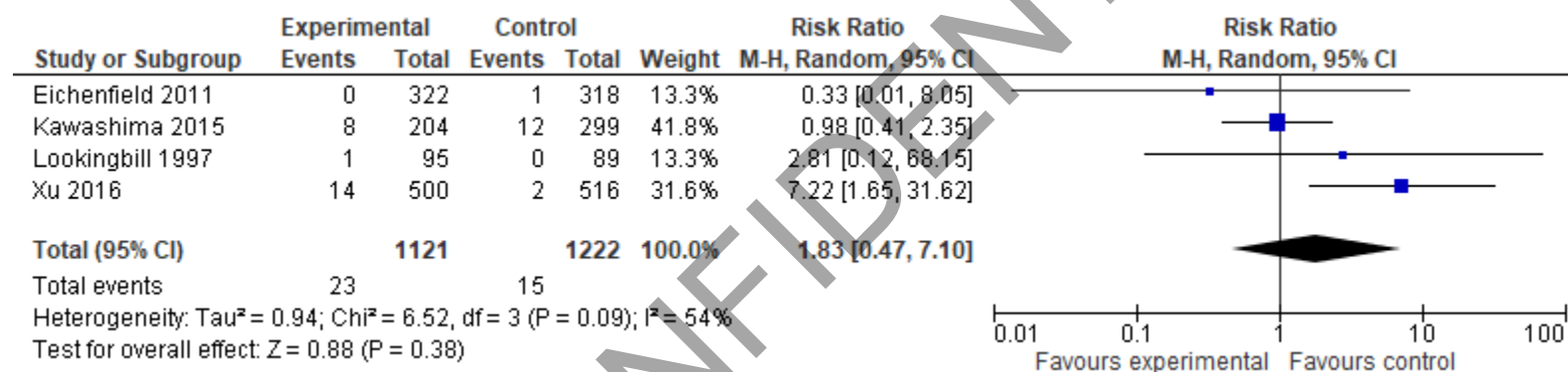
e-Figure 89. AE, Pruritus, Mild at 4 weeks, topical antibiotic + benzoyl peroxide vs. topical antibiotic



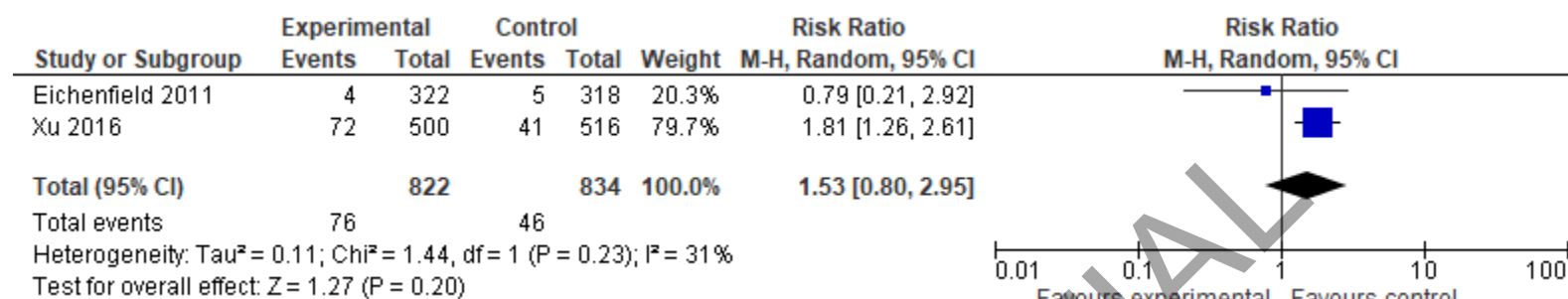
e-Figure 90. AE, Pruritus, Moderate at 4 weeks, topical antibiotic + benzoyl peroxide vs. topical antibiotic



e-Figure 91. AE, Pruritus at 12 weeks, topical antibiotic + benzoyl peroxide vs. topical antibiotic



e-Figure 92. AE, Any at 12 weeks, topical antibiotic + benzoyl peroxide vs. topical antibiotic



References

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7. Topical retinoid + topical antibiotic vs. vehicle

e-Table 18. GRADE Evidence Profile for topical retinoid + topical antibiotic vs. vehicle

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		

EGSS Evaluator's Global Severity Score, Success, at 12 weeks (≥ 2-grade reduction and clear/almost clear)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	150 and 148 patients with moderate and severe acne patients were randomized to receive clindamycin phosphate 1.2%/adapalene 0.15% gel or vehicle gel for 12 weeks. At 12 weeks, 30.3% and 8.1% of patients in clind/adap and vehicle groups, respectively, achieved treatment success (achieving a ≥ 2-grade reduction from baseline in Evaluator's Global Severity Score and clear/almost clear skin).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any at 12 weeks (mean absolute change from baseline)

1 ²	randomised trials	not serious	not serious	not serious	not serious	none	476	242	-	MD 8.6 lesions lower (12.84 lower to 4.36 lower)	⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Inflammatory at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^{a,b}	none	150 and 148 patients with moderate and severe acne patients were randomized to receive clindamycin phosphate 1.2%/adapalene 0.15% gel or vehicle gel for 12 weeks. At baseline, the mean non-inflammatory lesion counts were 38.2 ± 7.9 and 38.2 ± 9.2 for clind/adap and vehicle groups, respectively. The least squares absolute changes at 12 weeks from baseline in inflammatory lesions were -26.8 and -19.6 for clind/adap and vehicle groups, respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^{a,b}	none	150 and 148 patients with moderate and severe acne patients were randomized to receive clindamycin phosphate 1.2%/adapalene 0.15% gel or vehicle gel for 12 weeks. At baseline, the mean non-inflammatory lesion counts were 51.1 ± 18.4 and 50.7 ± 18.7 for clind/adap and vehicle groups, respectively. The least squares absolute changes at 12 weeks from baseline in inflammatory lesions were -30.0 and -21.8 for clind/adap and vehicle groups, respectively.				⊕⊕⊕○ Moderate	CRITICAL

Acne-specific quality of life questionnaire (Acne-QoL) at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^{a,b}	none	150 and 148 patients with moderate and severe acne patients were randomized to receive clindamycin phosphate 1.2%/adapalene 0.15% gel or vehicle gel for 12 weeks. At 12 weeks, clind/adap group had greater improvement in all 4 domains of Acne-QoL: self-perception (mean change from baseline, 8.5 vs. 5.9), role-emotion (7.6 vs. 4.4), role-social (5.3 vs. 3.6), and acne symptoms (6.6 vs. 4.9).				⊕⊕⊕○ Moderate	IMPORTANT

Acne severity, Patient assessment of improvement, Grade 0-1 at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	not serious	none	320/476 (67.2%)	128/242 (52.9%)	RR 1.27 (1.11 to 1.45)	143 more per 1,000 (from 58 more to 238 more)	⊕⊕⊕⊕ High	IMPORTANT

AE, Dermatitis, Leading to study withdrawal at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	0/148 (0.0%)	0/146 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Any, Leading to discontinuation at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	3/148 (2.0%)	2/146 (1.4%)	RR 1.48 (0.25 to 8.73)	7 more per 1,000 (from 10 fewer to 106 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pain, Leading to withdrawal at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^e	none	2/148 (1.4%)	0/146 (0.0%)	RR 4.93 (0.24 to 101.88)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Burning at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^e	none	1/148 (0.7%)	0/146 (0.0%)	RR 2.96 (0.12 to 72.07)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Dermatitis at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^e	none	2/148 (1.4%)	0/146 (0.0%)	RR 4.93 (0.24 to 101.88)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Dryness at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	9/148 (6.1%)	0/146 (0.0%)	RR 18.74 (1.10 to 319.15)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^e	none	5/148 (3.4%)	0/146 (0.0%)	RR 10.85 (0.61 to 194.52)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema, Severe at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^e	none	3/148 (2.0%)	0/146 (0.0%)	RR 6.91 (0.36 to 132.54)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Exfoliation at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^e	none	2/148 (1.4%)	1/146 (0.7%)	RR 1.97 (0.18 to 21.52)	7 more per 1,000 (from 6 fewer to 141 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Hyperpigmentation at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^e	none	3/148 (2.0%)	1/146 (0.7%)	RR 2.96 (0.31 to 28.12)	13 more per 1,000 (from 5 fewer to 186 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Irritation at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^e	none	3/148 (2.0%)	0/146 (0.0%)	RR 6.91 (0.36 to 132.54)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pain at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^e	none	5/148 (3.4%)	1/146 (0.7%)	RR 4.93 (0.58 to 41.71)	27 more per 1,000 (from 3 fewer to 279 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^e	none	1/148 (0.7%)	0/146 (0.0%)	RR 2.96 (0.12 to 72.07)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Scaling at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Topical antibiotic	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^e	none	2/148 (1.4%)	0/146 (0.0%)	RR 4.93 (0.24 to 101.88)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Stinging at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	0/148 (0.0%)	0/146 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

- Small sample size.
- The study did not report standard deviation values.
- Double zero study.
- CI included both appreciable benefits and harm. Small sample size.
- Wide CI included both appreciable benefits and harm. Small sample size.

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8. Topical retinoid + topical antibiotic vs. topical retinoid

e-Table 19. GRADE Evidence Profile for topical retinoid + topical antibiotic vs. topical retinoid

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Topical antibiotic	Topical retinoid	Relative (95% CI)	Absolute (95% CI)		
Investigator Global Assessment, Grade 0-1 at 12 weeks												
2 ^{1,2}	randomised trials	not serious	not serious	not serious	not serious	none	328/776 (42.3%)	252/764 (33.0%)	RR 1.28 (1.12 to 1.46)	92 more per 1,000 (from 40 more to 152 more)	⊕⊕⊕⊕ High	CRITICAL
AE, Any, Leading to discontinuation at 12 weeks												
2 ^{2,3}	randomised trials	not serious	not serious	not serious	serious ^a	none	0/386 (0.0%)	2/385 (0.5%)	RR 0.20 (0.01 to 4.15)	4 fewer per 1,000 (from 5 fewer to 16 more)	⊕⊕⊕○ Moderate	IMPORTANT
AE, Erythema at 12 weeks												
2 ^{2,3}	randomised trials	not serious	not serious	not serious	serious ^a	none	2/386 (0.5%)	4/384 (1.0%)	RR 0.62 (0.12 to 3.16)	4 fewer per 1,000 (from 9 fewer to 23 more)	⊕⊕⊕○ Moderate	IMPORTANT
AE, Any at 12 weeks												
2 ^{2,3}	randomised trials	not serious	not serious	not serious	serious ^a	none	10/386 (2.6%)	20/384 (5.2%)	RR 0.49 (0.24 to 1.04)	27 fewer per 1,000 (from 40 fewer to 2 more)	⊕⊕⊕○ Moderate	IMPORTANT

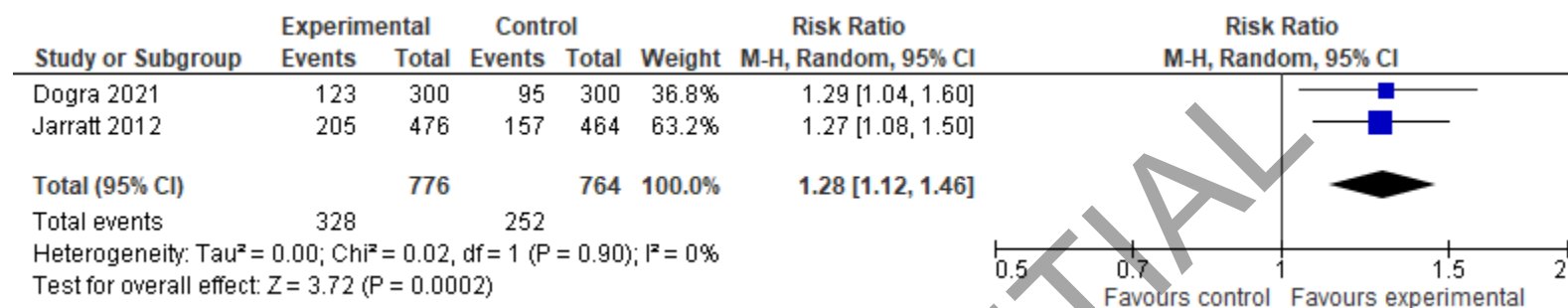
CI: confidence interval; RR: risk ratio

Explanations

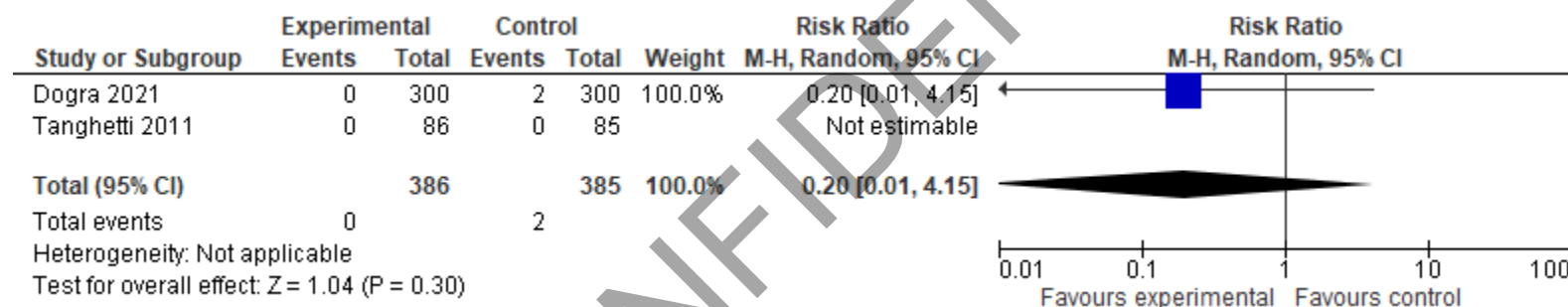
a. CI included both appreciable benefits and harm.

Forest plots

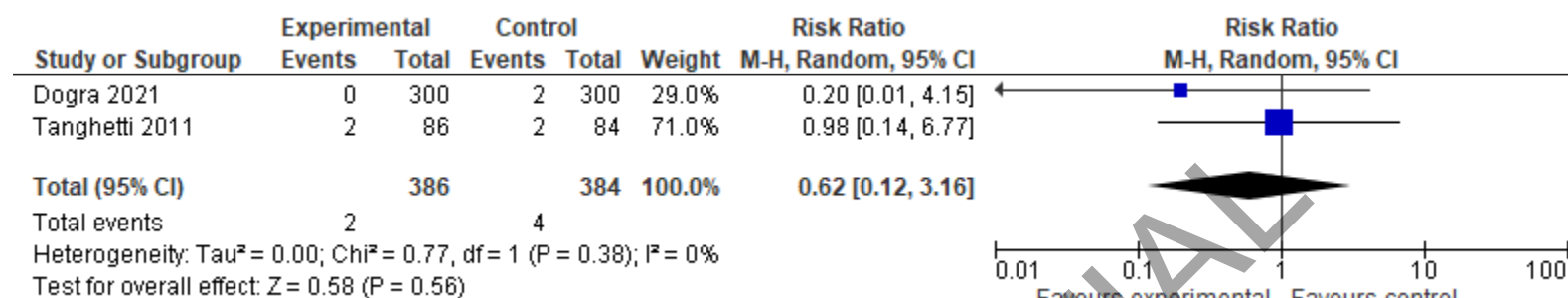
e-Figure 93. Investigator Global Assessment, Grade 0-1 at 12 weeks, topical retinoid + topical antibiotic vs. topical retinoid



e-Figure 94. AE, Any, Leading to discontinuation at 12 weeks, topical retinoid + topical antibiotic vs. topical retinoid



e-Figure 95. AE, Erythema at 12 weeks, topical retinoid + topical antibiotic vs. topical retinoid



e-Figure 96. AE, Any at 12 weeks, topical retinoid + topical antibiotic vs. topical retinoid



References

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2. Dogra S, Sumathy TK, Nayak C, et al. Efficacy and safety comparison of combination of 0.04% tretinoin microspheres plus 1% clindamycin versus their monotherapy in patients with acne vulgaris: a phase 3, randomized, double-blind study. *Journal of Dermatological Treatment*. 2021;32(8):925-933.
3. Tanghetti E, Dhawan S, Green L, et al. Clinical evidence for the role of a topical anti-inflammatory agent in comedonal acne: findings from a randomized study of dapsone gel 5% in combination with tazarotene cream 0.1% in patients with acne vulgaris. *J Drugs Dermatol*. 2011;10(7):783-792.

9. Topical retinoid + topical antibiotic vs. topical antibiotic

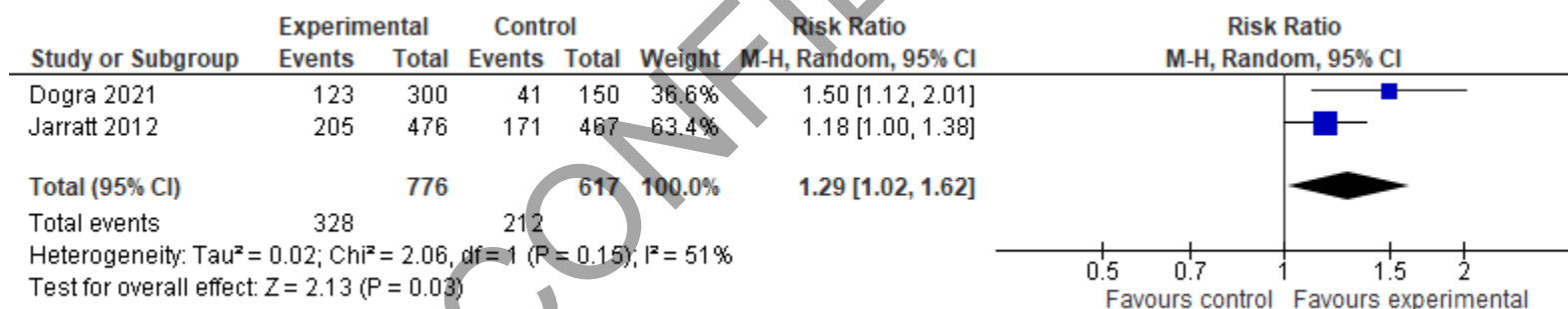
e-Table 20. GRADE Evidence Profile for topical retinoid + topical antibiotic vs. topical antibiotic

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Topical antibiotic	Topical antibiotic	Relative (95% CI)	Absolute (95% CI)		
Investigator Global Assessment, Grade 0-1 at 12 weeks												
2 ^{1,2}	randomised trials	not serious	not serious	not serious	not serious	none	328/776 (42.3%)	212/617 (34.4%)	RR 1.29 (1.02 to 1.62)	100 more per 1,000 (from 7 more to 213 more)	⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval; RR: risk ratio

Forest plot

e-Figure 97. Investigator Global Assessment, Grade 0-1 at 12 weeks, topical retinoid + topical antibiotic vs. topical antibiotic



References

1. Dogra S, Sumathy TK, Nayak C, et al. Efficacy and safety comparison of combination of 0.04% tretinoin microspheres plus 1% clindamycin versus their monotherapy in patients with acne vulgaris: a phase 3, randomized, double-blind study. *Journal of Dermatological Treatment*. 2021;32(8):925-933.
2. Jarratt MT, Brundage T. Efficacy and safety of clindamycin-tretinoin gel versus clindamycin or tretinoin alone in acne vulgaris: a randomized, double-blind, vehicle-controlled study. *J Drugs Dermatol*. 2012;11(3):318-326.

10. Topical retinoid + benzoyl peroxide vs. vehicle

e-Table 21. GRADE Evidence Profile for topical retinoid + benzoyl peroxide vs. vehicle

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
Investigator Global Assessment, Grade 0-1 at 4 weeks												
3 ^{1,2,3}	randomised trials	not serious	not serious	not serious	serious ^a	none	34/602 (5.6%)	15/600 (2.5%)	RR 1.87 (0.75 to 4.71)	22 more per 1,000 (from 6 fewer to 93 more)	⊕⊕⊕○ Moderate	CRITICAL
Investigator Global Assessment, Grade 0-1 at 12 weeks												
3 ^{1,2,3}	randomised trials	not serious	not serious	not serious	not serious	none	210/602 (34.9%)	95/600 (15.8%)	RR 2.19 (1.77 to 2.72)	188 more per 1,000 (from 122 more to 272 more)	⊕⊕⊕⊕ High	CRITICAL
Number of lesions, Inflammatory at 12 weeks (mean absolute change from baseline)												
2 ^{4,5}	randomised trials	not serious	not serious	not serious	serious ^b	none	In Stein Gold 2021 study, the mean absolute changes from baseline for topical retinoid + Benzoyl peroxide and vehicle groups were -26.7 (n: 150) and -19.6 (n: 148), respectively. In Weiss 2015 study, the mean absolute changes from baseline for topical retinoid + Benzoyl peroxide and vehicle groups were -35.2 (n: 106) and -15.5 (n: 34), respectively. The difference between the two groups was statistically significant. ^c			⊕⊕⊕○ Moderate	CRITICAL	

Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
4 ^{2,4,5,6}	randomised trials	not serious	not serious	not serious	serious ^b	none	In Stein Gold 2016 study, the mean percentage changes from baseline for topical retinoid + benzoyl peroxide and vehicle groups were -68.7 (n: 217) and -39.2 (n: 69), respectively. The difference between the two groups was statistically significant (p < 0.001). In Stein Gold 2021 study, the mean percentage changes from baseline for topical retinoid + benzoyl peroxide and vehicle groups were -68.1 (n: 150) and -50.4 (n: 148), respectively. The difference between the two groups was statistically significant (p < 0.01). In Webster 2020 study, the mean percentage changes from baseline for topical retinoid + benzoyl peroxide and vehicle groups were -60.8 (n: 116) and -30.7 (n: 115), respectively. In Weiss 2015 study, the mean percentage changes from baseline for topical retinoid + benzoyl peroxide and vehicle groups were -74.4 (n: 106) and -33 (n: 34), respectively. The difference between the two groups was statistically significant (p < 0.001). ^c				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (Pediatric to adolescent; mean percent change from baseline)

1 ⁷	randomised trials	not serious	not serious	not serious	serious ^b	none	The mean percentage changes from baseline for topical retinoid + Benzoyl peroxide and vehicle groups were -61.8% (n: 111) and -39.9% (n: 43), respectively. The difference between the two groups was statistically significant (p < 0.001). ^c				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (Adults; mean percent change from baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ⁷	randomised trials	not serious	not serious	not serious	serious ^b	none	The mean percentage changes from baseline for topical retinoid + Benzoyl peroxide and vehicle groups were -63.8% (n: 106) and -26.5% (n: 26), respectively. The difference between the two groups was statistically significant (p < 0.001). ^c				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (Sex: Females; mean percent change from baseline)

1 ⁷	randomised trials	not serious	not serious	not serious	serious ^b	none	The mean percentage changes from baseline for topical retinoid + Benzoyl peroxide and vehicle groups were -62.9% (n: 113) and -36.7%, (n: 36) respectively. The difference between the two groups was statistically significant (p < 0.001). ^c				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (Acne severity: severe, IGA 4; mean percent change from baseline)

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^b	none	The mean percentage changes from baseline for topical retinoid + Benzoyl peroxide and vehicle groups were -35.17% (n: 106) and -15.46% (n: 34), respectively. The difference between the two groups was statistically significant (p < 0.001). ^c				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean absolute change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
2 ^{4,5}	randomised trials	not serious	not serious	not serious	serious ^b	none	In Stein Gold 2021 study, the mean absolute changes from baseline for topical retinoid + Benzoyl peroxide and vehicle groups were -29.9 (n: 150) and -21.8 (n: 148), respectively. In Weiss 2015 study, the mean absolute changes from baseline for topical retinoid + Benzoyl peroxide and vehicle groups were -45.6 (n: 106) and -17.3 (n: 34), respectively. The difference between the two groups was statistically significant. ^c				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean percent change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	not serious	not serious	not serious	serious ^b	none	In Stein Gold 2016 study, the mean percentage changes from baseline for topical retinoid + benzoyl peroxide and vehicle groups were -68.3 (n: 217) and -37.4 (n: 69), respectively. The difference between the two groups was statistically significant (p < 0.001). In Stein Gold 2021 study, the mean percentage changes from baseline for topical retinoid + benzoyl peroxide and vehicle groups were -61.1 (n: 150) and -45.8 (n: 148), respectively. The difference between the two groups was statistically significant (p < 0.01). In Webster 2020 study, the mean percentage changes from baseline for topical retinoid + benzoyl peroxide and vehicle groups were -54.9 (n: 116) and -32.4 (n: 115), respectively. In Weiss 2015 study, the mean percentage changes from baseline for topical retinoid + benzoyl peroxide and vehicle groups were -72.1 (n: 106) and -30.8 (n: 34), respectively. The difference between the two groups was statistically significant (p < 0.001). ^c				⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Non-inflammatory at 12 weeks (Pediatric to adolescent; mean percent change from baseline)												
1 ⁷	randomised trials	not serious	not serious	not serious	serious ^b	none	The mean percentage changes from baseline for topical retinoid + Benzoyl peroxide and vehicle groups were -62.7% (n: 111) and -32.4% (n: 43), respectively. The difference between the two groups was statistically significant (p < 0.001). ^c				⊕⊕⊕○ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Non-inflammatory at 12 weeks (Adults; mean percent change from baseline)

1 ⁷	randomised trials	not serious	not serious	not serious	serious ^b	none	The mean percentage changes from baseline for topical retinoid + Benzoyl peroxide and vehicle groups were -62.4% (n: 106) and -34.8% (n: 26), respectively. The difference between the two groups was statistically significant (p < 0.001). c				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (Sex: Females; mean percent change from baseline)

1 ⁷	randomised trials	not serious	not serious	not serious	serious ^b	none	The mean percentage changes from baseline for topical retinoid + Benzoyl peroxide and vehicle groups were -60.8% (n: 113) and -32.4% (n: 36), respectively. The difference between the two groups was statistically significant (p < 0.001). c				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (Acne severity: severe, IGA 4; mean percent change from baseline)

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^b	none	The mean percentage changes from baseline for topical retinoid + Benzoyl peroxide and vehicle groups were -45.61% (n: 106) and -17.25% (n: 34), respectively. The difference between the two groups was statistically significant (p < 0.001). c				⊕⊕⊕○ Moderate	CRITICAL

Patient assessment of improvement, Global, Complete improvement at 12 weeks

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^d	none	19/204 (9.3%)	2/65 (3.1%)	RR 3.03 (0.72 to 12.65)	62 more per 1,000 (from 9 fewer to 358 more)	⊕⊕⊕○ Moderate	IMPORTANT

Patient assessment of improvement, Global, Marked improvement at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ⁶	randomised trials	not serious	not serious	not serious	serious ^e	none	90/204 (44.1%)	10/65 (15.4%)	RR 2.87 (1.59 to 5.18)	288 more per 1,000 (from 91 more to 643 more)	⊕⊕⊕○ Moderate	IMPORTANT

Patient assessment of improvement, Global, Moderate improvement at 12 weeks

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^e	none	74/204 (36.3%)	13/65 (20.0%)	RR 1.81 (1.08 to 3.05)	162 more per 1,000 (from 16 more to 410 more)	⊕⊕⊕○ Moderate	IMPORTANT

Patient assessment of improvement, Global, Minimal improvement at 12 weeks

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^e	none	12/204 (5.9%)	25/65 (38.5%)	RR 0.15 (0.08 to 0.29)	327 fewer per 1,000 (from 354 fewer to 273 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

Patient assessment of improvement, Global, No change at 12 weeks

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^e	none	5/204 (2.5%)	12/65 (18.5%)	RR 0.13 (0.05 to 0.36)	161 fewer per 1,000 (from 175 fewer to 118 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Any, Leading to discontinuation at 12 weeks

3 ^{3,4,6}	randomised trials	not serious	not serious	not serious	serious ^a	none	13/748 (1.7%)	4/521 (0.8%)	RR 2.21 (0.80 to 6.09)	9 more per 1,000 (from 2 fewer to 39 more)	⊕⊕⊕○ Moderate	IMPORTANT

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		

TEAE, Any, Leading to discontinuation at 12 weeks

2 ^{2,5}	randomised trials	not serious	not serious	not serious	not serious	none	13/263 (4.9%)	2/261 (0.8%)	RR 4.98 (1.29 to 19.27)	30 more per 1,000 (from 2 more to 140 more)	⊕⊕⊕⊕ High	IMPORTANT

AE, Dermatitis, Leading to study withdrawal at 12 weeks

1 ⁵	randomised trials	not serious	not serious	not serious	serious ^d	none	2/146 (1.4%)	0/146 (0.0%)	RR 5.00 (0.24 to 103.26)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pain, Leading to withdrawal at 12 weeks

1 ⁵	randomised trials	not serious	not serious	not serious	serious ^d	none	5/146 (3.4%)	0/146 (0.0%)	RR 11.00 (0.61 to 197.15)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Burning at 12 weeks

1 ⁵	randomised trials	not serious	not serious	not serious	serious ^d	none	8/146 (5.5%)	0/146 (0.0%)	RR 17.00 (0.99 to 291.85)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Burning, Mild at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	31/116 (26.7%)	12/115 (10.4%)	RR 2.56 (1.39 to 4.73)	163 more per 1,000 (from 41 more to 389 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Burning, Moderate at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
2 ^{2,6}	randomised trials	not serious	not serious	not serious	serious ^e	none	20/330 (6.1%)	2/183 (1.1%)	RR 6.46 (1.76 to 23.72)	60 more per 1,000 (from 8 more to 248 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Burning, Severe at 12 weeks

2 ^{2,6}	randomised trials	not serious	not serious	not serious	serious ^f	none	7/330 (2.1%)	0/183 (0.0%)	RR 4.37 (0.54 to 35.21)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Dryness at 12 weeks

2 ^{2,5}	randomised trials	not serious	not serious	not serious	not serious	none	16/263 (6.1%)	2/261 (0.8%)	RR 5.46 (1.42 to 20.97)	34 more per 1,000 (from 3 more to 153 more)	⊕⊕⊕⊕ High	IMPORTANT

AE, Dryness, Moderate at 12 weeks

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^d	none	4/212 (1.9%)	0/68 (0.0%)	RR 2.92 (0.16 to 53.47)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Dryness, Severe at 12 weeks

1 ⁶	randomised trials	not serious	not serious	not serious	serious ^d	none	0/212 (0.0%)	0/68 (0.0%)	RR 0.32 (0.01 to 16.17)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ⁵	randomised trials	not serious	not serious	not serious	serious ^d	none	2/146 (1.4%)	0/146 (0.0%)	RR 5.00 (0.24 to 103.26)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema, Mild at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^f	none	20/116 (17.2%)	21/115 (18.3%)	RR 0.94 (0.54 to 1.65)	11 fewer per 1,000 (from 84 fewer to 119 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema, Moderate

2 ^{2,6}	randomised trials	not serious	not serious	not serious	serious ^f	none	19/330 (5.8%)	7/183 (3.8%)	RR 1.74 (0.73 to 4.14)	28 more per 1,000 (from 10 fewer to 120 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema, Severe at 12 weeks

2 ^{2,5}	randomised trials	not serious	not serious	not serious	serious ^g	none	2/263 (0.8%)	0/261 (0.0%)	RR 5.00 (0.24 to 103.25)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Exfoliation at 12 weeks

2 ^{2,5}	randomised trials	not serious	not serious	not serious	serious ^g	none	8/263 (3.0%)	1/261 (0.4%)	RR 4.88 (0.83 to 28.76)	15 more per 1,000 (from 1 fewer to 106 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pain at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
2 ^{2,5}	randomised trials	not serious	not serious	not serious	not serious	none	26/263 (9.9%)	4/261 (1.5%)	RR 6.04 (1.24 to 29.49)	77 more per 1,000 (from 4 more to 437 more)	⊕⊕⊕⊕ High	IMPORTANT

AE, Dermatitis at 12 weeks

1 ⁵	randomised trials	not serious	not serious	not serious	serious ^d	none	3/146 (2.1%)	0/146 (0.0%)	RR 7.00 (0.36 to 134.33)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Hyperpigmentation at 12 weeks

1 ⁵	randomised trials	not serious	not serious	not serious	serious ^d	none	3/146 (2.1%)	1/146 (0.7%)	RR 3.00 (0.32 to 28.51)	14 more per 1,000 (from 5 fewer to 188 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Irritation at 12 weeks

1 ⁵	randomised trials	not serious	not serious	not serious	serious ^d	none	4/146 (2.7%)	0/146 (0.0%)	RR 9.00 (0.49 to 165.68)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus at 12 weeks

1 ⁵	randomised trials	not serious	not serious	not serious	serious ^d	none	2/146 (1.4%)	0/146 (0.0%)	RR 5.00 (0.24 to 103.26)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus, Mild at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	serious ^f	none	23/116 (19.8%)	22/115 (19.1%)	RR 1.04 (0.61 to 1.75)	8 more per 1,000 (from 75 fewer to 143 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus, Moderate at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^f	none	8/116 (6.9%)	3/115 (2.6%)	RR 2.64 (0.72 to 9.72)	43 more per 1,000 (from 7 fewer to 227 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus, Severe at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^h	none	0/116 (0.0%)	0/115 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Scaling at 12 weeks

1 ⁵	randomised trials	not serious	not serious	not serious	serious ^d	none	2/146 (1.4%)	0/146 (0.0%)	RR 5.00 (0.24 to 103.26)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Scaling, Mild at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^f	none	12/116 (10.3%)	11/115 (9.6%)	RR 1.08 (0.50 to 2.35)	8 more per 1,000 (from 48 fewer to 129 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Scaling, Moderate at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
2 ^{2,6}	randomised trials	not serious	not serious	not serious	serious ^f	none	5/330 (1.5%)	8/183 (4.4%)	RR 0.46 (0.14 to 1.53)	24 fewer per 1,000 (from 38 fewer to 23 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Scaling, Severe at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^h	none	0/117 (0.0%)	0/115 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Stinging at 12 weeks

1 ⁵	randomised trials	not serious	not serious	not serious	serious ^d	none	6/146 (4.1%)	0/146 (0.0%)	RR 13.00 (0.74 to 228.68)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Stinging, Mild at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	29/116 (25.0%)	16/115 (13.9%)	RR 1.80 (1.03 to 3.12)	111 more per 1,000 (from 4 more to 295 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Stinging, Moderate at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^d	none	6/116 (5.2%)	0/115 (0.0%)	RR 12.89 (0.73 to 226.19)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Stinging, Severe at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	serious ^d	none	6/116 (5.2%)	0/115 (0.0%)	RR 12.89 (0.73 to 226.19)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Any at 12 weeks

2 ^{3,4}	randomised trials	not serious	serious ⁱ	not serious	serious ^a	none	218/531 (41.1%)	124/452 (27.4%)	RR 1.23 (0.55 to 2.76)	63 more per 1,000 (from 123 fewer to 483 more)	⊕⊕○○ Low	IMPORTANT

AE, Any, Serious at 12 weeks

2 ^{2,5}	randomised trials	not serious	not serious	not serious	serious ^g	none	1/263 (0.4%)	0/261 (0.0%)	RR 2.95 (0.12 to 71.65)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Any at 12 weeks

3 ^{2,4,5}	randomised trials	not serious	not serious ^l	not serious	not serious	none	90/375 (24.0%)	50/295 (16.9%)	RR 1.77 (1.01 to 3.10)	131 more per 1,000 (from 2 more to 356 more)	⊕⊕⊕⊕ High	IMPORTANT

CI: confidence interval; RR: risk ratio

Explanations

- a. CI included both appreciable benefits and harm.
- b. Standard deviation values were not reported. Small sample size.
- c. n: number of patients.
- d. Wide CI included both appreciable benefits and harm. Small sample size.
- e. Small sample size.
- f. CI included both appreciable benefits and harm. Small sample size.

g. Wide CI included both appreciable benefits and harm.

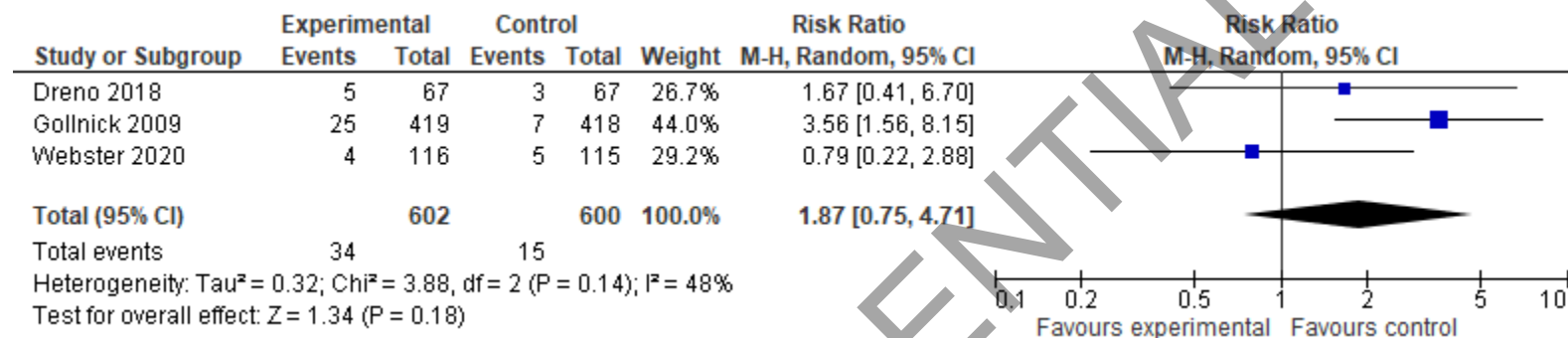
h. Double zero study.

i. $I^2 = 76\%$

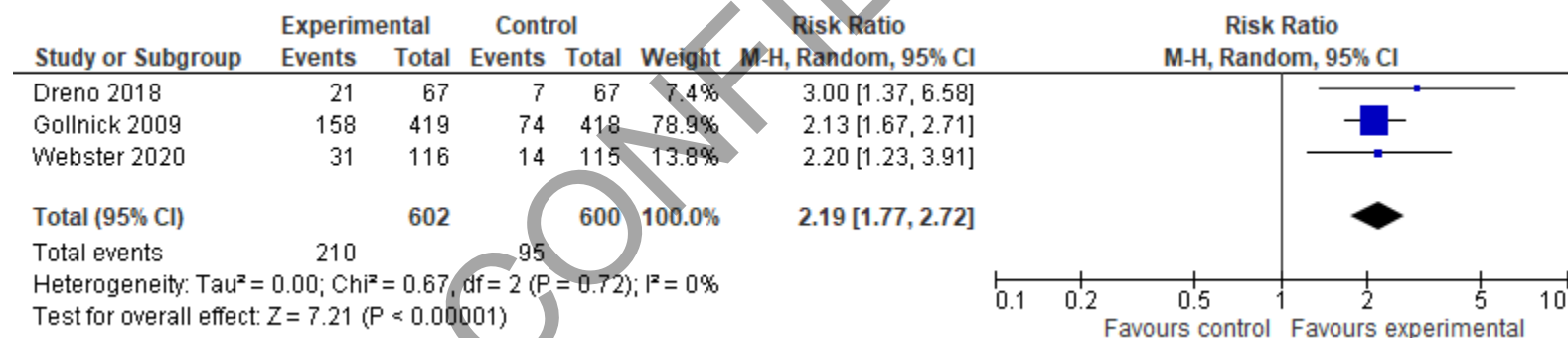
j. $I^2 = 71\%$

Forest plots

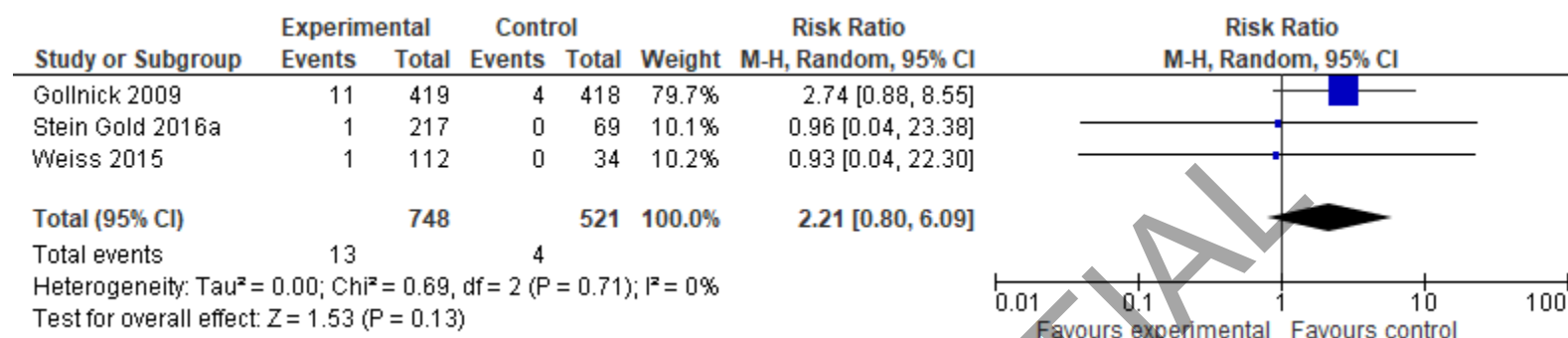
e-Figure 98. Investigator Global Assessment, Grade 0-1 at 4 weeks, topical retinoid + benzoyl peroxide vs. vehicle



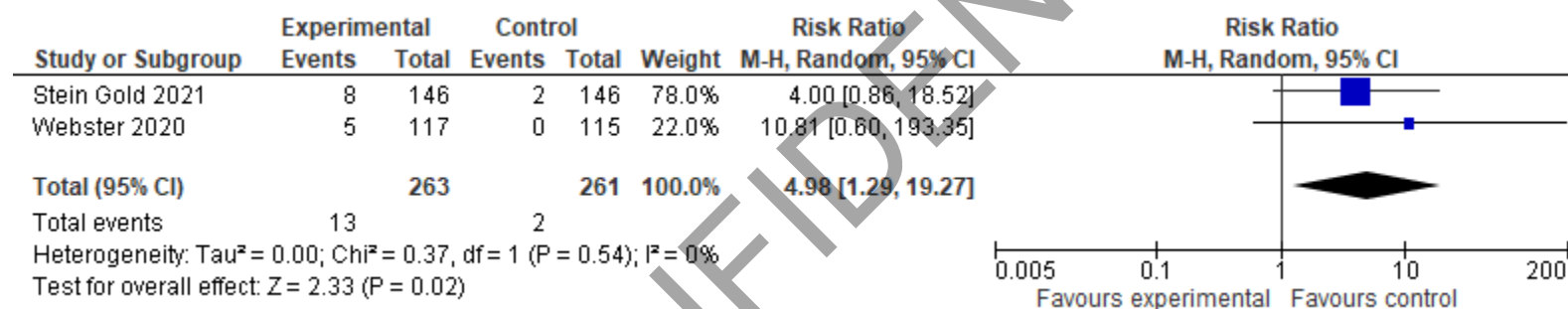
e-Figure 99. Investigator Global Assessment, Grade 0-1 at 12 weeks, topical retinoid + benzoyl peroxide vs. vehicle



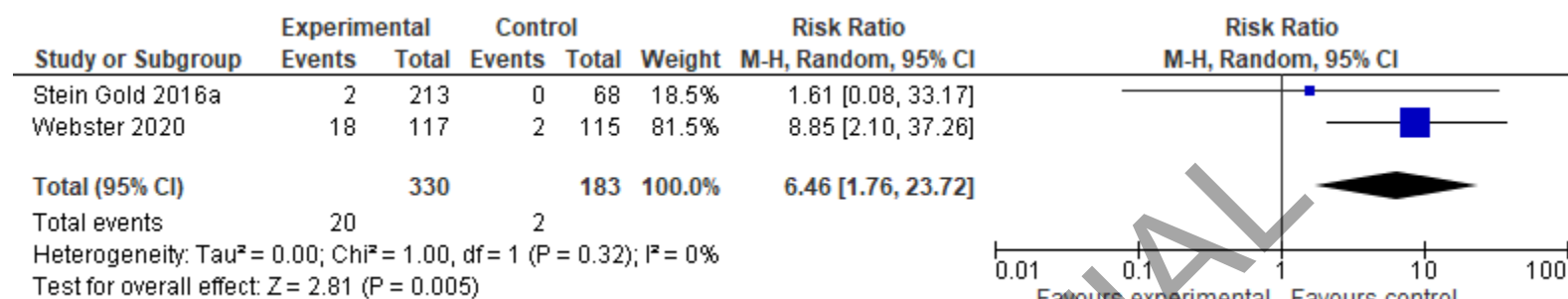
e-Figure 100. AE, Any, Leading to discontinuation at 12 weeks, topical retinoid + benzoyl peroxide vs. vehicle



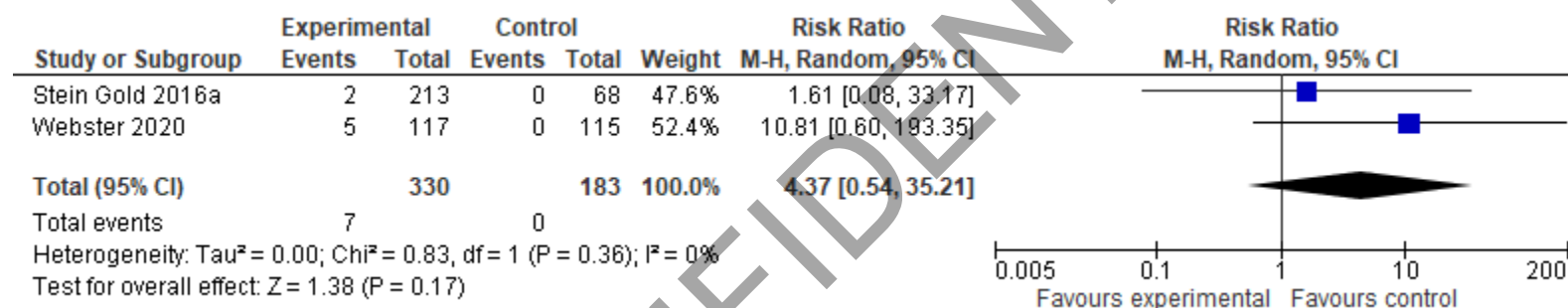
e-Figure 101. TEAE, Any, Leading to discontinuation at 12 weeks, topical retinoid + benzoyl peroxide vs. vehicle



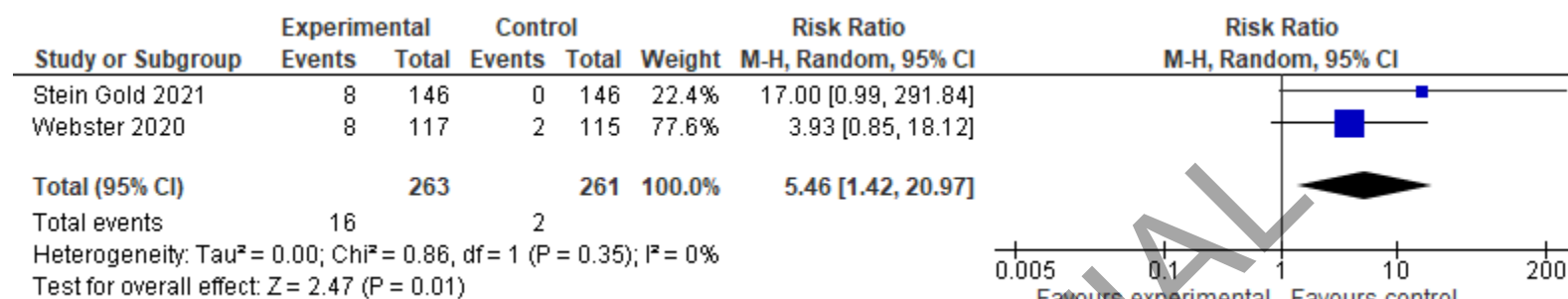
e-Figure 102. AE, Burning, Moderate at 12 weeks, topical retinoid + benzoyl peroxide vs. vehicle



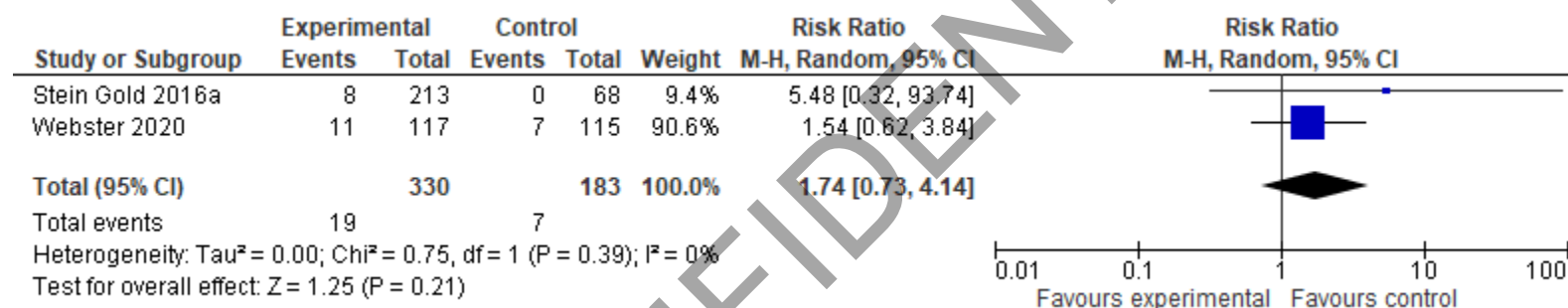
e-Figure 103. AE, Burning, Severe at 12 weeks, topical retinoid + benzoyl peroxide vs. vehicle



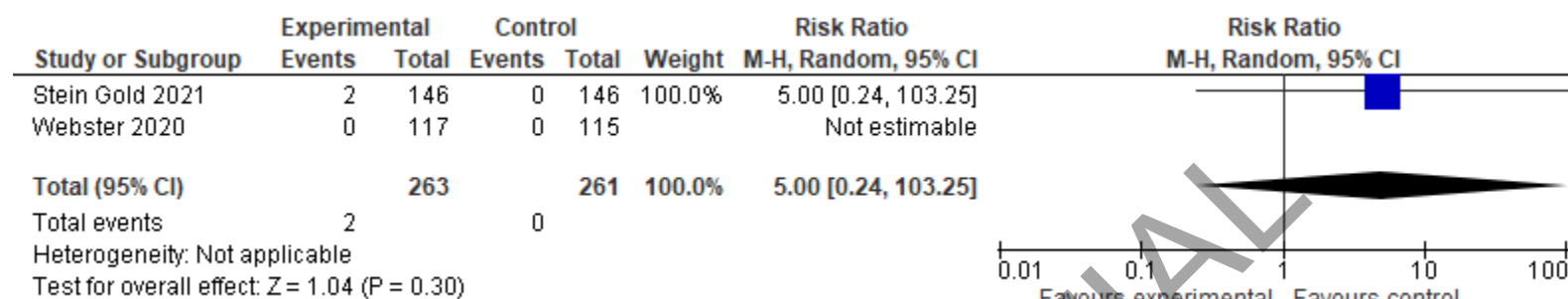
e-Figure 104. AE, Dryness at 12 weeks, topical retinoid + benzoyl peroxide vs. vehicle



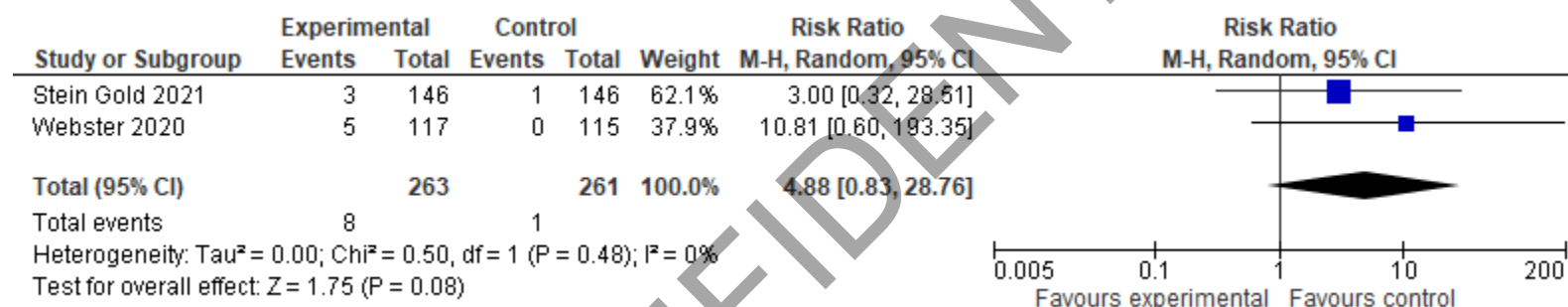
e-Figure 105. AE, Erythema, Moderate, topical retinoid + benzoyl peroxide vs. vehicle



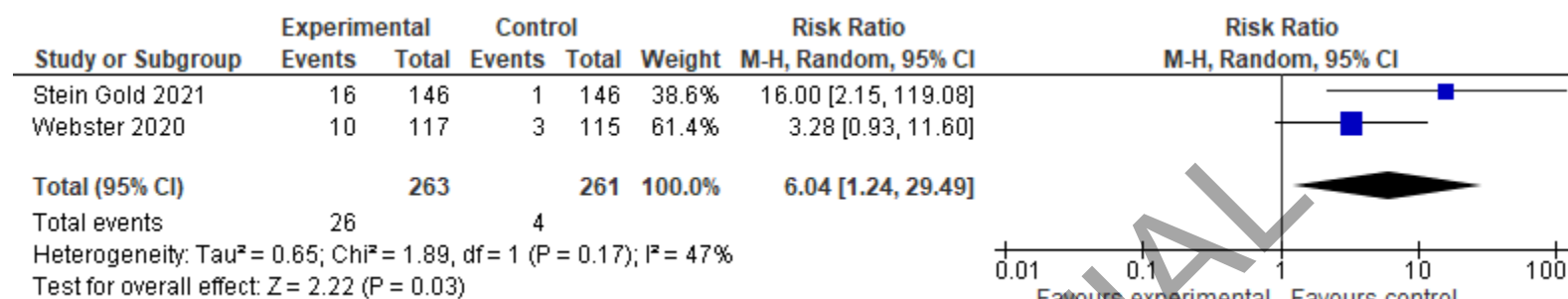
e-Figure 106. AE, Erythema, Severe at 12 weeks, topical retinoid + benzoyl peroxide vs. vehicle



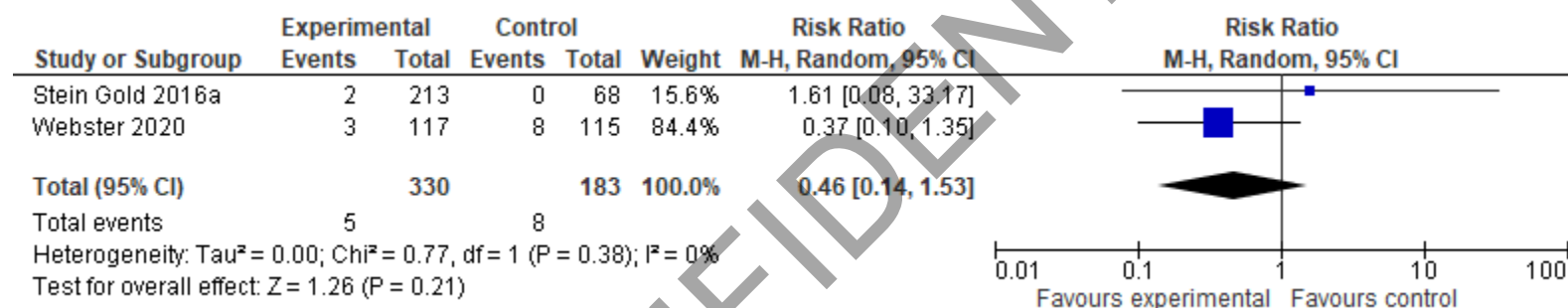
e-Figure 107. AE, Exfoliation at 12 weeks, topical retinoid + benzoyl peroxide vs. vehicle



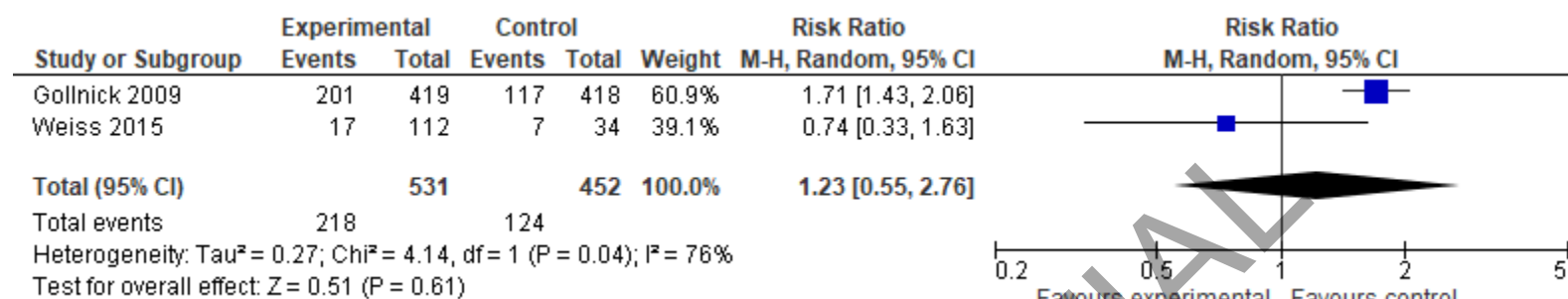
e-Figure 108. AE, Pain at 12 weeks, topical retinoid + benzoyl peroxide vs. vehicle



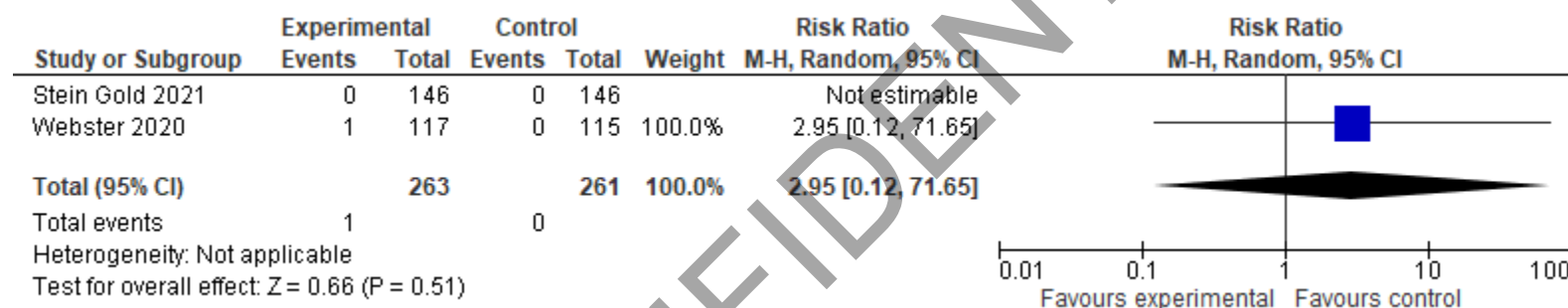
e-Figure 109. AE, Scaling, Moderate at 12 weeks, topical retinoid + benzoyl peroxide vs. vehicle



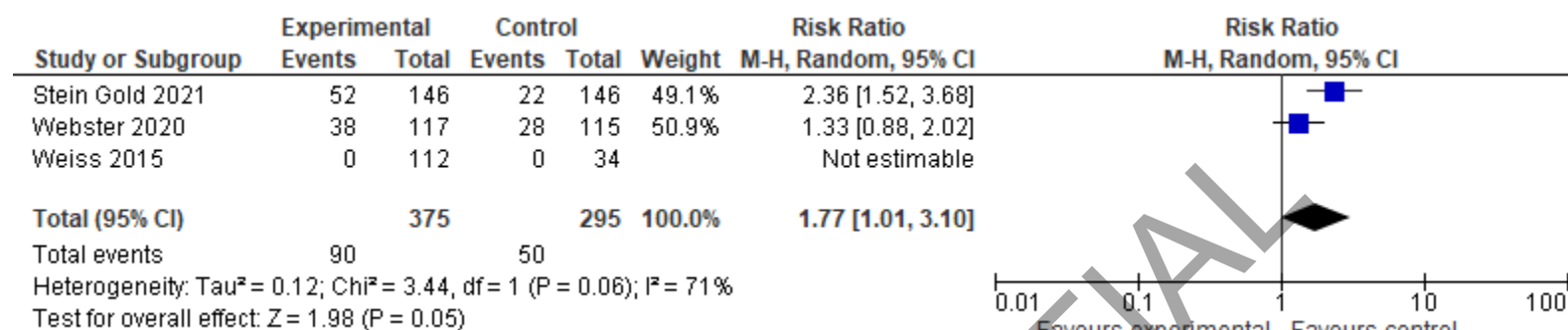
e-Figure 110. AE, Any at 12 weeks, topical retinoid + benzoyl peroxide vs. vehicle



e-Figure 111. AE, Any, Serious at 12 weeks, topical retinoid + benzoyl peroxide vs. vehicle



e-Figure 112. TEAE, Any at 12 weeks, topical retinoid + benzoyl peroxide vs. vehicle



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11. Topical retinoid + benzoyl peroxide vs. topical retinoid

e-Table 22. GRADE Evidence Profile for topical retinoid + benzoyl peroxide vs. topical retinoid

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Benzoyl peroxide	Topical retinoid	Relative (95% CI)	Absolute (95% CI)		
Investigator Global Assessment, Grade 0-1 at 4 weeks												
2 ^{1,2}	randomised trials	not serious	not serious	not serious	not serious	none	29/535 (5.4%)	9/536 (1.7%)	RR 3.19 (1.52 to 6.71)	37 more per 1,000 (from 9 more to 96 more)	⊕⊕⊕⊕ High	CRITICAL
Investigator Global Assessment, Grade 0-1 at 12 weeks												
2 ^{1,2}	randomised trials	not serious	not serious ^a	not serious	serious ^b	none	189/535 (35.3%)	120/536 (22.4%)	RR 1.43 (0.91 to 2.24)	96 more per 1,000 (from 20 fewer to 278 more)	⊕⊕⊕○ Moderate	CRITICAL

CI: confidence interval; RR: risk ratio

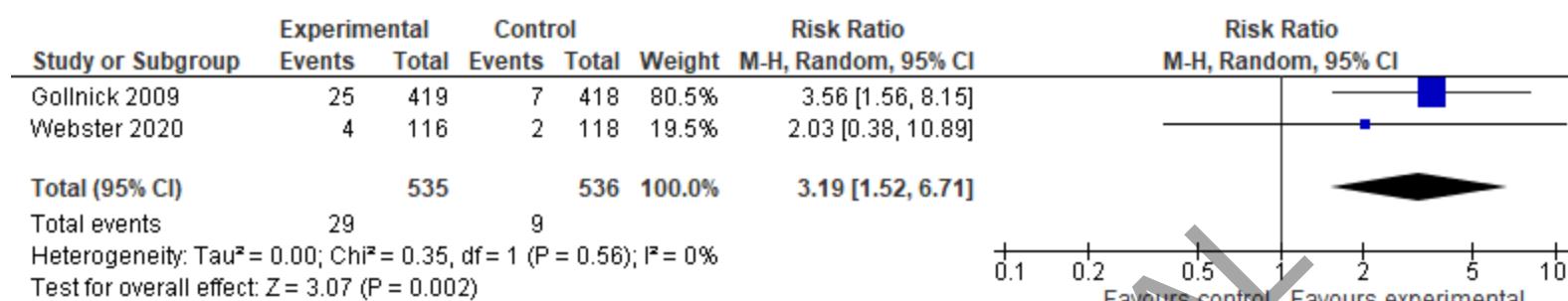
Explanations

a. $I^2 = 71\%$

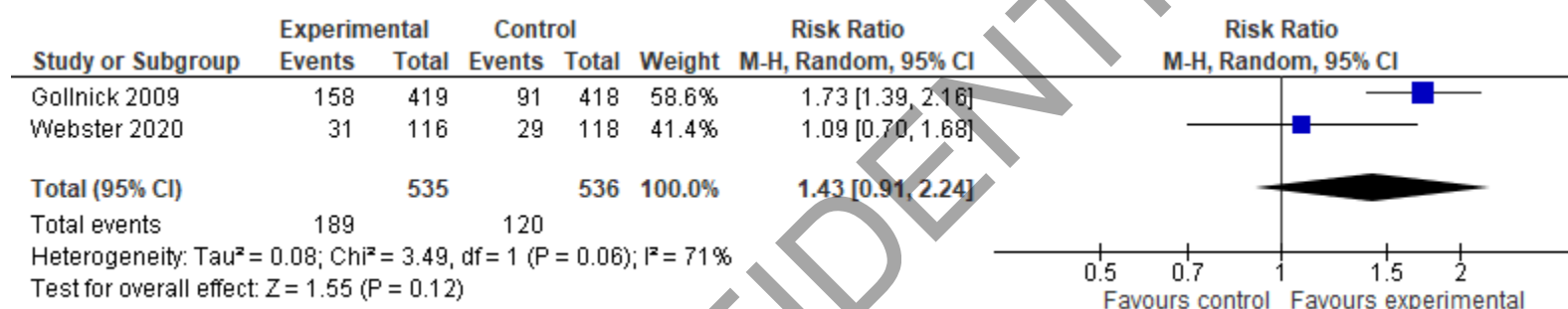
b. CI included both appreciable benefits and harm.

Forest plots

e-Figure 113. Investigator Global Assessment, Grade 0-1 at 4 weeks, topical retinoid + benzoyl peroxide vs. topical retinoid



e-Figure 114. Investigator Global Assessment, Grade 0-1 at 12 weeks, topical retinoid + benzoyl peroxide vs. topical retinoid



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1. Webster GF, Sugarman J, Levy-Hacham O, Toledano O. Microencapsulated Benzoyl Peroxide and Tretinoin for the Treatment of Acne Vulgaris: Results from a Phase 2 Multicenter, Double-Blind, Randomized, Vehicle-Controlled Study. *Skinmed*. 2020;18(6):343-351.
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12. Topical retinoid + Benzoyl peroxide vs. Benzoyl peroxide

e-Table 23. GRADE Evidence Profile for topical retinoid + benzoyl peroxide vs. benzoyl peroxide

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Benzoyl peroxide	Benzoyl peroxide	Relative (95% CI)	Absolute (95% CI)		
Investigator Global Assessment, Grade 0-1 at 4 weeks												
2 ^{1,2}	randomised trials	not serious	not serious	not serious	serious ^a	none	29/535 (5.4%)	31/533 (5.8%)	RR 0.93 (0.57 to 1.53)	4 fewer per 1,000 (from 25 fewer to 31 more)	⊕⊕⊕○ Moderate	CRITICAL
Investigator Global Assessment, Grade 0-1 at 12 weeks												
2 ^{1,2}	randomised trials	not serious	not serious	not serious	not serious	none	189/535 (35.3%)	136/533 (25.5%)	RR 1.39 (1.15 to 1.67)	100 more per 1,000 (from 38 more to 171 more)	⊕⊕⊕⊕ High	CRITICAL
AE, Any at 12 weeks												
2 ^{1,3}	randomised trials	not serious	not serious	not serious	not serious	none	254/504 (50.4%)	178/500 (35.6%)	RR 1.40 (1.22 to 1.62)	142 more per 1,000 (from 78 more to 221 more)	⊕⊕⊕⊕ High	IMPORTANT

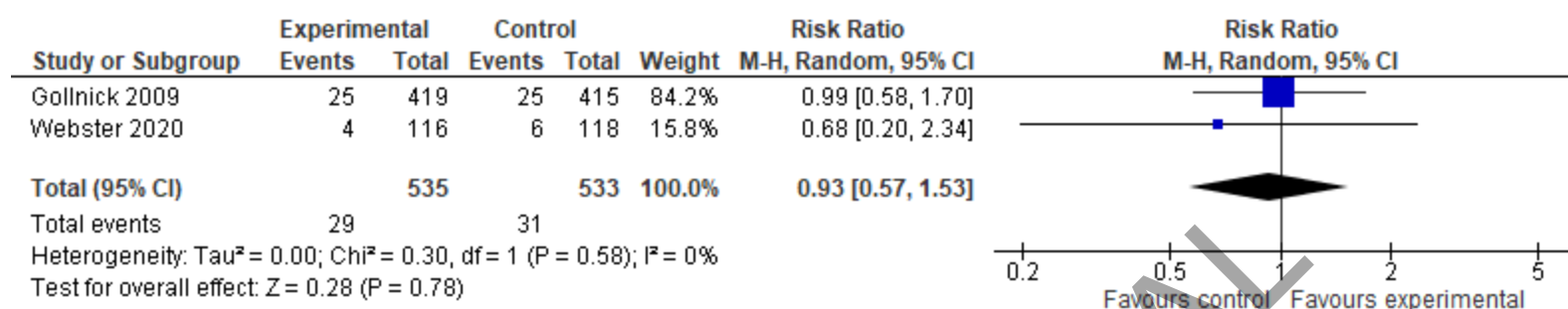
CI: confidence interval; RR: risk ratio

Explanations

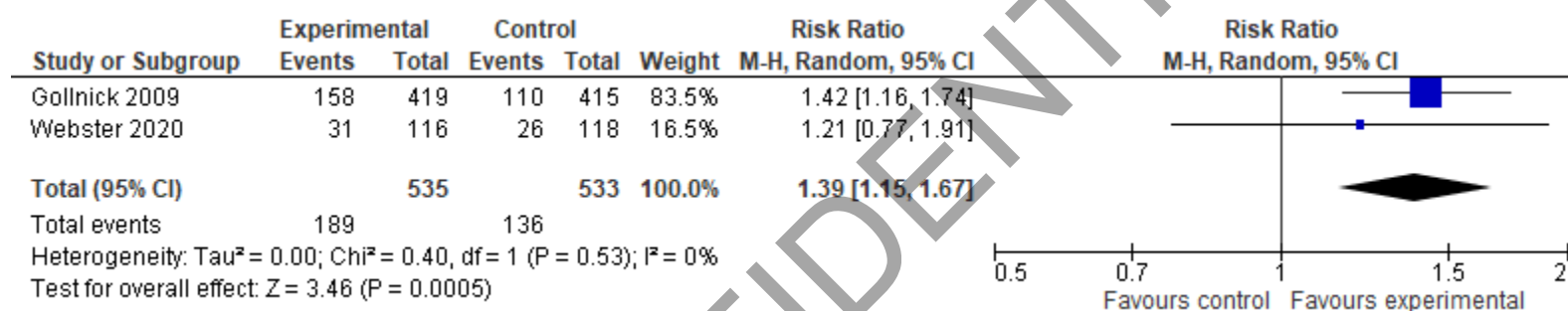
a. CI included both appreciable benefits and harm.

Forest plots

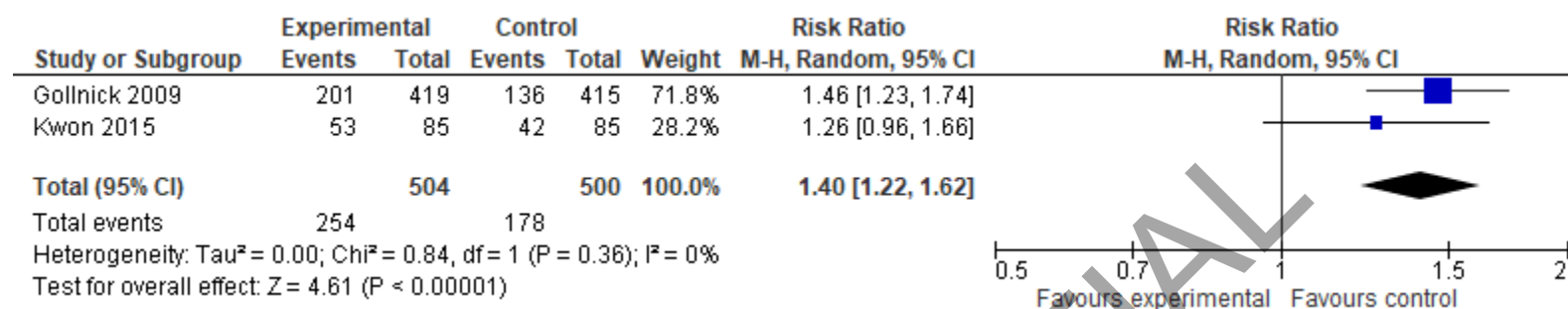
e-Figure 115. Investigator Global Assessment, Grade 0-1 at 4 weeks, topical retinoid + benzoyl peroxide vs. benzoyl peroxide



e-Figure 116. Investigator Global Assessment, Grade 0-1 at 12 weeks, topical retinoid + benzoyl peroxide vs. benzoyl peroxide



e-Figure 117. AE, Any at 12 weeks, topical retinoid + benzoyl peroxide vs. benzoyl peroxide



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3. Kwon HH, Park SY, Yoon JY, Min S, Suh DH. Do tutorials on application method enhance adapalene-benzoyl peroxide combination gel tolerability in the treatment of acne? *Journal of Dermatology.* 2015;42(11):1058-1065.

e-Table 24. GRADE Evidence Profile for clascoterone 1% (b.i.d.) vs. vehicle

Investigator Global Assessment, Grade 0-1 and ≥ 2 -grade reduction at 12 weeks (Study, Cb-03-01/26; 5-point scale)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clascoterone 1% (b.i.d.)	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	not serious	none	71/353 (20.1%)	23/355 (6.5%)	RR 3.10 (1.99 to 4.85)	136 more per 1,000 (from 64 more to 249 more)	⊕⊕⊕⊕ High	CRITICAL

Investigator Global Assessment, Grade 0-1 and ≥2-grade reduction at 12 weeks (5-point scale)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	6/70 (8.6%)	2/75 (2.7%)	RR 3.21 (0.67 to 15.40)	59 more per 1,000 (from 9 fewer to 384 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any at 12 weeks (Study, Cb-03-01/25; mean absolute change from baseline)

1 ²	randomised trials	not serious	not serious	not serious	not serious	none	The mean absolute changes from baseline for clascoterone 1% (b.i.d.) and vehicle groups were -39.1 (n: 287) and -28.8 (n: 290), respectively. The difference between the two groups was statistically significant (p < 0.001). ^c				⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Any at 12 weeks (Study, Cb-03-01/25; mean percent change from baseline)

1 ²	randomised trials	not serious	not serious	not serious	not serious	none	The mean percentage changes from baseline for clascoterone 1% (b.i.d.) and vehicle groups were -37% (n: 287) and -28.4% (n: 290), respectively. The difference between the two groups was statistically significant (p < 0.001). ^c				⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Any at 12 weeks (Study, Cb-03-01/26; mean absolute change from baseline)

1 ²	randomised trials	not serious	not serious	not serious	not serious	none	The mean absolute changes from baseline for clascoterone 1% (b.i.d.) and vehicle groups were -40 (n: 287) and -23.6 (n: 290), respectively. The difference between the two groups was statistically significant (p < 0.001). ^c				⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Any at 12 weeks (Study, Cb-03-01/26; mean percent change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clascoterone 1% (b.i.d.)	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	not serious	none	The mean percentage changes from baseline for clascoterone 1% (b.i.d.) and vehicle groups were -37.3% (n: 287) and -22.1% (n: 290), respectively. The difference between the two groups was statistically significant (p < 0.001). c			⊕⊕⊕⊕ High	CRITICAL	
Number of lesions, Inflammatory at 12 weeks (Study, Cb-03-01/25; mean absolute change from baseline)												
1 ²	randomised trials	not serious	not serious	not serious	not serious	none	The mean absolute changes from baseline for clascoterone 1% (b.i.d.) and vehicle groups were -19.3 (n: 287) and -15.5 (n: 290), respectively. The difference between the two groups was statistically significant (p = 0.003). c			⊕⊕⊕⊕ High	CRITICAL	
Number of lesions, Inflammatory at 12 weeks (Study, Cb-03-01/25; mean percent change from baseline)												
1 ²	randomised trials	not serious	not serious	not serious	not serious	none	The mean percentage changes from baseline for clascoterone 1% (b.i.d.) and vehicle groups were -44.8% (n: 287) and -36.5% (n: 290), respectively. The difference between the two groups was statistically significant (p = 0.005). c			⊕⊕⊕⊕ High	CRITICAL	
Number of lesions, Inflammatory at 12 weeks (Study, Cb-03-01/26; mean absolute change from baseline)												
1 ²	randomised trials	not serious	not serious	not serious	not serious	none	The mean absolute changes from baseline for clascoterone 1% (b.i.d.) and vehicle groups were -20 (n: 287) and -12.6 (n: 290), respectively. The difference between the two groups was statistically significant (p < 0.001). c			⊕⊕⊕⊕ High	CRITICAL	
Number of lesions, Inflammatory at 12 weeks (Study, Cb-03-01/26; mean percent change from baseline)												
1 ²	randomised trials	not serious	not serious	not serious	not serious	none	The mean percentage changes from baseline for clascoterone 1% (b.i.d.) and vehicle groups were -46.9% (n: 287) and -29.6% (n: 290), respectively. The difference between the two groups was statistically significant (p < 0.001). c			⊕⊕⊕⊕ High	CRITICAL	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clascoterone 1% (b.i.d.)	Vehicle	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Inflammatory at 12 weeks (Mean absolute change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	70	75	-	MD 2.8 lesions lower (7.2 lower to 1.6 higher)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (Study, Cb-03-01/25; mean absolute change from baseline)

1 ²	randomised trials	not serious	not serious	not serious	not serious	none	The mean absolute changes from baseline for clascoterone 1% (b.i.d.) and vehicle groups were -19.4 (n: 287) and -13 (n: 290), respectively. The difference between the two groups was statistically significant (p < 0.001). ^c				⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (Study, Cb-03-01/25; mean percent change from baseline)

1 ²	randomised trials	not serious	not serious	not serious	not serious	none	The mean percentage changes from baseline for clascoterone 1% (b.i.d.) and vehicle groups were -30.6% (n: 287) and -21.6% (n: 290), respectively. The difference between the two groups was statistically significant (p = 0.009). ^c				⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (Study, Cb-03-01/26; mean absolute change from baseline)

1 ²	randomised trials	not serious	not serious	not serious	not serious	none	The mean absolute changes from baseline for clascoterone 1% (b.i.d.) and vehicle groups were -19.4 (n: 287) and -10.8 (n: 290), respectively. The difference between the two groups was statistically significant (p < 0.001). ^c				⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (Study, Cb-03-01/26; mean percent change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clascoterone 1% (b.i.d.)	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	not serious	none	The mean percentage changes from baseline for clascoterone 1% (b.i.d.) and vehicle groups were -29.3% (n: 287) and -15.6% (n: 290), respectively. The difference between the two groups was statistically significant (p < 0.001). c				⊕⊕⊕⊕ High	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (Mean absolute change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	70	75	-	MD 9.9 lesions lower (16.2 lower to 3.6 lower)	⊕⊕⊕○ Moderate	CRITICAL

TEAE, Any, Leading to discontinuation at 12 weeks (Study, Cb-03-01/25)

1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	3/353 (0.8%)	4/355 (1.1%)	RR 0.75 (0.17 to 3.35)	3 fewer per 1,000 (from 9 fewer to 26 more)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Any, Leading to discontinuation at 12 weeks (Study, Cb-03-01/26)

1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	2/353 (0.6%)	8/355 (2.3%)	RR 0.25 (0.05 to 1.18)	17 fewer per 1,000 (from 21 fewer to 4 more)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Any, Related to treatment at 12 weeks (Study, Cb-03-01/25)

1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	4/353 (1.1%)	9/355 (2.5%)	RR 0.45 (0.14 to 1.44)	14 fewer per 1,000 (from 22 fewer to 11 more)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Any, Related to treatment at 12 weeks (Study, Cb-03-01/26)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clascoterone 1% (b.i.d.)	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	8/353 (2.3%)	13/355 (3.7%)	RR 0.62 (0.26 to 1.47)	14 fewer per 1,000 (from 27 fewer to 17 more)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Any at 12 weeks (Study, Cb-03-01/25)

1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	40/353 (11.3%)	41/355 (11.5%)	RR 0.98 (0.65 to 1.48)	2 fewer per 1,000 (from 40 fewer to 55 more)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Any at 12 weeks (Study, Cb-03-01/26)

1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	42/353 (11.9%)	50/355 (14.1%)	RR 0.84 (0.58 to 1.24)	23 fewer per 1,000 (from 59 fewer to 34 more)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Headache at 12 weeks (Study, Cb-03-01/25)

1 ²	randomised trials	not serious	not serious	not serious	serious ^f	none	2/353 (0.6%)	1/355 (0.3%)	RR 2.01 (0.18 to 22.08)	3 more per 1,000 (from 2 fewer to 59 more)	⊕⊕⊕○ Moderate	IMPORTANT

Headache at 12 weeks (Study, Cb-03-01/26)

1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	4/353 (1.1%)	3/355 (0.8%)	RR 1.34 (0.30 to 5.95)	3 more per 1,000 (from 6 fewer to 42 more)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Nasopharyngitis at 12 weeks (Study, Cb-03-01/25)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clascoterone 1% (b.i.d.)	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	6/353 (1.7%)	13/355 (3.7%)	RR 0.46 (0.18 to 1.21)	20 fewer per 1,000 (from 30 fewer to 8 more)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Nasopharyngitis at 12 weeks (Study, Cb-03-01/26)

1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	4/353 (1.1%)	7/355 (2.0%)	RR 0.57 (0.17 to 1.95)	8 fewer per 1,000 (from 16 fewer to 19 more)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Pain, Oropharyngeal at 12 weeks (Study, Cb-03-01/25)

1 ²	randomised trials	not serious	not serious	not serious	serious ^f	none	2/353 (0.6%)	1/355 (0.3%)	RR 2.01 (0.18 to 22.08)	3 more per 1,000 (from 2 fewer to 59 more)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Pain, Oropharyngeal at 12 weeks (Study, Cb-03-01/26)

1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	4/353 (1.1%)	4/355 (1.1%)	RR 1.01 (0.25 to 3.99)	0 fewer per 1,000 (from 8 fewer to 34 more)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Vomiting at 12 weeks (Study, Cb-03-01/25)

1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	2/353 (0.6%)	2/355 (0.6%)	RR 1.01 (0.14 to 7.10)	0 fewer per 1,000 (from 5 fewer to 34 more)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Vomiting at 12 weeks (Study, Cb-03-01/26)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clascoterone 1% (b.i.d.)	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	serious ^f	none	2/353 (0.6%)	1/355 (0.3%)	RR 2.01 (0.18 to 22.08)	3 more per 1,000 (from 2 fewer to 59 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Any, Serious at 12 weeks (Study, Cb-03-01/25)

1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	0/353 (0.0%)	1/355 (0.3%)	RR 0.34 (0.01 to 8.20)	2 fewer per 1,000 (from 3 fewer to 20 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Any, Serious at 12 weeks (Study, Cb-03-01/26)

1 ²	randomised trials	not serious	not serious	not serious	serious ^e	none	0/353 (0.0%)	1/355 (0.3%)	RR 0.34 (0.01 to 8.20)	2 fewer per 1,000 (from 3 fewer to 20 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Any at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	13/70 (18.6%)	17/75 (22.7%)	RR 0.82 (0.43 to 1.56)	41 fewer per 1,000 (from 129 fewer to 127 more)	⊕⊕⊕○ Moderate	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

- a. CI included both appreciable benefits and harm. Small sample size.
- b. Wide CI included both appreciable benefits and harm. Small sample size.
- c. n: number of patients
- d. Small sample size
- e. CI included both appreciable benefits and harm.
- f. Wide CI included both appreciable benefits and harm.

References

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14. Salicylic acid 0.5% vs. vehicle

e-Table 25. GRADE Evidence Profile for salicylic acid 0.5% vs. vehicle

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salicylic acid 0.5%	Vehicle	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any, <25% reduction at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	2/25 (8.0%)	9/24 (37.5%)	RR 0.21 (0.05 to 0.89)	296 fewer per 1,000 (from 356 fewer to 41 fewer)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, 25-49% reduction at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	5/25 (20.0%)	7/24 (29.2%)	RR 0.69 (0.25 to 1.87)	90 fewer per 1,000 (from 219 fewer to 254 more)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, ≥50% reduction at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	18/25 (72.0%)	7/24 (29.2%)	RR 2.47 (1.26 to 4.82)	429 more per 1,000 (from 76 more to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, 50-74% reduction at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	13/25 (52.0%)	4/24 (16.7%)	RR 3.12 (1.18 to 8.24)	353 more per 1,000 (from 30 more to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, ≥75% reduction at 12 weeks												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salicylic acid 0.5%	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	5/25 (20.0%)	4/24 (16.7%)	RR 1.20 (0.37 to 3.94)	33 more per 1,000 (from 105 fewer to 490 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any at 12 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	25 and 24 patients were randomized to receive salicylic acid 0.5% or vehicle, respectively. The mean percentage changes from baseline for salicylic acid 0.5% and vehicle groups were -38.4% and -24.6%, respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 4 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	25 and 24 patients were randomized to receive salicylic acid 0.5% or vehicle, respectively. The mean percentage changes from baseline for salicylic acid 0.5% and vehicle groups were -29.5% and -20%, respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	25 and 24 patients were randomized to receive salicylic acid 0.5% or vehicle, respectively. The mean percentage changes from baseline for salicylic acid 0.5% and vehicle groups were -54% and -29%, respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, Closed comedones at 12 weeks (mean percent change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salicylic acid 0.5%	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	25 and 24 patients were randomized to receive salicylic acid 0.5% or vehicle, respectively. The mean percentage changes from baseline for salicylic acid 0.5% and vehicle groups were -21% and -21%, respectively. The difference between the two groups was not statistically significant.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, Open comedones at 12 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	25 and 24 patients were randomized to receive salicylic acid 0.5% or vehicle, respectively. The mean percentage changes from baseline for salicylic acid 0.5% and vehicle groups were -39% and -28%, respectively. The difference between the two groups was statistically significant.				⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; RR: Risk ratio

Explanations

- Small sample size.
- CI included both appreciable benefits and harm. Small sample size.
- Standard deviation was not reported. Small sample size.

References

- Shalita AR. Treatment of mild and moderate acne vulgaris with salicylic acid in an alcohol-detergent vehicle. Cutis. 1981;28(5):556-558, 561.

15. Azelaic acid vs. vehicle

e-Table 26. GRADE Evidence Profile for azelaic acid vs. vehicle

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azelaic acid 20%	Vehicle	Relative (95% CI)	Absolute (95% CI)		
Acne severity index (ASI = Papules + [2 × pustules] + [0.25 x comedones]), mean percentage change from baseline, at 6 weeks												
1 ⁶¹	randomised trials	not serious	not serious	not serious	serious ^a	none	30 and 30 patients were randomized to receive azelaic acid 20% gel BID or vehicle, respectively. The mean percentage changes from baseline for azelaic acid 20% and vehicle groups were -65.2% and -21.3%, respectively. The difference between the two groups was statistically significant (p = 0.001).			⊕⊕⊕○ Moderate	CRITICAL	
Total lesions, percentage change from baseline, at 6 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	30 and 30 patients were randomized to receive azelaic acid 20% cream BID or vehicle, respectively. The mean percentage changes from baseline for azelaic acid 20% and vehicle groups were -60.6% and -19.9%, respectively. The difference between the two groups was statistically significant (p = 0.002).			⊕⊕⊕○ Moderate	CRITICAL	

Total lesion, 50-100% reduction at 3 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azelaic acid 20%	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	serious ^a	none	43 and 49 patients were randomized to receive azelaic acid 20% cream BID or vehicle, respectively. At 3 months, 64% of the AA patients had 50-100% reduction in total lesion counts, and only 36% of the vehicle patients had 50-100% reduction in the total lesion counts (Fisher's exact test, $\alpha=0.05$)				⊕⊕⊕○ Moderate	CRITICAL

Inflammatory lesions, percentage change from baseline, at 6 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	30 and 30 patients were randomized to receive azelaic acid 20% gel BID or vehicle, respectively. The mean percentage changes from baseline in papules for azelaic acid 20% and vehicle groups were -51.2% and -19.2%, respectively ($p = 0.003$). The mean percentage changes from baseline in pustules for azelaic acid 20% and vehicle groups were -42.1% and -17.8%, respectively ($p = 0.08$).				⊕⊕⊕○ Moderate	CRITICAL

Inflammatory lesions, change from baseline, at 3 months

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azelaic acid 20%	Vehicle	Relative (95% CI)	Absolute (95% CI)		
2 ^{2,3}	randomised trials	not serious	not serious	not serious	serious ^a	none	Cunliffe 1989: 20 and 20 patients were randomized to receive azelaic acid 20% cream BID or vehicle, respectively. AA showed significant benefit over placebo at 1, 2, and 3 months. 10 (50%) patients in AA had at least a 50% reduction in inflamed lesions by the end of the study, while only 1/20 (5%) in the placebo group achieved the same level of improvement. Katsambas 1989: 43 and 49 patients were randomized to receive azelaic acid 20% cream BID or vehicle, respectively. At baseline, the median number of lesions was 27.9 and 29.1 for azelaic acid 20% (BID) and vehicle, respectively. There were significant differences between the two groups after 2 and 3 months (Mann-Whitney U-test, $\alpha = 0.05$). After 3 months, AA and vehicle groups had a 72% and 47% decrease in the inflammatory lesion counts from the baseline, respectively.				⊕⊕⊕○ Moderate	CRITICAL

Noninflammatory lesions, percentage change from baseline, at 6 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azelaic acid 20%	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	30 and 30 patients were randomized to receive azelaic acid 20% gel BID or vehicle, respectively. The mean percentage changes from baseline in comedones for azelaic acid 20% and vehicle groups were -87.3% and -23.2%, respectively (p = 0.001).				⊕⊕⊕○ Moderate	CRITICAL

Non-inflammatory lesions, change from baseline, at 3 months

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azelaic acid 20%	Vehicle	Relative (95% CI)	Absolute (95% CI)		
2 ^{2,3}	randomised trials	not serious	not serious	not serious	serious ^a	none	Cunliffe 1989: 20 and 20 patients were randomized to receive azelaic acid 20% cream BID or vehicle, respectively. AA showed significant benefit over placebo at 2 and 3 months. 11 (55%) patients in AA had at least a 50% reduction in non-inflamed lesions by the end of the study, while only 4/20 (20%) in the placebo group achieved the same level of improvement. Katsamba 1989: 43 and 49 patients were randomized to receive azelaic acid 20% cream BID or vehicle, respectively. At baseline, the median number of lesions was 27.9 and 29.1 for azelaic acid 20% (BID) and vehicle, respectively. There were significant differences favoring AA at 1, 2, and 3 months (Mann-Whitney U-test, $\alpha = 0.05$). After 3 months, AA and vehicle groups had a 55.6% and 0% reduction in comedones from baseline, respectively.				⊕⊕⊕○ Moderate	CRITICAL

Local side effects

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azelaic acid 20%	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,2,3}	randomised trials	not serious	not serious	not serious	serious ^a	none	Iraji 2007: Side effects occurred in approximately 3% of patients in the azelaic acid-treated group and mainly consisted of pruritus, burning, stinging and tingling. They were generally transient and mild in nature. Katsambas 1989: 4 (9.3%), 2 (4.7%), 1 (2.3%), and 2 (4.7%) in the AA group reported burning, itching, scaling, and erythema, respectively. 1(2%), 2 (4.7%), and 1 (2%) in the vehicle group reported burning, scaling, and erythema, respectively. Cunliffe 1989: Side effects of treatments were transient with scaling, erythema, and burning noted in 5% of patients in both treatment groups. This frequency was observed in the placebo group for itching and stinging, but was twice this value for the azelaic acid treated patients.				⊕⊕⊕○ Moderate	IMPORTANT

CI: confidence interval

Explanations

- a. Small sample size.
b. Small sample size. SDs were not reported.

References

1. Iraj, F. Sadeghinia, A. Shahmoradi, Z. Siadat, A. H. Jooya, A. Efficacy of topical azelaic acid gel in the treatment of mild-moderate acne vulgaris. Indian J Dermatol Venereol Leprol; 2007.
2. Katsambas, A. Graupe, K. Stratigos, J. Clinical studies of 20% azelaic acid cream in the treatment of acne vulgaris. Comparison with vehicle and topical tretinoin. Acta Derm Venereol Suppl (Stockh); 1989.
3. Cunliffe, W. J. Holland, K. T. Clinical and laboratory studies on treatment with 20% azelaic acid cream for acne. Acta Derm Venereol Suppl (Stockh); 1989.

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e-Table 27. GRADE Evidence Profile for topical antibiotic vs. benzoyl peroxide

AE, Pruritus at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotic	Benzoyl peroxide	Relative (95% CI)	Absolute (95% CI)		
2 ^{1,2}	randomised trials	not serious	not serious	not serious	serious ^a	none	1/407 (0.2%)	2/415 (0.5%)	RR 0.64 (0.08 to 5.16)	2 fewer per 1,000 (from 4 fewer to 20 more)	⊕⊕⊕○ Moderate	IMPORTANT

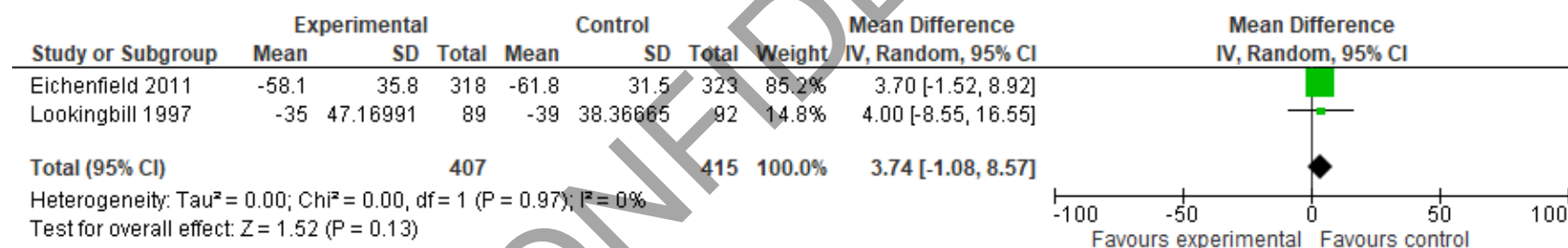
CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

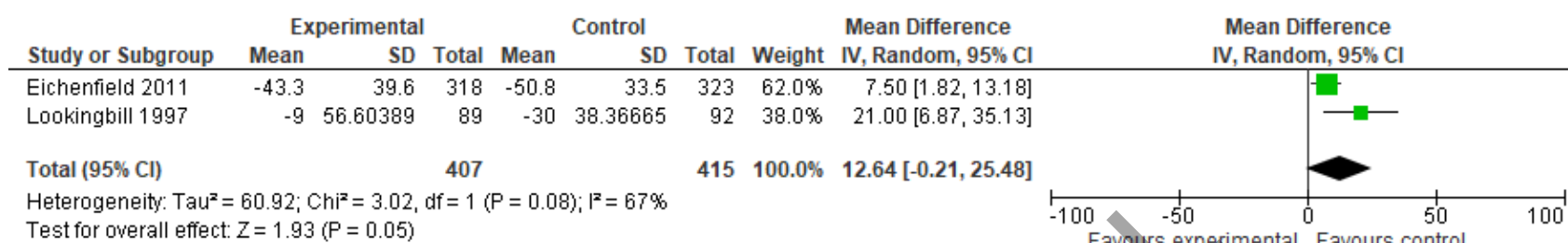
a. CI included both appreciable benefits and harm.

Forest plots

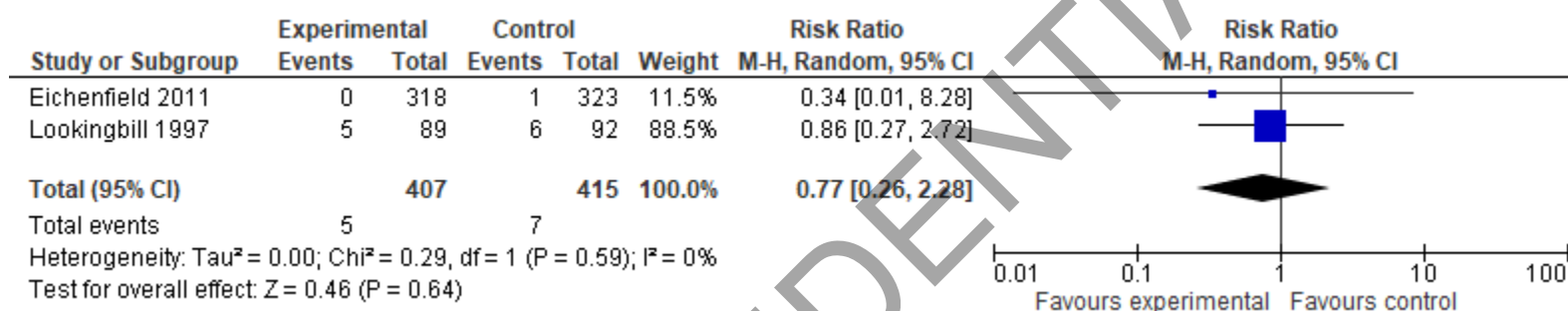
e-Figure 118. Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline), topical antibiotic vs. benzoyl peroxide



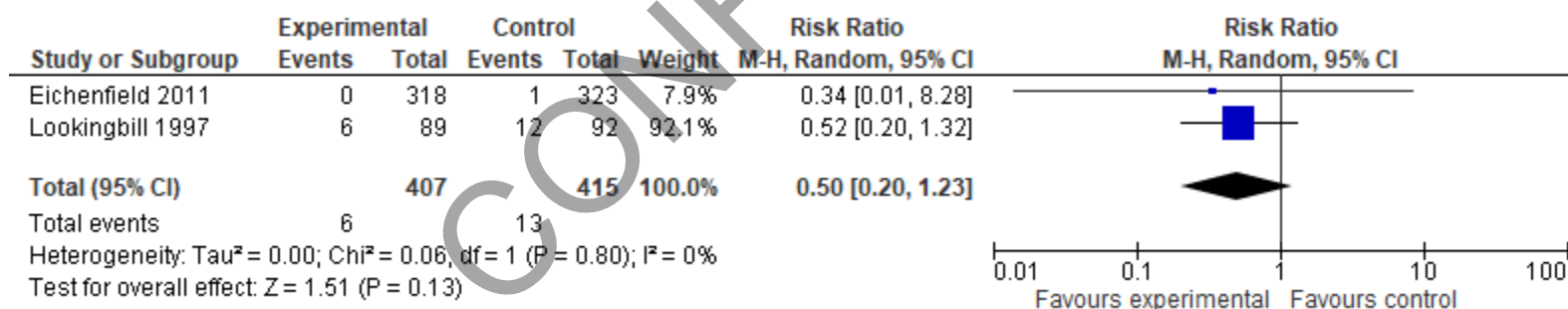
e-Figure 119. Number of lesions, Non-inflammatory at 12 weeks (mean percent change from baseline), topical antibiotic vs. benzoyl peroxide



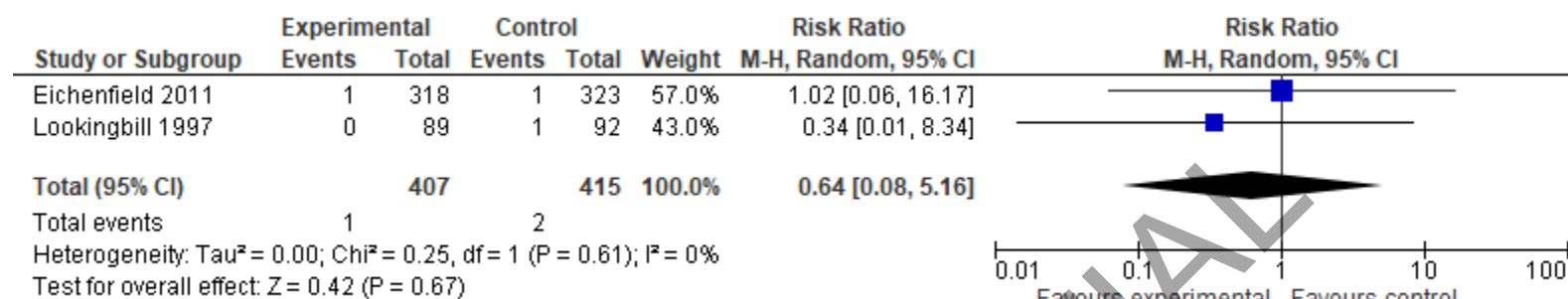
e-Figure 120. AE, Dryness at 12 weeks, topical antibiotic vs. benzoyl peroxide



e-Figure 121. AE, Erythema at 12 weeks, topical antibiotic vs. benzoyl peroxide



e-Figure 122. AE, Pruritus at 12 weeks, topical antibiotic vs. benzoyl peroxide



References

1. Lookingbill DP, Chalker DK, Lindholm JS, et al. Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: Combined results of two double-blind investigations. *Journal of the American Academy of Dermatology*. 1997;37(4):590-595.
2. Eichenfield LF, Alio Saenz AB. Safety and efficacy of clindamycin phosphate 1.2%-benzoyl peroxide 3% fixed-dose combination gel for the treatment of acne vulgaris: a phase 3, multicenter, randomized, double-blind, active- and vehicle-controlled study. *J Drugs Dermatol*. 2011;10(12):1382-1396.

17. Topical retinoid vs. benzoyl peroxide

e-Table 28. GRADE Evidence Profile for topical retinoid vs. benzoyl peroxide

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid	Benzoyl peroxide	Relative (95% CI)	Absolute (95% CI)		
Investigator Global Assessment, Grade 0-1 at 4 weeks												
2 ^{1,2}	randomised trials	not serious	not serious	not serious	not serious	none	9/536 (1.7%)	31/533 (5.8%)	RR 0.29 (0.14 to 0.60)	41 fewer per 1,000 (from 50 fewer to 23 fewer)	⊕⊕⊕⊕ High	CRITICAL
Investigator Global Assessment, Grade 0-1 at 12 weeks												
2 ^{1,2}	randomised trials	not serious	not serious	not serious	serious ^a	none	120/536 (22.4%)	136/533 (25.5%)	RR 0.90 (0.68 to 1.17)	26 fewer per 1,000 (from 82 fewer to 43 more)	⊕⊕⊕○ Moderate	CRITICAL

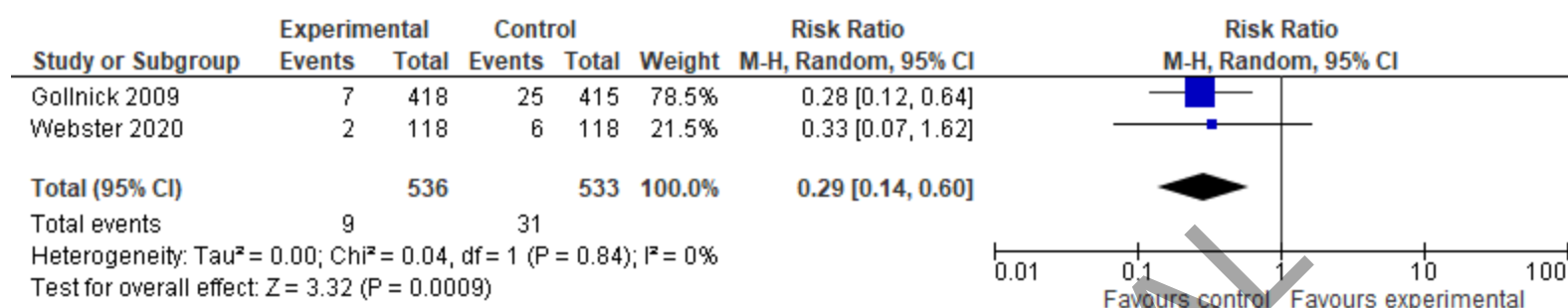
CI: Confidence interval; RR: Risk ratio

Explanations

a. CI included both appreciable benefits and harm.

Forest plots

e-Figure 123. Investigator Global Assessment, Grade 0-1 at 4 weeks, topical retinoid vs. benzoyl peroxide



e-Figure 124. Investigator Global Assessment, Grade 0-1 at 12 weeks, topical retinoid vs. benzoyl peroxide



References

1. Webster GF, Sugarman J, Levy-Hacham O, Toledano O. Microencapsulated Benzoyl Peroxide and Tretinoin for the Treatment of Acne Vulgaris: Results from a Phase 2 Multicenter, Double-Blind, Randomized, Vehicle-Controlled Study. *Skinmed*. 2020;18(6):343-351.
2. Gollnick HP, Draelos Z, Glenn MJ, et al. Adapalene-benzoyl peroxide, a unique fixed-dose combination topical gel for the treatment of acne vulgaris: a transatlantic, randomized, double-blind, controlled study in 1670 patients. *Br J Dermatol*. 2009;161(5):1180-1189.

18. Topical retinoid vs. topical antibiotic

e-Table 29. GRADE Evidence Profile for topical retinoid vs. topical antibiotic

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid	Topical antibiotic	Relative (95% CI)	Absolute (95% CI)		
Investigator Global Assessment, Grade 0-1 at 12 weeks												
2 ^{1,2}	randomised trials	not serious	not serious	not serious	serious ^a	none	252/764 (33.0%)	212/617 (34.4%)	RR 1.00 (0.81 to 1.23)	0 fewer per 1,000 (from 65 fewer to 79 more)	⊕⊕⊕○ Moderate	CRITICAL

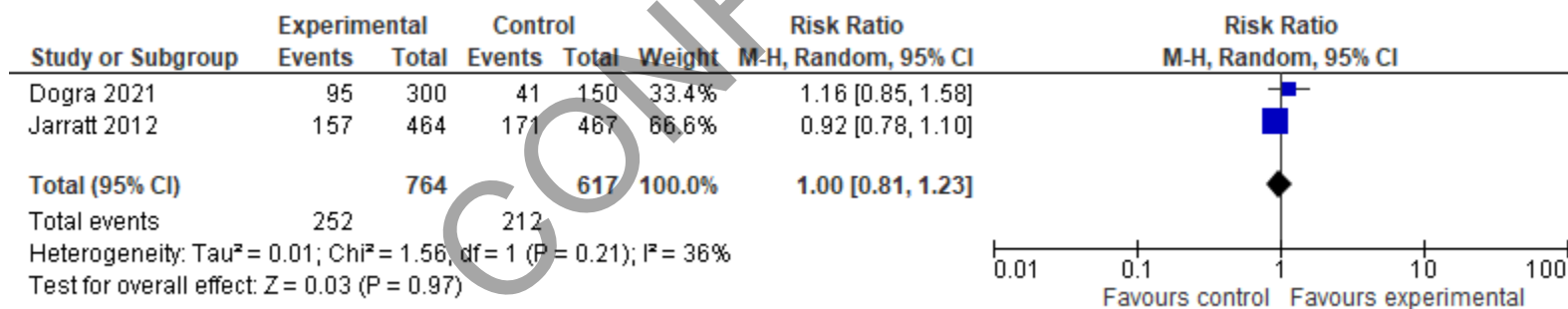
CI: Confidence interval; RR: Risk ratio

Explanations

a. CI included both appreciable benefits and harm.

Forest plot

e-Figure 125. Investigator Global Assessment, Grade 0-1 at 12 weeks, topical retinoid vs. topical antibiotic



References

1. Dogra S, Sumathy TK, Nayak C, et al. Efficacy and safety comparison of combination of 0.04% tretinoin microspheres plus 1% clindamycin versus their monotherapy in patients with acne vulgaris: a phase 3, randomized, double-blind study. *Journal of Dermatological Treatment*. 2021;32(8):925-933.

2. Jarratt MT, Brundage T. Efficacy and safety of clindamycin-tretinoin gel versus clindamycin or tretinoin alone in acne vulgaris: a randomized, double-blind, vehicle-controlled study. *J Drugs Dermatol.* 2012;11(3):318-326.

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19. Topical retinoid + topical antibiotic + benzoyl peroxide vs. vehicle

e-Table 30. GRADE Evidence Profile for **topical retinoid + topical antibiotic + benzoyl peroxide vs. vehicle**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Topical antibiotic + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Inflammatory at 12 weeks (mean absolute change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean absolute changes from baseline for topical retinoid + topical antibiotic + benzoyl peroxide and vehicle groups were -29.9 (n: 125) and -19.6 (n: 127), respectively. The difference between the two groups was statistically significant (p < 0.001). ^b			⊕⊕⊕○ Moderate	CRITICAL	
Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for topical retinoid + topical antibiotic + benzoyl peroxide and vehicle groups were -76.4% (n: 125) and -19.6% (n: 127), respectively. The difference between the two groups was statistically significant (p < 0.001). ^b			⊕⊕⊕○ Moderate	CRITICAL	
Number of lesions, Non-inflammatory at 12 weeks (mean absolute change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean absolute changes from baseline for topical retinoid + topical antibiotic + benzoyl peroxide and vehicle groups were -35.5 (n: 125) and -21.8 (n: 127), respectively. The difference between the two groups was statistically significant (p < 0.001). ^b			⊕⊕⊕○ Moderate	CRITICAL	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Topical antibiotic + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Non-inflammatory at 12 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for topical retinoid + topical antibiotic + benzoyl peroxide and vehicle groups were -71 (n: 125) and -45.8 (n: 127), respectively. The difference between the two groups was statistically significant (p < 0.001). ^b				⊕⊕⊕○ Moderate	CRITICAL

AE, Dermatitis, Leading to study withdrawal at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	0/141 (0.0%)	0/146 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Pain, Leading to withdrawal at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	2/141 (1.4%)	0/146 (0.0%)	RR 5.18 (0.25 to 106.88)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

TEAE, Any, Leading to discontinuation at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	4/141 (2.8%)	2/146 (1.4%)	RR 2.07 (0.39 to 11.13)	15 more per 1,000 (from 8 fewer to 139 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Burning at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Topical antibiotic + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	serious ^d	none	6/141 (4.3%)	0/146 (0.0%)	RR 13.46 (0.77 to 236.70)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Dermatitis at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	2/141 (1.4%)	0/146 (0.0%)	RR 5.18 (0.25 to 106.88)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Dryness at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^e	none	9/141 (6.4%)	0/146 (0.0%)	RR 19.67 (1.16 to 334.80)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	2/141 (1.4%)	0/146 (0.0%)	RR 5.18 (0.25 to 106.88)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema, Severe at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	0/141 (0.0%)	0/146 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Exfoliation at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Topical antibiotic + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	5/141 (3.5%)	1/146 (0.7%)	RR 5.18 (0.61 to 43.77)	29 more per 1,000 (from 3 fewer to 293 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Hyperpigmentation at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	2/141 (1.4%)	1/146 (0.7%)	RR 2.07 (0.19 to 22.59)	7 more per 1,000 (from 6 fewer to 148 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Irritation at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	3/141 (2.1%)	0/146 (0.0%)	RR 7.25 (0.38 to 139.04)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pain at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^e	none	11/141 (7.8%)	1/146 (0.7%)	RR 11.39 (1.49 to 87.08)	71 more per 1,000 (from 3 more to 590 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pruritus at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	3/141 (2.1%)	0/146 (0.0%)	RR 7.25 (0.38 to 139.04)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical retinoid + Topical antibiotic + Benzoyl peroxide	Vehicle	Relative (95% CI)	Absolute (95% CI)		

AE, Scaling at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	0/141 (0.0%)	0/146 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Stinging at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	3/141 (2.1%)	0/146 (0.0%)	RR 7.25 (0.38 to 139.04)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

CI: confidence interval; RR: risk ratio

Explanations

- Standard deviation values were not reported. Small sample size.
- n: number of patients.
- Double zero study.
- Wide CI included both appreciable benefits and harm. Small sample size.
- Small sample size.

References

- Stein Gold L, Baldwin H, Kircik LH, et al. Efficacy and Safety of a Fixed-Dose Clindamycin Phosphate 1.2%, Benzoyl Peroxide 3.1%, and Adapalene 0.15% Gel for Moderate-to-Severe Acne: A Randomized Phase II Study of the First Triple-Combination Drug. Am J Clin Dermatol. 2021;23(1):93-104.
- Stein Gold L, Weiss J, Rueda MJ, Liu H, Tangheiti E. Moderate and Severe Inflammatory Acne Vulgaris Effectively Treated with Single-Agent Therapy by a New Fixed-Dose Combination Adapalene 0.3 %/Benzoyl Peroxide 2.5 % Gel: A Randomized, Double-Blind, Parallel-Group, Controlled Study. American Journal of Clinical Dermatology. 2016;17(3):293-303.

e-Table 31. GRADE Evidence Profile for clindamycin 1% + salicylic acid 2% vs. clindamycin 1%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clindamycin 1% + Salicylic acid 2%	Clindamycin 1%	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Acne severity index at 12 weeks (Mean percent change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	14 and 14 patients were randomized to receive clindamycin 1% + salicylic acid 2% or clindamycin 1%. The mean percentage changes from baseline for clindamycin 1% + salicylic acid 2% and clindamycin 1% groups were -81.8% and -37.87%, respectively.				⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any at 12 weeks (Mean percent change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	14 and 14 patients were randomized to receive clindamycin 1% + salicylic acid 2% or clindamycin 1%. The mean percentage changes from baseline for clindamycin 1% + salicylic acid 2% and clindamycin 1% groups were -77.91% and -55.95%, respectively. The difference between the two groups was statistically significant (p = 0.039).				⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Inflammatory, Papules at 12 weeks (Mean percent change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	14 and 14 patients were randomized to receive clindamycin 1% + salicylic acid 2% or clindamycin 1%. The mean percentage changes from baseline for clindamycin 1% + salicylic acid 2% and clindamycin 1% groups were -84.5% and -26.63%, respectively. The difference between the two groups was statistically significant (p = 0.031).				⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Inflammatory, Pustules at 12 weeks (Mean percent change from baseline)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clindamycin 1% + Salicylic acid 2%	Clindamycin 1%	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	14 and 14 patients were randomized to receive clindamycin 1% + salicylic acid 2% or clindamycin 1%. The mean percentage changes from baseline for clindamycin 1% + salicylic acid 2% and clindamycin 1% groups were -90% and -80%, respectively. The difference between the two groups was not statistically significant.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, Closed comedones at 12 weeks (Mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	14 and 14 patients were randomized to receive clindamycin 1% + salicylic acid 2% or clindamycin 1%. The mean percentage changes from baseline for clindamycin 1% + salicylic acid 2% and clindamycin 1% groups were -87.05% and -31.28%, respectively. The difference between the two groups was statistically significant (p = 0.011).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, Open comedones at 12 weeks (Mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	14 and 14 patients were randomized to receive clindamycin 1% + salicylic acid 2% or clindamycin 1%. The mean percentage changes from baseline for clindamycin 1% + salicylic acid 2% and clindamycin 1% groups were -64.26% and -58.33%, respectively. The difference between the two groups was not statistically significant.				⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; RR: Risk ratio

Explanations

a. Standard deviation was not reported. Small sample size.

b. Small sample size.

References

1. NilFroushzadeh MA, Siadat AH, Baradaran EH, Moradi S. Clindamycin lotion alone versus combination lotion of clindamycin phosphate plus tretinoin versus combination lotion of clindamycin phosphate plus salicylic acid in the topical treatment of mild to moderate acne vulgaris: a randomized control trial. Indian J Dermatol Venereol Leprol. 2009;75(3):279-282.

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e-Table 32. GRADE Evidence Profile for clindamycin 1% + tretinoin 0.025% vs. clindamycin 1% + salicylic acid 2%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clindamycin 1% + Tretinoin 0.025%	Clindamycin 1% + Salicylic acid 2%	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Acne severity index at 12 weeks (Mean percent change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	14 and 14 patients were randomized to receive clindamycin 1% + tretinoin 0.025% or clindamycin 1% + salicylic acid 2%. The mean percentage changes from baseline for clindamycin 1% + tretinoin 0.025% and clindamycin 1% + salicylic acid 2% groups were -73.73% and -81.8%, respectively.		⊕⊕⊕○ Moderate		CRITICAL	
Number of lesions, Any at 12 weeks (Mean percent change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	14 and 14 patients were randomized to receive clindamycin 1% + tretinoin 0.025% or clindamycin 1% + salicylic acid 2%. The mean percentage changes from baseline for clindamycin 1% + tretinoin 0.025% and clindamycin 1% + salicylic acid 2% groups were -72% and -77.91%, respectively. The difference between the two groups was not statistically significant.		⊕⊕⊕○ Moderate		CRITICAL	
Number of lesions, Inflammatory, Papules at 12 weeks (Mean percent change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	14 and 14 patients were randomized to receive clindamycin 1% + tretinoin 0.025% or clindamycin 1% + salicylic acid 2%. The mean percentage changes from baseline for clindamycin 1% + tretinoin 0.025% and clindamycin 1% + salicylic acid 2% groups were -71.67% and -84.5%, respectively.		⊕⊕⊕○ Moderate		CRITICAL	
Number of lesions, Non-inflammatory, Closed comedones at 12 weeks (Mean percent change from baseline)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clindamycin 1% + Tretinoin 0.025%	Clindamycin 1% + Salicylic acid 2%	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	14 and 14 patients were randomized to receive clindamycin 1% + tretinoin 0.025% or clindamycin 1% + salicylic acid 2%. The mean percentage changes from baseline for clindamycin 1% + tretinoin 0.025% and clindamycin 1% + salicylic acid 2% groups were -60.94% and -87.05%, respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, Open comedones at 12 weeks (Mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	14 and 14 patients were randomized to receive clindamycin 1% + tretinoin 0.025% or clindamycin 1% + salicylic acid 2%. The mean percentage changes from baseline for clindamycin 1% + tretinoin 0.025% and clindamycin 1% + salicylic acid 2% groups were -67% and -64.26%, respectively.				⊕⊕⊕○ Moderate	CRITICAL

CI: confidence interval

Explanations

a. Small sample size. Standard deviation was not reported.

References

1. NilFroushzadeh MA, Siadat AH, Baradaran EH, Moradi S. Clindamycin lotion alone versus combination lotion of clindamycin phosphate plus tretinoin versus combination lotion of clindamycin phosphate plus salicylic acid in the topical treatment of mild to moderate acne vulgaris: a randomized control trial. Indian J Dermatol Venereol Leprol. 2009;75(3):279-282.

22. Supramolecular salicylic acid 2% vs. Adapalene 0.01% + Benzoyl peroxide 5%

e-Table 33. GRADE Evidence Profile for supramolecular salicylic acid 2% vs. adapalene 0.01% + benzoyl peroxide 5%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Supramolecular salicylic acid 2%	Adapalene 0.01% + Benzoyl peroxide 5%	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any at 4 weeks (mean percent change from baseline)												
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	31	31	-	MD 1.5 % higher (4.98 lower to 7.98 higher)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Inflammatory at 4 weeks (mean percent change from baseline)												
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	31	31	-	MD 1.9 % higher (5.33 lower to 9.13 higher)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Non-inflammatory at 4 weeks (mean percent change from baseline)												
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	31	31	-	MD 0.4 % lower (7.48 lower to 6.68 higher)	⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; MD: Mean difference

Explanations

a. RCT, Split face

b. CI included both appreciable benefits and harm. Small sample size.

References

1. Zheng Y, Yin S, Xia Y, et al. Efficacy and safety of 2% supramolecular salicylic acid compared with 5% benzoyl peroxide/0.1% adapalene in the acne treatment: a randomized, split-face, open-label, single-center study. *Cutaneous and Ocular Toxicology*. 2019;38(1):48-54.

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23. Clindamycin 1% + Salicylic acid 3% vs. Clindamycin 1% + All-trans retinoic acid

e-Table 34. GRADE Evidence Profile for clindamycin 1% + salicylic acid 3% vs. clindamycin 1% + all-trans retinoic acid

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clindamycin 1% + Salicylic acid 3%	Clindamycin 1% + All-trans retinoic acid	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Physician Global Assessment, Grade 0-1 at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	0/23 (0.0%)	2/23 (8.7%)	RR 0.20 (0.01 to 3.95)	70 fewer per 1,000 (from 86 fewer to 257 more)	⊕⊕⊕○ Moderate	CRITICAL
Acne severity, Physician Global Assessment, Grade 2 at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	10/23 (43.5%)	16/23 (69.6%)	RR 0.62 (0.36 to 1.07)	264 fewer per 1,000 (from 445 fewer to 49 more)	⊕⊕⊕○ Moderate	CRITICAL
Acne severity, Physician Global Assessment, Grade 3 at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	12/23 (52.2%)	4/23 (17.4%)	RR 3.00 (1.13 to 7.94)	348 more per 1,000 (from 23 more to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL
Investigator Global Assessment, Excellent at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	4/23 (17.4%)	6/23 (26.1%)	RR 0.67 (0.22 to 2.05)	86 fewer per 1,000 (from 203 fewer to 274 more)	⊕⊕⊕○ Moderate	CRITICAL

Investigator Global Assessment, Good at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clindamycin 1% + Salicylic acid 3%	Clindamycin 1% + All-trans retinoic acid	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	14/23 (60.9%)	16/23 (69.6%)	RR 0.88 (0.57 to 1.34)	83 fewer per 1,000 (from 299 fewer to 237 more)	⊕⊕⊕○ Moderate	CRITICAL
Investigator Global Assessment, Moderate at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	4/23 (17.4%)	0/23 (0.0%)	RR 9.00 (0.51 to 158.17)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, ≥50% reduction at 4 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	23/23 (100.0%)	23/23 (100.0%)	RR 1.00 (0.92 to 1.09)	0 fewer per 1,000 (from 80 fewer to 90 more)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any at 4 weeks (Mean)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	23	23	-	MD 7.7 lesions higher (1.89 higher to 13.51 higher)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Inflammatory at 4 weeks (Mean)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	23	23	-	MD 4.3 lesions higher (0.5 higher to 8.1 higher)	⊕⊕⊕○ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clindamycin 1% + Salicylic acid 3%	Clindamycin 1% + All-trans retinoic acid	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Non-inflammatory at 4 weeks (Mean)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	23	23	-	MD 3.9 lesions higher (0.03 lower to 7.83 higher)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, ≥50% reduction at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	8/23 (34.8%)	14/23 (60.9%)	RR 0.57 (0.30 to 1.09)	262 fewer per 1,000 (from 426 fewer to 55 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any at 12 weeks (Mean)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	23	23	-	MD 3.6 lesions higher (0.06 lower to 7.26 higher)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any at 12 weeks (Mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	23 and 23 patients were randomized to receive clindamycin 1% + salicylic acid 3% or clindamycin 1% + all-trans retinoic acid. The mean percentage changes from baseline for clindamycin 1% + salicylic acid 3% and clindamycin 1% + all-trans retinoic acid groups were 80.2% and 85.6%, respectively. The difference between the two groups was not statistically significant.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (Mean)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clindamycin 1% + Salicylic acid 3%	Clindamycin 1% + All-trans retinoic acid	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	23	23	-	MD 1.1 lesions higher (1.03 lower to 3.23 higher)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (Mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	23 and 23 patients were randomized to receive clindamycin 1% + salicylic acid 3% or clindamycin 1% + all-trans retinoic acid. The mean percentage changes from baseline for clindamycin 1% + salicylic acid 3% and clindamycin 1% + all-trans retinoic acid groups were 77.6% and 81.5%, respectively. The difference between the two groups was not statistically significant.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (Mean)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	23	23	-	MD 2.5 lesions higher (0.11 higher to 4.89 higher)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (Mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	23 and 23 patients were randomized to receive clindamycin 1% + salicylic acid 3% or clindamycin 1% + all-trans retinoic acid. The mean percentage changes from baseline for clindamycin 1% + salicylic acid 3% and clindamycin 1% + all-trans retinoic acid groups were 81.5% and 87.2%, respectively. The difference between the two groups was not statistically significant.				⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

- a. CI included both appreciable benefits and harm. Small sample size.
- b. Small sample size.
- c. Wide CI included both appreciable benefits and harm. Small sample size.
- d. Small sample size. Standard deviation values were not reported.

References

1. Babayeva L, Akarsu S, Fetil E, Gunes AT. Comparison of tretinoin 0.05% cream and 3% alcohol-based salicylic acid preparation in the treatment of acne vulgaris. J Eur Acad Dermatol Venereol. 2011;25(3):328-333.

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24. Tretinoin 0.02% + Clindamycin 0.8% + Glycolic acid 4% (Standard application therapy) vs. Clindamycin 0.8% + Tretinoin 0.02% + Glycolic acid 4% (Short contact therapy)

e-Table 35. GRADE Evidence Profile for tretinoin 0.02% + clindamycin 0.8% + glycolic acid 4% (standard application therapy) vs. clindamycin 0.8% + tretinoin 0.02% + glycolic acid 4% (short contact therapy)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tretinoin 0.02% + Clindamycin 0.8% + Glycolic acid 4% (Standard application therapy)	Clindamycin 0.8% + Tretinoin 0.02% + Glycolic acid 4% (Short contact therapy)	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Global Acne Grading System at 8 weeks (Mean; 5-point scale)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	At baseline, the mean values for tretinoin 0.02% + clindamycin 0.8% + glycolic acid 4% (standard application therapy) and clindamycin 0.8% + tretinoin 0.02% + glycolic acid 4% (short contact therapy) groups were 18.9 (n: 23) and 22.8 (n: 23), respectively. At 8 weeks, the mean values changed to 8.4 (n: 21) and 14.7 (n: 17) for tretinoin 0.02% + clindamycin 0.8% + glycolic acid 4% (standard application therapy) and clindamycin 0.8% + tretinoin 0.02% + glycolic acid 4% (short contact therapy) groups, respectively. The difference between the two groups was statistically significant (p = 0.005). ^b		⊕⊕⊕○ Moderate		CRITICAL	

Investigator Global Assessment at 8 weeks (Mean)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tretinoin 0.02% + Clindamycin 0.8% + Glycolic acid 4% (Standard application therapy)	Clindamycin 0.8% + Tretinoin 0.02% + Glycolic acid 4% (Short contact therapy)	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	At baseline, the mean values for tretinoin 0.02% + clindamycin 0.8% + glycolic acid 4% (standard application therapy) and clindamycin 0.8% + tretinoin 0.02% + glycolic acid 4% (short contact therapy) groups were 1.9 (n: 23) and 2.3 (n: 23), respectively. At 8 weeks, the mean values changed to 1 (n: 21) and 1.6 (n: 17) for tretinoin 0.02% + clindamycin 0.8% + glycolic acid 4% (standard application therapy) and clindamycin 0.8% + tretinoin 0.02% + glycolic acid 4% (short contact therapy) groups, respectively. The difference between the two groups was statistically significant (p = 0.005). ^b				⊕⊕⊕○ Moderate	CRITICAL

AE, Erythema/Dryness/Stinging/Burning, Tolerability at 4 weeks (Mean)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	At 4 weeks, the mean values were 1 (n: 21) and 2.9 (n: 17) for tretinoin 0.02% + clindamycin 0.8% + glycolic acid 4% (standard application therapy) and clindamycin 0.8% + tretinoin 0.02% + glycolic acid 4% (short contact therapy) groups, respectively. The difference between the two groups was statistically significant (p = 0.001). ^b				⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema/Dryness/Stinging/Burning, Tolerability at 8 weeks (Mean)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tretinoin 0.02% + Clindamycin 0.8% + Glycolic acid 4% (Standard application therapy)	Clindamycin 0.8% + Tretinoin 0.02% + Glycolic acid 4% (Short contact therapy)	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	At 8 weeks, the mean values were 1 (n: 21) and 2.5 (n: 17) for tretinoin 0.02% + clindamycin 0.8% + glycolic acid 4% (standard application therapy) and clindamycin 0.8% + tretinoin 0.02% + glycolic acid 4% (short contact therapy) groups, respectively. The difference between the two groups was statistically significant (p = 0.001). ^b				⊕⊕⊕○ Moderate	IMPORTANT

CI: confidence interval

Explanations

- a. Small sample size.
- b. n: number of patients
- c. Small sample size. Baseline values were not provided.

References

1. Bertolani MB, Rodighiero E, Gandolfi M, et al. Efficacy and tolerability of short contact therapy with tretinoin, clindamycin, and glycolic acid gel in acne: A randomized, controlled, assessor-blinded two-center trial: The MASCOTTE study. Dermatologic Therapy. 2021;34(1) (e14724).

Systemic Antibiotics

1. Doxycycline vs. placebo

e-Table 36. GRADE Evidence Profile for doxycycline vs. placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	placebo	Relative (95% CI)	Absolute (95% CI)		
Physician global assessment (follow up: 24 weeks; assessed with: 7-point scale)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	21 and 19 patients were randomized to receive doxycycline and placebo, respectively. Physician's Global Assessment (7-point scale) of facial acne at 24 weeks were 4.4 and 5.2 in doxycycline and placebo group (p=0.03).			⊕⊕⊕○ MODERATE	CRITICAL	
Treatment success (follow up: at least 12 weeks; assessed with: clear or almost clear and at least 2 grade improvements on PGA)												
2 ^{2,3}	randomised trials	not serious	not serious	not serious	not serious	none	49/285 (17.2%)	28/289 (9.7%)	RR 1.80 (1.17 to 2.77)	78 more per 1,000 (from 16 more to 171 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Total lesion (follow up: at least 12 weeks; assessed with: change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	placebo	Relative (95% CI)	Absolute (95% CI)		
2 ^{1,2}	randomised trials	not serious	not serious	not serious	serious ^b	none	82	86	-	MD 17.09 lower (34.84 lower to 0.66 higher)	⊕⊕⊕○ MODERATE	CRITICAL

Total lesion (follow up: at least 12 weeks; assessed with: percentage change from baseline)

2 ^{1,3}	randomised trials	not serious	not serious	not serious	serious ^c	none	224	222	-	MD 0 (7.63 lower to 7.63 higher)	⊕⊕⊕○ MODERATE	CRITICAL

Inflammatory lesion (follow up: at least 12 weeks; assessed with: change from baseline)

3 ^{1,2,3}	randomised trials	not serious	not serious ^d	not serious	serious ^e	none	285	289	-	MD 3.6 lower (8.78 lower to 1.59 higher)	⊕⊕⊕○ MODERATE	CRITICAL

Inflammatory lesion (follow up: at least 12 weeks; assessed with: percent change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	placebo	Relative (95% CI)	Absolute (95% CI)		
2 ^{1,3}	randomised trials	not serious	not serious	not serious	serious ^c	none	224	222	-	MD 3.2 lower (11.13 lower to 4.73 higher)	⊕⊕⊕○ MODERATE	CRITICAL

Inflammatory lesion (follow up: 4 weeks; assessed with: mean)

1 ⁴	randomised trials	not serious	not serious	not serious	serious ^f	none	28 and 34 acne patients were randomized to receive doxycycline 100mg/day or placebo, respectively, for 4 weeks. At baseline, the average number of inflammatory lesions on the left side of the face for doxycycline and placebo groups were 13.5 and 12.9, respectively. At 4 weeks, the average inflammatory lesion counts decreased to 8.6 and 14.4 for doxycycline and placebo groups, respectively, but the difference was statistically significant for doxycycline group only (p<0.001).				⊕⊕⊕○ MODERATE	CRITICAL

Noninflammatory lesion (follow up: at least 12 weeks; assessed with: change from baseline)

3 ^{1,2,3}	randomised trials	not serious	not serious ^g	not serious	serious ^h	none	306	308	-	MD 4.65 lower (13.6 lower to 4.29 higher)	⊕⊕⊕○ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	placebo	Relative (95% CI)	Absolute (95% CI)		

Noninflammatory lesion (follow up: at least 12 weeks; assessed with: percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	21 and 19 acne patients were randomized to receive doxycycline 100mg/day and placebo, respectively. At 6 months, the mean percentage changes from baseline for doxycycline and placebo groups were -53.6 and -10.6, respectively (SDs were not provided).			⊕⊕⊕○ MODERATE	CRITICAL

Serious AE

2 ^{2,3}	randomised trials	not serious	not serious	not serious	serious ⁱ	none	6/285 (2.1%)	5/289 (1.7%)	RR 1.23 (0.38 to 3.95)	4 more per 1,000 (from 11 fewer to 51 more)	⊕⊕⊕○ MODERATE	CRITICAL

Patient global assessment (follow up: at least 12 weeks; assessed with: 7-point scale)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	placebo	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	21 and 19 acne patients were randomized to receive doxycycline 100mg/day and placebo, respectively. At 6 months, the mean scores for the patient global assessment (7-point scale; 1, clear (100%); 2, almost clear (90% to <100%); 3, marked improvement (75% to <90%); 4, moderate improvement (50% to <75%); 5, fair improvement (25% to <50%); 6, no change; 7, worse) for doxycycline and placebo groups were 4.8 and 5.3, respectively (SDs were not provided).				⊕⊕⊕○ MODERATE	IMPORTANT

Subject assessment of facial acne improvement (follow up: at least 12 weeks; assessed with: Complete or Marked improvement)

1 ³	randomised trials	not serious	not serious	not serious	serious ⁱ	none	The between-group differences for DC 100mg versus placebo reached statistical significance at week 12 (LOCF; P=0.023) and week 16 (LOCF; P=0.036)				⊕⊕⊕○ MODERATE	IMPORTANT

Quality of life (follow up: at least 12 weeks; assessed with: DLQI/c-DLQI)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	placebo	Relative (95% CI)	Absolute (95% CI)		
1 ³	randomised trials	not serious	not serious	not serious	serious ^k	none	<u>DLQI</u>: The percent of subjects who scored their acne as having "no effect" or a "small effect" on quality of life increased from 52.8% at baseline to 79.1% at 16 weeks in doxycycline 100mg group, whereas it changed from 51.9% at baseline to 77.3% at 16 weeks in placebo group. <u>c-DLQI</u>: The percent of subjects who scored their acne as having "no effect" or a "small effect" on quality of life increased from 78.2% at baseline to 90.7% at 16 weeks in doxycycline 100mg group, whereas it change from 74.1% at baseline to 88.5% at 16 weeks in placebo group. The numbers of adults and children were not reported.				⊕⊕⊕○ MODERATE	IMPORTANT

Withdrawal due to AE

3 ^{1,2,3}	randomised trials	not serious	not serious	not serious	serious ⁱ	none	4/309 (1.3%)	1/314 (0.3%)	RR 2.25 (0.38 to 13.21)	4 more per 1,000 (from 2 fewer to 39 more)	⊕⊕⊕○ MODERATE	IMPORTANT

GI AE

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	placebo	Relative (95% CI)	Absolute (95% CI)		
2 ^{2,4}	randomised trials	not serious	not serious	not serious	serious ¹	none	14/89 (15.7%)	6/101 (5.9%)	RR 2.56 (1.05 to 6.25)	93 more per 1,000 (from 3 more to 312 more)	⊕⊕⊕○ MODERATE	IMPORTANT

IBD - Incident ulcerative colitis

1 ⁵	observational studies	not serious	not serious	not serious	not serious	none	-/0	-/0	HR 1.06 (0.53 to 2.12)	1 fewer per 1,000 (from 2 fewer to 1 fewer)	⊕⊕○○ LOW	IMPORTANT

IBD - Incident Crohn's disease

1 ⁵	observational studies	not serious	not serious	not serious	not serious	none	-/0	-/0	HR 2.25 (1.27 to 3.99)	2 fewer per 1,000 (from 4 fewer to 1 fewer)	⊕⊕○○ LOW	IMPORTANT

Any AE

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	placebo	Relative (95% CI)	Absolute (95% CI)		
3 ^{1,2,3}	randomised trials	not serious	serious ^m	not serious	serious ^h	none	77/311 (24.8%)	42/314 (13.4%)	RR 1.87 (0.85 to 4.12)	116 more per 1,000 (from 20 fewer to 417 more)	⊕⊕○○ LOW	IMPORTANT

Phototoxic reaction

1 ⁴	randomised trials	not serious	not serious	not serious	serious ⁿ	none	0/28 (0.0%)	0/34 (0.0%)	not estimable		⊕⊕⊕○ MODERATE	IMPORTANT

Change in microbiome (follow up: 6 months; assessed with: microbial colony count and antibiotic susceptibility testing)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	placebo	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^o	none	<u>Microbial colony counts</u>[*]: There were no statistically significant differences between or within the groups from baseline to 6 months in microbial colony counts, indicating that there was no change in the composition of the normal skin flora <u>Antibiotic susceptibility testing</u>[†]: Antibiotic susceptibility testing showed no differences between or within the study groups in the MICs obtained for doxycycline. There were no strong correlations between resistance to doxycycline and resistance to any of the 5 other antibiotics tested. The strongest correlation was between erythromycin and clindamycin resistance ($r=0.5$ to <0.70). Moderate correlations ($r=0.5$) were detected between doxycycline and both tetracycline and minocycline in some instances. There were no differences between the correlation coefficients for cross-resistance in the doxycycline 6-month samples and either the placebo 6-month samples or the doxycycline baseline samples. [*] Microbial samples of the surface of the skin were collected from a 2cm² area in the center of the brow at baseline and after 6 months of treatment				⊕⊕⊕○ MODERATE	IMPORTANT

Explanations

- a. Small sample size. Only means without SDs were provided.
- b. Small sample size
- c. One study did not report the SDs, therefore unable to pool the data. The CI included both appreciable benefits and harms.
- d. $I^2=57\%$
- e. CI included both appreciable benefits and harm
- f. This study reported the mean inflammatory counts at baseline and 4 weeks without reporting SDs.
- g. $I^2=67\%$
- h. wide CI included both appreciable benefits and harm
- i. Few events and wide CI included both appreciable benefits and harm
- j. This study only provided the statistical significance between the two groups.
- k. Failed to report the number of patients DLQI and c-DLQI were used to assess the quality of life.
- l. One study had no event in both arms. Data from only one study is presented here.
- m. $I^2=81\%$
- n. Double zero study.
- o. Only statistical differences between and within the groups were provided

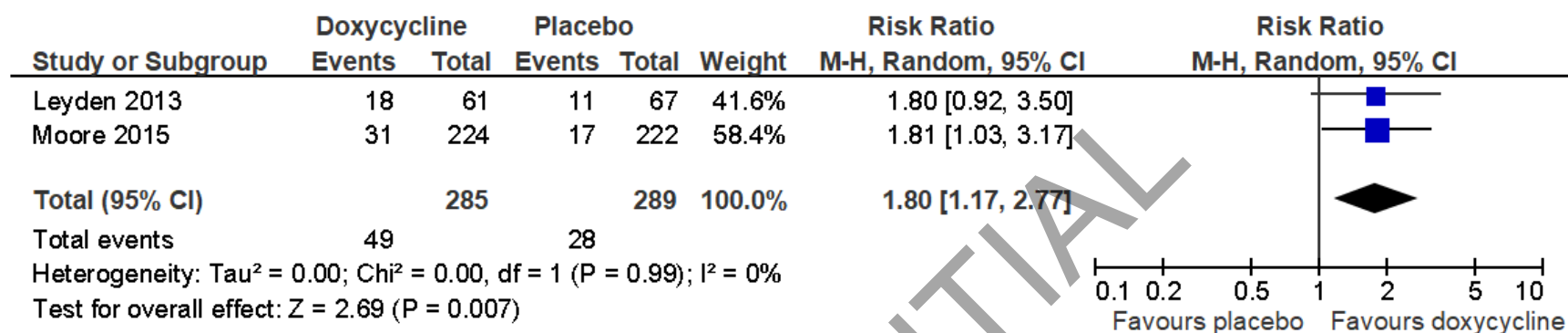
References

1. Skidmore, R., et al., *Effects of subantimicrobial-dose doxycycline in the treatment of moderate acne*. Arch Dermatol, 2003. **139**(4): p. 459-64.
2. Leyden, J.J., et al., *A randomized, phase 2, dose-ranging study in the treatment of moderate to severe inflammatory facial acne vulgaris with doxycycline calcium*. J Drugs Dermatol, 2013. **12**(6): p. 658-63.
3. Moore, A., et al., *Efficacy and Safety of Subantimicrobial Dose, Modified-Release Doxycycline 40 mg Versus Doxycycline 100 mg Versus Placebo for the treatment of Inflammatory Lesions in Moderate and Severe Acne: A Randomized, Double-Blinded, Controlled Study*. J Drugs Dermatol, 2015. **14**(6): p. 581-6.
4. Plewig, G., J.W. Petrozzi, and U. Berendes, *Double-blind study of doxycycline in acne vulgaris*. Arch Dermatol, 1970. **101**(4): p. 435-8.
5. Margolis, D.J., et al., *Potential association between the oral tetracycline class of antimicrobials used to treat acne and inflammatory bowel disease*. Am J Gastroenterol, 2010. **105**(12): p. 2610-6.

Forest Plots

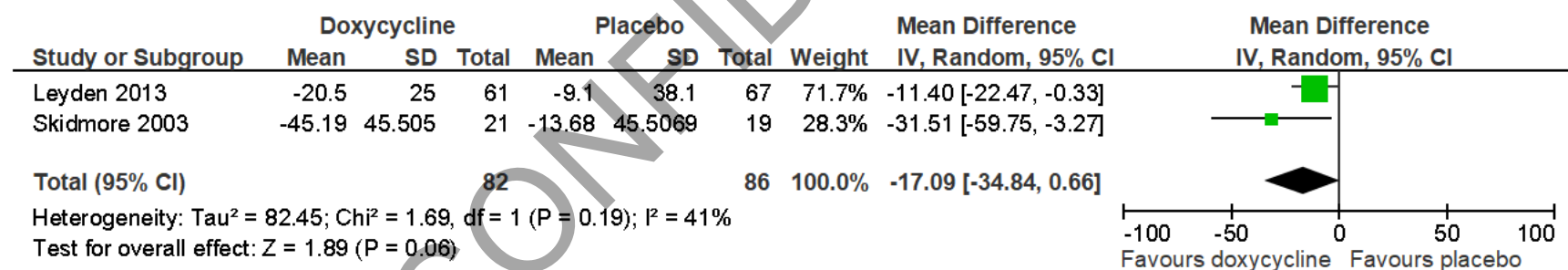
e-Figure 126. IGA, clear or almost clear and at least 2 grades improvement at 4 months, doxycycline vs. placebo

1.2 IGA - clear or almost clear and at least 2 grade improv. at 4 mos



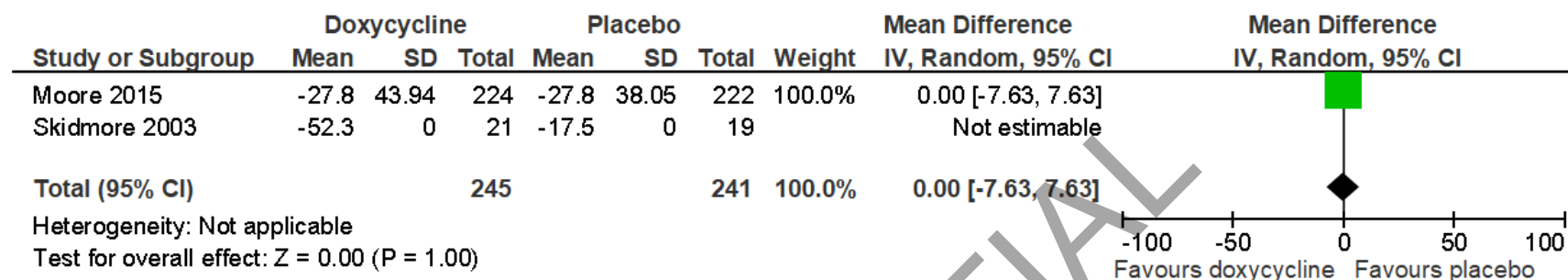
e-Figure 127. Total lesion, change from baseline, at 12 weeks, doxycycline vs. placebo

1.3 TL at 12+ weeks - Change from baseline



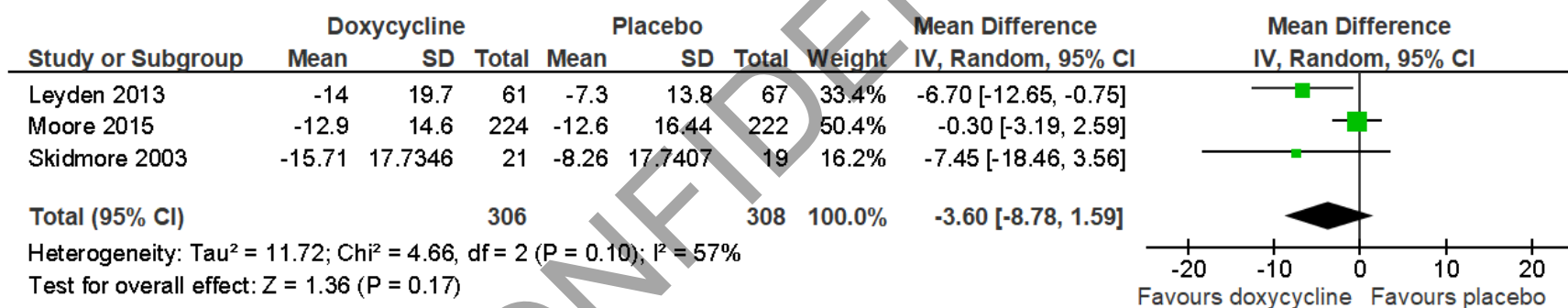
e-Figure 128. Total lesion, percentage change from baseline, at 12 weeks, doxycycline vs. placebo

1.4 TL at 12+ weeks - Percent change from baseline



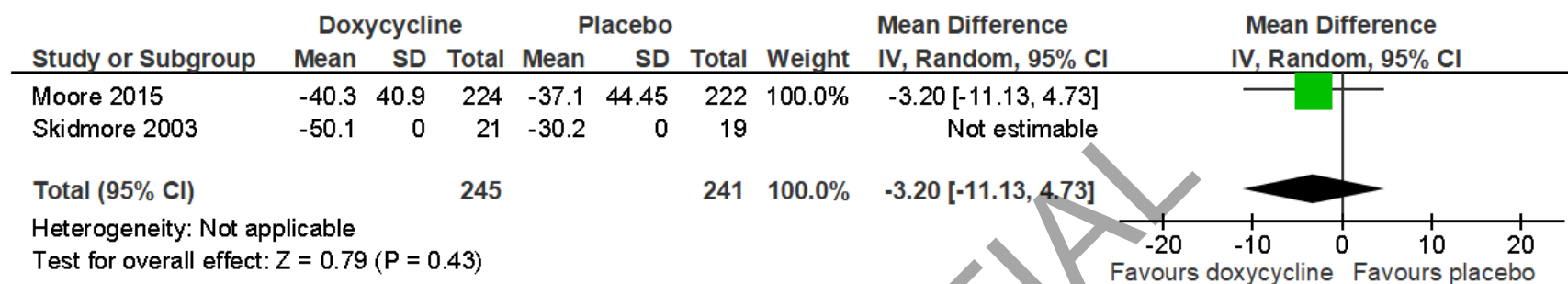
e-Figure 129. Inflammatory lesion, change from baseline, at 12+ weeks, doxycycline vs. placebo

1.5 IL at 12+ weeks - change from baseline



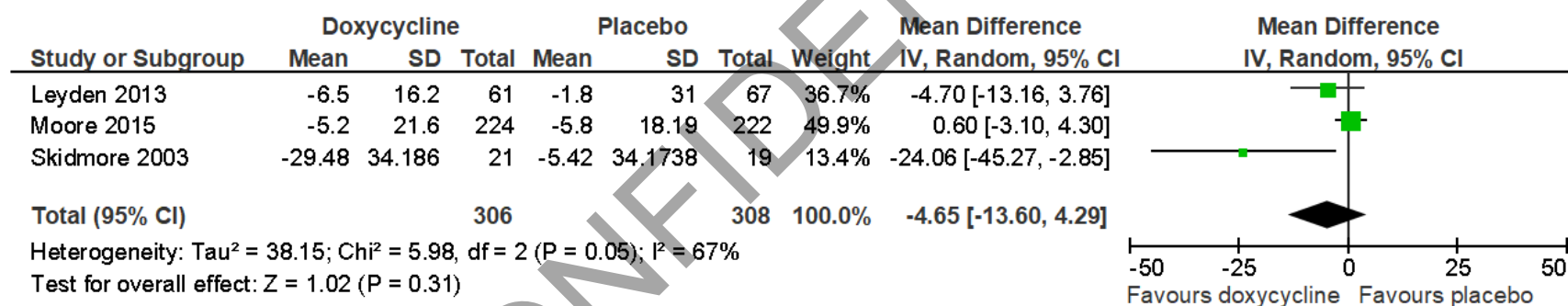
e-Figure 130. Inflammatory lesion, percentage change from baseline, at 12+ weeks, doxycycline vs. placebo

1.6 IL at 12+ weeks - percent change from baseline



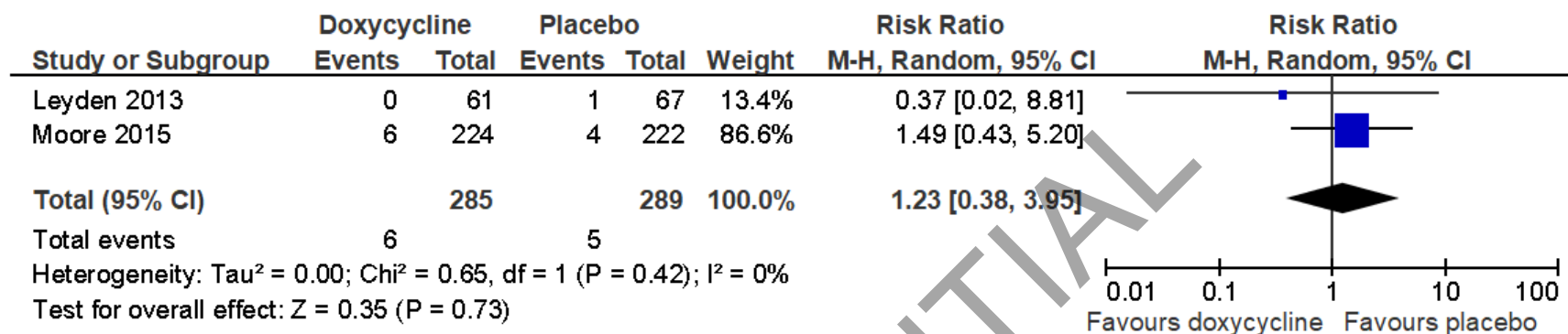
e-Figure 131. Noninflammatory lesion, change from baseline, at 12+ weeks, doxycycline vs. placebo

1.8 NIL at 12+ weeks - Change from baseline



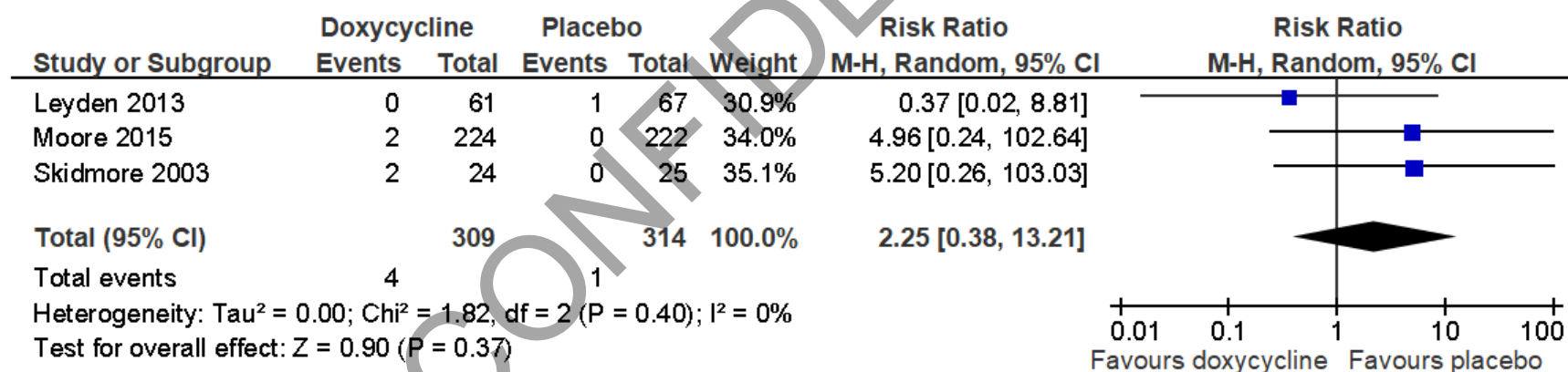
e-Figure 132. Serious AE, doxycycline vs. placebo

1.10 Serious AE



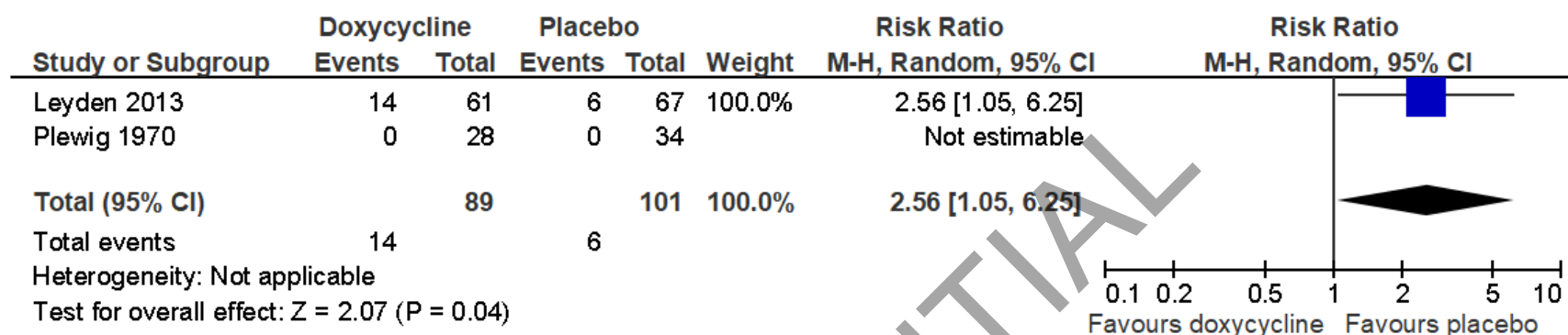
e-Figure 133. Withdrawal due to AE, doxycycline vs. placebo

1.14 Withdrawal due to AE



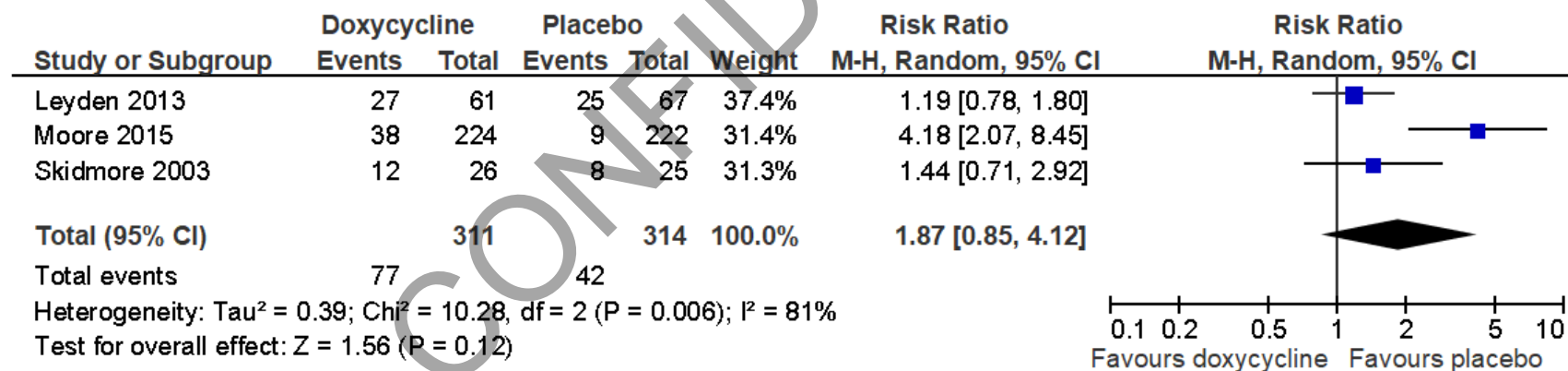
e-Figure 134. GI AE, doxycycline vs. placebo

1.15 GI AE



e-Figure 135. Any AE, doxycycline vs. placebo

1.17 Any AE



2. Doxycycline vs. azithromycin

e-Table 37. GRADE Evidence Profile for doxycycline vs. azithromycin

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	Azithromycin	Relative (95% CI)	Absolute (95% CI)		
Physician's global assessment (follow up: at least 12 weeks; assessed with: clear or almost clear)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	55/115 (47.8%)	47/109 (43.1%)	RR 1.11 (0.83 to 1.48)	47 more per 1,000 (from 73 fewer to 207 more)	⊕⊕⊕○ MODERATE	CRITICAL
Total lesion (follow up: at least 12 weeks; assessed with: change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	115 (-57 ± 22)	109 (-51 ± 21)	-	MD 6 lower (11.63 lower to 0.37 lower)	⊕⊕⊕○ MODERATE	CRITICAL

Total lesion (follow up: 12 weeks; assessed with: 80-100% Reduction)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	Azithromycin	Relative (95% CI)	Absolute (95% CI)		
2 ^{2,3}	randomised trials	not serious ^b	serious ^c	not serious	serious ^d	none	174/243 (71.6%)	91/243 (37.4%)	RR 1.68 (0.56 to 5.00)	255 more per 1,000 (from 165 fewer to 1,000 more)	⊕⊕○○ LOW	CRITICAL

Inflammatory lesion (follow up: at least 12 weeks; assessed with: change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	115 (-30 ± 12)	109 (-27 ± 12)	-	MD 3 lower (6.14 lower to 0.14 higher)	⊕⊕⊕○ MODERATE	CRITICAL

Inflammatory lesion (follow up: 12 weeks; assessed with: 80-100% reduction)

1 ⁴	randomised trials	not serious ^e	not serious	not serious	serious ^f	none	15/24 (62.5%)	11/21 (52.4%)	RR 1.19 (0.71 to 1.99)	100 more per 1,000 (from 152 fewer to 519 more)	⊕⊕⊕○ MODERATE	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	Azithromycin	Relative (95% CI)	Absolute (95% CI)		

Inflammatory lesion (follow up: 12 weeks; assessed with: $\geq 75\%$ reduction)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	68/115 (59.1%)	56/109 (51.4%)	RR 1.15 (0.91 to 1.46)	77 more per 1,000 (from 46 fewer to 236 more)	⊕⊕⊕○ MODERATE	CRITICAL

Withdrawal due to AE

1 ⁴	randomised trials	not serious ^e	not serious	not serious	serious ^f	none	0/24 (0.0%)	2/21 (9.5%)	RR 0.18 (0.01 to 3.47)	78 fewer per 1,000 (from 94 fewer to 235 more)	⊕⊕⊕○ MODERATE	IMPORTANT

Any AE

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	Azithromycin	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious ^g	not serious	not serious	serious ^d	none	0/50 (0.0%)	4/50 (8.0%)	RR 0.11 (0.01 to 2.01)	71 fewer per 1,000 (from 79 fewer to 81 more)	⊕⊕⊕○ MODERATE	IMPORTANT

Patients' global assessment (follow up: 12 weeks)

1 ⁴	randomised trials	not serious ^e	not serious	not serious	serious ^a	none	26 and 25 patients were randomized to receive i) doxycycline 100mg twice daily for the first month and once a daily for the second and third month or ii) azithromycin 500 mg/day on 3 consecutive days per week in the first, on 2 consecutive days per week in the second, and on 1 day per week in the third month. In doxycycline group (n=24), 12.5%, 62.5%, and 16.7% of patients had excellent, good, and moderate response, respectively, and 4.2%, 4.2%, and 0% had mild improvement, no change, and worsening, respectively. In azithromycin group (n=21), 14.3%, 38.1%, and 38.1% of patients had excellent, good, and moderate response, respectively, and 0%, 4.8%, and 4.8% had mild improvement, no change, and worsening, respectively.				⊕⊕⊕○ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

- a. Small sample size
- b. One study had unclear random sequence generation and allocation concealment The other study had unclear allocation concealment and blinding of patients and outcome assessors.
- c. $I^2=98\%$
- d. Wide CI included both appreciable benefits and harm.
- e. This study had unclear allocation concealment, unblinded patients, and high risk of attrition bias.
- f. Small sample size and a wide CI including both appreciable benefits and harm.
- g. This study had unclear random sequence generation and allocation concealment

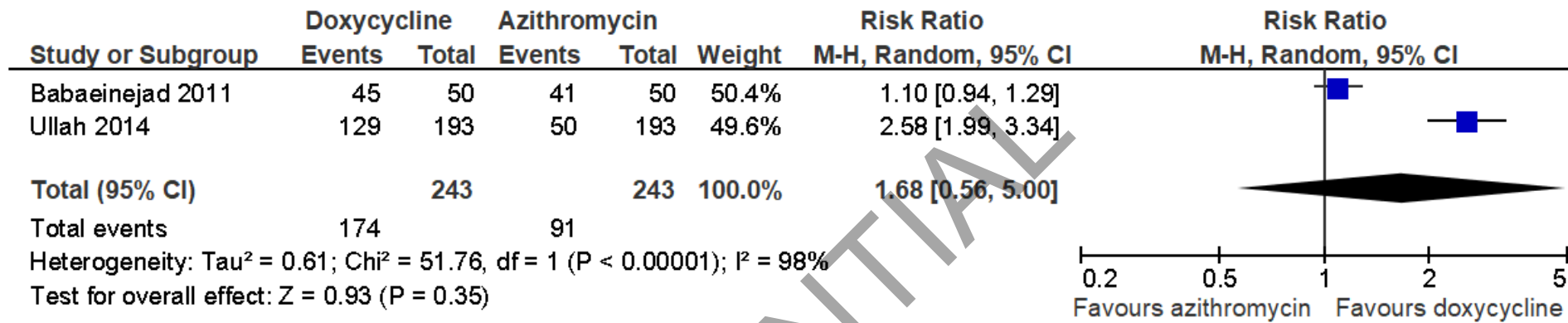
References

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2. Babaeinejad, S., E. Khodaeiani, and R.F. Fouladi, *Comparison of therapeutic effects of oral doxycycline and azithromycin in patients with moderate acne vulgaris: what is the role of age?* *Journal of dermatological treatment*, 2011. **22**(4): p. 206-210.
3. Ullah, G., et al., *Comparison of oral azithromycin with oral doxycycline in the treatment of acne vulgaris*. *J Ayub Med Coll Abbottabad*, 2014. **26**(1): p. 64-7.
4. Kus, S., D. Yucelten, and A. Aytug, *Comparison of efficacy of azithromycin vs. doxycycline in the treatment of acne vulgaris*. *Clin Exp Dermatol*, 2005. **30**(3): p. 215-20.

Forest plot

e-Figure 136. Total lesion, 80-100% reduction, at 12 weeks, doxycycline vs. azithromycin

4.4 TL, 80-100% Reduction at 12 weeks



3. Minocycline vs. placebo

e-Table 38. GRADE Evidence Profile for Minocycline vs. placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline	placebo	Relative (95% CI)	Absolute (95% CI)		
Percentage change in inflamed lesion counts												
4 ^{1, 2, 3, 4}	randomised trials	not serious ^a	not serious	not serious	not serious	none	708	401	-	MD 14.41 higher (8.44 higher to 20.39 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Percentage change in total lesion counts												
3 ^{1, 2, 3}	randomised trials	not serious ^b	not serious	not serious	not serious	none	674	364	-	MD 9.84 higher (4.84 higher to 14.84 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Investigator global severity, clear or almost clear												
3 ^{1, 2, 3}	randomised trials	not serious ^c	not serious	not serious	not serious	none	144/793 (18.2%)	35/364 (9.6%)	RR 1.82 (1.28 to 2.57)	79 more per 1,000 (from 27 more to 151 more)	⊕⊕⊕⊕ HIGH	CRITICAL

IBD - Incident inflammatory bowel disease (ulcerative colitis & Crohn's disease)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline	placebo	Relative (95% CI)	Absolute (95% CI)		
1 ⁵	observational studies	not serious ^f	not serious	not serious	not serious	none	-/0	-/0	HR 1.25 (0.82 to 1.89)	1 fewer per 1,000 (from 2 fewer to 1 fewer)	⊕⊕○○ LOW	IMPORTANT

Requiring therapy cessation

2 ^{3,6}	randomised trials	not serious ^g	not serious	not serious	serious ^e	none	19/208 (9.1%)	1/105 (1.0%)	RR 6.23 (1.20, 32.99)	80 fewer per 1,000 (from 130 fewer to 30 fewer)	⊕⊕⊕○ MODERATE	IMPORTANT

Gastro-intestinal disturbances

1 ³	randomised trials	not serious ^d	not serious	not serious	serious ^e	none	43/158 (27.2%)	18/51 (35.3%)	RR 0.77 (0.49 to 1.21)	81 fewer per 1,000 (from 180 fewer to 74 more)	⊕⊕⊕○ MODERATE	IMPORTANT

Any AE

1 ³	randomised trials	not serious ^d	not serious	not serious	serious ^e	none	103/158 (65.2%)	28/51 (54.9%)	RR 1.19 (0.90 to 1.56)	104 more per 1,000 (from 55 fewer to 307 more)	⊕⊕⊕○ MODERATE	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio; HR: Hazard Ratio

Explanations

- a. Two trials had unclear random sequence generation and allocation concealment and high risk of attrition bias (89% completed treatment, but dropouts and withdrawals totaled 15.3%). Another study had unclear random sequence generation and allocation concealment and high risk of attrition bias (only 182 of 269 patients were evaluable) and selective reporting bias (the specified outcomes were ILC, TLC, investigator and participant assessment, and photographs, but only inflammatory lesions were reported). The other study had unclear random sequence generation and allocation concealment.
- b. Two trials had unclear random sequence generation and allocation concealment and high risk of attrition bias (89% completed treatment, but dropouts and withdrawals totaled 15.3%). The other study had unclear random sequence generation and allocation concealment.
- c. Two trials had unclear random sequence generation and allocation concealment and high risk of attrition bias (89% completed treatment, but dropouts and withdrawals totaled 15.3%)
- d. This study had unclear random sequence generation and allocation concealment.
- e. Small sample size.
- f. This study followed up the patients for a mean of 3.6 years for no exposure group and 4.3 years for doxycycline group. However, there is a lack of knowledge regarding the time necessary between an antibiotics exposure and the risk of developing IBD.
- g. One study had unclear random sequence generation and allocation concealment. The other study had unclear random sequence generation and allocation concealment and high risk of attrition bias (7 of 50 dropped out, and all were in the minocycline group)

References

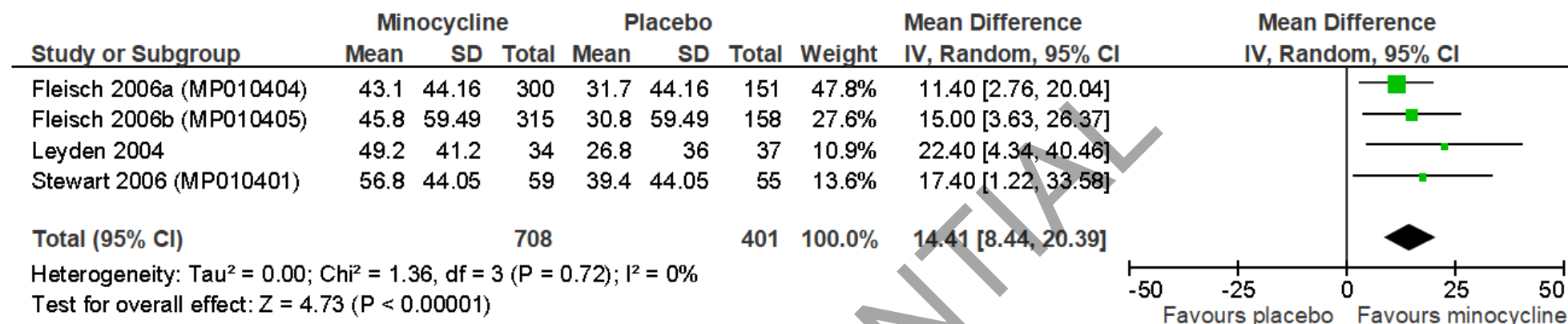
1. Fleischer, A.B., Jr., et al., *Safety and efficacy of a new extended-release formulation of minocycline*. Cutis, 2006 (MP010404). **78**(4 Suppl): p. 21-31.
2. Fleischer, A.B., Jr., et al., *Safety and efficacy of a new extended-release formulation of minocycline*. Cutis, 2006 (MP010405). **78**(4 Suppl): p. 21-31.
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4. Leyden, J., et al., *A systemic type 15-reductase inhibitor is ineffective in the treatment of acne vulgaris*. Journal of the American Academy of Dermatology, 2004. **50**(3): p. 443-447.
5. Margolis, D.J., et al., *Potential association between the oral tetracycline class of antimicrobials used to treat acne and inflammatory bowel disease*. Am J Gastroenterol, 2010. **105**(12): p. 2610-6.
6. Hersle, K. and H. Gisslen, *Minocycline in acne vulgaris: a double-blind study*. Curr Ther Res Clin Exp, 1976. **19**(3): p. 339-42.

Forest plots

e-Figure 137. Inflammatory lesion, percentage change from baseline, minocycline vs. placebo

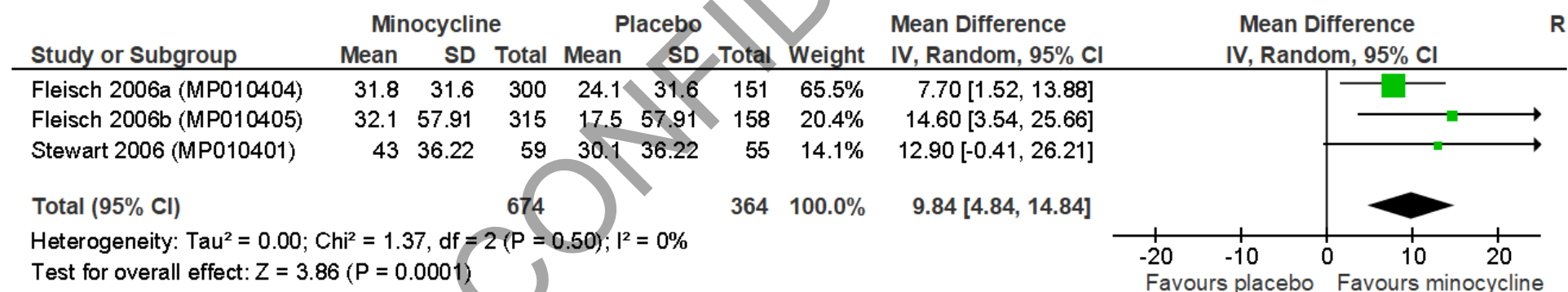
2 Minocycline versus placebo

2.1 Percentage change in inflamed lesion counts



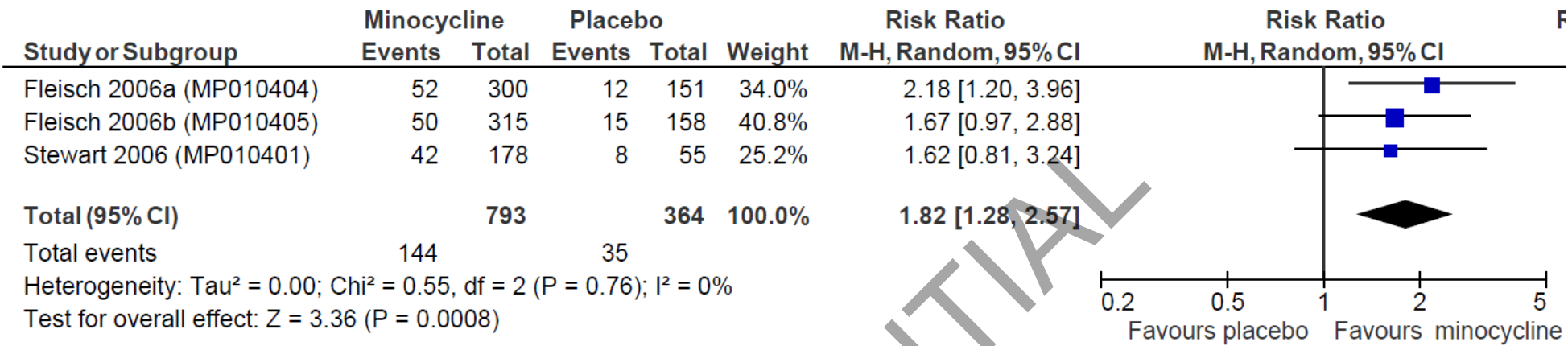
e-Figure 138. Total lesion, percentage change from baseline, minocycline vs. placebo

2.2 Percentage change in total lesion counts



e-Figure 139. IGA, clear or almost clear, minocycline vs. placebo

2.6 [Pooled] Investigator global assessment - clear or almost clear



4. Minocycline vs. doxycycline

e-Table 39. GRADE Evidence Profile for minocycline vs. doxycycline

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline	doxycycline	Relative (95% CI)	Absolute (95% CI)		
Physician's global assessment (follow up: 12 weeks; assessed with: treatment being effective and very effective on 4-pointing scale)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	27/31 (87.1%)	28/33 (84.8%)	RR 1.03 (0.84 to 1.25)	25 more per 1,000 (from 136 fewer to 212 more)	⊕⊕⊕○ MODERATE	CRITICAL
Patient's global assessment (follow up: 12 weeks; assessed with: treatment being effective and very effective on 4-pointing scale)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	28/31 (90.3%)	28/33 (84.8%)	RR 1.06 (0.89 to 1.28)	51 more per 1,000 (from 93 fewer to 238 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Withdrawal due to AE												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	3/39 (7.7%)	2/40 (5.0%)	1.54 (0.27, 8.71)	30 fewer per 1,000 (from 130 fewer to 80 more)	⊕⊕⊕○ MODERATE	IMPORTANT
GI AE												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	2/39 (5.1%)	1/40 (2.5%)	2.05 (0.19, 21.72)	30 fewer per 1,000 (from 110 fewer to 60 more)	⊕⊕⊕○ MODERATE	IMPORTANT

Any AE

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline	doxycycline	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	3/39 (7.7%)	2/40 (5.0%)	RR 1.54 (0.27 to 8.71)	27 more per 1,000 (from 37 fewer to 386 more)	⊕⊕⊕○ MODERATE	IMPORTANT

Reduction in *P. acnes* (follow up: 6 weeks)

1 ²	randomised trials	not serious ^b	not serious	serious ^c	serious ^a	none	60 patients were randomized to 3 groups of 20 each, for dosing with either minocycline 100mg BID, doxycycline 100mg BID, or tetracycline 500mg BID for 6 weeks. At baseline, log10/cm2 <i>P. acnes</i> were 6.35, 5.95, and 6.30 for minocycline, doxycycline, and tetracycline groups, respectively. At week 6, Minocycline group produced highly significant reductions in <i>P. acnes</i> on both cheeks and forehead compared with baseline (change in log10/cm2 <i>P. acnes</i> from baseline=2.05; p<=0.01). Doxycycline and tetracycline groups also produced significant reductions on both cheeks and forehead at 6 weeks (changes in log10/cm2 <i>P. acnes</i> at 6 week from baseline were 1.01 and 1.07 for doxycycline and tetracycline groups, respectively; both p<=0.01)				⊕⊕○○ LOW	IMPORTANT

Inflammatory bowel disease (follow up: varies)

1 ³	observational studies	not serious	not serious	not serious	serious ^d	none	When 94,487 acne patients were followed up for 406,294 person-years, IBD was noted in 41 individuals exposed to minocycline, 79 individuals exposed to tetracycline / oxytetracycline, 32 individuals exposed to doxycycline, and 55 (0.11 %) individuals not exposed to any of these antibiotics. Hazard ratios (HRs) for individual antibiotics were 1.19 (0.79, 1.79) for minocycline, 1.43 (1.02, 2.02) for tetracycline / oxytetracycline, and 1.63 (1.05, 2.52) for doxycycline. For ulcerative colitis, the				⊕○○○ VERY LOW	IMPORTANT

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline	doxycycline	Relative (95% CI)	Absolute (95% CI)		
							associations (HR) were 1.10 (0.76, 1.82) for minocycline, 1.27 (0.78, 2.07) for tetracycline /oxytetracycline, and 1.06 (0.53, 2.13) for doxycycline. For Crohn's disease (CD), the associations (HR) were 1.28 (0.72, 2.30) for minocycline, 1.61 (0.995, 2.63) for tetracycline / oxytetracycline, and 2.25 (1.27 4.00) for doxycycline.					

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease

Explanations

- Small sample size
- This study had unclear random sequence generation, allocation concealment, and outcome assessors and the participants were not blinded.
- This study enrolled healthy male and female subjects who had minimum *P. acnes* levels of 10,000 colony-forming units per cm² at baseline. It was not clear whether those subjects had a diagnosis of acne.
- Non-user group was used as a reference. No head-to-head comparison between doxycycline and minocycline.

References

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- Leyden, J.J., K. Kaidbey, and E. Gans, *The antimicrobial effects in vivo of minocycline, doxycycline and tetracycline in humans*. Journal of dermatological treatment, 1996. 7(4): p. 223-225.
- Margolis, D.J., et al., *Potential association between the oral tetracycline class of antimicrobials used to treat acne and inflammatory bowel disease*. Am J Gastroenterol, 2010. 105(12): p. 2610-6.

e-Table 40. GRADE Evidence Profile for minocycline vs. benzoyl peroxide

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline 100 mg ER od	benzoyl peroxide bd	Relative (95% CI)	Absolute (95% CI)		
Physician's global assessment (follow up: 18 weeks; assessed with: at least moderate improvement)												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	66/130 (50.8%)	74/130 (56.9%)	RR 0.89 (0.71 to 1.12)	63 fewer per 1,000 (from 165 fewer to 68 more)	⊕⊕⊕○ MODERATE	CRITICAL
Inflammatory lesion (follow up: 18 weeks; assessed with: change from baseline)												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	130	130	-	MD 0 (7.05 lower to 7.05 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Participants' global assessment (follow up: 18 weeks; assessed with: at least moderate improvement)												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	70/130 (53.8%)	78/130 (60.0%)	RR 0.90 (0.73 to 1.11)	60 fewer per 1,000 (from 162 fewer to 66 more)	⊕⊕⊕○ MODERATE	IMPORTANT

Requiring therapy cessation

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline 100 mg ER od	benzoyl peroxide bd	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	6/130 (4.6%)	9/130 (6.9%)	RR 0.67 (0.24 to 1.82)	23 fewer per 1,000 (from 53 fewer to 57 more)	⊕⊕⊕○ MODERATE	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

- a. This study had unblinded patients and high risk of attrition bias and selective reporting.
b. Small sample size.

References

- Ozolins, M., et al., *Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial.* Lancet, 2004. **364**(9452): p. 2188-95.

e-Table 41. GRADE Evidence Profile for minocycline 100mg er qd vs. erythromycin/benzoyl peroxide bid

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline 100 mg ER od	erythromycin/ benzoyl peroxide (ery/BP) bd	Relative (95% CI)	Absolute (95% CI)		
Physician's global assessment (follow up: 18 weeks; assessed with: at least moderate improvement)												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	66/130 (50.8%)	75/127 (59.1%)	RR 0.86 (0.69 to 1.07)	83 fewer per 1,000 (from 183 fewer to 41 more)	⊕⊕⊕○ MODERATE	CRITICAL
Inflammatory lesion (follow up: 18 weeks; assessed with: change from baseline)												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	130 (22.3 ± 29.9)	127 (24.5 ± 32.4)	-	MD 2.2 lower (9.83 lower to 5.43 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Participants' global assessment (follow up: 18 weeks; assessed with: at least moderate improvement)												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	70/130 (53.8%)	84/127 (66.1%)	RR 0.81 (0.67 to 1.00)	126 fewer per 1,000 (from 218 fewer to 0 fewer)	⊕⊕⊕○ MODERATE	IMPORTANT

Requiring therapy cessation

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline 100 mg ER od	erythromycin/ benzoyl peroxide (ery/BP) bd	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	6/130 (4.6%)	3/127 (2.4%)	RR 1.95 (0.50 to 7.64)	22 more per 1,000 (from 12 fewer to 157 more)	⊕⊕⊕○ MODERATE	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

- a. This study had unblinded patients and high risk of attrition bias and selective reporting.
b. Small sample size.

References

1. Ozolins, M., et al., *Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial.* Lancet, 2004. **364**(9452): p. 2188-95.

e-Table 42. GRADE Evidence Profile for Minocycline 100mg ER QD vs. erythromycin/benzoyl peroxide QD

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline 100 mg ER od	erythromycin od/benzoyl peroxide (ery/BP) od	Relative (95% CI)	Absolute (95% CI)		
Physician's global assessment (follow up: 12 weeks; assessed with: at least moderate improvement)												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	66/130 (50.8%)	78/131 (59.5%)	RR 0.85 (0.68 to 1.06)	89 fewer per 1,000 (from 191 fewer to 36 more)	⊕⊕⊕○ MODERATE	CRITICAL
Inflammatory lesion (follow up: 18 weeks; assessed with: change from baseline)												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	130 (22.3 ± 29.9)	131 (26.9 ± 29.7)	-	MD 4.6 lower (11.83 lower to 2.63 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Participants' global assessment (follow up: 18 weeks; assessed with: at least moderate improvement)												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	70/130 (53.8%)	82/131 (62.6%)	RR 0.86 (0.70 to 1.06)	88 fewer per 1,000 (from 188 fewer to 38 more)	⊕⊕⊕○ MODERATE	IMPORTANT

Requiring therapy cessation

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline 100 mg ER od	erythromycin od/benzoyl peroxide (ery/BP) od	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	6/130 (4.6%)	9/131 (6.9%)	RR 0.67 (0.25 to 1.83)	23 fewer per 1,000 (from 52 fewer to 57 more)	⊕⊕⊕○ MODERATE	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

- a. This study had unblinded patients and high risk of attrition bias and selective reporting.
b. Small sample size.

References

- Ozolins, M., et al., *Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial.* Lancet, 2004. **364**(9452): p. 2188-95.

7. Minocycline vs. tazarotene gel

e-Table 43. GRADE Evidence Profile for minocycline vs. tazarotene gel

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline 100 mg BID	tazarotene 0.1% gel QD	Relative (95% CI)	Absolute (95% CI)		
Physician's global assessment (follow up: 16 weeks; assessed with: ≥75% overall clinical improvement)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	21/31 (67.7%)	14/26 (53.8%)	RR 1.26 (0.82 to 1.94)	140 more per 1,000 (from 97 fewer to 506 more)	⊕⊕⊕○ MODERATE	CRITICAL
Inflammatory lesion (follow up: 12 weeks; assessed with: percentage change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	31 (66 ± 29.4)	26 (54 ± 25.1)	-	MD 12 higher (2.15 lower to 26.15 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Noninflammatory lesion (follow up: 12 weeks; assessed with: percentage change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	31 (52 ± 30.4)	26 (60 ± 22.9)	-	MD 8 lower (21.86 lower to 5.86 higher)	⊕⊕⊕○ MODERATE	CRITICAL

Requiring therapy cessation

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline 100 mg BID	tazarotene 0.1% gel QD	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	1/37 (2.7%)	0/36 (0.0%)	RR 2.92 (0.12 to 69.43)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ MODERATE	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. Small sample size.

b. Small sample size, few events, and wide CI including both appreciable benefits and harm.

Reference

1. Leyden, J., et al., *Comparison of tazarotene and minocycline maintenance therapies in acne vulgaris: a multicenter, double-blind, randomized, parallel-group study*. Arch Dermatol, 2006. **142**(5): p. 605-12.

8. Sarecycline vs. placebo

e-Table 44. GRADE Evidence Profile for sarecycline vs. placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sarecycline	placebo	Relative (95% CI)	Absolute (95% CI)		
Physician's global assessment (follow up: 12 weeks; assessed with: 2 grade reduction and clear or almost clear on IGA)												
2 ^{1,2}	randomised trials	not serious	not serious ^a	not serious	not serious	none	223/1002 (22.3%)	130/1000 (13.0%)	RR 1.73 (1.23 to 2.44)	95 more per 1,000 (from 30 more to 187 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Inflammatory lesion (follow up: 12 weeks; assessed with: change from baseline)												
3 ^{1,2,3}	randomised trials	not serious ^d	not serious	not serious	not serious	none	1072	1072	-	MD 4.59 lower (5.52 lower to 3.66 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Inflammatory lesion (follow up: 12 weeks; assessed with: percentage change from baseline)												
3 ^{1,2,3}	randomised trials	not serious ^d	not serious	not serious	not serious	none	1072	1072	-	MD 15.44 lower (19 lower to 11.89 lower)	⊕⊕⊕⊕ HIGH	CRITICAL

Noninflammatory lesion (follow up: 12 weeks; assessed with: change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sarecycline	placebo	Relative (95% CI)	Absolute (95% CI)		
2 ^{1,3}	randomised trials	not serious ^d	not serious	not serious	not serious	none	553	557	-	MD 3.53 lower (5.82 lower to 1.24 lower)	⊕⊕⊕⊕ HIGH	CRITICAL

Noninflammatory lesion (follow up: 12 weeks; assessed with: percentage change from baseline)

3 ^{1,2,3}	randomised trials	not serious ^d	not serious	not serious	not serious	none	553	557	-	MD 2.96 lower (11.89 lower to 5.96 higher)	⊕⊕⊕⊕ HIGH	CRITICAL

Withdrawal due to AE

4 ^{1,2,3,4}	observational studies	not serious ^e	not serious	not serious	serious ^f	none	31/1689 (1.8%)	14/1068 (1.3%)	RR 1.10 (0.41 to 2.95)	1 more per 1,000 (from 8 fewer to 26 more)	⊕○○○ VERY LOW	IMPORTANT

Any AE

4 ^{1,2,3,4}	observational studies	not serious ^e	not serious	not serious	serious ^f	none	538/1689 (31.9%)	312/1068 (29.2%)	RR 0.95 (0.83 to 1.08)	15 fewer per 1,000 (from 50 fewer to 23 more)	⊕○○○ VERY LOW	IMPORTANT

Serious AE

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sarecycline	placebo	Relative (95% CI)	Absolute (95% CI)		
4 ^{1, 2, 3, 4 f}	randomised trials	not serious ^e	not serious ^g	not serious	not serious	none	12/1689 (0.7%)	6/1068 (0.6%)	RR 1.29 (0.21 to 8.03)	2 more per 1,000 (from 4 fewer to 39 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Any GI AE

1 ⁴	observational studies	serious ⁱ	not serious	not serious	serious ^f	none	32/483 (6.6%)	0/0	not estimable		⊕○○○ VERY LOW	IMPORTANT

Candidiasis

3 ^{1, 2, 4 k}	randomised trials	not serious ^j	not serious	not serious	not serious	none	5/1477 (0.3%)	0/996 (0.0%)	RR 4.75 (0.54 to 41.67)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

Photosensitivity

2 ^{1, 2}	randomised trials	not serious	not serious	not serious	not serious	none	5/994 (0.5%)	1/996 (0.1%)	RR 3.66 (0.60 to 22.27)	3 more per 1,000 (from 0 fewer to 21 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

Inflammatory bowel disease

1 ²	randomised trials	not serious	not serious	not serious	serious ^h	none	1/513 (0.2%)	0/513 (0.0%)	RR 3.00 (0.12 to 73.47)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sarecycline	placebo	Relative (95% CI)	Absolute (95% CI)		

GI AE - nausea

3 ^{1,2,3}	randomised trials	not serious ^d	not serious	not serious	not serious	none	41/1206 (3.4%)	21/1068 (2.0%)	RR 1.57 (0.93 to 2.63)	11 more per 1,000 (from 1 fewer to 32 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

GI AE - abdominal pain

3 ^{1,2,3}	randomised trials	not serious ^d	not serious	not serious	not serious	none	13/1206 (1.1%)	7/1068 (0.7%)	RR 1.37 (0.53 to 3.56)	2 more per 1,000 (from 3 fewer to 17 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

GI AE - diarrhea

3 ^{1,2,3}	randomised trials	not serious ^d	not serious	not serious	not serious	none	14/1206 (1.2%)	14/1068 (1.3%)	RR 0.85 (0.40 to 1.83)	2 fewer per 1,000 (from 8 fewer to 11 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

GI AE - dyspepsia

1 ³	randomised trials	not serious ^b	not serious	not serious	serious ^{c,h}	none	3/212 (1.4%)	0/72 (0.0%)	RR 2.40 (0.13 to 45.89)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ MODERATE	IMPORTANT

GI AE- vomiting

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sarecycline	placebo	Relative (95% CI)	Absolute (95% CI)		
2 ^{1,2}	randomised trials	not serious	not serious	not serious	not serious	none	13/994 (1.3%)	9/996 (0.9%)	RR 1.45 (0.62 to 3.37)	4 more per 1,000 (from 3 fewer to 21 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

GI AE-abdominal discomfort

2 ^{1,2}	randomised trials	not serious	not serious	not serious	serious ^h	none	7/994 (0.7%)	3/996 (0.3%)	RR 2.11 (0.43 to 10.37)	3 more per 1,000 (from 2 fewer to 28 more)	⊕⊕⊕○ MODERATE	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

- I²=66%
- This study had high risk of selective reporting.
- Small sample size.
- One study had high risk of selective reporting.
- One study had high risk of selective reporting. Another study had high risk of bias due to the nature of a single arm cohort study (open label extension study of Moore 2018a and b).
- Only the data from the two RCTs (Moore 2018a and Moore 2018b) were pooled. Leyden 2018 reported no events in both groups, and Pariser 2019 reported that 5 of 483 patients who received sarecycline had serious AEs.
- I²=51
- Few events and wide CI
- This study had high risk of bias due to the nature of a single arm cohort study (open label extension study of Moore 2018a and b).
- One study had high risk of bias due to the nature of a single arm cohort study (open label extension study of Moore 2018a and b).
- Only the data from the two RCTs (Moore 2018a and Moore 2018b) were pooled. Pariser 2019 reported that 1 of 483 patients who received sarecycline had candidiasis.

References

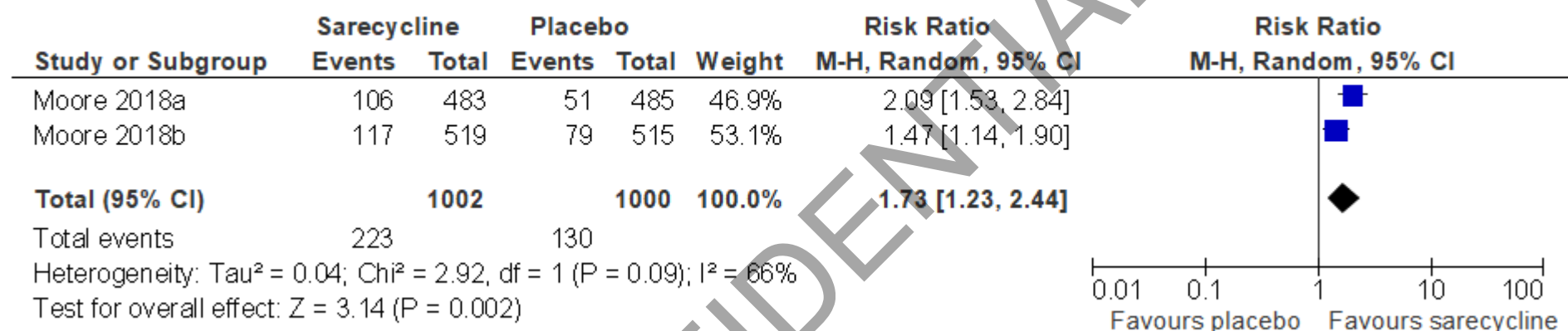
- Moore, A., et al., *Once-Daily Oral Sarecycline 1.5 mg/kg/day Is Effective for Moderate to Severe Acne Vulgaris: Results from Two Identically Designed, Phase 3, Randomized, Double-Blind Clinical Trials*. J Drugs Dermatol, 2018 (SC1401). 17(9): p. 987-996.
- Moore, A., et al., *Once-Daily Oral Sarecycline 1.5 mg/kg/day Is Effective for Moderate to Severe Acne Vulgaris: Results from Two Identically Designed, Phase 3, Randomized, Double-Blind Clinical Trials*. J Drugs Dermatol, 2018 (SC1402). 17(9): p. 987-996.

3. Leyden, J.J., et al., *Efficacy and Safety of Sarecycline, a Novel, Once-Daily, Narrow Spectrum Antibiotic for the Treatment of Moderate to Severe Facial Acne Vulgaris: Results of a Phase 2, Dose-Ranging Study*. J Drugs Dermatol, 2018. 17(3): p. 333-338.
4. Pariser, D.M., et al., *Safety and Tolerability of Sarecycline for the Treatment of Acne Vulgaris: Results from a Phase III, Multicenter, Open-Label Study and a Phase I Phototoxicity Study*. J Clin Aesthet Dermatol, 2019. 12(11): p. E53-e62.

Forest Plots

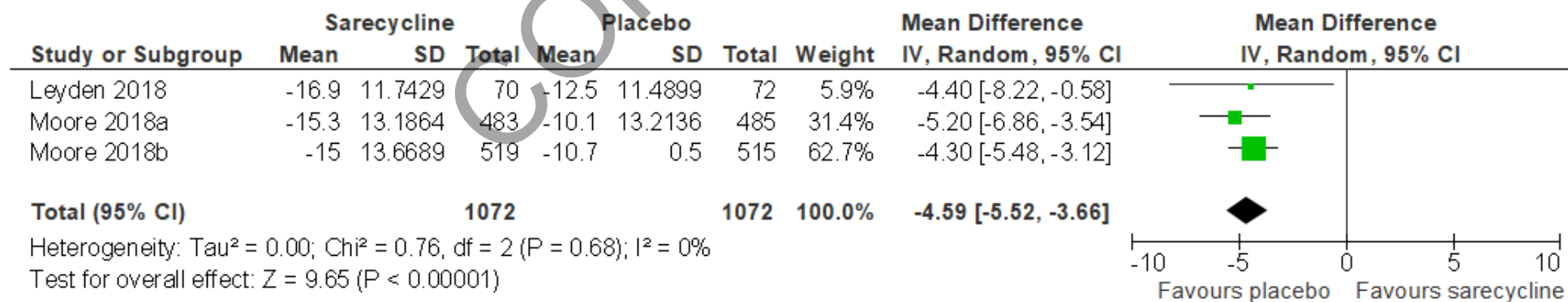
e-Figure 140. IGA, at least 2 grade reduction and clear or almost clear, at 12 weeks, sarecycline vs. placebo

14.1 Physician's global assessment, at least 2 grade reduction and clear or almost clear at 12 weeks



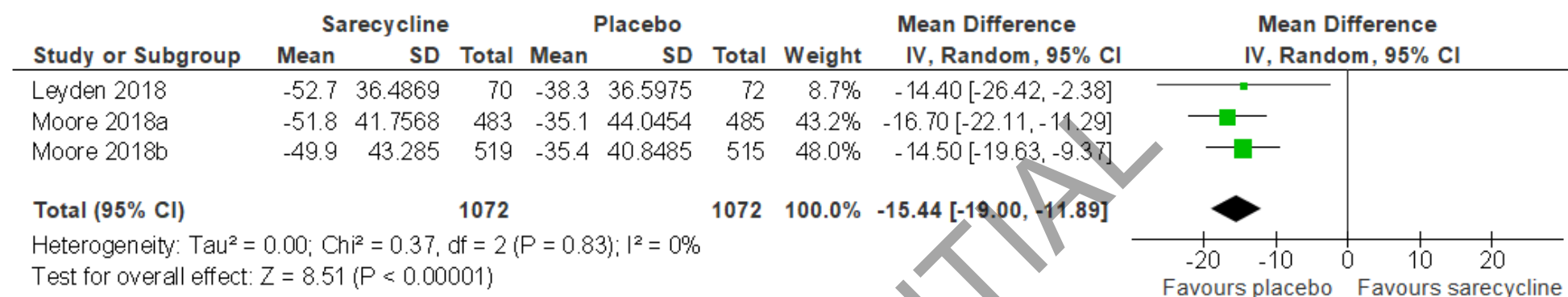
e-Figure 141. Inflammatory lesion, change from baseline, at 12 weeks, sarecycline vs. placebo

14.3 Inflammatory lesion, change from baseline at 12 weeks



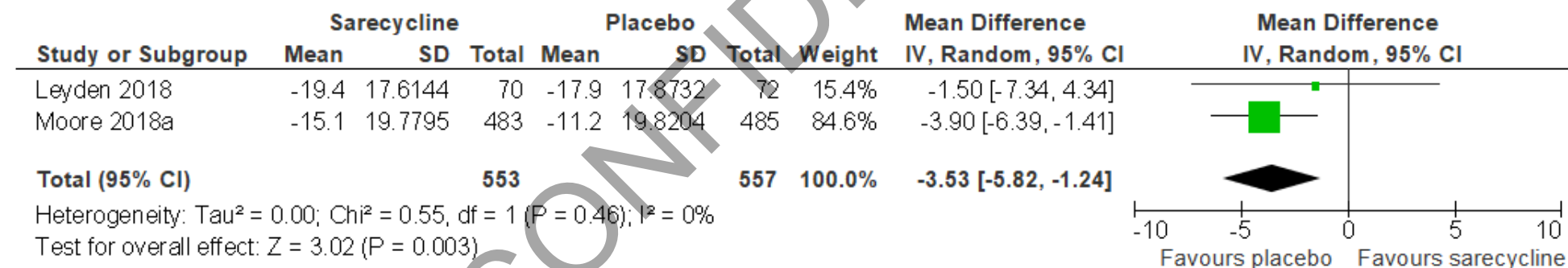
e-Figure 142. Inflammatory lesion, percentage change from baseline, at 12 weeks, sarecycline vs. placebo

14.4 Inflammatory lesion, percent change from baseline at 12 weeks



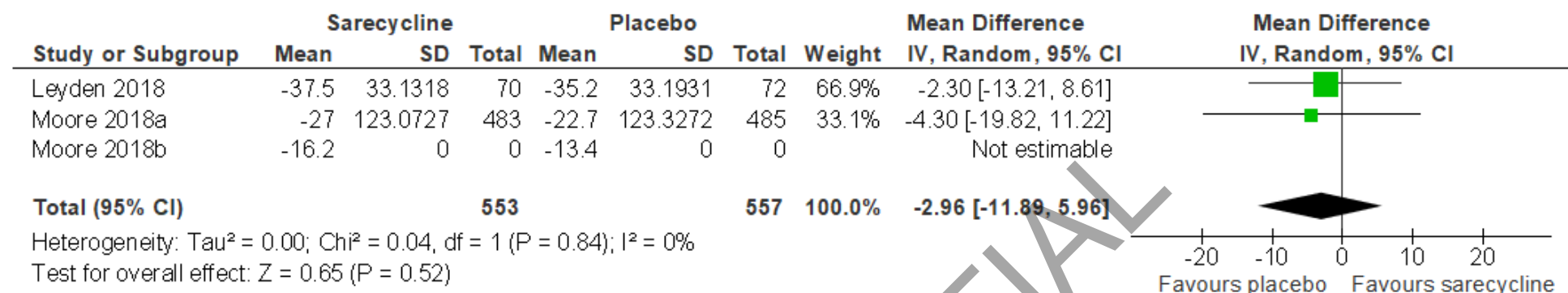
e-Figure 143. Noninflammatory lesion, change from baseline, at 12 weeks, sarecycline vs. placebo

14.5 NonInflammatory lesion, change from baseline at 12 weeks



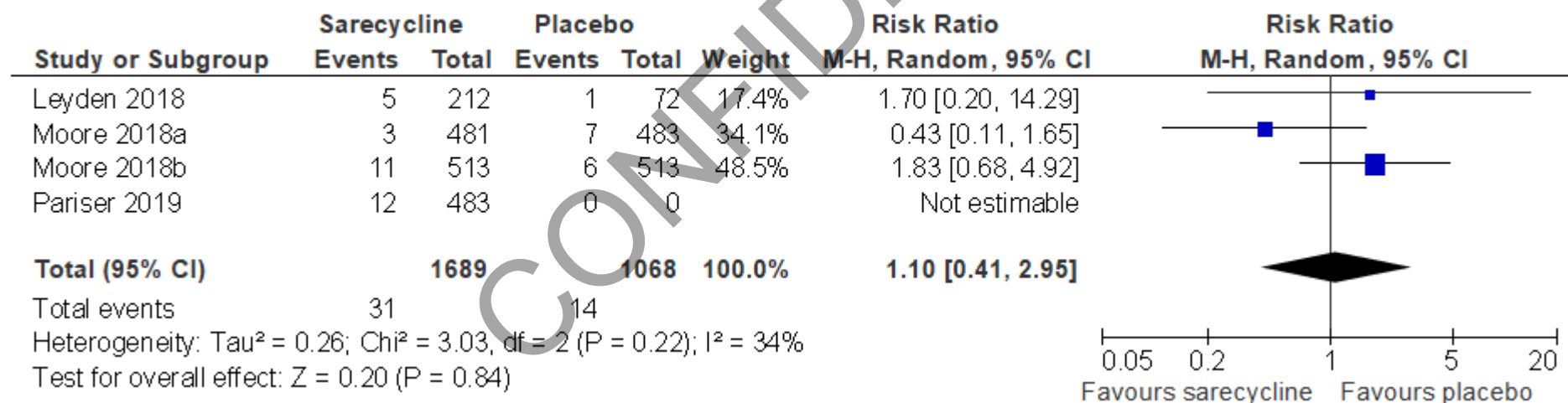
e-Figure 144. Noninflammatory lesion, percentage change from baseline, at 12 weeks, sarecycline vs. placebo

14.6 NonInflammatory lesion, percent change from baseline at 12 weeks



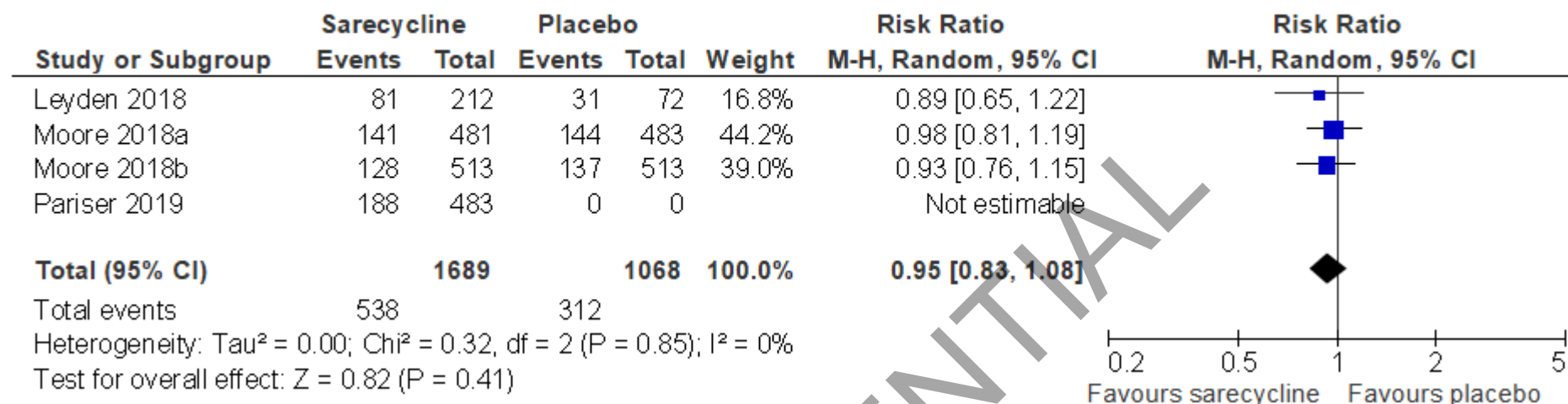
e-Figure 145. Withdrawal due to AE, sarecycline vs. placebo

14.7 Withdrawal due to AE



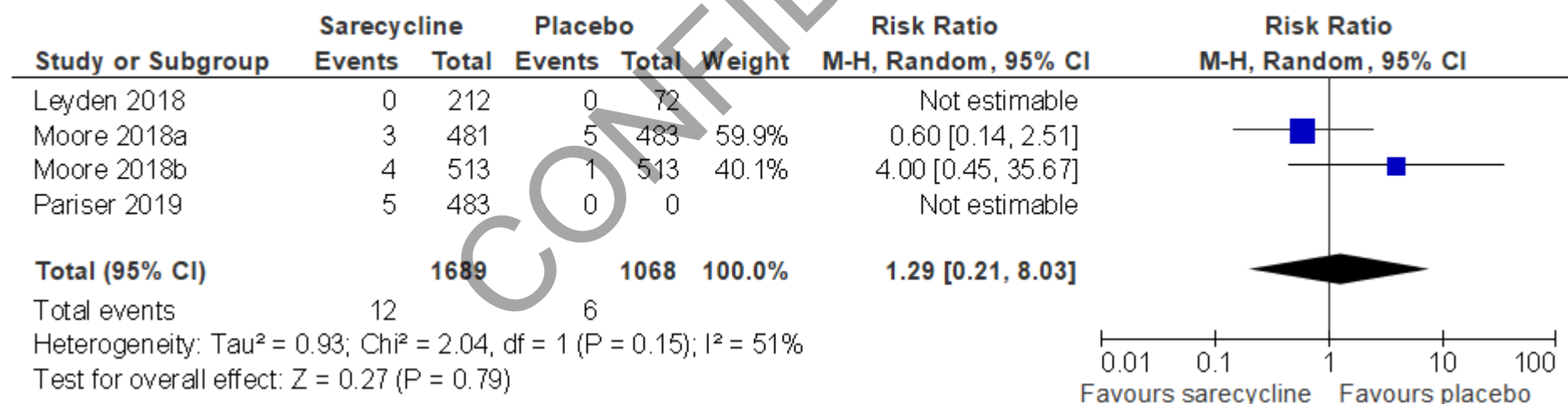
e-Figure 146. Any AE, sarecycline vs. placebo

14.8 Any AE



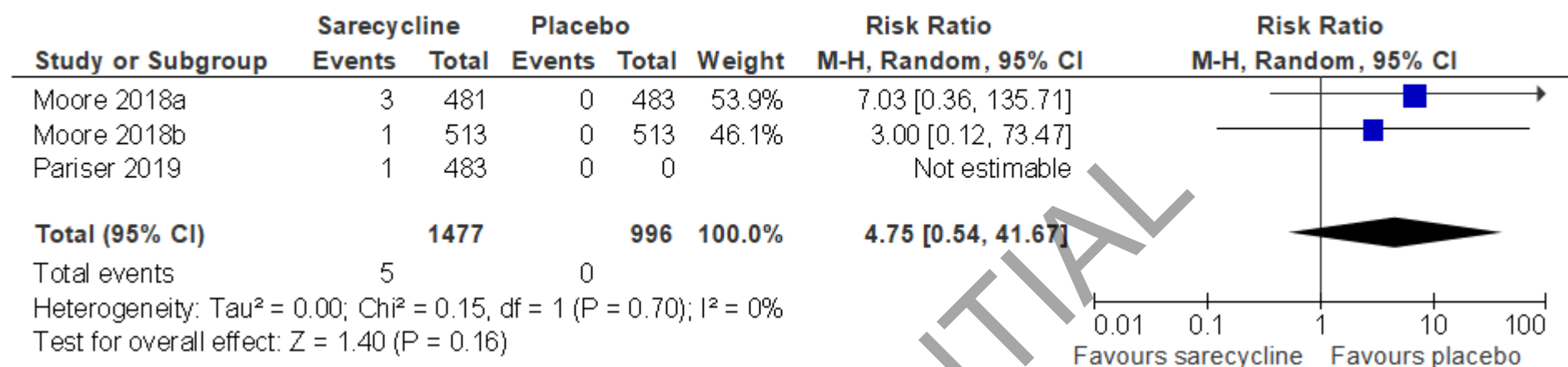
e-Figure 147. Serious AE, sarecycline vs. placebo

14.9 Serious AE



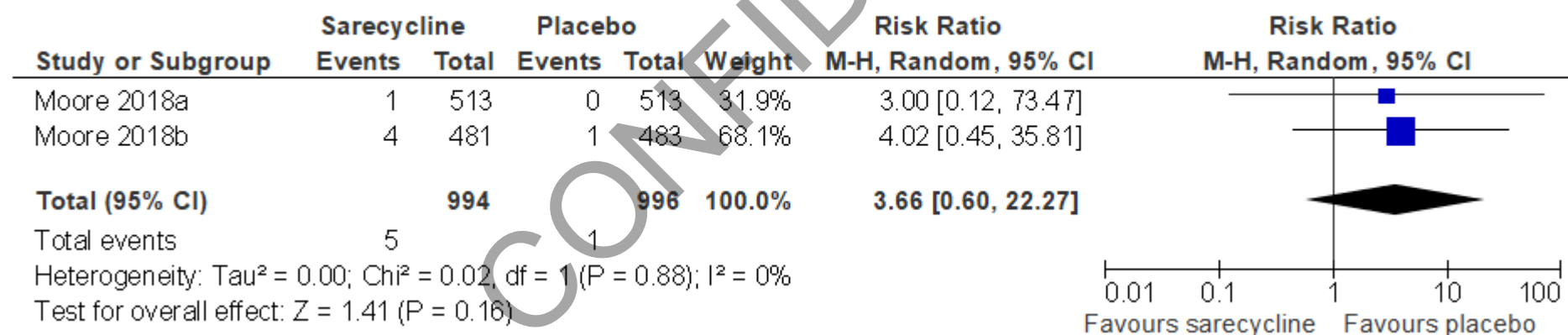
e-Figure 148. Candidiasis, sarecycline vs. placebo

14.11 Candidiasis



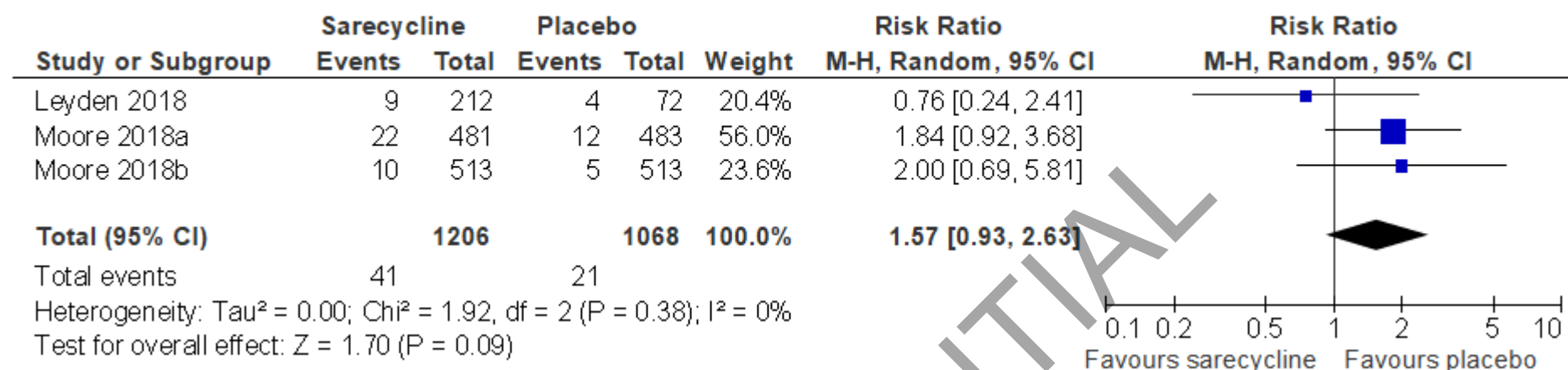
e-Figure 149. Withdrawal due to AE, sarecycline vs. placebo

14.12 Photosensitivity



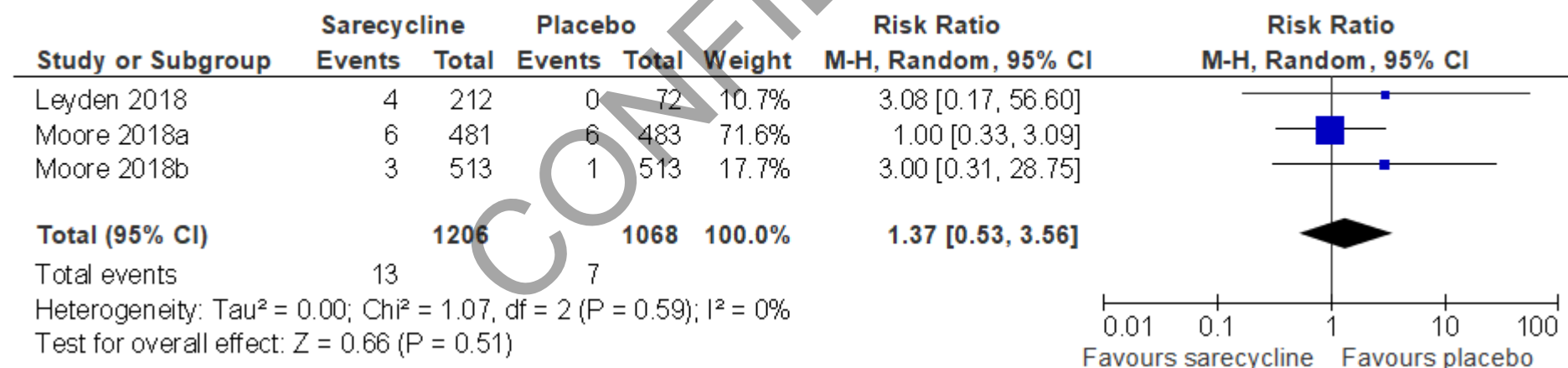
e-Figure 150. Nausea, sarecycline vs. placebo

14.14 GI AE - nausea



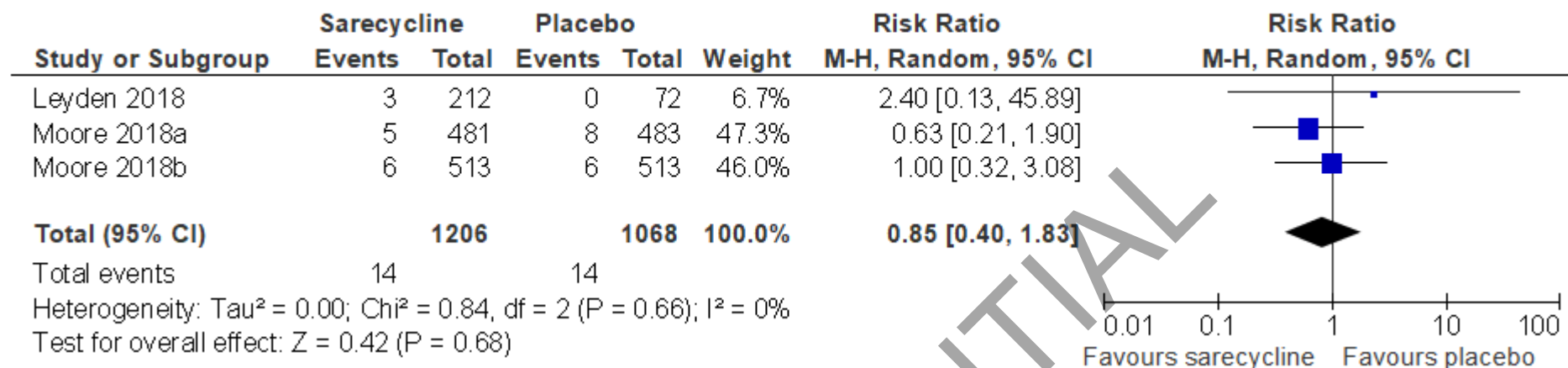
e-Figure 151. Abdominal pain, sarecycline vs. placebo

14.15 GI AE - abdominal pain



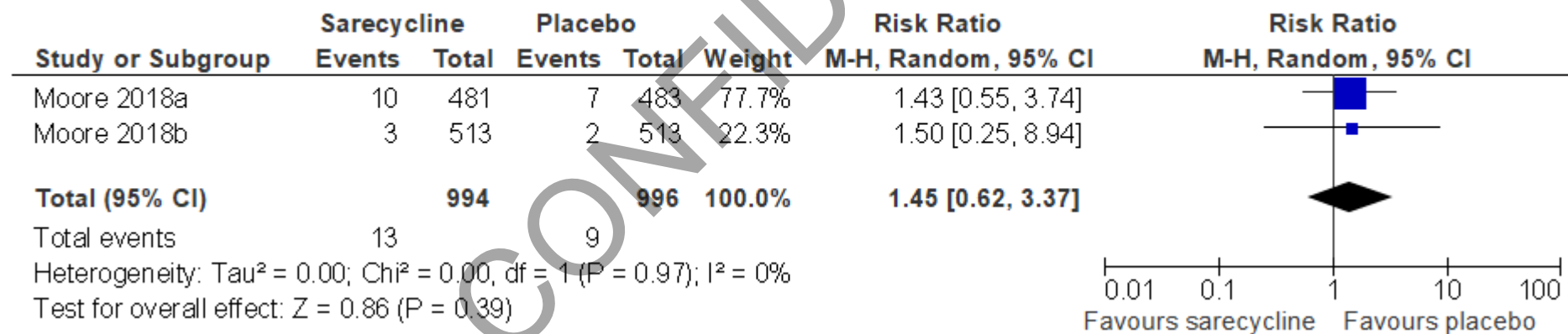
e-Figure 152. Diarrhea, sarecycline vs. placebo

14.16 GI AE - diarrhea



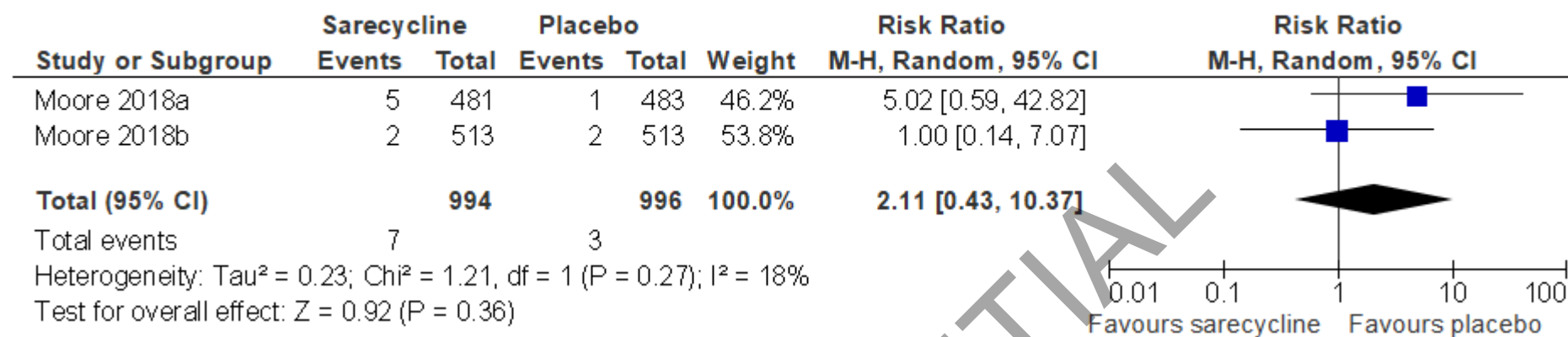
e-Figure 153. Vomiting, sarecycline vs. placebo

14.18 GI AE- vomiting



e-Figure 154. Abdominal discomfort, sarecycline vs. placebo

14.19 GI AE-abdominal discomfort



9. Azithromycin at different dosages

e-Table 45. GRADE Evidence Profile for azithromycin for 7 weeks vs. Azithromycin for 10 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin for 7 weeks	Azithromycin for 10 weeks	Relative (95% CI)	Absolute (95% CI)		
Inflammatory lesion (follow up: varies; assessed with: percentage change from baseline)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	Patients were randomized to receive a 3-day course of 500 mg azithromycin tablet once daily followed by one 500 mg azithromycin tablet per week for another 6 weeks in group A (n=36), 9 weeks in group B (n=34), and 12 weeks in group C (n=34). At the end of each treatment, the mean percentage changes from baseline in inflammatory lesions on face were -61 (range, -9, -100), -73 (range, -34, -100), and 74 (range, -29, -100) in Group A, B, and C, respectively.			⊕⊕○○ LOW	CRITICAL	
Inflammatory lesion (follow up: varies; assessed with: ≥75% reduction)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^c	none	14/36 (38.9%)	18/34 (52.9%)	RR 0.73 (0.44 to 1.23)	143 fewer per 1,000 (from 296 fewer to 122 more)	⊕⊕○○ LOW	CRITICAL
Any AE												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^c	none	11/36 (30.6%)	6/34 (17.6%)	RR 1.73 (0.72 to 4.16)	129 more per 1,000 (from 49 fewer to 558 more)	⊕⊕○○ LOW	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

- a. This study had unclear allocation concealment, unblinded participants and outcome assessors, and high risk of attrition bias (22.5% drop out).
- b. Small sample size; the percentage changes in inflammatory lesions were reported as means with ranges.
- c. Small sample size.

References

1. Basta-Juzbasic, A., et al., *A dose-finding study of azithromycin in the treatment of acne vulgaris*. Acta Dermatovenereol Croat, 2007. **15**(3): p. 141-7.

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e-Table 46. GRADE Evidence Profile for azithromycin for 7 weeks vs. azithromycin for 13 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin 7 weeks	Azithromycin 13 weeks	Relative (95% CI)	Absolute (95% CI)		
Inflammatory lesion (follow up: varies; assessed with: percentage change from baseline)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	Patients were randomized to receive a 3-day course of 500 mg azithromycin tablet once daily followed by one 500 mg azithromycin tablet per week for another 6 weeks in group A (n=36), 9 weeks in group B (n=34), and 12 weeks in group C (n=34). At the end of each treatment, the mean percentage changes from baseline in inflammatory lesions on face were -61 (range, -9, -100), -73 (range, -34, -100), and 74 (range, -29, -100) in Group A, B, and C, respectively.			⊕⊕○○ LOW	CRITICAL	
Inflammatory lesion (follow up: varies; assessed with: ≥75% reduction)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^c	none	14/36 (38.9%)	19/34 (55.9%)	RR 0.70 (0.42 to 1.16)	168 fewer per 1,000 (from 324 fewer to 89 more)	⊕⊕○○ LOW	CRITICAL
Any AE												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^c	none	11/34 (32.4%)	4/34 (11.8%)	RR 2.75 (0.97 to 7.79)	206 more per 1,000 (from 4 fewer to 799 more)	⊕⊕○○ LOW	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

- a. This study had unclear allocation concealment, unblinded participants and outcome assessors, and high risk of attrition bias (22.5% drop out).
- b. Small sample size; the percentage changes in inflammatory lesions were reported as means with ranges.
- c. Small sample size.

References

1. Basta-Juzbasic, A., et al., *A dose-finding study of azithromycin in the treatment of acne vulgaris*. Acta Dermatovenerol Croat, 2007. **15**(3): p. 141-7.

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e-Table 47. GRADE Evidence Profile for azithromycin for 10 weeks vs. azithromycin for 13 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin 10 weeks	Azithromycin 13 weeks	Relative (95% CI)	Absolute (95% CI)		
Inflammatory lesion (follow up: varies; assessed with: percentage change from baseline)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	Patients were randomized to receive a 3-day course of 500 mg azithromycin tablet once daily followed by one 500 mg azithromycin tablet per week for another 6 weeks in group A (n=36), 9 weeks in group B (n=34), and 12 weeks in group C (n=34). At the end of each treatment, the mean percentage changes from baseline in inflammatory lesions on face were -61 (range, -9, -100), -73 (range, -34, -100), and 74 (range, -29, -100) in Group A, B, and C, respectively.			⊕⊕○○ LOW	CRITICAL	
Inflammatory lesion (follow up: varies; assessed with: ≥75% reduction)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^c	none	18/34 (52.9%)	19/34 (55.9%)	RR 0.95 (0.61 to 1.46)	28 fewer per 1,000 (from 218 fewer to 257 more)	⊕⊕○○ LOW	CRITICAL
Any AE												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^c	none	6/34 (17.6%)	4/34 (11.8%)	RR 1.50 (0.46 to 4.84)	59 more per 1,000 (from 64 fewer to 452 more)	⊕⊕○○ LOW	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

- a. This study had unclear allocation concealment, unblinded participants and outcome assessors, and high risk of attrition bias (22.5% drop out).
- b. Small sample size; the percentage changes in inflammatory lesions were reported as means with ranges
- c. Small sample size.

References

1. Basta-Juzbasic, A., et al., *A dose-finding study of azithromycin in the treatment of acne vulgaris*. Acta Dermatovenerol Croat, 2007. **15**(3): p. 141-7.

CONFIDENTIAL

10. Trimethoprim/sulfamethoxazole vs. placebo

e-Table 48. GRADE Evidence Profile for trimethoprim/sulfamethoxazole vs. placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trimethoprim/sulfamethoxazole	placebo	Relative (95% CI)	Absolute (95% CI)		
Acne score at 5 weeks												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	43 patients were randomized to receive trimethoprim/sulfamethoxazole 80/400mg) daily or placebo for 5 weeks. The acne score was calculated based on the number of acne lesions of various degrees (Grade I: very small pustules without surrounding erythema and inflamed comedones; Grade II: inflamed papular infiltration with or without pustules; Grade III: deep-seated, larger erythematous, painful infiltrations with or without pustules) At baseline, the mean acne scores for trimethoprim/sulfamethoxazole and placebo were 105 and 69, respectively. At 5 weeks, the mean acne scores for the trimethoprim/sulfamethoxazole and placebo were 40 and 63, respectively. The change was statistically significant for trimethoprim/sulfamethoxazole group only.			⊕⊕⊕○ MODERATE	CRITICAL	
Total lesion (Comedones and pustules) at 4 weeks												
1 ²	randomised trials	serious ^c	not serious	not serious	serious ^b	none	40 patients were randomized to receive trimethoprim/sulfamethoxazole or placebo for 4 weeks, and 36 patients completed the trial (16 in trimethoprim/sulfamethoxazole and 17 in placebo). At 4 weeks, there was no significant difference in blackheads and pustules between the two groups (p>0.05).			⊕⊕○○ LOW	CRITICAL	

Withdrawal due to AE

1 ²	randomised trials	serious ^d	not serious	not serious	serious ^e	none	2/16 (12.5%)	0/17 (0.0%)	RR 5.29 (0.27 to 102.49)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	IMPORTANT

Any AE

1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^f	none	0/22 (0.0%)	0/21 (0.0%)	not estimable		⊕⊕⊕○ MODERATE	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

- This study had unclear random sequence generation. At baseline, the average acne scores in the two groups were significantly different: 105 and 69 in trimethoprim/sulfamethoxazole and placebo groups, respectively
- Small sample size
- This study had unclear random sequence generation and allocation concealment and high risk of attrition bias (25% dropout), and only p-value for the difference in the change from baseline between two groups is provided.
- This study had unclear random sequence generation and allocation concealment and high risk of attrition bias (25% dropout).
- Small sample size and few events.
- Small sample size and zero events in both arms.

References

- Hersle, K., *Trimethoprim-sulphamethoxazole in acne vulgaris. A double-blind study*. Dermatologica, 1972. **145**(3): p. 187-91.
- Macdonald, R.H., L.E. Macconnell, and I.R. Dunsmore, *Trimethoprim-sulphamethoxazole versus placebo in acne vulgaris*. Br J Clin Pract, 1972. **26**(2): p. 97-8.

e-Table 49. GRADE Evidence Profile for doxycycline vs. erythromycin

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	Erythromycin	Relative (95% CI)	Absolute (95% CI)		
Physician global assessment (follow up: 6 weeks; assessed with: change from baseline in Comprehensive Acne Severity Scale (0-5))												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	15 (1.1 ± 0.9)	14 (0.8 ± 0.1)	-	MD 0.3 higher (0.16 lower to 0.76 higher)	⊕⊕○○ LOW	CRITICAL

CI: Confidence interval; MD: Mean difference

Explanations

- a. This study had unclear random sequence generation and allocation concealment, unblinded patients and selective reporting (letter to editor).
- b. Small sample size

References

1. Cao, T., et al., *Anti-pruritic efficacies of doxycycline and erythromycin in the treatment of acne vulgaris: A randomized single-blinded pilot study*. Indian J Dermatol Venereol Leprol, 2018. **84**(4): p. 458-460.

e-Table 50. GRADE Evidence Profile for minocycline vs. doxycycline

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline	doxycycline	Relative (95% CI)	Absolute (95% CI)		
Physician's global assessment (follow up: 12 weeks; assessed with: treatment being effective and very effective on 4-pointing scale)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	27/31 (87.1%)	28/33 (84.8%)	RR 1.03 (0.84 to 1.25)	25 more per 1,000 (from 136 fewer to 212 more)	⊕⊕⊕○ MODERATE	CRITICAL
Patient's global assessment (follow up: 12 weeks; assessed with: treatment being effective and very effective on 4-pointing scale)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	28/31 (90.3%)	28/33 (84.8%)	RR 1.06 (0.89 to 1.28)	51 more per 1,000 (from 93 fewer to 238 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Withdrawal due to AE												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	3/39 (7.7%)	2/40 (5.0%)	1.54 (0.27, 8.71)	30 fewer per 1,000 (from 130 fewer to 80 more)	⊕⊕⊕○ MODERATE	IMPORTANT
GI AE												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	2/39 (5.1%)	1/40 (2.5%)	2.05 (0.19, 21.72)	30 fewer per 1,000 (from 110 fewer to 60 more)	⊕⊕⊕○ MODERATE	IMPORTANT

Any AE

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline	doxycycline	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	3/39 (7.7%)	2/40 (5.0%)	RR 1.54 (0.27 to 8.71)	27 more per 1,000 (from 37 fewer to 386 more)	⊕⊕⊕○ MODERATE	IMPORTANT

Reduction in *P. acnes* (follow up: 6 weeks)

1 ²	randomised trials	not serious ^b	not serious	serious ^c	serious ^a	none	60 patients were randomized to 3 groups of 20 each, for dosing with either minocycline 100mg BID, doxycycline 100mg BID, or tetracycline 500mg BID for 6 weeks. At baseline, log10/cm2 <i>P. acnes</i> were 6.35, 5.95, and 6.30 for minocycline, doxycycline, and tetracycline groups, respectively. At week 6, Minocycline group produced highly significant reductions in <i>P. acnes</i> on both cheeks and forehead compared with baseline (change in log10/cm2 <i>P. acnes</i> from baseline=2.05; p<=0.01). Doxycycline and tetracycline groups also produced significant reductions on both cheeks and forehead at 6 weeks (changes in log10/cm2 <i>P. acnes</i> at 6 week from baseline were 1.01 and 1.07 for doxycycline and tetracycline groups, respectively; both p<=0.01)				⊕⊕○○ LOW	IMPORTANT

Inflammatory bowel disease (follow up: varies)

1 ³	observational studies	not serious	not serious	not serious	serious ^d	none	When 94,487 acne patients were followed up for 406,294 person-years, IBD was noted in 41 individuals exposed to minocycline, 79 individuals exposed to tetracycline / oxytetracycline, 32 individuals exposed to doxycycline, and 55 (0.11 %) individuals not exposed to any of these antibiotics. Hazard ratios (HRs) for individual antibiotics were 1.19 (0.79, 1.79) for minocycline, 1.43 (1.02, 2.02) for tetracycline / oxytetracycline, and 1.63 (1.05, 2.52) for doxycycline. For ulcerative colitis, the				⊕○○○ VERY LOW	IMPORTANT

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline	doxycycline	Relative (95% CI)	Absolute (95% CI)		
							associations (HR) were 1.10 (0.76, 1.82) for minocycline, 1.27 (0.78, 2.07) for tetracycline /oxytetracycline, and 1.06 (0.53, 2.13) for doxycycline. For Crohn's disease (CD), the associations (HR) were 1.28 (0.72, 2.30) for minocycline, 1.61 (0.995, 2.63) for tetracycline / oxytetracycline, and 2.25 (1.27 4.00) for doxycycline.					

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease

Explanations

- Small sample size
- This study had unclear random sequence generation, allocation concealment, and outcome assessors and the participants were not blinded.
- This study enrolled healthy male and female subjects who had minimum *P. acnes* levels of 10,000 colony-forming units per cm² at baseline. It was not clear whether those subjects had a diagnosis of acne.
- Non-user group was used as a reference. No head-to-head comparison between doxycycline and minocycline.

References

- Ólafsson, J.H., et al., *Doxycycline versus minocycline in the treatment of acne vulgaris: A double-blind study*. Journal of Dermatological Treatment, 1989. 1(1): p. 15-17.
- Leyden, J.J., K. Kaidbey, and E. Gans, *The antimicrobial effects in vivo of minocycline, doxycycline and tetracycline in humans*. Journal of dermatological treatment, 1996. 7(4): p. 223-225.
- Margolis, D.J., et al., *Potential association between the oral tetracycline class of antimicrobials used to treat acne and inflammatory bowel disease*. Am J Gastroenterol, 2010. 105(12): p. 2610-6.

e-Table 51. GRADE Evidence Profile for minocycline vs. zinc gluconate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline 100 mg daily	zinc gluconate 30 mg bd	Relative (95% CI)	Absolute (95% CI)		
Inflammatory lesion, papules and pustules (follow up: 90 days; assessed with: percentage change from baseline)												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	161 (-61.92 ± 41.73)	157 (-45.50 ± 37.13)	-	MD 16.42 lower (25.1 lower to 7.74 lower)	⊕⊕⊕○ MODERATE	CRITICAL
Inflammatory lesion (follow up: 90 days; assessed with: 2/3 reduction in IL)												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	102/161 (63.4%)	49/157 (31.2%)	RR 2.03 (1.56 to 2.63)	321 more per 1,000 (from 175 more to 509 more)	⊕⊕⊕○ MODERATE	CRITICAL
Overall opinion on efficacy (100 mm VAS) - Clinician-assessed												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	155 (63.7 ± 27.0)	152 (50 ± 26.9)	-	MD 13.7 higher (7.67 higher to 19.73 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Overall opinion on efficacy (100 mm VAS) - Participant-assessed												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	148 (69.2 ± 24.2)	148 (52.5 ± 28.5)	-	MD 16.7 higher (10.68 higher to 22.72 higher)	⊕⊕⊕○ MODERATE	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline 100 mg daily	zinc gluconate 30 mg bd	Relative (95% CI)	Absolute (95% CI)		

Any AE

1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	36/169 (21.3%)	55/163 (33.7%)	RR 0.63 (0.44 to 0.91)	125 fewer per 1,000 (from 189 fewer to 30 fewer)	⊕⊕⊕○ MODERATE	IMPORTANT

Requiring therapy cessation

1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	4/169 (2.4%)	5/163 (3.1%)	RR 0.77 (0.21 to 2.82)	7 fewer per 1,000 (from 24 fewer to 56 more)	⊕⊕⊕○ MODERATE	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

- a. This study has unclear random sequence generation and allocation concealment.
- b. Small sample size

References

1. Dreno, B., et al., *Multicenter randomized comparative double-blind controlled clinical trial of the safety and efficacy of zinc gluconate versus minocycline hydrochloride in the treatment of inflammatory acne vulgaris*. *Dermatology*, 2001. **203**(2): p. 135-40.

e-Table 52. GRADE Evidence Profile for minocycline vs. clindamycin lotion

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline 50 mg bd	clindamycin 1% lotion bd	Relative (95% CI)	Absolute (95% CI)		
Participants' global assessment (assessed with: patient assessment of change in acne)												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	37/38 (97.4%)	40/42 (95.2%)	RR 1.02 (0.94 to 1.11)	19 more per 1,000 (from 57 fewer to 105 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Requiring therapy cessation												
2 ^{1,2}	randomised trials	not serious ^a	not serious	not serious	serious ^d	none	1/71 (1.4%)	1/75 (1.3%)	RR 1.11 (0.07 to 17.06)	1 more per 1,000 (from 12 fewer to 214 more)	⊕⊕⊕○ MODERATE	IMPORTANT
Any AE												
1 ²	randomised trials	not serious ^a	not serious	not serious	serious ^f	none	2/33 (6.1%)	2/33 (6.1%)	RR 1.00 (0.15 to 6.68)	0 fewer per 1,000 (from 52 fewer to 344 more)	⊕⊕⊕○ MODERATE	IMPORTANT

GI AE

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline 50 mg bd	clindamycin 1% lotion bd	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious ^a	not serious	not serious	serious ^f	none	1/33 (3.0%)	0/33 (0.0%)	RR 3.00 (0.13 to 71.07)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ MODERATE	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

- This study had unclear allocation concealment and blinding of outcome assessors.
- Small sample size
- One study had unclear allocation concealment and blinding of outcome assessors. The other study had unclear random sequence generation, allocation concealment, and attrition bias (6 participants were enrolled, but there were no details on how many participants were randomised to each group: It was assumed to be 33 due to matched pairs)
- Small sample size and zero events in both arms in one study.
- This study had unclear random sequence generation, allocation concealment, and attrition bias (6 participants were enrolled, but there were no details on how many participants were randomised to each group: It was assumed to be 33 due to matched pairs)
- Small sample size and wide CI including both appreciable benefits and harm

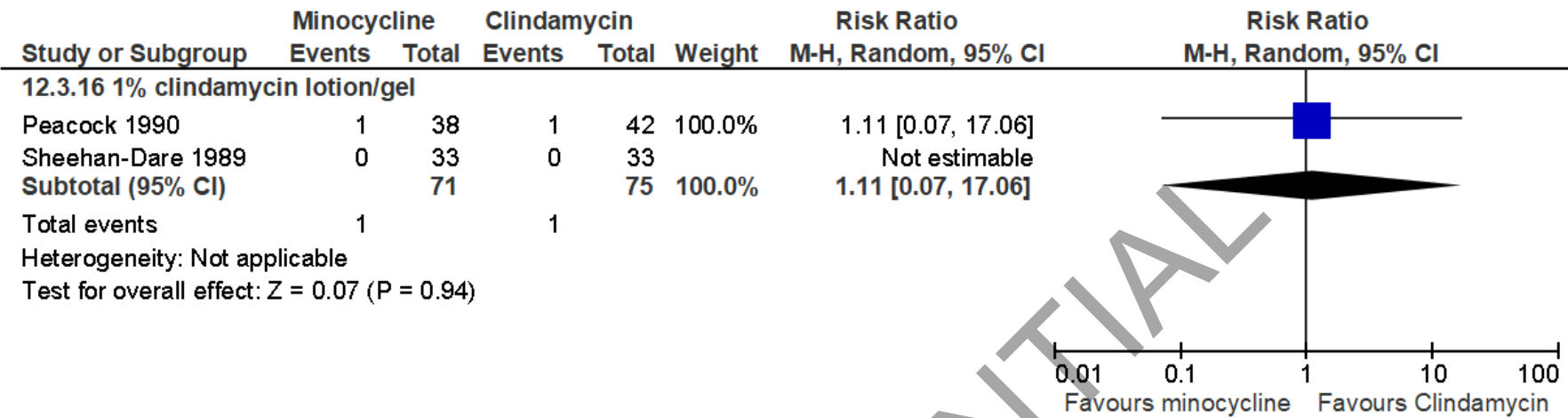
References

- Peacock, C., et al., *TOPICAL CLINDAMYCIN (DALACIN-T) COMPARED TO ORAL MINOCYCLINE (MINOCIN-50) IN TREATMENT OF ACNE-VULGARIS-A RANDOMIZED OBSERVER-BLIND CONTROLLED TRIAL IN 3 UNIVERSITY-STUDENT HEALTH CENTERS*. Clinical Trials Journal, 1990. **27**(3): p. 219-228.
- Sheehan-Dare, R.A., J. Papworth-Smith, and W.J. Cunliffe, *A double-blind comparison of topical clindamycin and oral minocycline in the treatment of acne vulgaris*. Acta Derm Venereol, 1990. **70**(6): p. 534-7.

Forest plot

e-Figure 155. Withdrawal due to AE, minocycline vs. clindamycin lotion

12.3 Requiring therapy cessation



e-Table 53. GRADE Evidence Profile for minocycline vs. doxycycline

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline 100 mg ER od	benzoyl peroxide bd	Relative (95% CI)	Absolute (95% CI)		
Physician's global assessment (follow up: 18 weeks; assessed with: at least moderate improvement)												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	66/130 (50.8%)	74/130 (56.9%)	RR 0.89 (0.71 to 1.12)	63 fewer per 1,000 (from 165 fewer to 68 more)	⊕⊕⊕○ MODERATE	CRITICAL
Inflammatory lesion (follow up: 18 weeks; assessed with: change from baseline)												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	130	130	-	MD 0 (7.05 lower to 7.05 higher)	⊕⊕⊕○ MODERATE	CRITICAL
Participants' global assessment (follow up: 18 weeks; assessed with: at least moderate improvement)												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	70/130 (53.8%)	78/130 (60.0%)	RR 0.90 (0.73 to 1.11)	60 fewer per 1,000 (from 162 fewer to 66 more)	⊕⊕⊕○ MODERATE	IMPORTANT

Requiring therapy cessation

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline 100 mg ER od	benzoyl peroxide bd	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	6/130 (4.6%)	9/130 (6.9%)	RR 0.67 (0.24 to 1.82)	23 fewer per 1,000 (from 53 fewer to 57 more)	⊕⊕⊕○ MODERATE	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

- a. This study had unblinded patients and high risk of attrition bias and selective reporting.
b. Small sample size.

References

- Ozolins, M., et al., *Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomised controlled trial.* Lancet, 2004. **364**(9452): p. 2188-95.

Hormonal Agents

1. Combined oral contraceptives vs. placebo

e-Table 54. GRADE Evidence Profile for combined oral contraceptives vs. placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral COC	placebo	Relative (95% CI)	Absolute (95% CI)		
Physician global assessment, clear or almost clear after cycle 6												
3 ^{1, 2, 3}	randomised trials	not serious ^{a, b}	not serious	not serious	not serious	none	191/499 (38.3%)	138/504 (27.4%)	RR 1.45 (1.06 to 1.97)	123 more per 1,000 (from 16 more to 266 more)	⊕⊕⊕⊕ High	CRITICAL
Physician global assessment, no, minimal or mild facial acne after cycle 6												
1 ⁴	randomised trials	not serious ^b	not serious	not serious	not serious	none	124/280 (44.3%)	82/275 (29.8%)	RR 1.49 (1.19 to 1.86)	146 more per 1,000 (from 57 more to 256 more)	⊕⊕⊕⊕ High	CRITICAL
Physician global assessment, Improvement after cycle 6												
3 ^{5, 6, 7}	randomised trials	not serious ^c	not serious	not serious	not serious	none	621/682 (91.1%)	302/422 (71.6%)	RR 1.29 (1.15 to 1.44)	208 more per 1,000 (from 107 more to 315 more)	⊕⊕⊕⊕ High	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral COC	placebo	Relative (95% CI)	Absolute (95% CI)		

Physician global assessment, VAS score, after cycle 6

1 ⁸	randomised trials	not serious ^d	not serious	not serious	serious ^e	none	Changes from baseline for both treatment groups revealed significant increases in investigator VAS scores, which were increasingly larger in the DSG-OC group over time. Significant differences at endpoint of about 11 mm (p = 0.04) showed a beneficial treatment effect for DSG-OC.*Used a 100-mm visual analog scale (VAS), with higher scores reflecting a better skin appearance*				⊕⊕⊕○ Moderate	CRITICAL

Total lesion, change from baseline after cycle 6

4, 2, 3, 6, 7	randomised trials	not serious ^f	not serious	not serious	not serious	none	474	485	-	MD 9.69 lower (14.58 lower to 4.8 lower)	⊕⊕⊕⊕ High	CRITICAL

Total lesion, percentage change from baseline after cycle 6

8 ^{1, 2, 3, 4, 5, 6, 7, 9}	randomised trials	not serious ^g	not serious	not serious	not serious	none	2182	1924	-	MD 16.6 lower (20.8 lower to 12.4 lower) ^h	⊕⊕⊕⊕ High	CRITICAL

Inflammatory lesion, change from baseline after cycle 6

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral COC	placebo	Relative (95% CI)	Absolute (95% CI)		
4 ^{2, 3, 6, 7}	randomised trials	not serious ^f	not serious	not serious	not serious	none	474	485	-	MD 3.23 lower (4.64 lower to 1.81 lower)	⊕⊕⊕⊕ High	CRITICAL

Inflammatory lesion, percentage change from baseline after cycle 6

9 ^{1, 2, 3, 4, 5, 6, 7, 9, 10}	randomised trials	not serious ⁱ	not serious	not serious	not serious	none	1727	1493	-	MD 15.81 lower (20.44 lower to 11.17 lower) ^j	⊕⊕⊕⊕ High	CRITICAL

Inflammatory lesion, >50% reduction after cycle 6

1 ¹⁰	randomised trials	not serious	not serious	not serious	serious ^e	none	161/251 (64.1%)	55/126 (43.7%)	RR 1.47 (1.18 to 1.83)	205 more per 1,000 (from 79 more to 362 more)	⊕⊕⊕○ Moderate	CRITICAL

Non-inflammatory lesion, change from baseline after cycle 6

4 ^{2, 3, 6, 7}	randomised trials	not serious ^f	not serious	not serious	not serious	none	474	485	-	MD 6.37 lower (10.87 lower to 1.88 lower)	⊕⊕⊕⊕ High	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral COC	placebo	Relative (95% CI)	Absolute (95% CI)		

Non-inflammatory lesion, percentage change from baseline after cycle 6

6 ^{2, 3, 4, 6, 7, 9}	randomised trials	not serious ^k	not serious	not serious	not serious	none	770	853	-	MD 19.45 lower (29.9 lower to 9 lower) ^l	⊕⊕⊕⊕ High	CRITICAL

Serious AE

2 ^{2, 4}	randomised trials	not serious ^m	not serious	not serious	not serious	none	2/471 (0.4%)	2/472 (0.4%)	RR 0.96 (0.14 to 6.49)	0 fewer per 1,000 (from 4 fewer to 23 more)	⊕⊕⊕⊕ High	CRITICAL

Patient global assessment, Improvement after cycle 6

4 ^{2, 3, 4, 6}	randomised trials	not serious ^f	not serious	not serious	not serious	none	487/591 (82.4%)	371/587 (63.2%)	RR 1.31 (1.17 to 1.48)	196 more per 1,000 (from 107 more to 303 more)	⊕⊕⊕⊕ High	IMPORTANT

Patient global assessment after cycle 6

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral COC	placebo	Relative (95% CI)	Absolute (95% CI)		
2 ^{8,10}	randomised trials	not serious ⁿ	not serious	not serious	serious ^e	none	Changes from baseline for both treatment groups in Katz 2000 revealed significant increases in patient VAS scores (a 100-mm visual analog scale with high scores reflecting a better skin appearance), which were increasingly larger in the DSG-OC group over time. Significant differences at the endpoint of about 14 mm ($p = 0.03$) showed a beneficial treatment effect for DSG-OC.⁸ At the end of cycle 6 in Plewig 2009 study, at least 70.5% of women taking EE/CMA rated the improvement of their moderate acne lesions as completely resolved (2.8%), excellent improved (37.1%) or satisfactory improved (30.7%), whereas 41.3% of women of the placebo group stated the improvement of their moderate acne lesions as at least satisfactory. "No moderate acne improvement" was reported by 11.6% of subjects taking EE/CMA compared with 19.8% of subjects taking placebo, and a "deterioration" was reported by 6% vs. 13.5% of subjects, respectively.¹⁰				⊕⊕⊕○ Moderate	IMPORTANT

Withdrawal due to AE

8 ^{1,2,4,5,7,9,10}	randomised trials	not serious ^p	not serious	not serious	not serious	none	104/2034 (5.1%)	48/1643 (2.9%)	RR 1.86 (1.32 to 2.62)	25 more per 1,000 (from 9 more to 47 more)	⊕⊕⊕⊕ High	IMPORTANT

Acne QoL, self-perception after cycle 6

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral COC	placebo	Relative (95% CI)	Absolute (95% CI)		
1 ⁴	randomised trials	not serious ^b	not serious	not serious	not serious	none	231	219	-	MD 3.45 higher (1.87 higher to 5.03 higher)	⊕⊕⊕⊕ High	IMPORTANT

Acne QoL, role-emotional, after cycle 6

1 ⁴	randomised trials	not serious ^b	not serious	not serious	not serious	none	231	219	-	MD 4.03 higher (2.41 higher to 5.65 higher)	⊕⊕⊕⊕ High	IMPORTANT

Acne QoL, role-social, after cycle 6

1 ⁴	randomised trials	not serious ^b	not serious	not serious	not serious	none	230	218	-	MD 2.58 higher (1.42 higher to 3.74 higher)	⊕⊕⊕⊕ High	IMPORTANT

Acne QoL, acne symptoms, after cycle 6

1 ⁴	randomised trials	not serious ^b	not serious	not serious	not serious	none	229	217	-	MD 2.96 higher (1.86 higher to 4.06 higher)	⊕⊕⊕⊕ High	IMPORTANT

Any AE

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	oral COC	placebo	Relative (95% CI)	Absolute (95% CI)		
4 ^{1,3,5,10}	randomised trials	not serious ^p	not serious	not serious	not serious	none	668/1236 (54.0%)	424/847 (50.1%)	RR 1.15 (1.07 to 1.24)	75 more per 1,000 (from 35 more to 120 more)	⊕⊕⊕⊕ High	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

- a. All 3 studies had high dropout rates ranging from 25.1% to 35.4%.
- b. 72% and 64% completed study in COC and placebo groups, respectively
- c. Two studies had high dropout rates (25.5% and 27.8%).
- d. 65.9% completed study
- e. Small sample size.
- f. All 4 studies had high dropout rates ranging from 25.5% to 35.4%.
- g. Eight studies had high dropout rates ranging from 25.1% to 35.4%
- h. Only 4 studies were pooled.
- i. Seven studies had high dropout rates ranging from 25.1% to 35.4%.
- j. Only 4 studies were pooled.
- k. All four studies had high dropout rates ranging from 27.8% to 35.4%.
- l. Only 3 studies were pooled.
- m. Both studies had high dropout rates (32.0% and 35.4%).
- n. One study had a dropout rate of 34.1%.
- o. Six studies had high dropout rates ranging from 25.1% to 35.4%.
- p. Two studies had high dropout rates (25.1% and 33.7%).

References

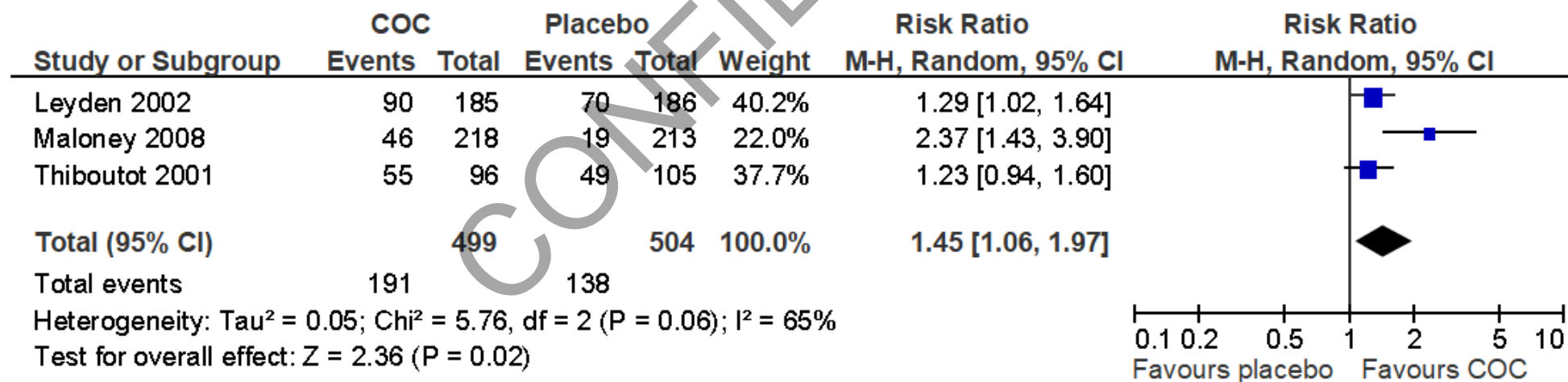
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6. Redmond, G.P., et al., *Norgestimate and ethinyl estradiol in the treatment of acne vulgaris: a randomized, placebo-controlled trial.* Obstet Gynecol, 1997. **89**(4): p. 615-22.
7. Lucky, A.W., et al., *Effectiveness of norgestimate and ethinyl estradiol in treating moderate acne vulgaris.* J Am Acad Dermatol, 1997. **37**(5 Pt 1): p. 746-54.
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10. Plewig, G., et al., *Efficacy of an oral contraceptive containing EE 0.03 mg and CMA 2 mg (Belara) in moderate acne resolution: a randomized, double-blind, placebo-controlled Phase III trial.* Contraception, 2009. **80**(1): p. 25-33.

Forest Plots

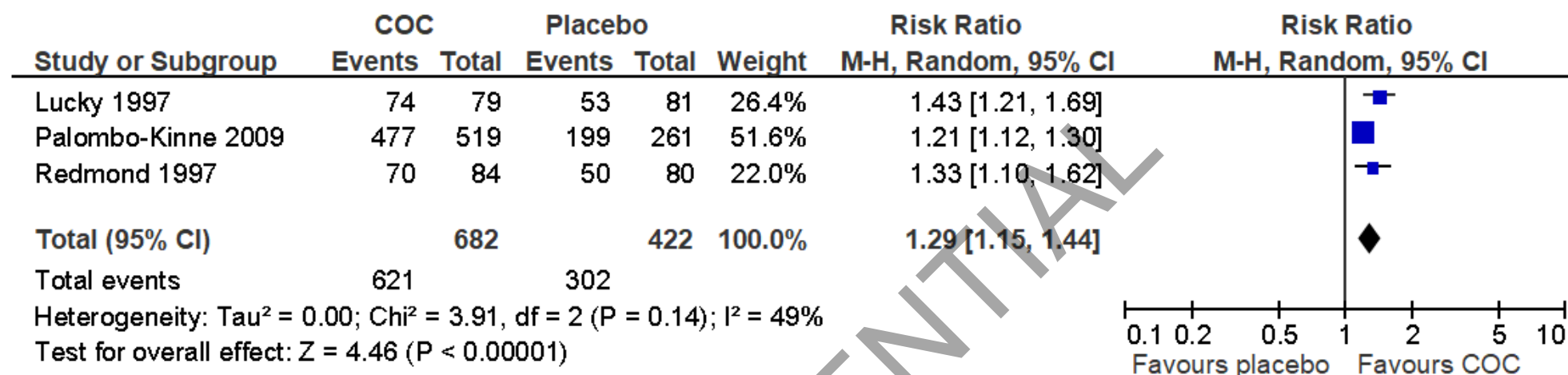
e-Figure 156. IGA, clear or almost clear after cycle 6, combined oral contraceptives vs. placebo

1.1 Physician global assessment, clear or almost clear after cycle 6



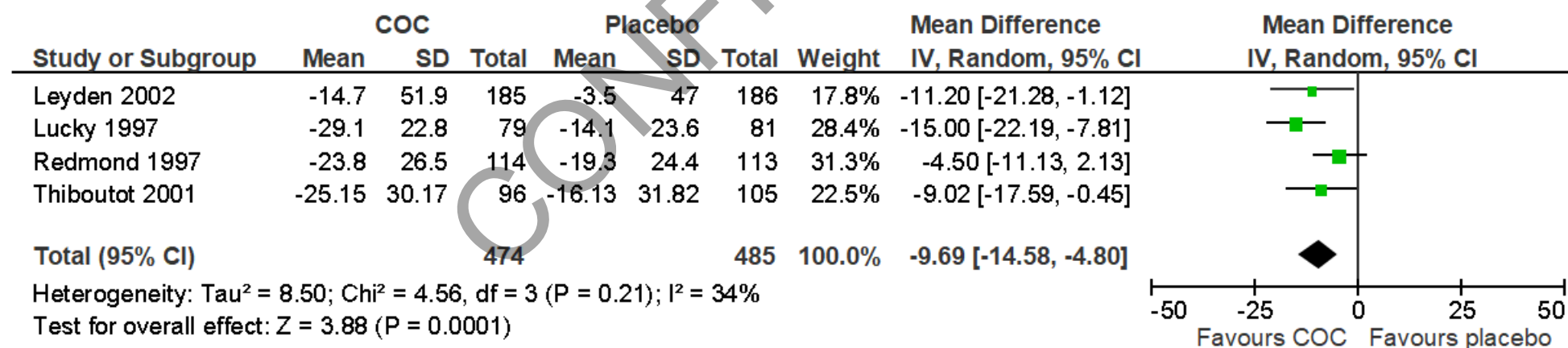
e-Figure 157. IGA, improvement, after cycle 6, combined oral contraceptives vs. placebo

1.3 Physician global assessment, Improvement after cycle 6



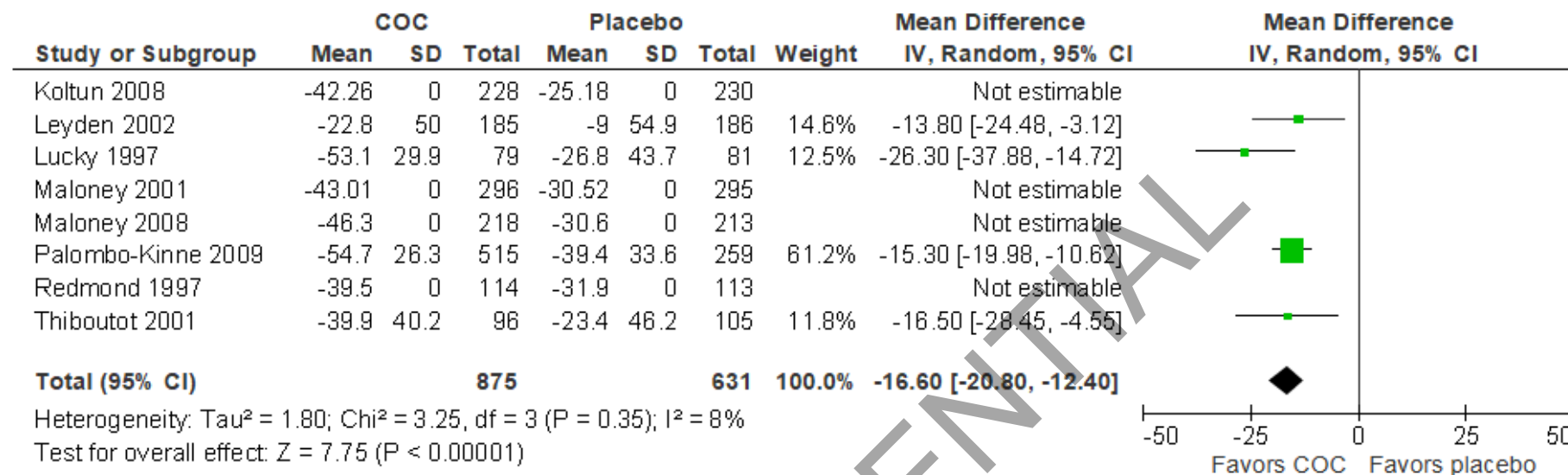
e-Figure 158. Total lesion, change from baseline, after cycle 6, combined oral contraceptives vs. placebo

1.6 Total lesion, change from baseline after cycle 6



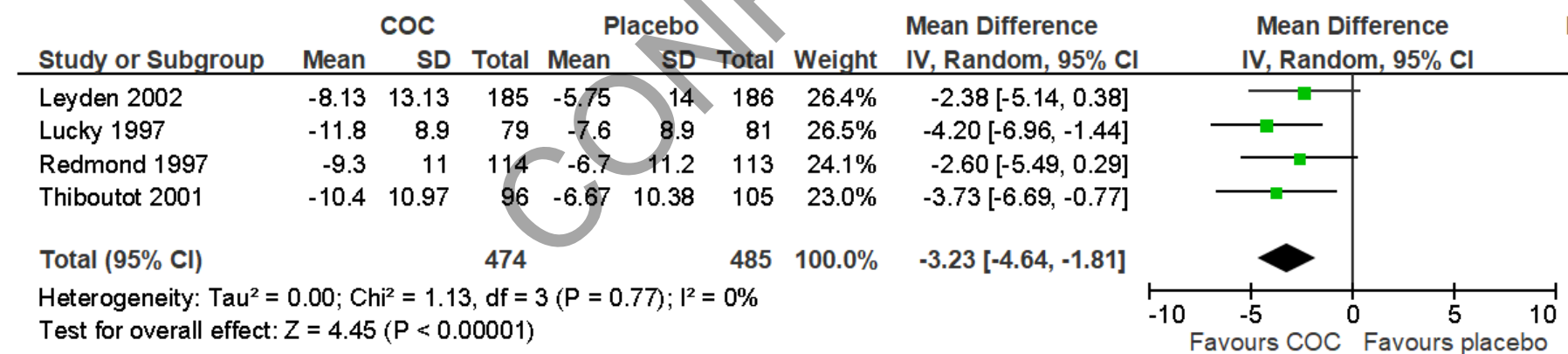
e-Figure 159. Total lesion, percentage change from baseline, after cycle 6, combined oral contraceptives vs. placebo

1.7 Total lesion, percentage change from baseline after cycle 6



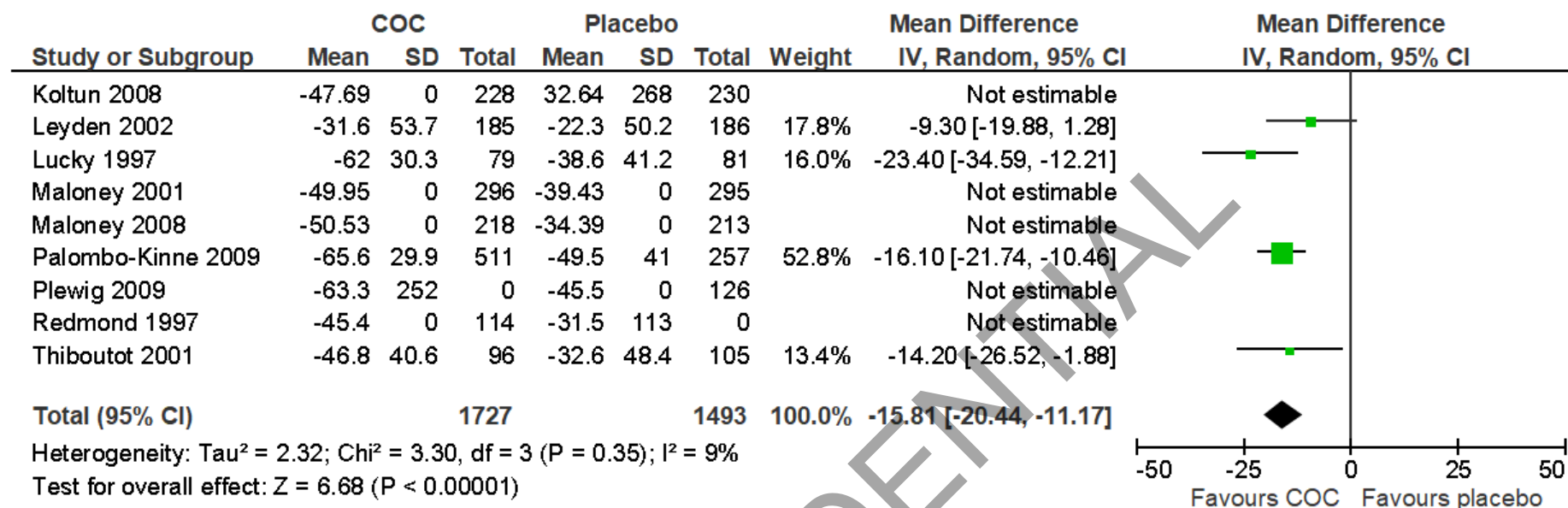
e-Figure 160. Inflammatory lesion, change from baseline, after cycle 6, combined oral contraceptives vs. placebo

1.8 Inflammatory lesion, change from baseline after cycle 6



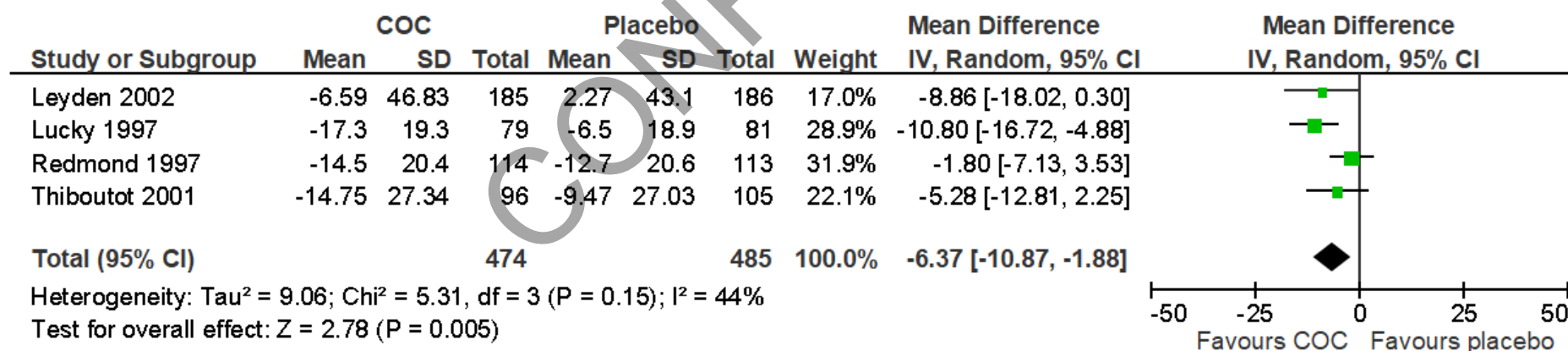
e-Figure 161. Inflammatory lesion, percentage change from baseline, after cycle 6, combined oral contraceptives vs. placebo

1.9 Inflammatory lesion, percentage change from baseline after cycle 6



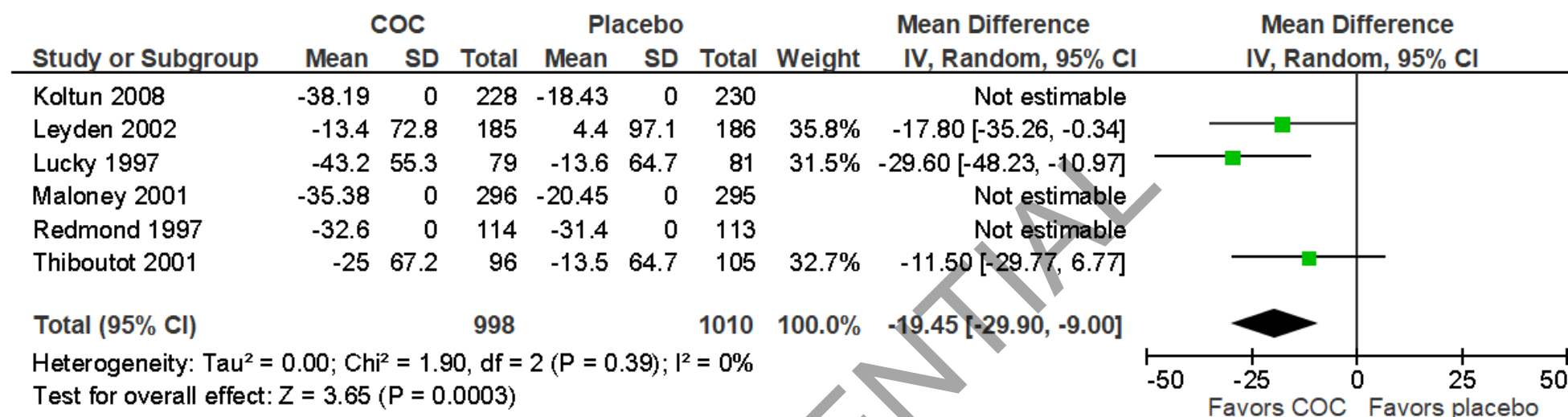
e-Figure 162. Non-inflammatory lesion, change from baseline, after cycle 6, combined oral contraceptives vs. placebo

1.11 Non-inflammatory lesion, change from baseline after cycle 6



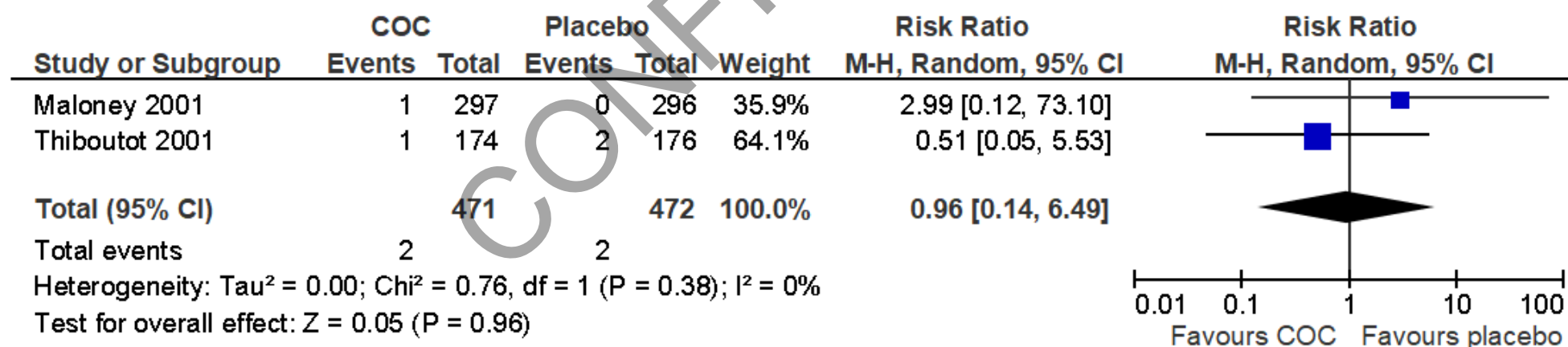
e-Figure 163. Non-inflammatory lesion, percentage change from baseline, after cycle 6, combined oral contraceptives vs. placebo

1.12 Non-inflammatory lesion, percentage change from baseline after cycle 6



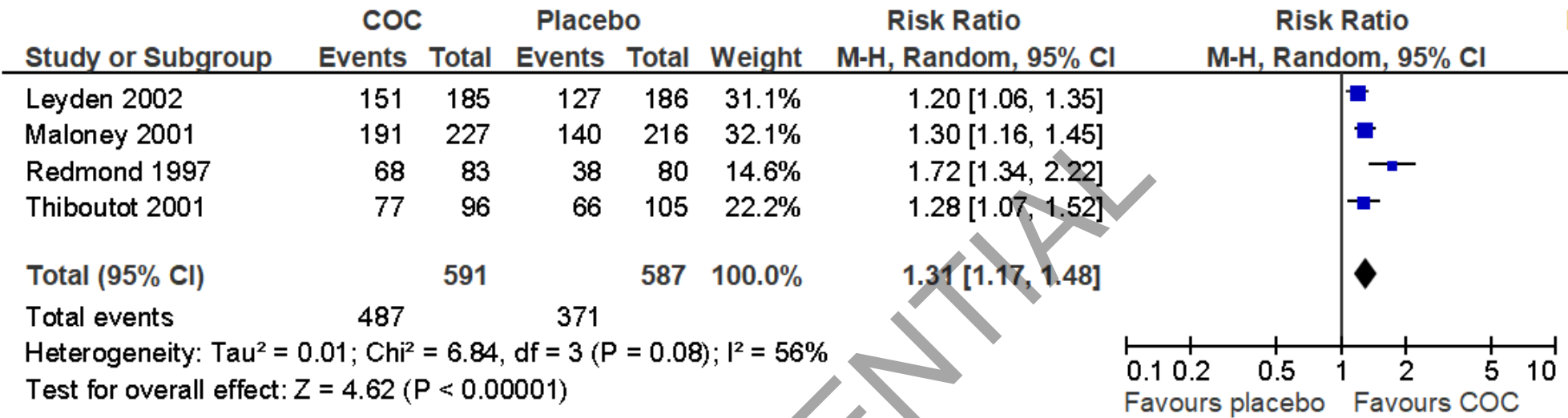
e-Figure 164. Serious AE, combined oral contraceptives vs. placebo

1.13 Serious AE



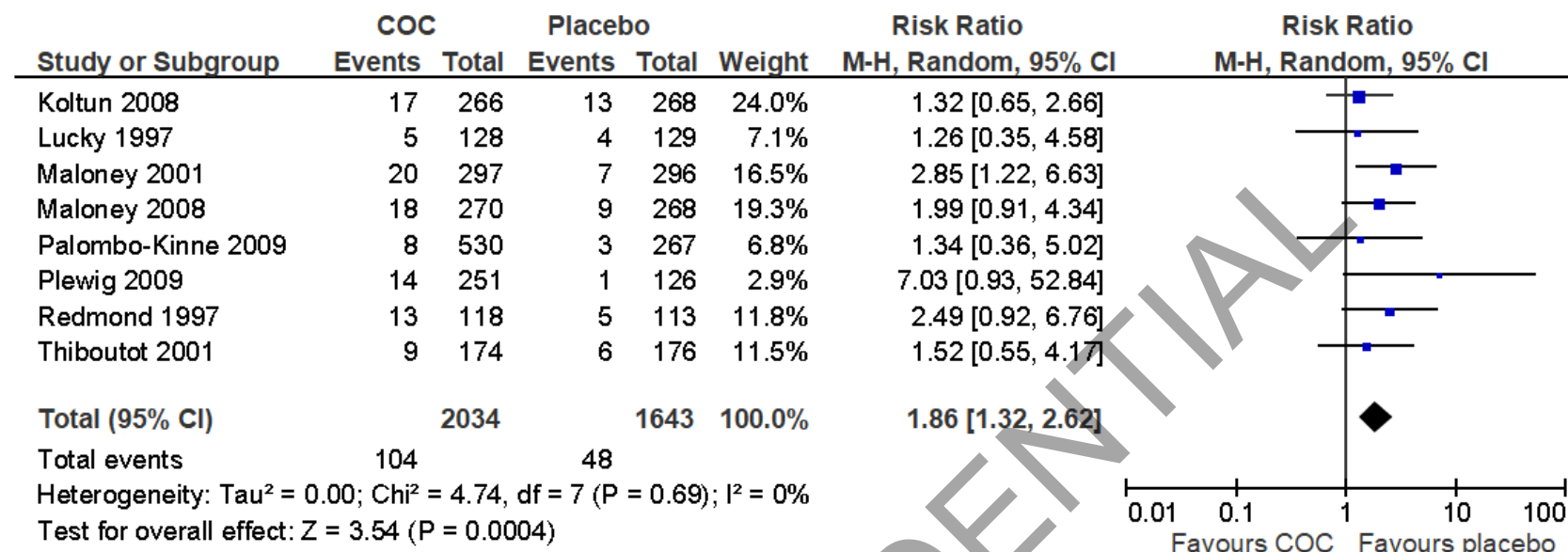
e-Figure 165. Patient global assessment, improvement, after cycle 6, combined oral contraceptives vs. placebo

1.14 Patient global assessment, Improvement after cycle 6



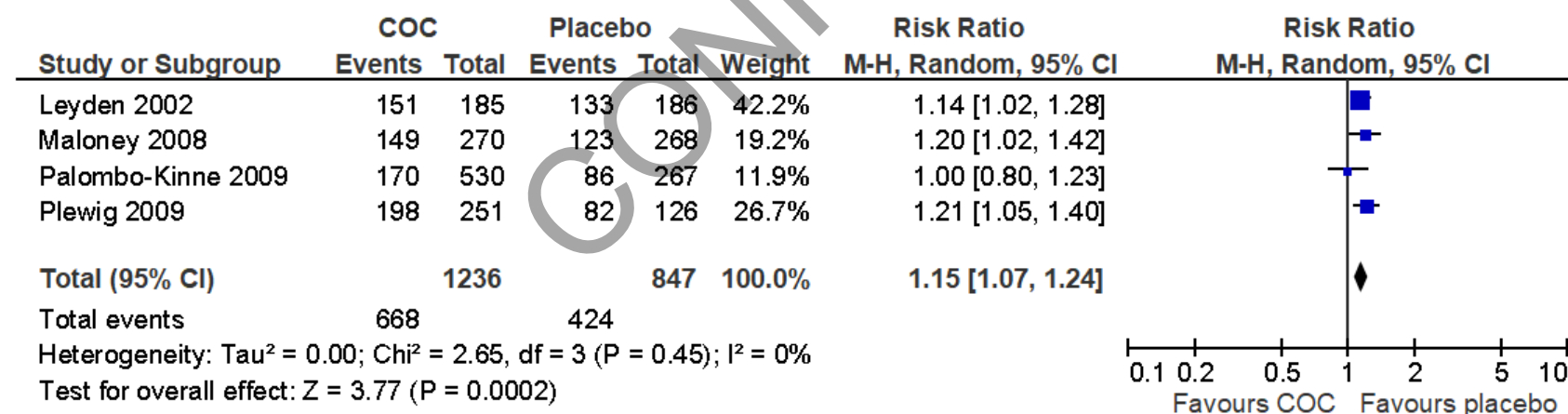
e-Figure 166. Withdrawal due to AE, combined oral contraceptives vs. placebo

1.16 Withdrawal due to AE



e-Figure 167. Any AE, combined oral contraceptives vs. placebo

1.17 Any AE



2. Spironolactone vs. placebo

e-Table 55. GRADE Evidence Profile for spironolactone vs. placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Spironolactone	placebo	Relative (95% CI)	Absolute (95% CI)		
Physician global assessment, clear or almost clear, at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	15/20 (75.0%)	6/20 (30.0%)	RR 2.50 (1.22 to 5.11)	450 more per 1,000 (from 66 more to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL
Physician global assessment, improved, at 12 weeks												
1 ²	randomised trials	not serious ^b	not serious	not serious	serious ^a	none	3/10 (30.0%)	1/6 (16.7%)	RR 1.80 (0.24 to 13.63)	133 more per 1,000 (from 127 fewer to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL
Physician global assessment, at least 2 grade improvement, at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	15/20 (75.0%)	6/20 (30.0%)	RR 2.50 (1.22 to 5.11)	450 more per 1,000 (from 66 more to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL
Total lesion, change from baseline, at 12 weeks												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Spironolactone	placebo	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	21 -18.2 ± 17.6	21 -38.0 ± 36.6	-	MD 19.75 higher (2.39 higher to 37.11 higher)	⊕⊕⊕○ Moderate	CRITICAL

Total lesion, >= 50% reduction, at 12 weeks

1 ³	randomised trials	not serious ^b	not serious	not serious	serious ^a	none	15/20 (75.0%)	4/20 (20.0%)	RR 3.75 (1.51 to 9.34)	550 more per 1,000 (from 102 more to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL

Inflammatory lesion, change from baseline, at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	21 -4.0 ± 7.1	21 -6.5 ± 5.9	-	MD 2.45 higher (1.52 lower to 6.42 higher)	⊕⊕⊕○ Moderate	CRITICAL

Noninflammatory lesion, change from baseline, at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	21 -25.0 ± 15.4	21 -35.1 ± 35.8	-	MD 10.1 higher (6.57 lower to 26.77 higher)	⊕⊕⊕○ Moderate	CRITICAL

Patient global assessment, improved, at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Spironolactone	placebo	Relative (95% CI)	Absolute (95% CI)		
2 ^{2,3}	randomised trials	serious ^c	not serious	not serious	serious ^a	none	24/31 (77.4%)	6/27 (22.2%)	RR 3.60 (1.75 to 7.42)	578 more per 1,000 (from 167 more to 1,000 more)	⊕⊕○○ Low	IMPORTANT

Withdrawal due to AE

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	0/20 (0.0%)	0/20 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

Menstrual irregularities

2 ^{1,2}	randomised trials	serious ^d	not serious	not serious	serious ^a	none	13/32 (40.6%)	0/27 (0.0%)	RR 10.89 (1.54 to 77.08)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ Low	IMPORTANT

Serum Potassium

7 1, 2, 4, 5, 6, 7, 8	observational studies	serious ^e	not serious	not serious	not serious	none	During the 12 weeks of the 2 spironolactone RCTs, no significant changes were seen in serum electrolytes in all groups.^{1, 2} When 108,547 acne patients who received spironolactone for at least 30 days were followed up for at least 6 months, 0.22% of patients experienced hyperkalemia (based on the ICD codes) during the course of spironolactone treatment, and 0.03% discontinued spironolactone within 30 days after the hyperkalemia diagnosis.⁴ A 4-year retrospective study evaluating 400 patients on spironolactone for the treatment of acne reported 6 hyperkalemia cases during 291.1 patient-year follow up.⁵ 974 healthy young women who took spironolactone for acne were followed up from December 2000 to March 2014, and 1,802 serum potassium measurements were undertaken while these patients were on spironolactone.³ Of 1,802 potassium measurements, 13 (0.72%) measurements showed mild hyperkalemia (between 5.1 and 6.0mEq/L). In 6 patients, the elevated value prompted successive testing within 1-3 weeks, revealing normal values in all cases. All patients with hyperkalemia were asymptomatic, and there were no reported adverse clinical events and the patients continued taking spironolactone. The baseline hyperkalemia rate, calculated based on the values obtained when taking and not taking spironolactone, was 0.76% (32 of 4,209), which was comparable to the 0.72% (13 of 1,802) rate of hyperkalemia in patients taking spironolactone.³ Spironolactone (200mg/day for the first 8 weeks followed by tapering 50mg every 4 weeks) was administered to 139 Japanese patients with acne,	⊕○○○ Very low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Spironolactone	placebo	Relative (95% CI)	Absolute (95% CI)		
							and potassium level was examined for 25 of the subjects. During up to 32 weeks of follow up, all 25 patients had their potassium levels within the normal range (3.5-5.0 mEq/L). ⁷					
							When 124 women on spironolactone for acne who had serum potassium level within the normal limits (3.5-5.0 mEq/L) were followed up for up to 12 months, three patients (ages, 42, 27, and 47 years) had incident hyperkalemia (≥ 5.1 mEq/L) at follow up (1-12 months after initiation of spironolactone). ⁸					

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

- Small sample size.
- Only 72% completed the study.
- Only 72% completed the study in both studies.
- Only 72% completed the study in one study.
- 5 studies were single arm studies.

References

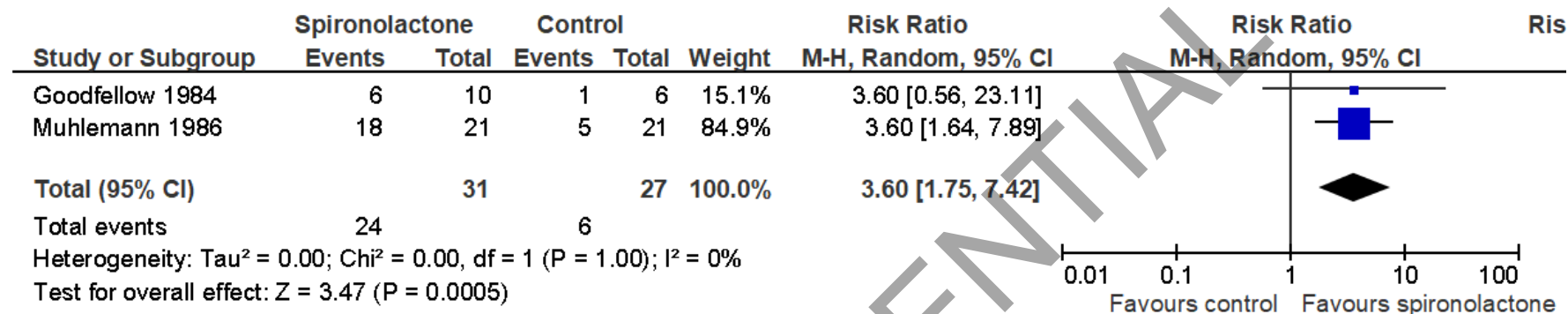
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Forest Plots

e-Figure 168. Patient global assessment, improved, at 12 weeks, spironolactone vs. placebo

9 Spironolactone versus placebo

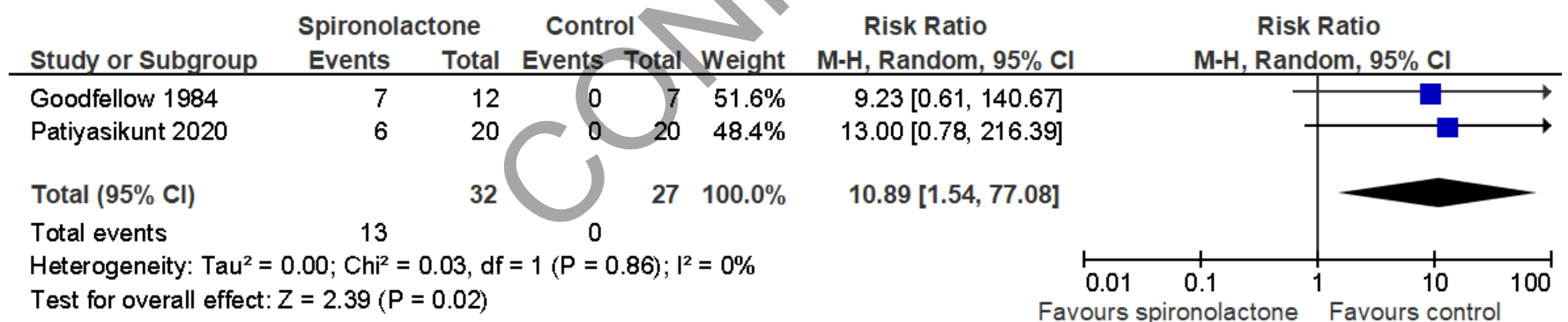
9.8 Patient global assessment, improved, at 12 weeks



e-Figure 169. Menstrual irregularities, spironolactone vs. placebo

9 Spironolactone versus placebo

9.9 Menstrual irregularities



3. DRSP 3 mg/EE 30 µg vs. LNG 150 µg/EE 30 µg

e-Table 56. GRADE Evidence Profile for DRSP 3 mg/EE 30 µg vs. LNG 150 µg/EE 30 µg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DRSP 3 mg / EE 30 µg	LNG 150 µg / EE 30 µg	Relative (95% CI)	Absolute (95% CI)		
Total lesion after Cycle 7												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	"Mean total lesion count decreased in the DRSP 3mg/EE 30 mg group with ongoing treatment, but remained relatively static in the LNG 150 mg/EE 30 mg group. Consistent with the changes in mean total lesion counts, there was a decrease in the proportion of subjects with acne in the DRSP 3mg/EE 30 mg group, but not in the LNG 150 mg/EE 30 mg group."			⊕⊕⊕○ Moderate	CRITICAL	
Deep vein thrombosis												
1 ¹	randomised trials	not serious ^a	not serious	not serious	not serious	none	1/282 (0.4%)	0/142 (0.0%)	RR 1.52 (0.06 to 36.98)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ High	CRITICAL
Serious AE												
1 ¹	randomised trials	not serious ^a	not serious	not serious	not serious	none	2/282 (0.7%)	0/142 (0.0%)	RR 2.53 (0.12 to 52.28)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ High	CRITICAL

Any AE

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DRSP 3 mg / EE 30 µg	LNG 150 µg / EE 30 µg	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious ^a	not serious	not serious	not serious	none	109/282 (38.7%)	62/142 (43.7%)	RR 0.89 (0.70 to 1.12)	48 fewer per 1,000 (from 131 fewer to 52 more)	⊕⊕⊕⊕ High	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

- a. Single blind (principal investigator was aware of treatment assignments. Only 66% completed the study).
b. Text describes decreases without any actual numbers or any statistical results.

References

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4. LNG 150 µg / EE 30 µg vs. DSG 150 µg / EE 30 µg

e-Table 57. GRADE Evidence Profile for LNG 150 µg / EE 30 µg vs. DSG 150 µg / EE 30 µg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG 150 µg / EE 30 µg	DSG 150 µg / EE 30 µg	Relative (95% CI)	Absolute (95% CI)		
Mean acne severity score after cycle 6												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	15 1.26 ± 0.56	18 0.78 ± 0.66	-	MD 0.48 higher (0.06 higher to 0.9 higher)	⊕⊕○○ Low	CRITICAL
Mean total lesion count after cycle 9												
1 ²	randomised trials	not serious ^c	not serious	not serious	serious ^b	none	9 17.6 ± 7.6	7 11.3 ± 3.3	-	MD 6.3 higher (0.77 higher to 11.83 higher)	⊕⊕⊕○ Moderate	CRITICAL
Total lesion, percentage change from baseline, after cycle 9												
1 ²	randomised trials	not serious ^c	not serious	not serious	serious ^b	none	In subjects completing 9 months of therapy, acne decreased by 52.8% in the LNG/EE group (n = 9) and by 58.5% in the DSG/EE (n = 7) (between groups: P not significant)			⊕⊕⊕○ Moderate	CRITICAL	

Withdrawal due to AE

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG 150 µg / EE 30 µg	DSG 150 µg / EE 30 µg	Relative (95% CI)	Absolute (95% CI)		
2 ^{1,2}	randomised trials	serious ^d	not serious	not serious	serious ^b	none	4/45 (8.9%)	3/43 (7.0%)	RR 1.27 (0.30 to 5.35)	19 more per 1,000 (from 49 fewer to 303 more)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; MD: Mean difference

Explanations

a. Limited methods reporting. Only 52% completed the study.

b. Small sample size.

c. only 52.9% completed the study.

d. One study had limited methods reporting and 52% of study completion rate. The other study had 52.9% completed the study.

References

1. Palatsi, R., et al., *Serum total and unbound testosterone and sex hormone binding globulin (SHBG) in female acne patients treated with two different oral contraceptives*. Acta Derm Venereol, 1984. **64**(6): p. 517-23.
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5. DSG 150 µg / EE 20 µg vs. LNG 100 µg / EE 20 µg

e-Table 58. GRADE Evidence Profile for DSG 150 µg / EE 20 µg vs. LNG 100 µg / EE 20 µg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DSG 150 µg / EE 20 µg	LNG 100 µg / EE 20 µg	Relative (95% CI)	Absolute (95% CI)		
Improvement in comedones after cycle 6												
1 ¹	randomised trials	serious ^a	not serious	not serious	not serious	none	71/266 (26.7%)	49/258 (19.0%)	RR 1.41 (1.02 to 1.94)	78 more per 1,000 (from 4 more to 179 more)	⊕⊕⊕○ Moderate	CRITICAL
Improvement in papules after cycle 6												
1 ¹	randomised trials	serious ^a	not serious	not serious	not serious	none	63/266 (23.7%)	61/258 (23.6%)	RR 1.00 (0.74 to 1.36)	0 fewer per 1,000 (from 61 fewer to 85 more)	⊕⊕⊕○ Moderate	CRITICAL
Improvement in pustules after cycle 6												
1 ¹	randomised trials	serious ^a	not serious	not serious	not serious	none	46/266 (17.3%)	32/258 (12.4%)	RR 1.39 (0.92 to 2.12)	48 more per 1,000 (from 10 fewer to 139 more)	⊕⊕⊕○ Moderate	CRITICAL

Improvement in nodules after cycle 6

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DSG 150 µg / EE 20 µg	LNG 100 µg / EE 20 µg	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	not serious	none	14/266 (5.3%)	17/258 (6.6%)	RR 0.80 (0.40 to 1.59)	13 fewer per 1,000 (from 40 fewer to 39 more)	⊕⊕⊕○ Moderate	CRITICAL

Withdrawal due to AE

1 ¹	randomised trials	serious ^a	not serious	not serious	not serious	none	10/500 (2.0%)	26/498 (5.2%)	RR 0.38 (0.19 to 0.79)	32 fewer per 1,000 (from 42 fewer to 11 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

Scores for Psychological General Well-Being Index after cycle 6

1 ¹	randomised trials	serious ^a	not serious	not serious	not serious	none	263	253	-	MD 1.1 higher (0.83 lower to 3.03 higher)	⊕⊕⊕○ Moderate	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **HR:** Hazard Ratio

Explanations

a. Open label study. Only 77% completed the study.

References

1. Winkler, U.H., H. Ferguson, and J.A. Mulders, *Cycle control, quality of life and acne with two low-dose oral contraceptives containing 20 microg ethinylestradiol*. Contraception, 2004. **69**(6): p. 469-76.

6. NGM/EE (triphasic) vs. DSG/EE (biphasic)

e-Table 59. GRADE Evidence Profile for NGM/EE (triphasic) vs. DSG/EE (biphasic)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NGM/EE (triphasic)	DSG/EE (biphasic)	Relative (95% CI)	Absolute (95% CI)		
Physician global assessment, excellent or good, after cycle 6												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	81/93 (87.1%)	71/95 (74.7%)	RR 1.17 (1.01 to 1.34)	127 more per 1,000 (from 7 more to 254 more)	⊕⊕⊕○ Moderate	CRITICAL
Total lesion, change from baseline after cycle 6												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	93 -13.4 ± 9.7	95 -11.9 ± 10.1	-	MD 1.5 lower (4.33 lower to 1.33 higher)	⊕⊕⊕○ Moderate	CRITICAL
Total lesion, percentage change from baseline, after cycle 6												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	93 -74.4 ± 35.2	95 -65.1 ± 35.2	-	MD 9.3 lower (19.36 lower to 0.76 higher)	⊕⊕⊕○ Moderate	CRITICAL

Papules, change from baseline after cycle 6

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NGM/EE (triphasic)	DSG/EE (biphasic)	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	93 -3.5 ± 5.1	95 -2.8 ± 4.6	-	MD 0.7 lower (2.09 lower to 0.69 higher)	⊕⊕⊕○ Moderate	CRITICAL

Pustules and Nodules, change from baseline after cycle 6

1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	93 -0.9 ± 2.3	95 -1.0 ± 2.1	-	MD 0.1 higher (0.53 lower to 0.73 higher)	⊕⊕⊕○ Moderate	CRITICAL

Comedones, change from baseline after cycle 6

1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	93 -9.0 ± 6.3	95 -8.2 ± 7.4	-	MD 0.8 lower (2.76 lower to 1.16 higher)	⊕⊕⊕○ Moderate	CRITICAL

Serious AE

1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	2/100 (2.0%)	0/101 (0.0%)	RR 5.05 (0.25 to 103.87)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	CRITICAL

Patient global assessment, excellent or good after cycle 6

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NGM/EE (triphasic)	DSG/EE (biphasic)	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	86/93 (92.5%)	91/95 (95.8%)	RR 0.97 (0.90 to 1.04)	29 fewer per 1,000 (from 96 fewer to 38 more)	⊕⊕○○ Low	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

- a. Study subjects were not blinded.
- b. Small sample size.

References

1. Jaisamram, U., et al., *A comparison of multiphasic oral contraceptives containing norgestimate or desogestrel in acne treatment: a randomized trial*. Contraception, 2014. 90(5): p. 535-41.

7. DRSP 3 mg / EE 30 µg vs. NGM 180-215-250 µg / EE 35 µg

e-Table 60. GRADE Evidence Profile for DRSP 3 mg / EE 30 µg vs. NGM 180-215-250 µg / EE 35 µg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DRSP 3 mg / EE 30 µg	NGM 180-215-250 µg / EE 35 µg	Relative (95% CI)	Absolute (95% CI)		
Physician global assessment, Improvement of facial acne after cycle 6												
1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	527/551 (95.6%)	524/569 (92.1%)	RR 1.04 (1.01 to 1.07)	37 more per 1,000 (from 9 more to 64 more)	⊕⊕⊕⊕ High	CRITICAL
Total lesion, percentage change from baseline after cycle 6												
1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	547	561	-	MD 3.3 lower (6.45 lower to 0.15 lower)	⊕⊕⊕⊕ High	CRITICAL
Total lesion, change from baseline after cycle 6												
1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	547	561	-	MD 2.6 lower (5.72 lower to 0.52 higher)	⊕⊕⊕⊕ High	CRITICAL
Inflammatory lesion, percentage change from baseline after cycle 6												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DRSP 3 mg / EE 30 µg	NGM 180-215-250 µg / EE 35 µg	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	547	561	-	MD 2.4 lower (5.97 lower to 1.17 higher)	⊕⊕⊕⊕ High	CRITICAL

Inflammatory lesion, change from baseline after cycle 6

1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	547	561	-	MD 0.5 lower (1.86 lower to 0.86 higher)	⊕⊕⊕⊕ High	CRITICAL

Open comedone, percentage change from baseline after cycle 6

1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	547	561	-	MD 9.3 lower (17.59 lower to 1.01 lower)	⊕⊕⊕⊕ High	CRITICAL

Open comedone, change from baseline after cycle 6

1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	547	561	-	MD 1.5 lower (3.17 lower to 0.17 higher)	⊕⊕⊕⊕ High	CRITICAL

Closed comedone, percentage change from baseline after cycle 6

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DRSP 3 mg / EE 30 µg	NGM 180-215-250 µg / EE 35 µg	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	547	561	-	MD 5.2 lower (13.45 lower to 3.05 higher)	⊕⊕⊕⊕ High	CRITICAL

Closed comedone, change from baseline after cycle 6

1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	547	561	-	MD 0.6 lower (2.1 lower to 0.9 higher)	⊕⊕⊕⊕ High	CRITICAL

Serious adverse event

1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	18/566 (3.2%)	2/582 (0.3%)	RR 9.25 (2.16 to 39.70)	28 more per 1,000 (from 4 more to 133 more)	⊕⊕⊕⊕ High	CRITICAL

Patient global assessment, improvement of facial acne after cycle 6

1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	512/550 (93.1%)	505/567 (89.1%)	RR 1.05 (1.01 to 1.08)	45 more per 1,000 (from 9 more to 71 more)	⊕⊕⊕⊕ High	IMPORTANT

Discontinuation due to adverse event

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DRSP 3 mg / EE 30 µg	NGM 180-215-250 µg / EE 35 µg	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	18/566 (3.2%)	23/582 (4.0%)	RR 0.80 (0.44 to 1.47)	8 fewer per 1,000 (from 22 fewer to 19 more)	⊕⊕⊕⊕ High	IMPORTANT

Any AE

1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	92/566 (16.3%)	106/582 (18.2%)	RR 0.89 (0.69 to 1.15)	20 fewer per 1,000 (from 56 fewer to 27 more)	⊕⊕⊕⊕ High	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

References

1. Thorneycroft, H., H. Gollnick, and I. Schellschmidt, *Superiority of a combined contraceptive containing drospirenone to a triphasic preparation containing norgestimate in acne treatment*. *Cutis*, 2004. **74**(2): p. 123-30.

8. LNG 100 µg / EE 20 µg vs. NA 1 mg / EE 20 µg

e-Table 61. GRADE Evidence Profile for LNG 100 µg / EE 20 µg vs. NA 1 mg / EE 20 µg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LNG 100 µg / EE 20 µg	NA 1 mg / EE 20 µg	Relative (95% CI)	Absolute (95% CI)		
Total lesion, change from baseline after cycle 3 (subgroup of women with >= 15 lesions at baseline)												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	11 -18.4 ± 15.8	8 -20.9 ± 16.5	-	MD 2.5 higher (12.26 lower to 17.26 higher)	⊕⊕⊕○ Moderate	CRITICAL
Discontinuation due to side effects												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^c	none	0/30 (0.0%)	1/28 (3.6%)	RR 0.31 (0.01 to 7.35)	25 fewer per 1,000 (from 35 fewer to 227 more)	⊕⊕⊕○ Moderate	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

a. Open label study.

b. Small sample size. Included a subgroup of women with ≥ 15 lesions at baseline.

c. Small sample size.

References

1. Thorneycroft, I.H., et al., *Effect of low-dose oral contraceptives on androgenic markers and acne*. Contraception, 1999. 60(5): p. 255-62.

e-Table 62. GRADE Evidence Profile for metformin vs. placebo in PCOS

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metformin	placebo in PCOS	Relative (95% CI)	Absolute (95% CI)		
Presence of acne at 4 months												
1 ¹	randomised trials	not serious ^a	not serious	serious ^b	serious ^c	none	At baseline, 10/20 (50%), 8/20 (40%), and 7/30 (35%) in metformin, metformin + cal/VitD, and placebo, respectively, had acne. At 4 months, 0/20 (0%), 4/20 (20%), and 7/30 (35%) in metformin, metformin + cal/VitD, and placebo, respectively, had acne.		⊕⊕○○ Low		CRITICAL	

CI: confidence interval; PCOS: polycystic ovary syndrome

Explanations

a. Unclear randomization methods and allocation concealment.

b. Enrolled women aged 20-40 years with PCOS; At baseline, 10/20 (50%), 8/20 (40%), and 7/30 (35%) in metformin, metformin + cal/VitD, and placebo, respectively, had acne.

c. Small sample size.

References

1. Tehrani, H.G., F. Mostajeran, and S. Shahsavari, *The effect of calcium and vitamin D supplementation on menstrual cycle, body mass index and hyperandrogenism state of women with polycystic ovarian syndrome*. J Res Med Sci, 2014. **19**(9): p. 875-80.

e-Table 63. GRADE Evidence Profile for metformin vs. COC in PCOS

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metformin	COC	Relative (95% CI)	Absolute (95% CI)		
Physician global assessment, Cook acne score, at 6 months												
1 ¹	randomised trials	serious ^a	not serious	serious ^b	serious ^c	none	Thirty-six adolescent females (12-21yo) with signs and symptoms suggesting PCOS were randomized to receive metformin or COC. Cook severity scores at baseline were 1.1 ± 0.40 and 2.1 ±0.53 in metformin and COC, respectively. Acne score showed no consistent change over time for the metformin group but decreased for the OCP group (p <0.05 - not considered significant due to multiple comparisons rule).			⊕○○○ Very low	CRITICAL	
Improvement in Acne at 3 months (subgroup of women with acne at baseline)												
1 ²	randomised trials	serious ^a	not serious	not serious	serious ^d	none	2/4 (50.0%)	4/5 (80.0%)	RR 0.63 (0.21 to 1.83)	296 fewer per 1,000 (from 632 fewer to 664 more)	⊕⊕○○ Low	CRITICAL

Patient global assessment at 12 months

Certainty assessment							№ of patients		Effect		Certainty	Importance	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metformin	COC	Relative (95% CI)	Absolute (95% CI)			
2 ^{3,4}	randomised trials	serious ^e	not serious	serious ^f	serious ^c	none	Ninety women with PCOS were randomized to receive i) metformin 1g BID, ii) metformin plus COC (DSG/EE 140mg/30mg) or iii) COC. At 12 months, the median changes in PCOS-VAS acne subscore were -0.4 (IQR, -2.0, 0.1) and -1.8 (IQR, -4.0, 0) in metformin (n=19) and COC (n=23), respectively. PCOS-VAS consisted of a horizontal line from 0mm to 100 mm, ranging from no discomfort at the 0mm mark to severe discomfort at the 100mm mark. ³ Fifty-two women with PCOS were randomized to receive metformin 500mg three times daily or COC (CYP/EE 2mg/35ug) daily. At baseline, the patient's own quantitative self-assessment scores for acne were 3.4 and 2.0 in metformin and COC, respectively. Both groups believed that acne improved significantly by self-assessment. At 6 months, the scores decreased to 2.9 and 1.2 in metformin and COC, respectively (between group p value was not provided). At 12 months, the acne self-assessments were 1.9 and 1.0 in metformin and COC, respectively (the between group p value was 0.36) ⁴					⊕○○○ Very low	IMPORTANT
Presence of acne at 4 months													
1 ⁵	randomised trials	serious ^a	not serious	serious ^g	serious ^c	none	At baseline, 23/47 in metformin and 17/22 in COC had acne. At 4 months after the treatment, 19/47 in metformin and 13/22 in COC had acne.					⊕○○○ Very low	

CI: Confidence interval; RR: Risk ratio

Explanations

- a. Minimal methods reporting.
- b. Enrolled adolescent females (12-21yo) with signs and symptoms suggesting PCOS;
- c. Small sample size.
- d. This study enrolled women with PCOS, and at baseline only 4/12 and 5/12 in metformin and COC, respectively, had acne.
- e. One study had minimal methods reporting. The other study had 34% dropouts.
- f. Both studies enrolled women with PCOS.
- g. Enrolled young women with PCOS. At baseline, 23/47 in metformin and 17/22 in COC had acne.

References

1. Allen, H.F., et al., *Randomized controlled trial evaluating response to metformin versus standard therapy in the treatment of adolescents with polycystic ovary syndrome*. J Pediatr Endocrinol Metab, 2005. **18**(8): p. 761-8.
2. Mhao, N.S., et al., *A comparative study to illustrate the benefits of using ethinyl estradiol-cyproterone acetate over metformin in patients with polycystic ovarian syndrome*. Diabetes Metab Syndr, 2016. **10**(1 Suppl 1): p. S95-8.
3. Altinok, M.L., et al., *Effect of 12-month treatment with metformin and/or oral contraceptives on health-related quality of life in polycystic ovary syndrome*. Gynecol Endocrinol, 2018. **34**(10): p. 859-863.
4. Harborne, L., et al., *Metformin or antiandrogen in the treatment of hirsutism in polycystic ovary syndrome*. J Clin Endocrinol Metab, 2003. **88**(9): p. 4116-23.
5. Cetinkalp, S., et al., *The effects of rosiglitazone, metformin, and estradiol-cyproterone acetate on lean patients with polycystic ovary syndrome*. The Endocrinologist, 2009. **19**(3): p. 94-97.

11. Metformin plus COC vs. COC in PCOS

e-Table 64. GRADE Evidence Profile for metformin plus COC vs. COC in PCOS

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metformin plus COC	COC in PCOS	Relative (95% CI)	Absolute (95% CI)		
Physician global assessment, global acne grading system, at 3 months												
1 ¹	randomised trials	not serious	not serious	serious ^a	serious ^b	none	Eighty-two women with PCOS were randomized to receive Diane 35 (cyproterone acetate 2mg and ethinylestradiol 35 µg) with metformin (415mg BID titrated up to maximum tolerable dosage; n=41) or Diane 35 alone (n=41). At baseline, global acne grading system (GAGS) scores were 3.50 ± 1.35 and 3.45 ± 1.45 in Diane 35 plus metformin and Diane 35, respectively. At 3 months, GAGS decreased to 0.54 ± 0.02 and 0.45 ± 0.04 in Diane 35 plus metformin and Diane 35, respectively (both within group p values were less than 0.01; between group p was 0.79).			⊕⊕○○ Low	CRITICAL	
Patient global assessment, PCOS-VAS acne score, change from baseline, at 12 months												
1 ²	randomised trials	serious ^c	not serious	serious ^a	serious ^b	none	At 12 months, the median changes in PCOS-VAS acne subscore were -2.6 (IQR, -5.3, 0.0) and -1.8 (IQR, -4.0, 0) in metformin plus OCP group (n=23) and OCP (n=23), respectively. PCOS-VAS consisted of a horizontal line from 0mm to 100 mm, ranging from no discomfort at the 0mm mark to severe discomfort at the 100mm mark.			⊕○○○ Very low	IMPORTANT	

Explanations

a. Enrolled women with PCOS.

b. Small sample size.

c. Minimal methods reporting.

References

1. Feng, W., et al., *Management of polycystic ovarian syndrome with Diane-35 or Diane-35 plus metformin*. Gynecol Endocrinol, 2016. **32**(2): p. 147-50.
2. Altinok, M.L., et al., *Effect of 12-month treatment with metformin and/or oral contraceptives on health-related quality of life in polycystic ovary syndrome*. Gynecol Endocrinol, 2018. **34**(10): p. 859-863.

CONFIDENTIAL

12. Metformin + tetracycline + BPO vs. tetracycline + BPO

e-Table 65. GRADE Evidence Profile for metformin + tetracycline + BPO vs. tetracycline + BPO

Certainty assessment							№ of patients		Effect		Certaint y	Importanc e
№ of studie s	Study design	Risk of bias	Inconsisten cy	Indirectne ss	Imprecisio n	Other consideratio ns	Metformin+tetracycline+B PO	tetracycline+B PO	Relativ e (95% CI)	Absolut e (95% CI)		
Physician global assessment, clear or almost clear or at least 2 grade improvement at 12 weeks												
1 ¹	randomise d trials	not seriou s	not serious	not serious	serious ^a	none	26/39 (66.7%)	16/37 (43.2%)	RR 1.54 (1.00 to 2.37)	234 more per 1,000 (from 0 fewer to 592 more)	⊕⊕⊕ ○ Moderate	CRITICAL
Total lesion at 12 weeks												
1 ¹	randomise d trials	not seriou s	not serious	not serious	serious ^a	none	At baseline, the total lesion counts for metformin group and control group were 54.3 ± 21.69 and 56.5 ± 19.86, respectively. Both groups showed comparable improvements at Week 12, -71.4% in the metformin group versus -65.3% in the control group (p=0.278).			⊕⊕⊕ ○ Moderate	CRITICAL	
Inflammatory lesion at 12 weeks												
1 ¹	randomise d trials	not seriou s	not serious	not serious	serious ^a	none	At baseline, the inflammatory lesion counts for metformin group and control group were 35.7 ± 15.73 and 37.1 ± 19.38, respectively. The metformin group performed beter with an 83.1% reduction compared to a 75.6% reduction in the control group for inflammatory lesion counts at Week 12 (p=0.064).			⊕⊕⊕ ○ Moderate	CRITICAL	

Noninflammatory lesion at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metformin+tetracycline+BP	tetracycline+BP	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	At baseline, the noninflammatory lesion counts for metformin group and control group were 19.1 ± 17.78 and 19.4 ± 12.95 , respectively. The metformin group had a greater reduction of 44.9% compared to 37.4% in the control group ($p = .445$) at Week 12.				⊕⊕⊕ ○ Moderate	CRITICAL

Cardiff Acne Disability Index, change from baseline, at 12 weeks

1 ¹	randomised trials	serious ^b	not serious	not serious	serious ^a	none	39	37	-	MD 0.6 higher (0.96 lower to 2.16 higher)	⊕⊕○ ○ Low	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

- a. Small sample size.
- b. Patients were not blinded.

References

1. Robinson, S., Z. Kwan, and M.M. Tang, *Metformin as an adjunct therapy for the treatment of moderate to severe acne vulgaris: A randomized open-labeled study*. Dermatol Ther, 2019. **32**(4): p. e12953.

13. Metformin and hypocaloric diet with PRN acne symptomatic treatment vs. PRN acne symptomatic treatment*

e-Table 66. GRADE Evidence Profile for metformin and hypocaloric diet with PRN acne symptomatic treatment vs. PRN acne symptomatic treatment*

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metformin and hypocaloric diet with PRN symptomatic treatment	PRN symptomatic treatment	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	20 young male patients (17-24) with acne resistant to common standard therapies were randomized to receive metformin 500 mg twice daily with a hypocaloric diet (1500-2000 kcal, rich in fruits, vegetables, and fish, low in carbohydrates) or no treatment. All patients continued the symptomatic anti-acne treatment (bland detergent and a sebostatic cream based on azelaic acid and nicotinamide) as needed. At baseline, global acne grading system (GAGS) scores were 25.1 ± 8.9 and 24.9 ± 7.6 in metformin and no treatment groups, respectively. At 6 months, GAGS scores decreased to 14.1 ± 10.4 and 19.4 ± 7.4 in metformin (p<0.03 for within group difference) and no treatment (no p provided), respectively.				⊕⊕○○ Low	CRITICAL

CI: Confidence interval; RR: Risk ratio

* Metformin: 500 mg twice daily; Hypocaloric diet: 1,500-2,000 kcal, rich in fruits, vegetables, and fish, low in carbohydrates; PRN symptomatic treatment: bland detergent and a sebostatic cream based on azelaic acid and nicotinamide

Explanations

a. Minimal methods reporting.

b. Small sample size.

References

1. Fabbrocini, G., et al., *Low glycaemic diet and metformin therapy: a new approach in male subjects with acne resistant to common treatments*. Clin Exp Dermatol, 2016. **41**(1): p. 38-42.

14. Metformin plus lifestyle change vs. lifestyle change in PCOS *

e-Table 67. GRADE Evidence Profile for metformin plus lifestyle change vs. lifestyle change in PCOS *

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metformin plus lifestyle change	lifestyle change in PCOS	Relative (95% CI)	Absolute (95% CI)		
Total lesion, change from baseline, at 6 months												
2 ^{1,2}	randomised trials	not serious ^a	not serious	serious ^b	serious ^c	none	54	57	-	MD 0.39 lower (2.33 lower to 1.56 higher)	⊕⊕○○ Low	CRITICAL

CI: Confidence interval; **MD:** Mean difference

* Lifestyle change: A combined intervention of diet and exercise was employed with the goal of achieving an average weight loss of at least 7% from initial body weight over 6 months, with a prescription of 150 minutes/week of exercise combined with a low-calorie diet

Explanations

- a. Only 33.3% completed the study in one study.
- b. One study enrolled obese adolescents with PCOS. The other study enrolled women with PCOS.
- c. Small sample size.

References

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15. Metformin plus exercise vs. exercise in PCOS *

e-Table 68. GRADE Evidence Profile for metformin plus exercise vs. exercise in PCOS

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metformin plus exercise	exercise in PCOS	Relative (95% CI)	Absolute (95% CI)		
Presence of acne at 6 months												
1 ¹	randomised trials	not serious	not serious	serious ^a	serious ^b	none	At baseline, the metformin group had 8 (24.24%) patients with acne and the control group had 6 (18.18%) patients with acne. At the end of treatment at 6 months, 8 (24.24%) in the metformin group and 3 (9.09%) in the control group had acne (both within group p-values were greater than 0.05)			⊕⊕○○ Low		

* Marching for 30 minutes to achieve a heart rate of ≥ 120 beats/min

Explanations

a. Enrolled women with PCOS. At baseline, the metformin group had 8 (24.24%) patients with acne and the control group had 6 (18.18%) patients with acne.

b. Small sample size.

References

1. Tiwari, N., S. Pasrija, and S. Jain, *Randomised controlled trial to study the efficacy of exercise with and without metformin on women with polycystic ovary syndrome*. Eur J Obstet Gynecol Reprod Biol, 2019. **234**: p. 149-154.

Isotretinoin

16. Isotretinoin vs. placebo

e-Table 69. GRADE Evidence Profile for isotretinoin vs. placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	isotretinoin	placebo	Relative (95% CI)	Absolute (95% CI)		
Total lesion at 16 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	29 3.2±5.1	29 8.6±8.2	-	MD 5.4 lower (8.91 lower to 1.89 lower)	⊕⊕⊕○ Moderate	CRITICAL
Cyst, percentage change from baseline at 1 and 2 months												
1 ²	randomised trials	serious ^b	not serious	not serious	serious ^a	none	16 and 17 patients were randomized to receive isotretinoin and placebo, respectively. The mean number of cystic lesions in the isotretinoin group (n=16) decreased by 17% at 1 month and by 33% at 2 months. However, the mean number of cystic lesions in the placebo group (n=17) increased by 33 % after 1 month, and 8 patients were switched to receive isotretinoin due to worsening of acne (mean % increase in lesions: 61%). After 2 months, the remaining 9 patients in the placebo group had a mean increase in lesions of 58%, and 5 of those were switched to receive isotretinoin.			⊕⊕○○ Low	CRITICAL	
Serious AE												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	0/29 (0.0%)	0/30 (0.0%)	RR 1.03 (0.23 to 4.71)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	isotretinoin	placebo	Relative (95% CI)	Absolute (95% CI)		

DLQI change from baseline at 16 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	29	29	-	MD 2.7 lower (4.13 lower to 1.27 lower)	⊕⊕⊕○ Moderate	IMPORTANT

Withdrawal due to AE

2 ^{1,2}	randomised trials	not serious	not serious	not serious	serious ^a	none	2/29 (6.9%)	0/30 (0.0%)	RR 5.17 (0.26 to 103.21) ^c	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

Any neuropsychiatric AE

5 ^{3,4,5,6}	observational studies	not serious	serious ^d	not serious	not serious	none	7932/71064 (11.2%)	13727/1006193 (13.6%)	RR 0.88 (0.77 to 1.00) ^e	16 fewer per 1,000 (from 31 fewer to 0 fewer)	⊕⊕○○ Low	IMPORTANT

Moderately elevated liver enzymes

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	1/29 (3.4%)	0/30 (0.0%)	RR 3.10 (0.13 to 73.14)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT
							Additional data on elevated liver enzymes from single-arm cohort studies are summarized in Table 9.					

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	isotretinoin	placebo	Relative (95% CI)	Absolute (95% CI)		

Inflammatory bowel disease

7 ⁷ , 8, 9, 10, 11, 12, 13	observational studies	not serious ^f	not serious ^g	not serious ^h	not serious	none	205/83085 (0.2%)	31359/10299303 (0.3%)	RR 1.13 (0.89 to 1.43)	1 more per 1,000 (from 0 fewer to 1 more)	⊕⊕○○ Low	IMPORTANT

Any AE

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	28/29 (96.6%)	26/30 (86.7%)	RR 1.11 (0.95 to 1.30)	95 more per 1,000 (from 43 fewer to 260 more)	⊕⊕⊕○ Moderate	IMPORTANT

Abnormal lipid

1 ^{1,2}	randomised trials	serious ^b	not serious	not serious	serious ^a	none	Rademaker 2014 - There were no significant changes in haematological or biochemical indices including lipids during the blinded phase (29 patients in each arm; treated for 16 weeks) and open-label phase (16 weeks, both groups received isotretinoin). Peck 1982 - No elevations in serum cholesterol were observed during the study period. Additional data on elevated lipid levels from single-arm cohort studies are summarized in Table 10.			⊕⊕○○ Low	

Abnormal CBC

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	isotretinoin	placebo	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a		There were no significant changes in haematological or biochemical indices including lipids, during the study period.				-	
							Additional data on CBC abnormal levels from single-arm cohort studies are summarized in Table 11 .					

Explanations

a. Small sample size.

b. 8, 5, and 1 patients from the placebo group switched to receive isotretinoin at 1 month, 2 months, and 3 months, respectively, and their data were not accounted. In methods, they measured the numbers of cysts, papules, and pustules, but only the number of cysts was reported in the results (high risk of selective reporting).

c. None of the patients withdrew from Peck 1982 study and its data was not pooled.

d. $I^2 = 80\%$

e. Three studies compared the rates of neuropsychiatric AE between isotretinoin and oral antibiotics (see the subgroup analysis in **e-Figure 171**. Any neuropsychiatric AE, isotretinoin vs. placebo).

f. One cohort study is of low quality (NewCastle Ottawa score of 5) due to no follow-up duration reported and the lack of demonstration that IBD was not present at start of study.

g. $I^2 = 62\%$

h. One study included a small portion of non-acne patients: 20 (3.5%) of the Isotretinoin exposed population received isotretinoin for non-acne indications (2.1% for rosacea and 0.5% for folliculitis) and 44 (8.8%) of the non-exposed group received isotretinoin for rosacea (1.6%), folliculitis (1.1%), or discussion of isotretinoin use in the setting of dermatologic procedure (1.7%).

References

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4. Paljarvi, T., et al., *Isotretinoin and adverse neuropsychiatric outcomes: retrospective cohort study using routine data*. Br J Dermatol, 2022.
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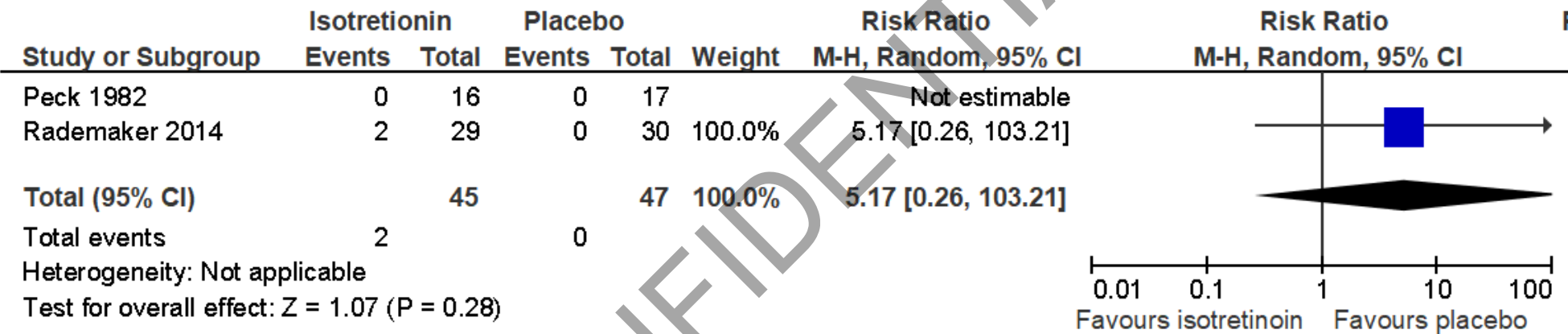
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Forest Plots

e-Figure 170. Withdrawal due to AE, isotretinoin vs. placebo

1 Isotretinoin versus placebo

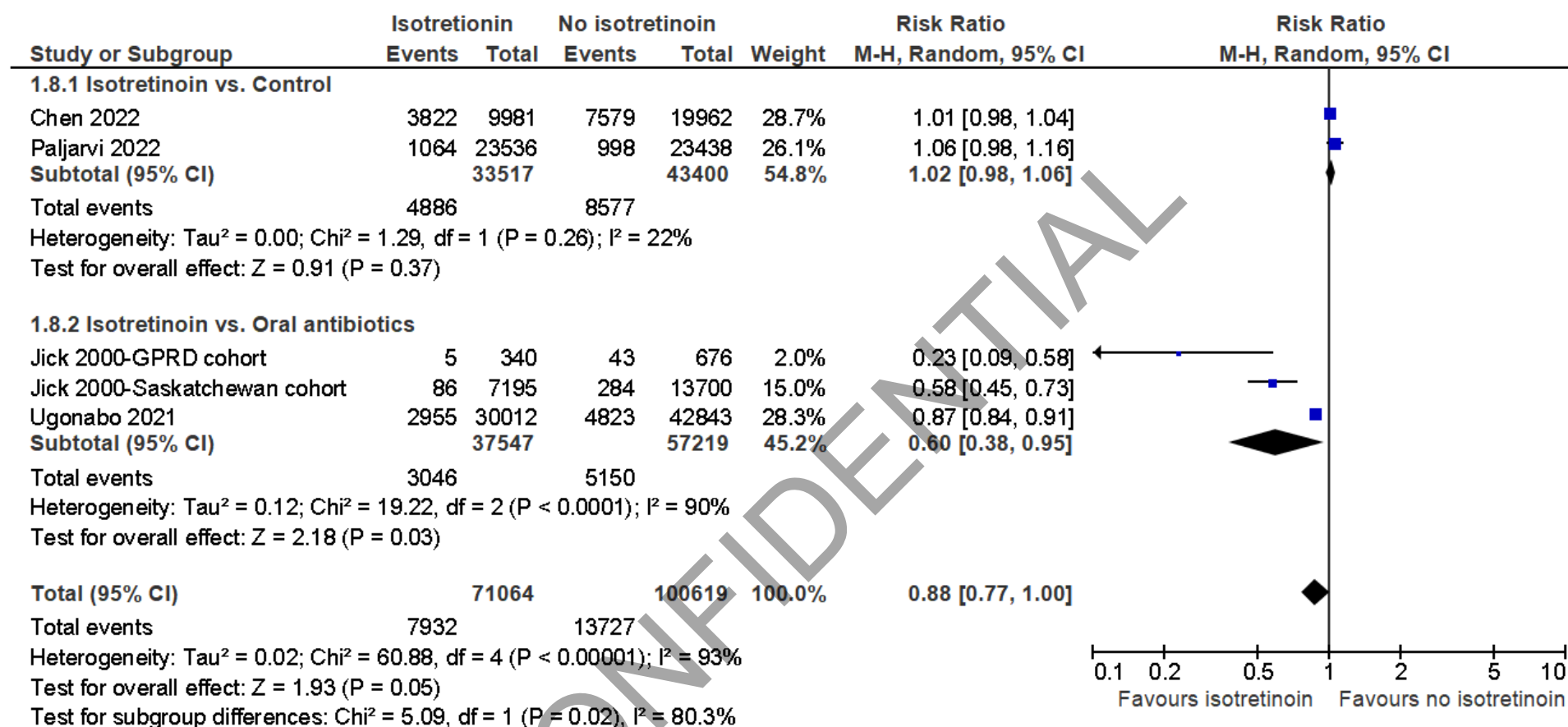
1.5 Withdrawal due to AE



e-Figure 171. Any neuropsychiatric AE, isotretinoin vs. placebo

1 Isotretinoin versus placebo

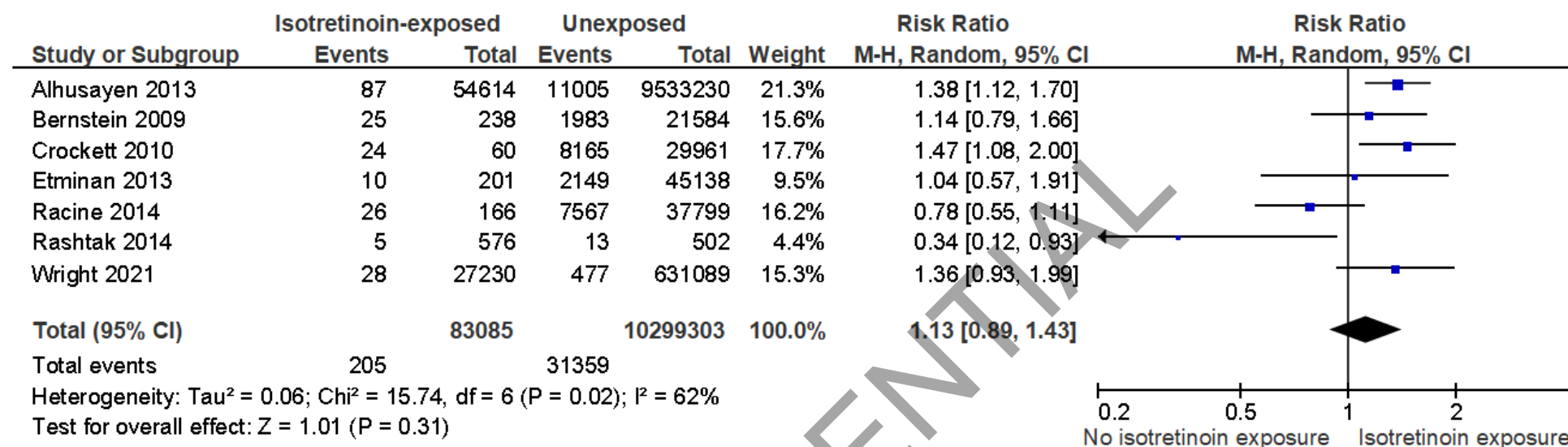
1.8 Any neuropsychiatric AE



e-Figure 172. Inflammatory bowel disease, isotretinoin vs. placebo

1 Isotretinoin versus placebo

1.11 Inflammatory bowel disease



Additional data from single arm cohort studies

e-Table 70. Additional data from single arm cohort studies - abnormal liver enzyme levels with isotretinoin use

Study ID	Isotretinoin dosages	Outcomes	Definition	Time point	Total patients	# of patients (%) experiencing the abnormality
Amichai 2006 ¹	Isotretinoin 0.3-0.4 mg/kg/day	Marked increase in triglycerides	Up to 4 times that of the normal range	At 4 weeks or 10 weeks after the treatment initiation	638	1 (0.2%)
Barbieri 2020 ²	Not reported	Abnormal AST, Grade 1, n (%)	The National Cancer Institute Common Terminology Criteria for Adverse Events	1 month	725	29 (4.0%)
		Abnormal AST, Grade 2, n (%)				1 (0.1%)
		Abnormal AST, Grade 3, n (%)				1 (0.1%)
		Abnormal AST, Grade 4, n (%)				0 (0%)
		Abnormal AST, Grade 1, n (%)		2 months	818	45 (5.5%)
		Abnormal AST, Grade 2, n (%)				2 (0.2%)
		Abnormal AST, Grade 3, n (%)				0 (0%)
		Abnormal AST, Grade 4, n (%)				0 (0%)
		Abnormal AST, Grade 1, n (%)		3 months	742	49 (6.6%)
		Abnormal AST, Grade 2, n (%)				1 (0.1%)
		Abnormal AST, Grade 3, n (%)				1 (0.1%)
		Abnormal AST, Grade 4, n (%)				0 (0%)
		Abnormal AST, Grade 1, n (%)		4 months	644	38 (5.9%)
		Abnormal AST, Grade 2, n (%)				0 (0%)
		Abnormal AST, Grade 3, n (%)				0 (0%)
		Abnormal AST, Grade 4, n (%)				0 (0%)
		Abnormal AST, Grade 1, n (%)		5 months	441	26 (5.9%)
		Abnormal AST, Grade 2, n (%)				1 (0.2%)
		Abnormal AST, Grade 3, n (%)				0 (0%)
		Abnormal AST, Grade 4, n (%)				0 (0%)
		Abnormal AST, Grade 1, n (%)		6 months	239	16 (6.7%)

		Abnormal AST, Grade 2, n (%)			1 (0.4%)
		Abnormal AST, Grade 3, n (%)			0 (0%)
		Abnormal AST, Grade 4, n (%)			0 (0%)
		Abnormal ALT, Grade 1, n (%)	1 month	703	26 (3.7%)
		Abnormal ALT, Grade 2, n (%)			1 (0.1%)
		Abnormal ALT, Grade 3, n (%)			0 (0%)
		Abnormal ALT, Grade 4, n (%)			0 (0%)
		Abnormal ALT, Grade 1, n (%)	2 months	796	43 (5.4%)
		Abnormal ALT, Grade 2, n (%)			0 (0%)
		Abnormal ALT, Grade 3, n (%)			1 (0.1%)
		Abnormal ALT, Grade 4, n (%)			0 (0%)
		Abnormal ALT, Grade 1, n (%)	3 months	739	34 (4.6%)
		Abnormal ALT, Grade 2, n (%)			0 (0%)
		Abnormal ALT, Grade 3, n (%)			2 (0.3%)
		Abnormal ALT, Grade 4, n (%)			0 (0%)
		Abnormal ALT, Grade 1, n (%)	4 months	632	24 (3.8%)
		Abnormal ALT, Grade 2, n (%)			0 (0%)
		Abnormal ALT, Grade 3, n (%)			4 (0.6%)
		Abnormal ALT, Grade 4, n (%)			0 (0%)
		Abnormal ALT, Grade 1, n (%)	5 months	241	13 (3.1%)
		Abnormal ALT, Grade 2, n (%)			0 (0%)
		Abnormal ALT, Grade 3, n (%)			0 (0%)
		Abnormal ALT, Grade 4, n (%)			0 (0%)
		Abnormal ALT, Grade 1, n (%)	6 months		7 (2.9%)
		Abnormal ALT, Grade 2, n (%)			2 (0.8%)
		Abnormal ALT, Grade 3, n (%)			0 (0%)
		Abnormal ALT, Grade 4, n (%)			0 (0%)
Evaristo 2019 ³	Isotretinoin 0.33 mg/kg/day (avg total/dosage/weight, 127.61mg/kg)	ALT & AST levels above the upper reference limit	"Most treatments lasted for between 9 and 12 months (57.64%)."	279	29 (10.4%)
		ALT & AST levels above the upper reference limit requiring monitoring		279	22 (7.9%)

		ALT & AST levels above the upper reference limit requiring treatment suspension			279	13 (4.7%)
Ghaffarpour 2006 ⁴	Isotretinoin 0.75 mg/kg/day, then maintenance dose of 20 mg/kg after lesions are healed (mean cumulative isotretinoin dose 72.5 mg/kg)	Elevated liver enzymes	Less than 2-fold increase	Mean follow up, 4.4 years	132	1 (0.8%)
Kizilyel 2014 ⁵	Isotretinoin 0.5-1 mg/kg per day	ALT & AST levels above the upper reference limit requiring treatment suspension		3 months	279	13 (4.7%)
			High (≥ 40 U/L)			3 (0.9%)
			Normal (<40 U/L)	6 months	322	209 (64.9%)
		ALT Levels	High (≥ 40 U/L)			4 (1.2%)
			Normal (<40 U/L)	3 months	322	263 (81.7%)
			High (≥ 40 U/L)			11 (3.4%)
			Normal (<40 U/L)	6 months	322	201 (62.4%)
			High (≥ 40 U/L)			11 (3.4%)

e-Table 71. Additional data from single arm cohort studies - abnormal lipid levels with isotretinoin use

Study ID	Isotretinoin dosages	Outcomes	Definition	Time point	Total patients	# of patients (%) experiencing the abnormality
Amichai 2006 ¹	Isotretinoin 0.3-0.4 mg/kg/day	Elevated serum lipids	"Slight increase"	At 4 weeks or 10 weeks after the treatment initiation	638	27 (4.23%)
Barbieri 2020 ²	Isotretinoin	Abnormal triglyceride, Grade 1, n (%) Abnormal triglyceride, Grade 2, n (%) Abnormal triglyceride, Grade 3, n (%) Abnormal triglyceride, Grade 4, n (%) Abnormal triglyceride, Grade 1, n (%)	The National Cancer Institute Common Terminology Criteria for Adverse Events	1 month 2 months	737 856	146 (19.8%) 18 (2.4%) 1 (0.1%) 0 (0%) 190 (22.2%)

Abnormal triglyceride, Grade 2, n (%)			21 (2.5%)
Abnormal triglyceride, Grade 3, n (%)			4 (0.5%)
Abnormal triglyceride, Grade 4, n (%)			0 (0%)
Abnormal triglyceride, Grade 1, n (%)	3 months	793	234 (29.5%)
Abnormal triglyceride, Grade 2, n (%)			30 (3.8%)
Abnormal triglyceride, Grade 3, n (%)			6 (0.7%)
Abnormal triglyceride, Grade 4, n (%)			0 (0%)
Abnormal triglyceride, Grade 1, n (%)	4 months	666	195 (29.3%)
Abnormal triglyceride, Grade 2, n (%)			38 (5.6%)
Abnormal triglyceride, Grade 3, n (%)			0 (0%)
Abnormal triglyceride, Grade 4, n (%)			0 (0%)
Abnormal triglyceride, Grade 1, n (%)	5 months	440	144 (32.7%)
Abnormal triglyceride, Grade 2, n (%)			16 (3.7%)
Abnormal triglyceride, Grade 3, n (%)			2 (0.4%)
Abnormal triglyceride, Grade 4, n (%)			0 (0%)
Abnormal triglyceride, Grade 1, n (%)	6 months	236	92 (39.0%)
Abnormal triglyceride, Grade 2, n (%)			13 (5.3%)
Abnormal triglyceride, Grade 3, n (%)			0 (0%)
Abnormal triglyceride, Grade 4, n (%)			0 (0%)
Abnormal total cholesterol, Grade 1, n (%)	1 month	526	101 (19.2%)
Abnormal total cholesterol, Grade 2, n (%)			2 (0.4%)
Abnormal total cholesterol, Grade 3, n (%)			0 (0%)
Abnormal total cholesterol, Grade 4, n (%)			0 (0%)
Abnormal total cholesterol, Grade 1, n (%)	2 months	606	123 (20.3%)
Abnormal total cholesterol, Grade 2, n (%)			2 (0.2%)
Abnormal total cholesterol, Grade 3, n (%)			0 (0%)
Abnormal total cholesterol, Grade 4, n (%)			0 (0%)
Abnormal total cholesterol, Grade 1, n (%)	3 months	556	115 (20.7%)
Abnormal total cholesterol, Grade 2, n (%)			3 (0.5%)
Abnormal total cholesterol, Grade 3, n (%)			0 (0%)
Abnormal total cholesterol, Grade 4, n (%)			0 (0%)
Abnormal total cholesterol, Grade 1, n (%)	4 months	461	113 (24.5%)
Abnormal total cholesterol, Grade 2, n (%)			6 (1.3%)
Abnormal total cholesterol, Grade 3, n (%)			0 (0%)
Abnormal total cholesterol, Grade 4, n (%)			0 (0%)

		Abnormal total cholesterol, Grade 1, n (%) Abnormal total cholesterol, Grade 2, n (%) Abnormal total cholesterol, Grade 3, n (%) Abnormal total cholesterol, Grade 4, n (%) Abnormal total cholesterol, Grade 1, n (%) Abnormal total cholesterol, Grade 2, n (%) Abnormal total cholesterol, Grade 3, n (%) Abnormal total cholesterol, Grade 4, n (%)		5 months 6 months	172	74 (25.4%) 3 (1.0%) 0 (0%) 0 (0%) 45 (26.1%) 2 (1.1%) 0 (0%) 0 (0%)
Evaristo 2019 ⁴	Isotretinoin 0.33 mg/kg/day	Cholesterol and/or triglycerides levels above upper reference limit Elevated cholesterol and/or triglycerides levels requiring monitoring Elevated cholesterol and/or triglycerides levels requiring suspension of treatment needed		"Most treatments lasted for between 9 and 12 months (57.64%)." 279 279 279	279 279 279	46 (16.5%) 9 (3.2%) 1 (0.3%)
Ghaffarpour 2006 ⁴	Isotretinoin 0.75 mg/kg/day, then maintenance dose of 20 mg/kg after lesions are healed (mean cumulative isotretinoin dose 72.5 mg/kg)	Hypertriglyceridemia Hypercholesterolemia		Mean follow up, 4.4 years	132 132	19 (14.3%) 9 (6.8%)
Kizilyel 2014 ⁵	Isotretinoin 0.5-1 mg/kg per day	Triglyceride Levels LDL Levels	Normal (<150 mg/dL) Borderline high (150-199 mg/dL) High (200-499 mg/dL) Very High (≥ 500 mg/dL) Normal (<150 mg/dL) Borderline high (150-199 mg/dL) High (200-499 mg/dL) Very High (≥ 500 mg/dL) Optima (<100 mg/dL) Above Normal (100-129 mg/dL)	3 months 6 months 3 months	322 322 322 322 322 322 322 322 322 322	197 (61.2%) 38 (11.8%) 22 (6.8%) 1 (0.3%) 145 (45%) 36 (11.2%) 16 (5%) 0 (0%) 89 (27.6%) 98 (30.4%)

			Borderline high (130-159 mg/dL)		322	54 (16.85)
			High (160-189 mg/dL)		322	12 (3.7%)
			Very High (≥ 190 mg/dL)		322	5 (1.6%)
			Optima (<100 mg/dL)	6 months	322	60 (18.6%)
			Above Normal (100-129 mg/dL)		322	84 (26.1%)
			Borderline high (130-159 mg/dL)		322	44 (13.7%)
			High (160-189 mg/dL)		322	8 (2.5%)
			Very High (≥ 190 mg/dL)		322	1 (0.3%)
		HDL Levels	Low (<40 mg/dL)	3 months	322	63 (19.6%)
			Normal (40-59 mg/dL)		322	154 (47.8%)
			High (≥ 60 mg/dL)		322	41 (12.7%)
			Low (<40 mg/dL)	6 months	322	48 (14.9%)
			Normal (40-59 mg/dL)		322	117 (36.3%)
			High (≥ 60 mg/dL)		322	33 (10.2%)
Yap 2017 ⁶	Isotretinoin 10 mg/day	Serum lipid level increase	Less than 20% the upper limit	Mean follow up, 24 weeks	150	4 (2.7%)

e-Table 72. Additional data from single arm cohort studies - abnormal CBC levels with isotretinoin use

Study ID	Isotretinoin dosages	Outcomes	Definition	Time point	Total patients	# of patients (%) experiencing the abnormality
Barbieri 2020 ¹		Abnormal WBC, Grade 1, n (%)	The National Cancer Institute Common Terminology Criteria for Adverse Events	1 month	493	33 (6.7%)
		Abnormal WBC, Grade 2, n (%)				3 (0.6%)
		Abnormal WBC, Grade 3, n (%)				0 (0%)
		Abnormal WBC, Grade 4, n (%)				0 (0%)
		Abnormal WBC, Grade 1, n (%)		2 months	535	38 (7.1%)
		Abnormal WBC, Grade 2, n (%)				2 (0.4%)
		Abnormal WBC, Grade 3, n (%)				0 (0%)
		Abnormal WBC, Grade 4, n (%)				0 (0%)
		Abnormal WBC, Grade 1, n (%)		3 months	470	31 (6.6%)
		Abnormal WBC, Grade 2, n (%)				2 (0.4%)
		Abnormal WBC, Grade 3, n (%)				0 (0%)

Abnormal WBC, Grade 4, n (%)			0 (0%)
Abnormal WBC, Grade 1, n (%)	4 months	425	31 (7.3%)
Abnormal WBC, Grade 2, n (%)			2 (0.5%)
Abnormal WBC, Grade 3, n (%)			0 (0%)
Abnormal WBC, Grade 4, n (%)			0 (0%)
Abnormal WBC, Grade 1, n (%)	5 months	278	20 (7.2%)
Abnormal WBC, Grade 2, n (%)			1 (0.4%)
Abnormal WBC, Grade 3, n (%)			0 (0%)
Abnormal WBC, Grade 4, n (%)			0 (0%)
Abnormal WBC, Grade 1, n (%)	6 months	149	15 (10.1%)
Abnormal WBC, Grade 2, n (%)			1 (0.7%)
Abnormal WBC, Grade 3, n (%)			0 (0%)
Abnormal WBC, Grade 4, n (%)			0 (0%)
Abnormal platelet, Grade 1, n (%)	1 month	500	11 (2.2%)
Abnormal platelet, Grade 2, n (%)			0 (0%)
Abnormal platelet, Grade 3, n (%)			0 (0%)
Abnormal platelet, Grade 4, n (%)			0 (0%)
Abnormal platelet, Grade 1, n (%)	2 months	522	12 (2.3%)
Abnormal platelet, Grade 2, n (%)			0 (0%)
Abnormal platelet, Grade 3, n (%)			1 (0.2%)
Abnormal platelet, Grade 4, n (%)			0 (0%)
Abnormal platelet, Grade 1, n (%)	3 months	467	7 (1.5%)
Abnormal platelet, Grade 2, n (%)			0 (0%)
Abnormal platelet, Grade 3, n (%)			0 (0%)
Abnormal platelet, Grade 4, n (%)			0 (0%)
Abnormal platelet, Grade 1, n (%)	4 months	417	5 (1.2%)
Abnormal platelet, Grade 2, n (%)			0 (0%)
Abnormal platelet, Grade 3, n (%)			0 (0%)
Abnormal platelet, Grade 4, n (%)			0 (0%)
Abnormal platelet, Grade 1, n (%)	5 months	276	8 (2.9%)
Abnormal platelet, Grade 2, n (%)			0 (0%)
Abnormal platelet, Grade 3, n (%)			0 (0%)
Abnormal platelet, Grade 4, n (%)			0 (0%)
Abnormal platelet, Grade 1, n (%)	6 months	143	2 (1.4%)
Abnormal platelet, Grade 2, n (%)			0 (0%)

		Abnormal platelet, Grade 3, n (%)				0 (0%)
		Abnormal platelet, Grade 4, n (%)				0 (0%)
Evaristo 2019 ⁴	Isotretinoin 0.33 mg/kg/day	Hemogram	Mild Normocytic anemia (hemoglobin of 11.8 g/dl)	"Most treatments lasted for between 9 and 12 months (57.64%)."	279	1 (0.4%)

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17. Traditional dosing vs. intermittent dosing

e-Table 73. GRADE Evidence Profile for traditional dosing vs. intermittent dosing

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Traditional QD	Intermittent dosing	Relative (95% CI)	Absolute (95% CI)		
Physician global assessment, GAGS, at 24 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	16	17	-	MD 1.75 lower (3.38 lower to 0.12 lower)	⊕⊕⊕○ Moderate	CRITICAL
Physician global assessment, FDA global grade (1-4), at 6 months												
1 ²	randomised trials	serious ^b	not serious	not serious	serious ^a	none	Patients were randomized to receive isotretinoin 0.5mg/kg/day for the first 10 days of each month for 6 months (Group 1, N=22), isotretinoin 0.5mg/kg/day every day for 1 month, then 0.5mg/kg/day for the first 10 days of each month for the next 5 months (Group 2, N=19) and isotretinoin 0.5mg/kg/day every day for 6 months. The FDA global grade in each group was found to be significantly decreased compared with baseline values at the end of treatment (P < 0.001). Differences were also significant in each group at the end of follow-up period (P < 0.001). There were no statistically significant differences between the three treatment groups (P = 0.554). However, when patients were evaluated according to the FDA global grade, there was a statistically significant difference between groups 1 and 3 at the end of the 12-month follow-up period (P = 0.002). The difference between groups 2 and 3 was also close to the statistical significance (P = 0.053).				⊕⊕○○ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Traditional QD	Intermittent dosing	Relative (95% CI)	Absolute (95% CI)		

Total acne load, change from baseline at 16 weeks

1 ³	randomised trials	not serious	not serious	not serious	serious ^a	none	120 patients were randomized to receive i) isotretinoin 1mg/kg/day every day (Group A) , ii) 1mg/kg/day every other day(Group B), iii) 1mg/kg/day for 1week out of 4 weeks(Group C), and iv) 20mg every other day(Group D) for 16 weeks. Total acne load was calculated by multiplying the total number of each type of lesion with its severity index (Non-inflamed comedones, open and closed (no erythema) - 0.5; Comedones/papules with surrounding erythema - 1; Superficial pustules < 2 mm with no or little erythema - 1; Pustules with a diameter > 2 mm - 2; Pustules with a significant erythema - 2; Deep infiltrates with or without pustules/ nodules/isolated cysts - 3) and adding them together. At baseline, total acne loads were 110.14 (range, 48-265), 119 (range, 4-222), 129.25 (range, 17-366), and 131.6 (range, 26-366) in Group A, B, C, and D, respectively (p<0.5). At the end of treatment at 16 weeks, the mean acne score reductions were 7.74 (range, 0-27), 20 (range, 1-53), 29.92 (range, 0-46), and 8.13 (range, 0-56) in Group A, B, C, and D, respectively (p<0.001).				⊕⊕⊕○ Moderate	CRITICAL

Inflammatory lesion at 24 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	16	17	-	MD 3.87 lower (5.57 lower to 2.17 lower)	⊕⊕⊕○ Moderate	CRITICAL

noninflammatory lesion, at 24 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Traditional QD	Intermittent dosing	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	16	17	-	MD 4.53 lower (6.89 lower to 2.17 lower)	⊕⊕⊕○ Moderate	CRITICAL

Patient global assessment at 24 weeks

1 ¹	randomised trials	serious ^c	not serious	not serious	serious ^a	none	16	17	-	MD 0.25 lower (0.72 lower to 0.22 higher)	⊕⊕○○ Low	IMPORTANT

Withdrawal due to AE

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	2/30 (6.7%)	0/30 (0.0%)	RR 5.00 (0.25 to 99.95)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

Recurrence at 1 year after the completion of 6-month treatment

1 ¹	randomised trials	serious ^d	not serious	not serious	serious ^a	none	2/16 (12.5%)	9/17 (52.9%)	RR 0.24 (0.06 to 0.93)	402 fewer per 1,000 (from 498 fewer to 37 fewer)	⊕⊕○○ Low	IMPORTANT

Elevated LFT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Traditional QD	Intermittent dosing	Relative (95% CI)	Absolute (95% CI)		
3 ^{1,2,3}	randomised trials	not serious	not serious	not serious	serious ^{e,f}	none	2/57 (3.5%)	0/115 (0.0%)	RR 5.25 (0.56 to 49.26)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

Elevated triglyceride

3 ^{1,2,3}	randomised trials	not serious	not serious	not serious	serious ^{e,f}	none	3/57 (5.3%)	1/115 (0.9%)	RR 4.83 (0.73 to 32.02)	33 more per 1,000 (from 2 fewer to 270 more)	⊕⊕⊕○ Moderate	IMPORTANT

Muscular cramps or pains

1 ²	randomised trials	serious ^b	not serious	not serious	serious ^g	none	0/19 (0.0%)	0/41 (0.0%)	not estimable		⊕⊕○○ Low	IMPORTANT

Bone/joint aches and pains

1 ²	randomised trials	serious ^b	not serious	not serious	serious ^g	none	0/19 (0.0%)	0/41 (0.0%)	not estimable		⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

- a. Small sample size.
- b. Limited methods reporting.
- c. Patients were not blinded.
- d. only 16/30 and 17/30 were assessed for recurrence at 1 year after the completion of 6 months of treatment.
- e. Small sample and few events lead to a wide CI.
- f. Akman 2007 had no events in both groups, therefore were not pooled.
- g. Small sample size. Double-zero study

References

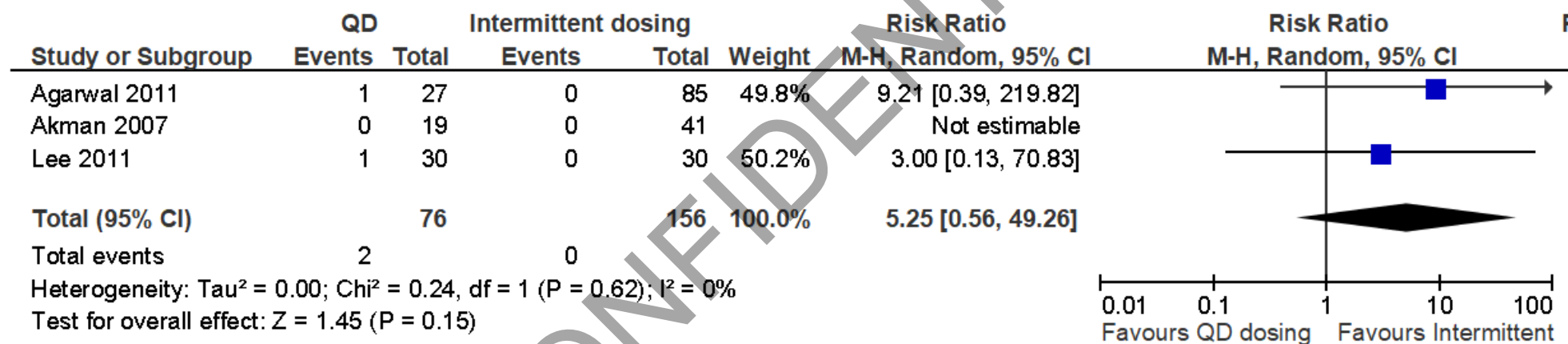
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Forest plots

e-Figure 173. Elevated LFT, traditional vs. intermittent dosing

29 [Pooled] Traditional vs. Intermittent

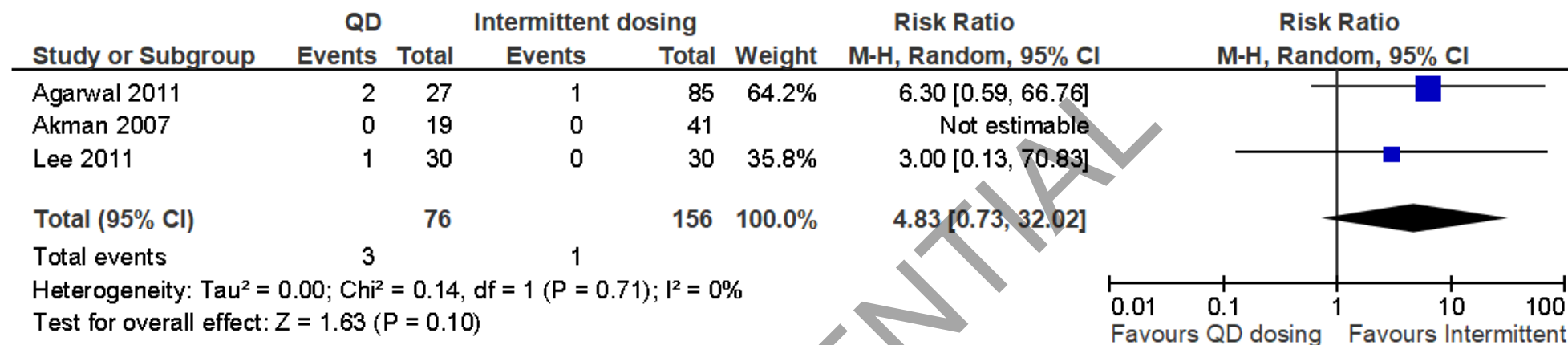
29.2 Elevated LFT



e-Figure 174. Elevated lipids, traditional vs. intermittent dosing

29 [Pooled] Traditional vs. Intermittent

29.3 Elevated lipids



e-Table 74. GRADE Evidence Profile for isotretinoin-Lidose vs. conventional isotretinoin*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isotretinoin-Lidose	conventional isotretinoin	Relative (95% CI)	Absolute (95% CI)		
Physician global assessment, treatment success, at 20 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	326/387 (84.2%)	351/395 (88.9%)	RR 0.95 (0.90 to 1.00)	44 fewer per 1,000 (from 89 fewer to 0 fewer)	⊕⊕⊕⊕ High	CRITICAL
Total lesion at 20 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	At baseline, the mean nodule lesion facial and truncal counts were 18.4 and 17.7 in the isotretinoin-Lidose and conventional isotretinoin, respectively. After 20 weeks of treatment, isotretinoin-Lidose reduced the facial and truncal nodule lesion counts to 1.6 and conventional isotretinoin reduced the lesion count to 1.3			⊕⊕⊕⊕ High	CRITICAL	
Total lesion, >=90% reduction, at 20 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	310/403 (76.9%)	332/410 (81.0%)	RR 0.95 (0.88 to 1.02)	40 fewer per 1,000 (from 97 fewer to 16 more)	⊕⊕⊕⊕ High	CRITICAL

Withdrawal due to AE

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isotretinoin-Lidose	conventional isotretinoin	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	19/464 (4.1%)	15/460 (3.3%)	RR 1.26 (0.65 to 2.44)	8 more per 1,000 (from 11 fewer to 47 more)	⊕⊕⊕⊕ High	IMPORTANT

Psychiatric AE

1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	29/464 (6.3%)	27/461 (5.9%)	RR 1.07 (0.64 to 1.77)	4 more per 1,000 (from 21 fewer to 45 more)	⊕⊕⊕⊕ High	IMPORTANT

Any AE

1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	428/464 (92.2%)	413/460 (89.8%)	RR 1.03 (0.99 to 1.07)	27 more per 1,000 (from 9 fewer to 63 more)	⊕⊕⊕⊕ High	IMPORTANT

Arthralgia and epistaxis

1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	Arthralgia and epistaxis were frequently reported with similar incidence in both treatment groups.				⊕⊕⊕⊕ High	IMPORTANT

CI: Confidence interval; RR: Risk ratio

* Both groups received 0.5mg/kg/day during the first 4 weeks, then received 1mg/kg/day in the next 16 weeks.

References

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1. Traditional dosage (0.5-1.0mg/kg/day) vs. low dosage (<0.5mg/kg/day)

e-Table 75. GRADE Evidence Profile for traditional dosage (0.5-1.0mg/kg/day) vs. low dosage (<0.5mg/kg/day)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Traditional isotretinoin	low dosage isotretinoin	Relative (95% CI)	Absolute (95% CI)		
Physician global assessment, GAGS, at 24 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	16	17	-	MD 0.18 lower (1.78 lower to 1.42 higher)	⊕⊕⊕○ Moderate	CRITICAL
Acne grade at Week 16 (0-10 scale on face, back and chest)												
1 ²	randomised trials	not serious	not serious	not serious	serious ^a	none	All 1mg/kg/day, 0.5mg/kg/day, and 0.1mg/day groups had a gradual reduction in acne grade over the 16-week treatment with a final improvement of 70%. There was no difference in effectiveness between the doses. At baseline, the mean acne grades on the face were 2.25, 2.15, and 1.64 in 1.0mg/kg/day, 0.5mg/kg/day, and 0.1mg/kg/day groups, respectively. At 16 weeks, the mean acne grades on the face were 0.47, 0.50, 0.34 in 1.0mg/kg/day, 0.5mg/kg/day, and 0.1mg/kg/day groups, respectively (data are from Figure 1 using WebPlotDigitizer).			⊕⊕⊕○ Moderate	CRITICAL	

Total lesion count, face, at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Traditional isotretinoin	low dosage isotretinoin	Relative (95% CI)	Absolute (95% CI)		
1 ³	randomised trials	not serious	not serious	not serious	serious ^a	none	At baseline, the mean lesion counts on the face were 15.3, 12.1, and 14.0 in 1.0mg/kg/day, 0.5mg/day, and 0.1mg/kg/day groups, respectively. At the end of treatment at week 20, the mean lesion counts on the face were 1.7, 2.6, and 2.9 in 1.0mg/kg/day, 0.5mg/day, and 0.1mg/kg/day groups, respectively (p>0.05). At baseline, the mean lesion counts on the trunk were 38.8, 33.9, and 40.3 in 1.0mg/kg/day, 0.5mg/day, and 0.1mg/kg/day groups, respectively. At the end of treatment at week 20, the mean lesion counts on the face were 20.0, 9.6, and 14.8 in 1.0mg/kg/day, 0.5mg/day, and 0.1mg/kg/day groups, respectively (p>0.05).				⊕⊕⊕○ Moderate	CRITICAL

Inflammatory lesion at 24 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	16	17	-	MD 0.15 lower (1.51 lower to 1.21 higher)	⊕⊕⊕○ Moderate	CRITICAL

Noninflammatory lesion, at 24 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	16	17	-	MD 0.83 lower (3.24 lower to 1.58 higher)	⊕⊕⊕○ Moderate	CRITICAL

Patient global assessment at 24 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Traditional isotretinoin	low dosage isotretinoin	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^b	not serious	not serious	serious ^a	none	16	17	-	MD 0.7 lower (1.13 lower to 0.27 higher)	⊕⊕○○ Low	IMPORTANT

Withdrawal due to AE

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	2/30 (6.7%)	0/30 (0.0%)	RR 5.00 (0.25 to 99.95)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

Recurrence at 1 year after the completion of 6-month treatment

1 ¹	randomised trials	serious ^c	not serious	not serious	serious ^a	none	2/16 (12.5%)	3/17 (17.6%)	RR 0.71 (0.14 to 3.70)	51 fewer per 1,000 (from 152 fewer to 476 more)	⊕⊕○○ Low	IMPORTANT

Increased LFT

2 ^{1,3}	randomised trials	not serious	not serious	not serious	serious ^a	none	10/79 (12.7%)	15/122 (12.3%)	RR 1.19 (0.57 to 2.46)	23 more per 1,000 (from 53 fewer to 180 more)	⊕⊕⊕○ Moderate	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Traditional isotretinoin	low dosage isotretinoin	Relative (95% CI)	Absolute (95% CI)		

Decreased HDL

1 ³	randomised trials	not serious	not serious	not serious	serious ^a	none	8/49 (16.3%)	15/92 (16.3%)	RR 1.00 (0.46 to 2.20)	0 fewer per 1,000 (from 88 fewer to 196 more)	⊕⊕⊕○ Moderate	IMPORTANT

Increased triglyceride

2 ^{1,3}	randomised trials	not serious	not serious	not serious	serious ^a	none	13/79 (16.5%)	7/122 (5.7%)	RR 3.20 (1.39 to 7.38)	126 more per 1,000 (from 22 more to 366 more)	⊕⊕⊕○ Moderate	IMPORTANT

Increased platelet

1 ³	randomised trials	not serious	not serious	not serious	serious ^a	none	4/49 (8.2%)	7/92 (7.6%)	RR 1.07 (0.33 to 3.49)	5 more per 1,000 (from 51 fewer to 189 more)	⊕⊕⊕○ Moderate	IMPORTANT

Bone and joint pain

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Traditional isotretinoin	low dosage isotretinoin	Relative (95% CI)	Absolute (95% CI)		
1 ³	randomised trials	not serious	not serious	not serious	serious ^a	none	15/49 (30.6%)	19/92 (20.7%)	RR 1.48 (0.83 to 2.65)	99 more per 1,000 (from 35 fewer to 341 more)	⊕⊕⊕○ Moderate	IMPORTANT

Muscle cramps

1 ³	randomised trials	not serious	not serious	not serious	serious ^a	none	11/49 (22.4%)	13/92 (14.1%)	RR 1.59 (0.77 to 3.28)	83 more per 1,000 (from 32 fewer to 322 more)	⊕⊕⊕○ Moderate	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

- Small sample size.
- Patients were not blinded.
- only 16/30 and 17/30 were assessed for recurrence at 1 year after the completion of 6 months of treatment.

References

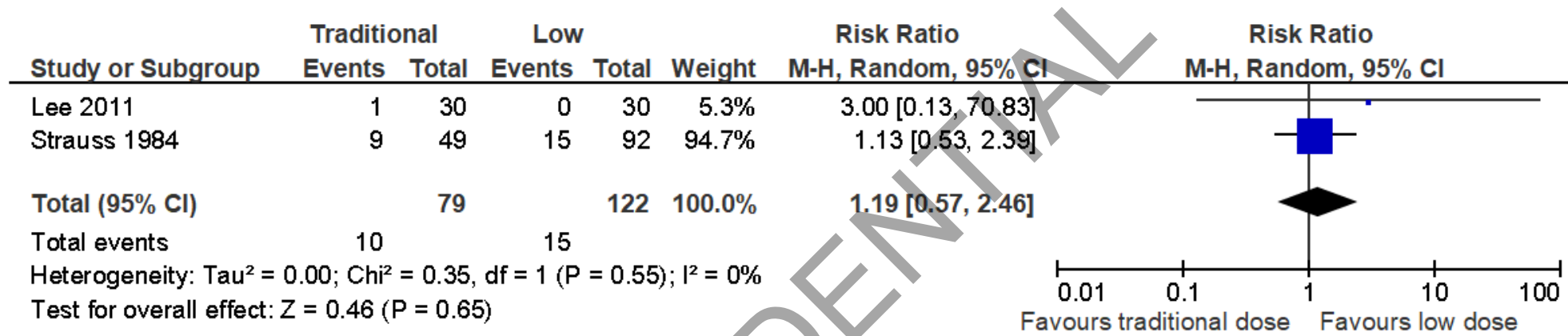
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Forest plots

e-Figure 175. Increased LFT, traditional dosing vs. low dosing

28 [pooled] Traditional vs. Low

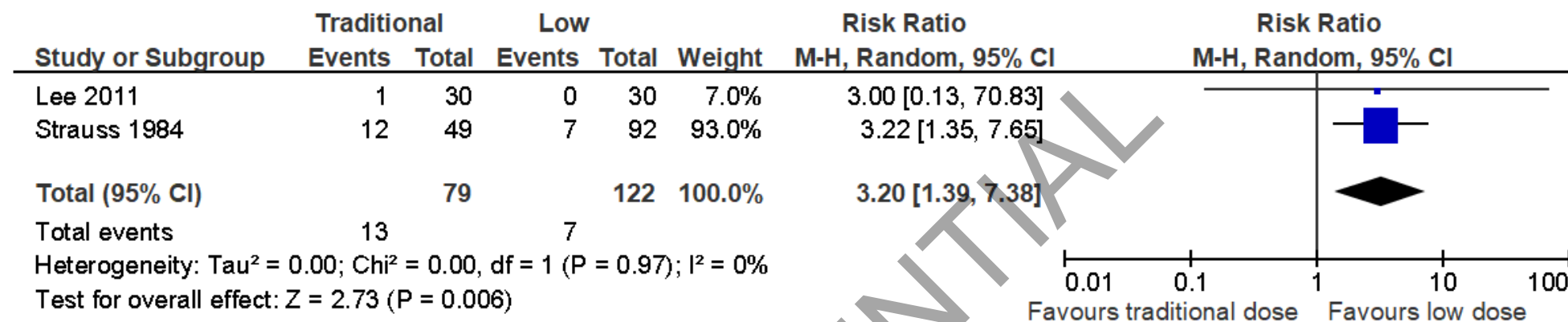
28.2 Increased LFT



e-Figure 176. Increased triglyceride, traditional dosing vs. low dosing

28 [pooled] Traditional vs. Low

28.4 Increased triglyceride



16. Isotretinoin 20mg QD vs. 20mg EOD for 24 weeks

e-Table 76. GRADE Evidence Profile for isotretinoin 20mg QD vs. 20mg EOD for 24 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isotretinoin 20mg QD	20mg EOD for 24 weeks	Relative (95% CI)	Absolute (95% CI)		
Total acne load at 6 months												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	118	116	-	MD 2.08 lower (3.51 lower to 0.65 lower)	⊕⊕○○ Low	CRITICAL
Lesion count, >90% reduction, at 24 weeks												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	116/118 (98.3%)	109/116 (94.0%)	RR 1.05 (0.99 to 1.10)	47 more per 1,000 (from 9 fewer to 94 more)	⊕⊕○○ Low	CRITICAL
Abnormal LFT (no details provided)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^c	none	3/118 (2.5%)	1/116 (0.9%)	RR 2.95 (0.31 to 27.94)	17 more per 1,000 (from 6 fewer to 232 more)	⊕⊕○○ Low	IMPORTANT
Abnormal lipid profile (no details provided)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^c	none	4/118 (3.4%)	1/116 (0.9%)	RR 3.93 (0.45 to 34.66)	25 more per 1,000 (from 5 fewer to 290 more)	⊕⊕○○ Low	IMPORTANT

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isotretinoin 20mg QD	20mg EOD for 24 weeks	Relative (95% CI)	Absolute (95% CI)		

Arthralgia

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^c	none	1/118 (0.8%)	0/116 (0.0%)	RR 2.95 (0.12 to 71.67)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ Low	IMPORTANT

Myalgia

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^c	none	2/118 (1.7%)	2/116 (1.7%)	RR 0.98 (0.14 to 6.86)	0 fewer per 1,000 (from 15 fewer to 101 more)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

- Minimal methods reporting.
- Small sample size.
- The small sample size and rare events resulted in a wide CI.

References

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17. Isotretinoin 0.5-1.0mg/kg/day once daily vs. 0.5-1.0 mg/kg/day divided as twice daily

e-Table 77. GRADE Evidence Profile for isotretinoin 0.5-1.0mg/kg/day once daily vs. 0.5-1.0 mg/kg/day divided as twice daily

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	0.5-1.0 mg/kg/day once daily	0.5-1.0 mg/kg/day divided as twice daily	Relative (95% CI)	Absolute (95% CI)		
Global acne score at 20 weeks (median treatment duration, 22 weeks)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	Both groups showed marked clinical improvement. In the once-daily dosing group, the median GAS significantly decreased from 34 to 0 after treatment (p < 0.001). In the twice-daily dosing group, the median GAS significantly decreased from 31 to 0 after treatment (p < 0.001). However, the difference between the post-treatment results of the two groups was not statistically significant (p = 0.8).			⊕⊕○○ Low	CRITICAL	
Elevated AST(between 41IU/L and 100 IU/L)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	1/26 (3.8%)	2/32 (6.3%)	RR 0.62 (0.06 to 6.41)	24 fewer per 1,000 (from 59 fewer to 338 more)	⊕⊕○○ Low	IMPORTANT

Elevated ALT(between 41IU/L and 100 IU/L)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	0.5-1.0 mg/kg/day once daily	0.5-1.0 mg/kg/day divided as twice daily	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	5/26 (19.2%)	2/32 (6.3%)	RR 3.08 (0.65 to 14.58)	130 more per 1,000 (from 22 fewer to 849 more)	⊕⊕○○ Low	IMPORTANT

Elevated total cholesterol (between 201 mg/dL and 300 mg/dL)

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	7/26 (26.9%)	18/32 (56.3%)	RR 0.48 (0.24 to 0.97)	293 fewer per 1,000 (from 428 fewer to 17 fewer)	⊕⊕○○ Low	IMPORTANT

Elevated triglyceride (between 150 mg/dL and 375 mg/dL)

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	4/26 (15.4%)	14/32 (43.8%)	RR 0.35 (0.13 to 0.94)	284 fewer per 1,000 (from 381 fewer to 26 fewer)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

- a. Limited methods reporting.
- b. Small sample size.

References

1. Ahmad, H.M., *Analysis of clinical efficacy, side effects, and laboratory changes among patients with acne vulgaris receiving single versus twice daily dose of oral isotretinoin.* Dermatol Ther, 2015. **28**(3): p. 151-7.

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18. Isotretinoin vs. systemic antibiotics

e-Table 78. GRADE Evidence Profile for isotretinoin vs. systemic antibiotics

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isotretinoin	Oral antibiotics	Relative (95% CI)	Absolute (95% CI)		
Physician's global evaluation (follow-up: 16 weeks; assessed with: photographic evidence)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	Dapsone did not appear to produce any significant benefit based on the photographic evaluation. The subjects on 13-cis retinoic acid showed a significant improvement for the face from week 8 (P < 0.01) to week 36 (P < 0.001) and for the back and chest from week 20 (P < 0.05) to week 36 (P<0.0005 and P<0.01, respectively).				⊕⊕○○ Low	CRITICAL
Total lesion, 100% reduction, at the end of treatment												
1 ²	randomised trials	serious ^c	not serious	not serious	serious ^b	none	24/30 (80.0%)	6/30 (20.0%)	RR 4.00 (1.91 to 8.36)	600 more per 1,000 (from 182 more to 1,000 more)	⊕⊕○○ Low	CRITICAL
Total lesion, 75-99% reduction, at the end of treatment												
1 ²	randomised trials	serious ^c	not serious	not serious	serious ^b	none	5/30 (16.7%)	9/30 (30.0%)	RR 0.56 (0.21 to 1.46)	132 fewer per 1,000 (from 237 fewer to 138 more)	⊕⊕○○ Low	CRITICAL

Inflammatory lesion

2 ^{1,3}	randomised trials	serious ^a	not serious	not serious	serious ^b	none	Prendiville 1988 Total of 40 patients were randomized to receive dapsone 100 mg daily for 16 weeks or 13-cis retinoic acid, 40mg daily for 16 weeks (Author did not report how many were randomized to each group), and 17 from each group completed the study. Lesion counts (pustules, nodules, and cysts) were assessed during the treatment and for a follow up period of 20 weeks. [Face and neck] At 16 weeks, there was a reduction in lesions in the dapsone-treated patients ($P < 0.05$) which was maintained on follow-up to 36 weeks. The 13-cis retinoic acid group showed a highly significant improvement ($p < 0.0001$) from week 16 to completion of the follow-up period. Comparison of the groups showed the 13-cis retinoic acid treated patients to have significantly fewer lesions at 20 weeks ($P < 0.01$) and at 28 and 36 weeks ($P < 0.05$) when compared with the dapsone group. [Chest and back] There was no significant reduction in lesions on the chest and back in the dapsone group. The 13-cis retinoic acid treated patients showed a significant improvement ($P < 0.01$) from week 16 to 36. Pigatto 1986 A total of 24 patients with severe cystic acne were randomized to receive either isotretinoin 1mg/kg/day for 10 weeks, then 0.5mg/day for another 10 weeks or minocycline 100mg day for 10 weeks, then 50 mg/day for another 10 weeks. Patients treated with isotretinoin ($n=12$) continued to improve, while the acne of the minocycline-treated group ($n=12$) remained unchanged, leading to a significantly different number of cysts ($p < 0.02$) at week 20 (mean number of cysts 1.2 vs. 8.9 in isotretinoin and minocycline, respectively; data are from Figure 1 using WebPlotDigitizer).	⊕⊕○○ Low	CRITICAL

Lab abnormalities

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isotretinoin	Oral antibiotics	Relative (95% CI)	Absolute (95% CI)		
2 ^{2,3}	randomised trials	serious ^a	not serious	not serious	serious ^d	none	Pigatto 1986 Neither isotretinoin nor minocycline induced any clinically significant changes in hepatic function, blood chemistry, urinalysis, or lipid metabolism ALT: In the minocycline-treated group, 3 patients had slight but persistent abnormal elevations of alkaline phosphatase during therapy. TC: No patients in isotretinoin group had abnormal total cholesterol level. 7 minocycline patients fell to levels below the range of normal during therapy. TG: Triglyceride levels rose above the normal range in 4 patients in the isotretinoin group. In the minocycline group, the triglyceride level fell below the range of normal in 6 patients, while the mean triglyceride values remained stable. HDL-C: Our results showed a decrease in the mean HDL-C level during the first 10 weeks of isotretinoin therapy but by the end of treatment, HDL-C was enhanced by isotretinoin, leading to normal values ($p < 0.05$). Wahab2008 A total of 60 patients with moderate to severe acne were 1:1 randomized to receive isotretinoin 0.5-1mg/kg/day for 5 months or azithromycin 500mg three days a week for 3 months. In the isotretinoin group, 3 patients showed a transient rise in serum lipids especially triglycerides but not of the patients had levels enough to warrant stoppage of the drugs.				⊕⊕○○ Low	IMPORTANT

Patient's global evaluation (follow-up: 16 weeks; assessed with: Visual analog scale)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isotretinoin	Oral antibiotics	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	The patients on dapsone recorded a significant (p<0.01) improvement at 16 weeks which was not maintained at week 36. The 13-cis retinoic acid groups recorded a highly significant improvement (p<0.001) from the eighth week of treatment to completion of the follow-up period. Between drug comparisons at week 16-36 showed a highly significant (p<0.001) result in favour of 13-cis retinoic acid.				⊕⊕○○ Low	IMPORTANT

Withdrawal due to AE

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	0/20 (0.0%)	1/20 (5.0%)	RR 0.33 (0.01 to 7.72)	33 fewer per 1,000 (from 50 fewer to 336 more)	⊕⊕○○ Low	IMPORTANT

Recurrence, during the post treatment period

1 ²	randomised trials	serious ^c	not serious	not serious	serious ^b	none	5/30 (16.7%)	10/30 (33.3%)	RR 0.50 (0.19 to 1.29)	167 fewer per 1,000 (from 270 fewer to 97 more)	⊕⊕○○ Low	IMPORTANT

Nausea

1 ³	randomised trials	serious ^a	not serious	not serious	serious ^d	none	0/12 (0.0%)	1/12 (8.3%)	RR 0.33 (0.01 to 7.45)	56 fewer per 1,000 (from 82 fewer to 538 more)	⊕⊕○○ Low	IMPORTANT

Nausea and abdominal discomfort, mild

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isotretinoin	Oral antibiotics	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	serious ^c	not serious	not serious	serious ^b	none	0/30 (0.0%)	3/30 (10.0%)	RR 0.14 (0.01 to 2.65)	86 fewer per 1,000 (from 99 fewer to 165 more)	⊕⊕○○ Low	IMPORTANT

Vomiting

1 ³	randomised trials	serious ^a	not serious	not serious	serious ^d	none	0/12 (0.0%)	3/12 (25.0%)	RR 0.14 (0.01 to 2.50)	215 fewer per 1,000 (from 248 fewer to 375 more)	⊕⊕○○ Low	IMPORTANT

Diarrhea

1 ³	randomised trials	serious ^a	not serious	not serious	serious ^d	none	0/12 (0.0%)	2/12 (16.7%)	RR 0.20 (0.01 to 3.77)	133 fewer per 1,000 (from 165 fewer to 462 more)	⊕⊕○○ Low	IMPORTANT

Photosensitivity

1 ³	randomised trials	serious ^a	not serious	not serious	serious ^d	none	0/12 (0.0%)	1/12 (8.3%)	RR 0.33 (0.01 to 7.45)	56 fewer per 1,000 (from 82 fewer to 538 more)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

a. Limited methods reporting.

b. Small sample size.

c. Minimal methods reporting. The isotretinoin group received the treatment for 5 months and the azithromycin group received 500 mg three days a week for 3 months. Topical adjuvant therapy (e.g., erythromycin lotion followed by adapalene) was given in both groups

d. A small sample size and rare event rate resulted in a wide CI

References

1. Prendiville, J.S., R.A. Logan, and R. Russell-Jones, *A comparison of dapsone with 13-cis retinoic acid in the treatment of nodular cystic acne*. Clin Exp Dermatol, 1988. **13**(2): p. 67-71.
2. Wahab, M.A., et al., *Isotretinoin versus weekly pulse dose azithromycin in the treatment of acne-a comparative study*. Journal of Pakistan Association of Dermatology, 2008. **18**(1): p. 9-14.
3. Pigatto, P.D., et al., *Isotretinoin versus minocycline in cystic acne: a study of lipid metabolism*. Dermatologica, 1986. **172**(3): p. 154-9.

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e-Table 79. GRADE Evidence Profile for isotretinoin vs. systemic antibiotics plus a topical agent

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isotretinoin	Systemic antibiotics plus a topical agent	Relative (95% CI)	Absolute (95% CI)		
Physician's global evaluation, at least two grade reduction from baseline, at week 20												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	120/133 (90.2%)	98/133 (73.7%)	RR 1.22 (1.09 to 1.38)	162 more per 1,000 (from 66 more to 280 more)	⊕⊕⊕○ Moderate	CRITICAL
Physician's global assessment (follow-up: 24 weeks; assessed with: good or very good response)												
1 ²	randomised trials	serious ^b	not serious	not serious	serious ^a	none	34/35 (97.1%)	45/50 (90.0%)	RR 1.08 (0.97 to 1.20)	72 more per 1,000 (from 27 fewer to 180 more)	⊕⊕○○ Low	CRITICAL
Lesion counts, percentage changes from baseline, at week 20												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	At week 20, ISO was superior to D+A/BPO in the reduction of nodules (95.6% vs. 88.7%), papules/pustules (95.2% vs. 79.6%), comedones (92.3% vs. 75.9%) and total lesions (92.9% vs. 78.2%, respectively) (all P < 0.01). In the D+A/BPO group, 96.0% had ≥ 75% reduction in nodules compared with 98.0% for ISO.				⊕⊕⊕○ Moderate	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isotretinoin	Systemic antibiotics plus a topical agent	Relative (95% CI)	Absolute (95% CI)		

Inflammatory lesion (follow-up: 24 weeks; assessed with: percentage change from baseline)

1 ²	randomised trials	serious ^b	not serious	not serious	serious ^a	none	35	50	-	MD 8.9 higher (0.13 higher to 17.67 higher)	⊕⊕○○ Low	

Noninflammatory lesion (follow-up: 24 weeks; assessed with: percentage change from baseline)

1 ²	randomised trials	serious ^b	not serious	not serious	serious ^a	none	35	50	-	MD 14 higher (0.2 higher to 27.8 higher)	⊕⊕○○ Low	

Serious adverse effects

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	1/133 (0.8%)	0/133 (0.0%)	RR 3.00 (0.12 to 72.98)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	CRITICAL

Withdrawal due to AE

2 ^{1,2}	randomised trials	not serious	not serious	not serious	serious ^a	none	4/168 (2.4%)	8/183 (4.4%)	RR 0.59 (0.19 to 1.85)	18 fewer per 1,000 (from 35 fewer to 37 more)	⊕⊕⊕○ Moderate	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isotretinoin	Systemic antibiotics plus a topical agent	Relative (95% CI)	Absolute (95% CI)		

Increased triglycerides, alanine aminotransferase and aspartate aminotransferase

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	6/133 (4.5%)	0/133 (0.0%)	RR 13.00 (0.74 to 228.47)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

Hypercholesterolemia

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	0/133 (0.0%)	1/133 (0.8%)	RR 0.33 (0.01 to 8.11)	5 fewer per 1,000 (from 7 fewer to 53 more)	⊕⊕⊕○ Moderate	IMPORTANT

Any AE

1 ²	randomised trials	serious ^b	not serious	not serious	serious ^a	none	23/35 (65.7%)	18/50 (36.0%)	RR 1.83 (1.18 to 2.84)	299 more per 1,000 (from 65 more to 662 more)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; MD: mean difference; RR: Risk ratio;

Explanations

a. Small sample size

b. This study had unclear risk of random sequence generation and selective reporting and high risk of selection bias (no allocation concealment was used) and performance/detection bias (open label)

References

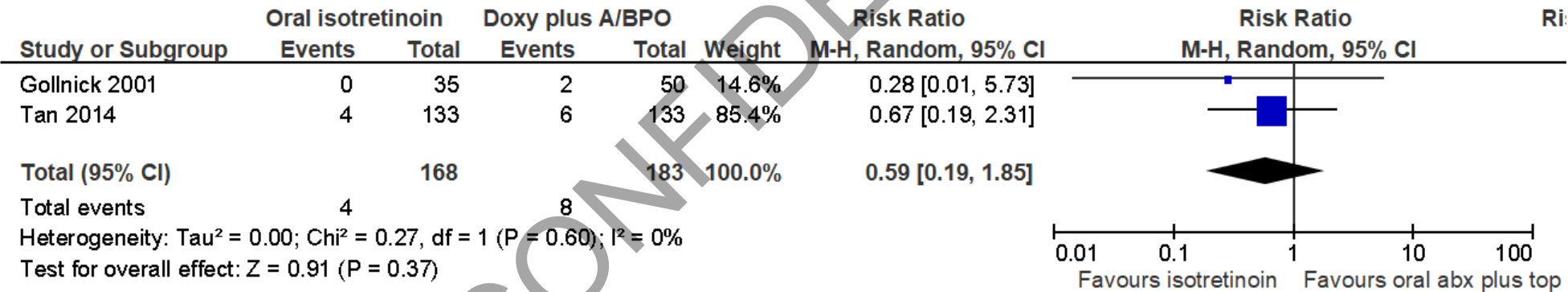
1. Tan, J., et al., *A treatment for severe nodular acne: a randomized investigator-blinded, controlled, noninferiority trial comparing fixed-dose adapalene/benzoyl peroxide plus doxycycline vs. oral isotretinoin*. Br J Dermatol, 2014. **171**(6): p. 1508-16.
2. Gollnick, H.P., K. Graupe, and R.P. Zaumseil, *Comparison of combined azelaic acid cream plus oral minocycline with oral isotretinoin in severe acne*. Eur J Dermatol, 2001. **11**(6): p. 538-44.

Forest plot

e-Figure 177. Withdrawal due to AE, isotretinoin vs. antibiotic plus a topical agent

30 [Pooled] Isotretinoin versus antibiotics plus a topical agent

30.9 Withdrawal due to AE wtih gollnick



e-Table 80. GRADE Evidence Profile for isotretinoin plus topical agents vs. isotretinoin

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	isotretinoin plus topical agents	isotretinoin	Relative (95% CI)	Absolute (95% CI)		
Physician global assessment, Global acne assessment score (Range 0-5), at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	29	29	-	MD 0.2 lower (0.33 lower to 0.07 lower)	⊕⊕⊕○ Moderate	CRITICAL
Physician global assessment, clear, at 6 months												
1 ²	randomised trials	serious ^b	not serious	not serious	serious ^a	none	13/30 (43.3%)	12/30 (40.0%)	RR 1.08 (0.59 to 1.97)	32 more per 1,000 (from 164 fewer to 388 more)	⊕⊕○○ Low	CRITICAL
Physician global assessment, Clear or excellence (>= 75 reduction in acne score) at 6 months												
1 ²	randomised trials	serious ^b	not serious	not serious	serious ^{a,c}	none	22/30 (73.3%)	19/30 (63.3%)	RR 1.16 (0.82 to 1.64)	101 more per 1,000 (from 114 fewer to 405 more)	⊕⊕○○ Low	CRITICAL

Withdrawal due to AE

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	isotretinoin plus topical agents	isotretinoin	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	serious ^b	not serious	not serious	serious ^a	none	0/30 (0.0%)	0/30 (0.0%)	not estimable		⊕⊕○○ Low	IMPORTANT

Any AE

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	18/29 (62.1%)	3/29 (10.3%)	RR 6.00 (1.98 to 18.18)	517 more per 1,000 (from 101 more to 1,000 more)	⊕⊕⊕○ Moderate	IMPORTANT

Photosensitivity

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	1/29 (3.4%)	0/29 (0.0%)	RR 3.00 (0.13 to 70.74)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

Burning sensation

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	7/29 (24.1%)	2/29 (6.9%)	RR 3.50 (0.79 to 15.45)	172 more per 1,000 (from 14 fewer to 997 more)	⊕⊕⊕○ Moderate	IMPORTANT

Erythema/irritation

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	isotretinoin plus topical agents	isotretinoin	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	4/29 (13.8%)	1/29 (3.4%)	RR 4.00 (0.48 to 33.66)	103 more per 1,000 (from 18 fewer to 1,000 more)	⊕⊕⊕○ Moderate	IMPORTANT

Dryness

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	3/29 (10.3%)	0/29 (0.0%)	RR 7.00 (0.38 to 129.74)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

Exfoliation

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	1/29 (3.4%)	0/29 (0.0%)	RR 3.00 (0.13 to 70.74)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	IMPORTANT

Flare-ups (erythema, edema, and fresh papular and pustular lesions)

1 ²	randomised trials	serious ^b	not serious	not serious	serious ^a	none	6/30 (20.0%)	3/30 (10.0%)	RR 2.00 (0.55 to 7.27)	100 more per 1,000 (from 45 fewer to 627 more)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

- a. Small sample size.
- b. Open label study; 20/30 in combo and 15/30 in isotretinoin alone groups completed the study
- c. For comedones, papules, and pustules (for each) lesion counts great than 20 gets 4 points, between 15-19 gets 3, between 11-14 gets 2, fewer than 10 gets 1. For nodules and cysts, lesion counts greater than 10 gets 4 points, between 6-10 gets 3, and fewer than 6 gets 2 points.
- d. A small sample size and few events resulted in a wide CI.

References

1. Faghihi, G., et al., *The efficacy of 5% dapsone gel plus oral isotretinoin versus oral isotretinoin alone in acne vulgaris: A randomized double-blind study*. Adv Biomed Res, 2014. **3**: p. 177.
2. Dhir, R., et al., *Oral isotretinoin is as effective as a combination of oral isotretinoin and topical anti-acne agents in nodulocystic acne*. Indian J Dermatol Venereol Leprol, 2008. **74**(2): p. 187.

Physical Modalities

A. Peels vs. Control

1. Glycolic acid 40% vs. Control

e-Table 81. GRADE Evidence Profile for glycolic acid 40% vs. control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glycolic acid 40%	Control	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any at 4 weeks (mean)												
1 1,a	randomised trials	not serious	not serious	not serious	serious ^b	none	25	25	-	MD 4.63 lesions lower (6.65 lower to 2.61 lower)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any at 8 weeks (mean)												
1 1,a	randomised trials	not serious	not serious	not serious	serious ^b	none	25	25	-	MD 5.71 lesions lower (8.68 lower to 2.75 lower)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Inflammatory at 4 weeks (mean)												
1 1,a	randomised trials	not serious	not serious	not serious	serious ^b	none	25	25	-	MD 4.71 lesions lower (6.74 lower to 2.69 lower)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 8 weeks (mean)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glycolic acid 40%	Control	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	25	25	-	MD 5.86 lesions lower (8.89 lower to 2.82 lower)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks (mean)

1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	25	25	-	MD 6.63 lesions lower (9.49 lower to 3.77 lower)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (mean)

1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	25	25	-	MD 7.35 lesions lower (10.89 lower to 3.8 lower)	⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; MD: Mean difference

Explanations

- a. RCT, Split face
b. Small sample size

References

1. Kaminaka, C., et al., *Clinical evaluation of glycolic acid chemical peeling in patients with acne vulgaris: A randomized, double-blind, placebo-controlled, split-face comparative study*. Dermatologic Surgery, 2014. **40**(3): p. 314-322.

2. Glycolic acid 70% + Salicylic acid 20% + Doxycycline vs. Doxycycline

e-Table 82. GRADE Evidence Profile for glycolic acid 70% + salicylic acid 20% + doxycycline vs. doxycycline

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glycolic acid 70% + Salicylic acid 20% + Doxycycline	Doxycycline	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Bespoke, Unknown scale at 12 weeks (median)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	15 and 15 patients were randomized to receive glycolic acid 70% + salicylic acid 20% + doxycycline and doxycycline, respectively. At baseline, the median values of acne severity for glycolic acid 70% + salicylic acid 20% and doxycycline groups were 2 (range: 2-4) and 2 (range: 2-4), respectively. At 12 weeks, the median values changed to 2 (range: 0-2, n: 13) and 2 (range: 0-2, n: 12) for glycolic acid 70% + salicylic acid 20% + doxycycline and doxycycline groups, respectively. The difference between the two treatment groups was not significant. ^b		⊕⊕⊕○ Moderate		CRITICAL	
Number of lesions, Any at 12 weeks (median)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	At baseline, the median number of lesions for glycolic acid 70% + salicylic acid 20% + doxycycline and doxycycline groups was 23 (range: 8-40) and 17 (range: 10-38), respectively. At 12 weeks, the median values changed to 2 (range: 0-7, n: 13) and 3 (range: 2-7, n: 12) for glycolic acid 70% + salicylic acid 20% + doxycycline and doxycycline groups, respectively. The difference between the two treatment groups was not significant. ^b		⊕⊕⊕○ Moderate		CRITICAL	

Patient assessment of improvement, Global, VAS (1-4) at 12 weeks (median)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glycolic acid 70% + Salicylic acid 20% + Doxycycline	Doxycycline	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	At baseline, the median values of patient satisfaction for glycolic acid 70% + salicylic acid 20% + doxycycline and doxycycline groups were 2 (range: 1-3) and 2 (range: 1-3), respectively. At 12 weeks, the median values changed to 4 (range: 3-4, n: 13) and 3 (range: 3-4, n: 12) for glycolic acid 70% + salicylic acid 20% + doxycycline and doxycycline groups, respectively. The difference between the two treatment groups was significant (p = 0.001). ^b				⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval

Explanations

a. Small sample size

b. n: number of patients at the follow-up.

References

1. Zayed, A.A., et al., *Sequential peeling as a monotherapy for treatment of milder forms of acne vulgaris*. Journal of Cosmetic Dermatology, 2020. **19(6)**: p. 1381-1387.

Comparing Different Peeling Agents

3. Trichloroacetic acid 25% vs. Azelaic acid 20% + Salicylic acid 20%

e-Table 83. GRADE Evidence Profile for trichloroacetic acid 25% vs. azelaic acid 20% + salicylic acid 20%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trichloroacetic acid 25%	Azelaic acid 20% + Salicylic acid 20%	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Non-inflammatory at 4 weeks (mean)												
1 1,a	randomised trials	not serious	not serious	not serious	serious ^b	none	34	34	-	MD 1.21 lesions lower (3.9 lower to 1.48 higher)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Non-inflammatory at 8 weeks (mean)												
1 1,a	randomised trials	not serious	not serious	not serious	serious ^b	none	34	34	-	MD 1.21 lesions lower (3.9 lower to 1.48 higher)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Inflammatory at 4 weeks (mean)												
1 1,a	randomised trials	not serious	not serious	not serious	serious ^b	none	34	34	-	MD 1.45 lesions higher (0.28 lower to 3.18 higher)	⊕⊕⊕○ Moderate	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trichloroacetic acid 25%	Azelaic acid 20% + Salicylic acid 20%	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Inflammatory at 8 weeks (mean)

1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	34	34	-	MD 0.17 lesions lower (1.65 lower to 1.31 higher)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, Improvement at 8 weeks

1 ^{1,a,c}	randomised trials	not serious	not serious	not serious	serious ^d	none	27/34 (79.4%)	29/34 (85.3%)	OR 0.67 (0.08 to 5.47)	58 fewer per 1,000 (from 536 fewer to 117 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Improvement at 8 weeks

1 ^{1,a,e}	randomised trials	not serious	not serious	not serious	serious ^b	none	29/34 (85.3%)	34/34 (100.0%)	OR 0.08 (0.00 to 2.30)	0 fewer per 1,000 (from 0 fewer to -)	⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; MD: Mean difference; OR: Odds ratio

Explanations

a. RCT, Split face

b. Small sample size.

- c. The number of comedones (open and closed)
- d. Small sample size resulting in a wide CI including both appreciable benefits and harm
- e. The number of papules and pustules

References

1. Abdel Hay, R., et al., *Clinical and dermoscopic evaluation of combined (salicylic acid 20% and azelaic acid 20%) versus trichloroacetic acid 25% chemical peel in acne: an RCT*. Journal of Dermatological Treatment, 2019. **30**(6): p. 572-577.

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4. Trichloroacetic acid 25% vs. Salicylic acid 30%

e-Table 84. GRADE Evidence Profile for trichloroacetic acid 25% vs. salicylic acid 30%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trichloroacetic acid 25%	Salicylic acid 30%	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any, <0% reduction at 10 weeks												
1 1,a	randomised trials	not serious	not serious	not serious	serious ^b	none	2/20 (10.0%)	1/20 (5.0%)	OR 2.11 (0.10 to 42.57)	50 more per 1,000 (from 45 fewer to 641 more)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, 0-10% reduction at 10 weeks												
1 1,a	randomised trials	not serious	not serious	not serious	serious ^c	none	1/20 (5.0%)	0/20 (0.0%)	not estimable		⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, >=10% reduction at 10 weeks												
1 1,a	randomised trials	not serious	not serious	not serious	serious ^c	none	17/20 (85.0%)	19/20 (95.0%)	OR 0.30 (0.02 to 5.41)	99 fewer per 1,000 (from 675 fewer to 40 more)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, 10-20% reduction at 10 weeks												
1 1,a	randomised trials	not serious	not serious	not serious	serious ^c	none	1/20 (5.0%)	1/20 (5.0%)	OR 1.00 (0.04 to 27.29)	0 fewer per 1,000 (from 48 fewer to 540 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, 21-50% reduction at 10 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trichloroacetic acid 25%	Salicylic acid 30%	Relative (95% CI)	Absolute (95% CI)		
1 1,a	randomised trials	not serious	not serious	not serious	serious ^b	none	4/20 (20.0%)	9/20 (45.0%)	OR 0.31 (0.03 to 2.75)	248 fewer per 1,000 (from 426 fewer to 242 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, >50% reduction at 10 weeks

1 1,a	randomised trials	not serious	not serious	not serious	serious ^b	none	12/20 (60.0%)	9/20 (45.0%)	OR 1.83 (0.22 to 15.01)	150 more per 1,000 (from 297 fewer to 475 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Papules and pustules, <0% reduction at 10 weeks

1 1,a,d	randomised trials	not serious	not serious	not serious	serious ^b	none	5/20 (25.0%)	1/20 (5.0%)	OR 6.33 (0.38 to 105.52)	200 more per 1,000 (from 30 fewer to 797 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Papules and pustules, 0-10% reduction at 10 weeks

1 1,a,d	randomised trials	not serious	not serious	not serious	serious ^b	none	1/20 (5.0%)	2/20 (10.0%)	OR 0.47 (0.02 to 9.55)	50 fewer per 1,000 (from 98 fewer to 415 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Papules and pustules, ≥10% reduction at 10 weeks

1 1,a,d	randomised trials	not serious	not serious	not serious	serious ^c	none	14/20 (70.0%)	17/20 (85.0%)	OR 0.41 (0.04 to 4.09)	151 fewer per 1,000 (from 665 fewer to 109 more)	⊕⊕⊕○ Moderate	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trichloroacetic acid 25%	Salicylic acid 30%	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Inflammatory, Papules and pustules, 10-20% reduction at 10 weeks

1 ^{1,a,d}	randomised trials	not serious	not serious	not serious	serious ^c	none	3/20 (15.0%)	0/20 (0.0%)	not estimable		⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Papules and pustules, 21-50% reduction at 10 weeks

1 ^{1,a,d}	randomised trials	not serious	not serious	not serious	serious ^c	none	6/20 (30.0%)	5/20 (25.0%)	OR 1.29 (0.14 to 11.46)	51 more per 1,000 (from 205 fewer to 543 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Papules and pustules, >50% reduction at 10 weeks

1 ^{1,a,d}	randomised trials	not serious	not serious	not serious	serious ^b	none	5/20 (25.0%)	12/20 (60.0%)	OR 0.22 (0.03 to 1.93)	352 fewer per 1,000 (from 557 fewer to 143 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, <0% reduction at 10 weeks

1 ^{1,a,e}	randomised trials	not serious	not serious	not serious	serious ^c	none	4/20 (20.0%)	0/20 (0.0%)	not estimable		⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, 0-10% reduction at 10 weeks

1 ^{1,a,e}	randomised trials	not serious	not serious	not serious	serious ^c	none	0/20 (0.0%)	4/20 (20.0%)	OR 0.09 (0.00 to 2.78)	178 fewer per 1,000 (from -- to 210 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, >=10% reduction at 10 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trichloroacetic acid 25%	Salicylic acid 30%	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a,e}	randomised trials	not serious	not serious	not serious	serious ^c	none	16/20 (80.0%)	16/20 (80.0%)	OR 1.00 (0.10 to 9.88)	0 fewer per 1,000 (from 514 fewer to 175 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, 10-20% reduction at 10 weeks

1 ^{1,a,e}	randomised trials	not serious	not serious	not serious	serious ^c	none	2/20 (10.0%)	0/20 (0.0%)	not estimable		⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, 21-50% reduction at 10 weeks

1 ^{1,a,e}	randomised trials	not serious	not serious	not serious	serious ^b	none	5/20 (25.0%)	2/20 (10.0%)	OR 3.00 (0.26 to 34.78)	150 more per 1,000 (from 72 fewer to 694 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, >50% reduction at 10 weeks

1 ^{1,a,e}	randomised trials	not serious	not serious	not serious	serious ^c	none	9/20 (45.0%)	14/20 (70.0%)	OR 0.35 (0.04 to 2.95)	250 fewer per 1,000 (from 615 fewer to 173 more)	⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; OR: Odds ratio

Explanations

- a. RCT, Split face
- b. Small sample size resulting in a wide CI including both appreciable benefits and harm
- c. Small sample size.
- d. Papules and pustules, Total improvement (Good or fair or poor)
- e. Comedones, Total improvement

References

1. Abdel Meguid, A.M., D. Abd Elaziz Ahmed Attallah, and H. Omar, *Trichloroacetic acid versus salicylic acid in the treatment of acne vulgaris in dark-skinned patients*. Dermatologic Surgery, 2015. **41**(12): p. 1398-1404.

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5. Salicylic acid 30% vs Jessner's solution

e-Table 85. GRADE Evidence Profile for salicylic acid 30% vs Jessner's solution

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salicylic acid 30%	Jessner's solution	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Michaëlsson at 4 weeks (median)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	At baseline, the median score for salicylic acid 30% and Jessner's solution was 17 and 17, respectively. At 4 weeks, the median score decreased to 6.75 and 7.75 for salicylic acid 30% and Jessner's solution sides, respectively. The difference between the two treatments was not significant (p = 0.684).			⊕⊕⊕○ Moderate	CRITICAL	
Acne severity, Michaëlsson at 8 weeks (median)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	At baseline, the median score for salicylic acid 30% and Jessner's solution was 17 and 17, respectively. At 8 weeks, the median score decreased to 5.5 and 6 for salicylic acid 30% and Jessner's solution sides, respectively. The difference between the two treatments was not significant (p = 0.684).			⊕⊕⊕○ Moderate	CRITICAL	
Acne severity, Michaëlsson at 12 weeks (mean percent change from baseline)												
1 ²	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for salicylic acid 30% and Jessner's solution groups were -60.35% and -34.12%, respectively. The difference between the two treatment groups was significant (p = 0.002).			⊕⊕⊕○ Moderate	CRITICAL	

Acne severity, Michaëlsson, 21-50% decrease at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salicylic acid 30%	Jessner's solution	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	serious ^a	none	3/20 (15.0%)	14/20 (70.0%)	RR 0.21 (0.07 to 0.63)	553 fewer per 1,000 (from 651 fewer to 259 fewer)	⊕⊕⊕○ Moderate	CRITICAL

Acne severity, Michaëlsson, >50% decrease at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^a	none	17/20 (85.0%)	4/20 (20.0%)	RR 4.25 (1.74 to 10.41)	650 more per 1,000 (from 148 more to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 4 weeks (median)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	At baseline, the median number of inflammatory lesions for salicylic acid 30% and Jessner's solution was 7 and 7, respectively. At 4 weeks, the median number of inflammatory lesions decreased to 2 and 3 for salicylic acid 30% and Jessner's solution, respectively. The difference between the two treatments was not significant (p = 0.989).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 8 weeks (median)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salicylic acid 30%	Jessner's solution	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	At baseline, the median number of inflammatory lesions for salicylic acid 30% and Jessner's solution was 7 and 7, respectively. At 8 weeks, the median number of inflammatory lesions decreased to 1.5 and 2 for salicylic acid 30% and Jessner's solution, respectively. The difference between the two treatments was not significant (p = 0.989).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Pustules at 12 weeks (mean percent change from baseline)

1 ²	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for salicylic acid 30% and Jessner's solution groups were -70.28% and -76.70%, respectively. The difference between the two treatment groups was not significant (p = 0.57).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Papules at 12 weeks (mean percent change from baseline)

1 ²	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for salicylic acid 30% and Jessner's solution groups were -71.00% and -61.52%, respectively. The difference between the two treatment groups was not significant (p = 0.87).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks (median)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	At baseline, the median number of non-inflammatory lesions for salicylic acid 30% and Jessner's solution was 16.5 and 20, respectively. At 4 weeks, the median number of non-inflammatory lesions decreased to 6.5 and 8 for salicylic acid 30% and Jessner's solution, respectively. The difference between the two treatments was not significant (p = 0.228).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (median)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salicylic acid 30%	Jessner's solution	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	At baseline, the median number of non-inflammatory lesions for salicylic acid 30% and Jessner's solution was 16.5 and 20, respectively. At 8 weeks, the median number of non-inflammatory lesions decreased to 5.5 and 6 for salicylic acid 30% and Jessner's solution, respectively. The difference between the two treatments was not significant (p = 0.228).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean percent change from baseline)

12 ^b	randomised trials	not serious	not serious	not serious	serious ^a	none	20 and 20 patients were randomized to receive salicylic acid 30% or Jessner's solution, respectively. The mean percentage changes from baseline for salicylic acid 30% and Jessner's solution groups were -53.42% and -26.33%, respectively. The difference between the two treatment groups was significant (p = 0.001).			⊕⊕⊕○ Moderate	CRITICAL

Patient assessment of improvement, Global, Very good at 8 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^{a,c}	none	4/34 (11.8%)	6/34 (17.6%)	OR 0.80 (0.10 to 6.75)	30 fewer per 1,000 (from 155 fewer to 415 more)	⊕⊕⊕○ Moderate	CRITICAL

Patient assessment of improvement, Global, Good at 8 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salicylic acid 30%	Jessner's solution	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^{a,c}	none	16/34 (47.1%)	13/34 (38.2%)	OR 1.44 (0.21 to 10.03)	89 more per 1,000 (from 267 fewer to 479 more)	⊕⊕⊕○ Moderate	CRITICAL

Patient assessment of improvement, Global, No change at 8 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^{a,c}	none	13/34 (38.2%)	13/34 (38.2%)	OR 1.00 (0.14 to 7.03)	0 fewer per 1,000 (from 303 fewer to 431 more)	⊕⊕⊕○ Moderate	CRITICAL

Patient assessment of improvement, Global, Worse at 8 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^{a,c}	none	0/34 (0.0%)	2/34 (5.9%)	OR 0.16 (0.01 to 6.28)	49 fewer per 1,000 (from 58 fewer to 223 more)	⊕⊕⊕○ Moderate	CRITICAL

AE, Hyperpigmentation at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salicylic acid 30%	Jessner's solution	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	serious ^a	none	1/20 (5.0%)	3/20 (15.0%)	RR 0.33 (0.04 to 2.94)	100 fewer per 1,000 (from 144 fewer to 291 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Burning and irritation at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^a	none	13/20 (65.0%)	9/20 (45.0%)	RR 1.44 (0.81 to 2.58)	198 more per 1,000 (from 85 fewer to 711 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema at 12 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^a	none	6/20 (30.0%)	4/20 (20.0%)	RR 1.50 (0.50 to 4.52)	100 more per 1,000 (from 100 fewer to 704 more)	⊕⊕⊕○ Moderate	IMPORTANT

CI: Confidence interval; OR: Odds ratio; RR: Risk ratio

Explanations

a. Small sample size

b. Comedone count

c. CI includes appreciable benefits and harm

References

1. How, K.N., et al., *Efficacy and safety of Jessner's solution peel in comparison with salicylic acid 30% peel in the management of patients with acne vulgaris and postacne hyperpigmentation with skin of color: a randomized, double-blinded, split-face, controlled trial*. International Journal of Dermatology, 2020. **59(7)**: p. 804-812.
2. Dayal, S., et al., *Jessner's solution vs. 30% salicylic acid peels: a comparative study of the efficacy and safety in mild-to-moderate acne vulgaris*. Journal of Cosmetic Dermatology, 2017. **16(1)**: p. 43-51.

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6. Salicylic acid 30% vs. Mandelic acid

e-Table 86. GRADE Evidence Profile for salicylic acid 30% vs. mandelic acid

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salicylic acid 30%	Mandelic acid	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Michaëlsson at 12 weeks (mean absolute change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^{a,b}	none	25	25	-	MD 4 higher (4.13 lower to 12.13 higher)	⊕⊕⊕○ Moderate	CRITICAL
Acne severity, Michaëlsson at 12 weeks (mean percent change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for salicylic acid 30% and mandelic acid groups were -78.56% and -76.31%, respectively. The difference between the two treatment groups was not significant (p = 0.12).			⊕⊕⊕○ Moderate	CRITICAL	
Acne severity, Michaëlsson, >50% decrease at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	25/25 (100.0%)	25/25 (100.0%)	not estimable		⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Inflammatory, Papules at 12 weeks (mean percent change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for salicylic acid 30% and mandelic acid groups were -76.9% and -85.98%, respectively. The difference between the two treatment groups was significant (p = 0.004).			⊕⊕⊕○ Moderate	CRITICAL	
Number of lesions, Inflammatory, Pustules at 12 weeks (mean percent change from baseline)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salicylic acid 30%	Mandelic acid	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for salicylic acid 30% and mandelic acid groups were -95.33% and -95.69%, respectively. The difference between the two treatment groups was not significant (p = 0.86).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Noninflammatory, Comedones at 12 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for salicylic acid 30% and mandelic acid groups were -73.4% and -59.66%, respectively. The difference between the two treatment groups was statistically significant (p = 0.044).				⊕⊕⊕○ Moderate	CRITICAL

AE, Hyperpigmentation at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	3/25 (12.0%)	0/25 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Burning and irritation at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	20/25 (80.0%)	1/25 (4.0%)	RR 20.00 (2.90 to 137.48)	760 more per 1,000 (from 76 more to 1,000 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salicylic acid 30%	Mandelic acid	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	9/25 (36.0%)	2/25 (8.0%)	RR 4.50 (1.08 to 18.77)	280 more per 1,000 (from 6 more to 1,000 more)	⊕⊕⊕○ Moderate	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

a. Small sample size

b. CI includes both appreciable benefits and harm

References

1. Dayal, S., K.D. Kalra, and P. Sahu, *Comparative study of efficacy and safety of 45% mandelic acid versus 30% salicylic acid peels in mild-to-moderate acne vulgaris*. Journal of Cosmetic Dermatology, 2020. **19**(2): p. 393-399.

7. Jessner's solution vs. Glycolic acid 50% + Salicylic acid

e-Table 87. GRADE Evidence Profile for Jessner's solution vs. glycolic acid 50% + salicylic acid

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Jessner's solution	Glycolic acid 50% + Salicylic acid	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Global Evaluation Acne, Decreased by 1 at 4 weeks												
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	5/20 (25.0%)	5/20 (25.0%)	OR 1.00 (0.11 to 9.14)	0 fewer per 1,000 (from 215 fewer to 503 more)	⊕⊕○○ Low	CRITICAL
Acne severity, Global Evaluation Acne, Did not change at 4 weeks												
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	13/20 (65.0%)	15/20 (75.0%)	OR 0.62 (0.07 to 5.43)	100 fewer per 1,000 (from 576 fewer to 192 more)	⊕⊕○○ Low	CRITICAL
Acne severity, Global Evaluation Acne, Mild improvement at 4 weeks												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Jessner's solution	Glycolic acid 50% + Salicylic acid	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	8/20 (40.0%)	7/20 (35.0%)	OR 1.24 (0.15 to 10.30)	50 more per 1,000 (from 275 fewer to 497 more)	⊕⊕○○ Low	CRITICAL

Acne severity, Global Evaluation Acne, Moderate improvement at 4 weeks

1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	4/20 (20.0%)	5/20 (25.0%)	OR 0.75 (0.08 to 7.13)	50 fewer per 1,000 (from 224 fewer to 454 more)	⊕⊕○○ Low	CRITICAL

Acne severity, Global Evaluation Acne, No improvement at 4 weeks

1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	7/20 (35.0%)	8/20 (40.0%)	OR 0.81 (0.10 to 6.72)	49 fewer per 1,000 (from 338 fewer to 418 more)	⊕⊕○○ Low	CRITICAL

Number of lesions, Any at 4 weeks (mean)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Jessner's solution	Glycolic acid 50% + Salicylic acid	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^d	none	The total lesion count in the glycolic acid 50% + salicylic acid group decreased from the mean value of 16.80 at baseline to 12.45 at week 4 (p = 0.008). Similar results were obtained in Jessner's solution group, which decreased from the mean value of 17.95 at baseline to 12.35 at week 4 (P = .001). However, the differences in lesion count between the glycolic acid 50% + salicylic acid group and Jessner's solution group were not statistically significant (P > .05).				⊕⊕○○ Low	CRITICAL

Patient assessment of improvement, Global, 76-100% at 4 weeks

1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	0/20 (0.0%)	1/20 (5.0%)	OR 0.32 (0.01 to 12.45)	33 fewer per 1,000 (from 49 fewer to 346 more)	⊕⊕○○ Low	CRITICAL

Patient assessment of improvement, Global, Marked at 4 weeks

1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	1/20 (5.0%)	2/20 (10.0%)	OR 0.47 (0.02 to 9.55)	50 fewer per 1,000 (from 98 fewer to 415 more)	⊕⊕○○ Low	CRITICAL

Patient assessment of improvement, Global, Minimal (<25%) at 4 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Jessner's solution	Glycolic acid 50% + Salicylic acid	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	6/20 (30.0%)	5/20 (25.0%)	OR 1.29 (0.14 to 11.46)	51 more per 1,000 (from 205 fewer to 543 more)	⊕⊕○○ Low	CRITICAL

Patient assessment of improvement, Global, Moderate at 4 weeks

1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	6/20 (30.0%)	3/20 (15.0%)	OR 2.43 (0.24 to 24.10)	150 more per 1,000 (from 109 fewer to 660 more)	⊕⊕○○ Low	CRITICAL

Patient assessment of improvement, Global, No change at 4 weeks

1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	7/20 (35.0%)	9/20 (45.0%)	OR 0.66 (0.08 to 5.45)	99 fewer per 1,000 (from 389 fewer to 367 more)	⊕⊕○○ Low	CRITICAL

CI: Confidence interval; OR: Odds ratio

Explanations

a. RCT, Split face

b. Limited methods reporting and unblinded patients

- c. Small sample size leading to a wide CI including both appreciable benefits and harm
- d. Small sample size.

References

1. In Jae, J., et al., *Comparative study of buffered 50% glycolic acid (pH 3.0) + 0.5% salicylic acid solution vs Jessner's solution in patients with acne vulgaris*. Journal of Cosmetic Dermatology, 2018. **17(5)**: p. 797-801.

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8. Glycolic acid 70% vs. Amino fruit acid

e-Table 88. GRADE Evidence Profile for glycolic acid 70% vs. amino fruit acid

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glycolic acid 70%	Amino fruit acid	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Inflammatory, Papules and pustules at 4 weeks (mean)												
11.a	randomised trials	serious ^b	not serious	not serious	serious ^e	none	24	24	-	MD 1.41 lesions higher (0.68 lower to 3.5 higher)	⊕⊕○○ Low	CRITICAL
Number of lesions, Inflammatory, Papules and pustules at 8 weeks (mean)												
11.a	randomised trials	serious ^b	not serious	not serious	serious ^e	none	24	24	-	MD 0.59 lesions lower (2.46 lower to 1.28 higher)	⊕⊕○○ Low	CRITICAL
Number of lesions, Inflammatory, Papules and pustules at 24 weeks (mean)												
11.a	randomised trials	serious ^b	not serious	not serious	serious ^e	none	24	24	-	MD 0.12 lesions lower (2.71 lower to 2.47 higher)	⊕⊕○○ Low	CRITICAL
Number of lesions, Non-inflammatory at 4 weeks (mean)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glycolic acid 70%	Amino fruit acid	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a,d}	randomised trials	serious ^b	not serious	not serious	serious ^e	none	24	24	-	MD 0.5 lesion lower (20.65 lower to 19.65 higher)	⊕⊕○○ Low	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (mean)

1 ^{1,a,d}	randomised trials	serious ^b	not serious	not serious	serious ^e	none	24	24	-	MD 0.29 lesions higher (15.31 lower to 15.89 higher)	⊕⊕○○ Low	CRITICAL

Number of lesions, Non-inflammatory at 24 weeks (mean)

1 ^{1,a,d}	randomised trials	serious ^b	not serious	not serious	serious ^e	none	24	24	-	MD 1.16 lesions higher (4.29 lower to 6.61 higher)	⊕⊕○○ Low	CRITICAL

AE, Erythema at 24 weeks

1 ¹	randomised trials	serious ^b	not serious	not serious	serious ^c	none	24/24 (100.0%)	24/24 (100.0%)	not estimable		⊕⊕○○ Low	IMPORTANT

AE, Edema at 24 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glycolic acid 70%	Amino fruit acid	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^e	none	22/24 (91.7%)	12/24 (50.0%)	OR 11.00 (1.04 to 116.78)	417 more per 1,000 (from 10 more to 492 more)	⊕⊕○○ Low	IMPORTANT

AE, Frosting at 24 weeks

1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^e	none	7/24 (29.2%)	4/24 (16.7%)	OR 2.06 (0.23 to 18.30)	125 more per 1,000 (from 123 fewer to 619 more)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; MD: Mean difference; OR: Odds ratio

Explanations

- a. RCT, Split face
- b. Limited methods reporting, unblinded patients, and risk of attrition bias (20% dropout)
- c. Small sample size
- d. Comedones; blackheads and whiteheads
- e. Small sample size leading to a wide CI including both appreciable benefits and harm

References

1. Ilknur, T., et al., *Glycolic acid peels versus amino fruit acid peels for acne*. J Cosmet Laser Ther, 2010. **12**(5): p. 242-5.

9. Salicylic acid 30% vs. Glycolic acid 30%

e-Table 89. GRADE Evidence Profile for salicylic acid 30% vs. glycolic acid 30%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salicylic acid 30%	Glycolic acid 30%	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any at 4 weeks (mean percent change from baseline)												
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	20 patients were randomized to receive salicylic acid 30% on one half of the face and glycolic acid 30% on the other half, every 2 weeks for a total of six treatments. At 4 weeks, the mean percentage changes from baseline for salicylic acid 30% and glycolic acid 30% sides were -47% and -43%, respectively. The difference between the two treatments was not significant (p > 0.05).			⊕⊕⊕○ Moderate	CRITICAL	
Number of lesions, Any at 8 weeks (mean percent change from baseline)												
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	At 8 weeks, the mean percentage changes from baseline for salicylic acid 30% and glycolic acid 30% sides were -81% and -75%, respectively. The difference between the two treatments was not significant (p > 0.05).			⊕⊕⊕○ Moderate	CRITICAL	

CI: Confidence interval

Explanations

a. RCT, Split face

b. Small sample size.

References

1. Kessler, E., et al., *Comparison of alpha- and beta-hydroxy acid chemical peels in the treatment of mild to moderately severe facial acne vulgaris*. Dermatol Surg, 2008. **34**(1): p. 45-50; discussion 51.

e-Table 90. GRADE Evidence Profile for Jessner's solution vs. glycolic acid 70%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Jessner's solution	Glycolic acid 70%	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Leeds, 0 point reduction at 4 weeks												
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^{b,c}	none	9/26 (34.6%)	9/26 (34.6%)	OR 1.00 (0.13 to 7.67)	0 fewer per 1,000 (from 282 fewer to 456 more)	⊕⊕⊕○ Moderate	CRITICAL
Acne severity, Leeds, 0.25 point reduction at 4 weeks												
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^{b,c}	none	11/26 (42.3%)	10/26 (38.5%)	OR 1.17 (0.16 to 8.83)	38 more per 1,000 (from 294 fewer to 462 more)	⊕⊕⊕○ Moderate	CRITICAL

Acne severity, Leeds, 0.5 point reduction at 4 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Jessner's solution	Glycolic acid 70%	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^{b,c}	none	3/26 (11.5%)	4/26 (15.4%)	OR 0.72 (0.07 to 7.37)	38 fewer per 1,000 (from 141 fewer to 419 more)	⊕⊕⊕○ Moderate	CRITICAL

Acne severity, Leeds, 0.75 point reduction at 4 weeks

1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^{b,c}	none	1/26 (3.8%)	2/26 (7.7%)	OR 0.48 (0.02 to 9.52)	38 fewer per 1,000 (from 75 fewer to 365 more)	⊕⊕⊕○ Moderate	CRITICAL

Acne severity, Leeds, 1 point reduction at 4 weeks

1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^{b,c}	none	2/26 (7.7%)	1/26 (3.8%)	OR 2.08 (0.11 to 41.30)	38 more per 1,000 (from 34 fewer to 584 more)	⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; OR: Odds ratio

Explanations

a. RCT, Split face

- b. Small sample size
- c. CI include appreciable benefits and harm

References

1. Kim, S.W., et al., *Glycolic acid versus Jessner's solution: which is better for facial acne patients? A randomized prospective clinical trial of split-face model therapy*. *Dermatol Surg*, 1999. **25**(4): p. 270-3.

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11. Alpha hydroxy acid 4% + Negative pressure vs. Alpha hydroxy acid 4%

e-Table 91. GRADE Evidence Profile for alpha hydroxy acid 4% + negative pressure vs. alpha hydroxy acid 4%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alpha hydroxy acid 4% + Negative pressure	Alpha hydroxy acid 4%	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Non-inflammatory, Closed comedones at 4 weeks (mean percent change from baseline)												
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	23 patients were randomized to receive alpha hydroxy acid 4% + negative pressure on half of the face and alpha hydroxy acid 4% on the other half. The mean percent change from baseline of non-inflammatory lesions (closed comedones) for the alpha hydroxy acid 4% + negative pressure and alpha hydroxy acid 4% sides were 8.91% and 6.2%, respectively.			⊕⊕○○ Low	CRITICAL	
Number of lesions, Non-inflammatory, Open comedones at 4 weeks (mean percent change from baseline)												
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	The mean percent change from baseline of non-inflammatory lesions (open comedones) for the alpha hydroxy acid 4% + negative pressure and alpha hydroxy acid 4% sides were 20.09% and 11.17%, respectively.			⊕⊕○○ Low	CRITICAL	
AE, Burning and irritation at 4 weeks												
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^{c,d}	none	0/23 (0.0%)	2/23 (8.7%)	OR 0.18 (0.01 to 6.20)	70 fewer per 1,000 (from 86 fewer to 284 more)	⊕⊕○○ Low	IMPORTANT

AE, Itching at 4 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alpha hydroxy acid 4% + Negative pressure	Alpha hydroxy acid 4%	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^{c,d}	none	0/23 (0.0%)	1/23 (4.3%)	RR 0.32 (0.01 to 12.45)	30 fewer per 1,000 (from 43 fewer to 498 more)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; OR: Odds ratio; RR: Risk ratio

Explanations

- a. RCT, Split face
- b. Unclear allocation concealment and open label study
- c. Small sample size and no CIs or p-values provided
- d. CI includes appreciable benefits and harm

References

1. Kim, S.J., et al., *The effect of physically applied alpha hydroxyl acids on the skin pore and comedone*. International Journal of Cosmetic Science, 2015. **37(5)**: p. 519-525.

Peel vs. Other Acne Treatment (Oral or Topical)

12. Trichloroacetic acid 25% vs. Tretinoin 0.1% + Benzoyl peroxide 5%

e-Table 92. GRADE Evidence Profile for trichloroacetic acid 25% vs. tretinoin 0.1% + benzoyl peroxide 5%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trichloroacetic acid 25%	Tretinoin 0.1% + Benzoyl peroxide 5%	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Leeds at 12 weeks (mean)												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	At baseline, the mean values of acne severity score for trichloroacetic acid 25% and tretinoin 0.1% + benzoyl peroxide 5% groups were 2.08 (SD: 0.95) and 2.02 (SD: 1.01), respectively. At 12 weeks, the mean values decreased to 0.68 (SD: 0.50) and 0.65 (SD: 0.47) for trichloroacetic acid 25% and trichloroacetic acid 25% and tretinoin 0.1% + benzoyl peroxide 5% groups, respectively. The difference between the two treatment groups was not significant.			⊕⊕○○ Low	CRITICAL	
AE, Any, Trace at 12 weeks												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^c	none	7/15 (46.7%)	5/13 (38.5%)	RR 1.21 (0.51 to 2.91)	81 more per 1,000 (from 188 fewer to 735 more)	⊕⊕○○ Low	CRITICAL

Number of lesions, Any, >75% reduction at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trichloroacetic acid 25%	Tretinoin 0.1% + Benzoyl peroxide 5%	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^c	none	6/15 (40.0%)	5/13 (38.5%)	RR 1.04 (0.41 to 2.62)	15 more per 1,000 (from 227 fewer to 623 more)	⊕⊕○○ Low	CRITICAL

AE, Any, Mild at 12 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^c	none	6/15 (40.0%)	6/13 (46.2%)	RR 0.87 (0.37 to 2.04)	60 fewer per 1,000 (from 291 fewer to 480 more)	⊕⊕○○ Low	IMPORTANT

AE, Any, Moderate at 12 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^c	none	2/15 (13.3%)	2/13 (15.4%)	RR 0.87 (0.14 to 5.32)	20 fewer per 1,000 (from 132 fewer to 665 more)	⊕⊕○○ Low	IMPORTANT

Number of lesions, Any, 50-75% reduction at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trichloroacetic acid 25%	Tretinoin 0.1% + Benzoyl peroxide 5%	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^c	none	9/15 (60.0%)	8/13 (61.5%)	RR 0.97 (0.54 to 1.77)	18 fewer per 1,000 (from 283 fewer to 474 more)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

- a. Limited methods reporting and unblinded patients
- b. Small sample size
- c. Small sample size and wide CI including appreciable benefits and harm

References

1. Leheta, T.M., *Role of the 585-nm pulsed dye laser in the treatment of acne in comparison with other topical therapeutic modalities*. J Cosmet Laser Ther, 2009. 11(2): p. 118-24.

13. Glycolic acid 70% + Salicylic acid 20% vs. Doxycycline

e-Table 93. GRADE Evidence Profile for glycolic acid 70% + salicylic acid 20% vs. doxycycline

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glycolic acid 70% + Salicylic acid 20%	Doxycycline	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Bespoke, Unknown scale at 12 weeks (median)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	15 and 15 patients were randomized to receive glycolic acid 70% + salicylic acid 20% and doxycycline, respectively. At baseline, the median values of acne severity for glycolic acid 70% + salicylic acid 20% and doxycycline groups were 2 (range: 2-4) and 2 (range: 2-4), respectively. At 12 weeks, the median values changed to 2 (range: 0-2, n: 14) and 2 (range: 0-2, n: 12) for glycolic acid 70% + salicylic acid 20% and doxycycline groups, respectively. The difference between the two treatment groups was not significant (p = 0.39). ^b			⊕⊕⊕○ Moderate	CRITICAL	
Number of lesions, Any at 12 weeks (median)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	At baseline, the median number of lesions for glycolic acid 70% + salicylic acid 20% and doxycycline groups was 17 (range: 10-38) and 17 (range: 10-38), respectively. At 12 weeks, the median values changed to 2 (range: 0-6, n: 14) and 3 (range: 2-7, n: 12) for glycolic acid 70% + salicylic acid 20% and doxycycline groups, respectively. The difference between the two treatment groups was not significant (p = 0.14). ^b			⊕⊕⊕○ Moderate	CRITICAL	

Patient assessment of improvement, Global, VAS (1-4) at 12 weeks (median)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glycolic acid 70% + Salicylic acid 20%	Doxycycline	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	At baseline, the median values of patient satisfaction for glycolic acid 70% + salicylic acid 20% and doxycycline groups were 2 (range: 1-3) and 2 (range: 1-3), respectively. At 12 weeks, the median values changed to 4 (range: 3-4, n: 14) and 3 (range: 3-4, n: 12) for glycolic acid 70% + salicylic acid 20% and doxycycline groups, respectively. The difference between the two treatment groups was significant (p = 0.001). ^b				⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval

Explanations

a. Small sample size

b. n: number of patients at the follow-up.

References

1. Zayed, A.A., et al., *Sequential peeling as a monotherapy for treatment of milder forms of acne vulgaris*. Journal of Cosmetic Dermatology, 2020. **19(6)**: p. 1381-1387.

Peel vs. Laser/Light/Photodynamic Therapy

14. Trichloroacetic acid 25% vs. Pulsed dye laser

e-Table 94. GRADE Evidence Profile for trichloroacetic acid 25% vs. pulsed dye laser

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trichloroacetic acid 25%	Pulsed dye laser	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Leeds at 12 weeks (mean)												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	At baseline, the mean values of acne severity score for trichloroacetic acid 25% and pulsed dye laser groups were 2.08 (SD: 0.95) and 1.67 (SD: 0.93), respectively. At 12 weeks, the mean values decreased to 0.68 (SD: 0.50) and 0.56 (SD: 0.57) for trichloroacetic acid 25% and pulsed dye laser groups, respectively. The difference between the two treatment groups was not significant.			⊕⊕○○ Low	CRITICAL	
Number of lesions, Any, >75% reduction at 12 weeks												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	6/15 (40.0%)	6/13 (46.2%)	RR 0.87 (0.37 to 2.04)	60 fewer per 1,000 (from 291 fewer to 480 more)	⊕⊕○○ Low	CRITICAL
Number of lesions, Any, 50-75% reduction at 12 weeks												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	9/15 (60.0%)	7/13 (53.8%)	RR 1.11 (0.58 to 2.14)	59 more per 1,000 (from 226 fewer to 614 more)	⊕⊕○○ Low	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Trichloroacetic acid 25%	Pulsed dye laser	Relative (95% CI)	Absolute (95% CI)		

AE, Any, Mild at 12 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	6/15 (40.0%)	5/13 (38.5%)	RR 1.04 (0.41 to 2.62)	15 more per 1,000 (from 227 fewer to 623 more)	⊕⊕○○ Low	IMPORTANT

AE, Any, Moderate at 12 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	2/15 (13.3%)	3/13 (23.1%)	RR 0.58 (0.11 to 2.94)	97 fewer per 1,000 (from 205 fewer to 448 more)	⊕⊕○○ Low	IMPORTANT

AE, Any, Trace at 12 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	7/15 (46.7%)	5/13 (38.5%)	RR 1.21 (0.51 to 2.91)	81 more per 1,000 (from 188 fewer to 735 more)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

- a. Limited methods reporting and unblinded patients
- b. Small sample size and wide CI including appreciable benefits and harm

References

1. Leheta, T.M., *Role of the 585-nm pulsed dye laser in the treatment of acne in comparison with other topical therapeutic modalities*. J Cosmet Laser Ther, 2009. **11**(2): p. 118-24.

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15. Salicylic acid 30% vs. Pneumatic broadband light

e-Table 95. GRADE Evidence Profile for salicylic acid 30% vs. pneumatic broadband light

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salicylic acid 30%	Pneumatic broadband light	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Global Acne Grading Score, Modified at 4 weeks (median)												
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	12 patients were randomized to receive salicylic acid 30% on half of the face and pneumatic broadband light on the other half. At baseline, the median values of acne severity for salicylic acid 30% and pneumatic broadband light sides were 15 (range: 4-31) and 16 (range: 4-31), respectively. At 4 weeks, the median values changed to 10 (range: 6-21) and 10 (range: 4-27) for salicylic acid 30% and pneumatic broadband light sides, respectively. The difference between the two treatment groups was not significant (p = 0.79).			⊕⊕○○ Low	CRITICAL	
Acne severity, Global Acne Grading Score, Modified at 12 weeks (median)												
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	At baseline, the median values of acne severity for salicylic acid 30% and pneumatic broadband light sides were 15 (range: 4-31) and 16 (range: 4-31), respectively. At 12 weeks, the median values changed to 9 (range: 4-16) and 10 (range: 4-18) for salicylic acid 30% and pneumatic broadband light sides, respectively. The difference between the two treatment groups was not significant (p = 0.5).			⊕⊕○○ Low	CRITICAL	
Quality of life, Bespoke at 4 weeks (median)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salicylic acid 30%	Pneumatic broadband light	Relative (95% CI)	Absolute (95% CI)		
11, ^a	randomised trials	serious ^b	not serious	not serious	serious ^c	none	At baseline, the median values of quality of life for salicylic acid 30% and pneumatic broadband light sides were 4.5 (range: 0-13) and 4 (range: 0-13), respectively. At 4 weeks, the median values changed to 2 (range: 0-13) and 2.5 (range: 0-13) for salicylic acid 30% and pneumatic broadband light sides, respectively. The difference between the two treatment groups was not significant (p = 0.16).				⊕⊕○○ Low	IMPORTANT

Quality of life, Bespoke at 8 weeks (median)

11, ^a	randomised trials	serious ^b	not serious	not serious	serious ^c	none	At baseline, the median values of quality of life for salicylic acid 30% and pneumatic broadband light sides were 4.5 (range: 0-13) and 4 (range: 0-13), respectively. At 12 weeks, the median values changed to 3 (range: 0-11) and 3 (range: 0-15) for salicylic acid 30% and pneumatic broadband light sides, respectively. The difference between the two treatment groups was significant (p = 0.05).				⊕⊕○○ Low	IMPORTANT

CI: Confidence interval

Explanations

- a. RCT, Split face
- b. Limited methods reporting and unblinded patients
- c. Small sample size

References

1. Thuangtong, R., et al., *Comparison of salicylic acid 30% peel and pneumatic broadband light in the treatment of mild to moderately severe facial acne vulgaris*. *Cutis*, 2017. **100(1)**: p. 43-48.

16. Salicylic acid 10% vs. Combined 470 nm blue light and 660 nm red light

e-Table 96. GRADE Evidence Profile for salicylic acid 10% vs. combined 470 nm blue light and 660 nm red light

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Salicylic acid 10%	Combined 470 nm blue light and 660 nm red light	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Non-inflammatory, Comedones at 9 weeks (mean absolute change from baseline)												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	11 and 11 patients were randomized to receive salicylic acid 10% or combined 470 nm blue light and 660 nm red light, respectively. The mean absolute changes from baseline for salicylic acid 10% and combined 470 nm blue light and 660 nm red light groups were -19.01% and -16.16%, respectively. The difference between the two treatment groups was not significant.				⊕⊕○○ Low	CRITICAL
Number of lesions, Inflammatory, Pustules at 9 weeks (mean absolute change from baseline)												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	The mean absolute changes from baseline for salicylic acid 10% and combined 470 nm blue light and 660 nm red light groups were -6.08% and -13.06%, respectively. The difference between the two treatment groups was significant (p < 0.05).				⊕⊕○○ Low	CRITICAL
Number of lesions, Inflammatory, Papules (mean absolute change from baseline)												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	The mean absolute changes from baseline for salicylic acid 10% and combined 470 nm blue light and 660 nm red light groups were -7.11% and -8.15%, respectively. The difference between the two treatment groups was not significant.				⊕⊕○○ Low	CRITICAL

CI: Confidence interval

Explanations

- a. Limited methods reporting and unblinded patients.
- b. Small sample size and no CI or p-value reported.

References

1. Alba, M.N., et al., *Clinical comparison of salicylic acid peel and LED-Laser phototherapy for the treatment of Acne vulgaris in teenagers*. Journal of Cosmetic & Laser Therapy, 2017. **19**(1): p. 49-53.

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Laser/Light/Photodynamic Therapy vs. Control

17. Single microneedle radiofrequency vs. Control

e-Table 97. GRADE Evidence Profile for single microneedle radiofrequency vs. control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single microneedle radiofrequency	Control	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any at 4 weeks (mean percent change from baseline)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	29	28	-	MD 1.14 % lower (31.82 lower to 29.54 higher)	⊕⊕○○ Low	CRITICAL
Number of lesions, Any at 8 weeks (mean percent change from baseline)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	29	28	-	MD 18.55 % lower (48.8 lower to 11.7 higher)	⊕⊕○○ Low	CRITICAL
Number of lesions, Any at 12 weeks (mean percent change from baseline)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	29	28	-	MD 15.73 % lower (56.39 lower to 24.93 higher)	⊕⊕○○ Low	CRITICAL

Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single microneedle radiofrequency	Control	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^c	none	29	28	-	MD 14.02 % lower (27.49 lower to 0.55 lower)	⊕⊕○○ Low	CRITICAL

AE, Any, Serious at 12 weeks

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^c	none	0/29 (0.0%)	0/28 (0.0%)	not estimable		⊕⊕○○ Low	CRITICAL

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

- a. Limited methods reporting and unblinded patients.
- b. Wide CI includes both appreciable benefits and harm
- c. Small sample size.

References

1. Ahn, G.R., et al., *Selective Sebaceous Gland Electrothermolysis Using a Single Microneedle Radiofrequency Device for Acne Patients: A Prospective Randomized Controlled Study*. Lasers in Surgery and Medicine, 2020. **52(5)**: p. 396-401.

18. Infrared LED vs. Control

e-Table 98. GRADE Evidence Profile for infrared led vs. control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Infrared LED	Control	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Comprehensive Acne Severity Scale at 4 weeks (mean)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	At baseline, the mean values of acne severity for 905-nm infrared laser and control groups were 19.45 and 21.55, respectively. At 4 weeks, the mean values changed to 11.40 and 29.60 for 905-nm infrared laser and control groups, respectively. The difference between the two treatment groups was significant (p = 0.0001).			⊕⊕○○ Low	CRITICAL	

CI: Confidence interval

Explanations

- a. Limited methods reporting and open label study
- b. Small sample size

References

1. Mahran, H.G. and K.M. Drbala, *Efficacy of twelve sessions of 905nm infrared laser on acne vulgaris*. Annals of Clinical and Analytical Medicine, 2019. **11(3)**: p. 191-195.

e-Table 99. GRADE Evidence Profile for blue light vs. control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Blue light	Control	Relative (95% CI)	Absolute (95% CI)		
Investigator Global Assessment, >=1 grade reduction at 12 weeks												
11.a	randomised trials	not serious	not serious	not serious	serious ^b	none	79/89 (88.8%)	62/89 (69.7%)	OR 3.44 (1.55 to 7.64)	191 more per 1,000 (from 84 more to 249 more)	⊕⊕⊕○ Moderate	CRITICAL
Investigator Global Assessment, >=2 grade reduction at 4 weeks												
11.a	randomised trials	not serious	not serious	not serious	serious ^b	none	6/89 (6.7%)	0/89 (0.0%)	OR 13.93 (0.77 to 251.19)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	CRITICAL
Investigator Global Assessment, >=2 grade reduction at 8 weeks												
11.a	randomised trials	not serious	not serious	not serious	serious ^b	none	28/89 (31.5%)	9/89 (10.1%)	OR 4.08 (1.79 to 9.28)	213 more per 1,000 (from 66 more to 410 more)	⊕⊕⊕○ Moderate	CRITICAL
Investigator Global Assessment, >=2 grade reduction at 12 weeks												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Blue light	Control	Relative (95% CI)	Absolute (95% CI)		
11,a	randomised trials	not serious	not serious	not serious	serious ^b	none	46/89 (51.7%)	16/89 (18.0%)	OR 4.88 (2.47 to 9.66)	337 more per 1,000 (from 171 more to 499 more)	⊕⊕⊕○ Moderate	CRITICAL

Investigator Global Assessment, 0 or 1 grade reduction at 12 weeks

11,a	randomised trials	not serious	not serious	not serious	serious ^b	none	29/89 (32.6%)	10/89 (11.2%)	OR 3.82 (1.73 to 8.44)	214 more per 1,000 (from 67 more to 404 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, >=40% reduction at 4 weeks

11,a	randomised trials	not serious	not serious	not serious	serious ^b	none	32/89 (36.0%)	13/89 (14.6%)	OR 3.28 (1.58 to 6.81)	213 more per 1,000 (from 67 more to 392 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, >=40% reduction at 12 weeks

11,a	randomised trials	not serious	not serious	not serious	serious ^b	none	73/89 (82.0%)	41/89 (46.1%)	OR 5.34 (2.70 to 10.57)	360 more per 1,000 (from 237 more to 440 more)	⊕⊕⊕○ Moderate	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Blue light	Control	Relative (95% CI)	Absolute (95% CI)		

Number of lesion, any at 12 weeks (mean percent change from baseline)

1 ²	randomised trials	not serious	not serious	not serious	serious ^b	none	26 and 15 patients were randomized to receive 414 nm blue light or control, respectively. The mean percentage changes from baseline for 414 nm blue light and control groups were -50.08% and 2.45%, respectively.		⊕⊕⊕○ Moderate	CRITICAL

Quality of life, Cardiff Acne Disability Index at 12 weeks

1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	The comparison of quality of life scores showed a decrease of 40% in the 415/446 nm blue light hemifaces, whereas an increase in scores of 20% was reported for the control group.		⊕⊕⊕○ Moderate	IMPORTANT

CI: confidence interval; OR: odds ratio

Explanations

- a. RCT, Split face
- b. Small sample size

References

1. Antoniou, C. Dessinioti, C. Sotiriadis, D. Kalokasidis, K. Kontochristopoulos, G. Petridis, A. Rigopoulos, D. Vezina, D. Nikolis, A. A multicenter, randomized, split-face clinical trial evaluating the efficacy and safety of chromophore gel-assisted blue light phototherapy for the treatment of acne. International Journal of Dermatology; 2016.
2. Ash, C. Harrison, A. Drew, S. Whittall, R. A randomized controlled study for the treatment of acne vulgaris using high-intensity 414 nm solid state diode arrays. 2015.

e-Table 100. GRADE Evidence Profile for intense pulsed light vs. control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intense pulsed light	Control	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Inflammatory, Papules and pustules at 9 weeks (mean absolute change from baseline)												
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	30 patients were randomized to receive intense pulsed light on half of the face and control on the other half. The mean absolute changes from baseline for intense pulsed light and control sides were -3.2% and -3.1%, respectively. The difference between the two treatment sides was not significant (p > 0.05).			⊕⊕○○ Low	CRITICAL	
Number of lesions, Inflammatory at 21 weeks (mean percent change from baseline)												
1 ^{2,a}	randomised trials	serious ^e	not serious	not serious	serious ^d	none	23	12	-	MD 65.1 % higher (29.61 lower to 159.81 higher)	⊕⊕○○ Low	CRITICAL
Number of lesions, Non-inflammatory at 21 weeks (mean percent change from baseline)												
1 ^{2,a}	randomised trials	serious ^e	not serious	not serious	serious ^d	none	23	12	-	MD 28.5 % lower (146.89 lower to 89.89 higher)	⊕⊕○○ Low	CRITICAL

AE, Crusting and Hyperpigmentation at 21 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intense pulsed light	Control	Relative (95% CI)	Absolute (95% CI)		
12, ^a	randomised trials	serious ^e	not serious	not serious	serious ^d	none	2/23 (8.7%)	0/12 (0.0%)	OR 6.58 (0.25 to 171.78)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

- a. RCT, Split face
- b. Limited methods reporting and unblinded patients
- c. Small sample size
- d. Small sample size and CI including both appreciable benefits and harm
- e. Limited methods reporting, unblinded patients, and risk of attrition bias (23% dropout)

References

1. Chang, S.E., et al., *Treatment of facial acne papules and pustules in Korean patients using an intense pulsed light device equipped with a 530- to 750-nm filter*. Dermatol Surg, 2007. **33**(6): p. 676-9.
2. Yeung, C.K., et al., *A comparative study of intense pulsed light alone and its combination with photodynamic therapy for the treatment of facial acne in Asian skin*. Lasers Surg Med, 2007. **39**(1): p. 1-6.

e-Table 101. GRADE Evidence Profile for 1450 nm diode laser vs. control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1450 nm diode laser	Control	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Leeds at 4 weeks (median)												
1 1,a	randomised trials	serious ^b	not serious	not serious	serious ^c	none	At baseline, the median grade for 1450-nm diode laser and control was 3 (range: 0-11) and 3 (range: 1-10), respectively. At 4 weeks, the median grade changed to 3 (range: 1-11) and 3 (range: 1-11) for 1450-nm diode laser and control, respectively.			⊕⊕○○ Low	CRITICAL	
Acne severity, Leeds at 8 weeks (median)												
1 1,a	randomised trials	serious ^b	not serious	not serious	serious ^c	none	At baseline, the median grade for 1450-nm diode laser and control was 3 (range: 0-11) and 3 (range: 1-10), respectively. At 8 weeks, the median grade changed to 2 (range: 1-11) and 2 (range: 1-11) for 1450-nm diode laser and control, respectively.			⊕⊕○○ Low	CRITICAL	
Acne severity, Leeds at 24 weeks (median)												
1 1,a	randomised trials	serious ^b	not serious	not serious	serious ^c	none	At baseline, the median grade for 1450-nm diode laser and control was 3 (range: 0-11) and 3 (range: 1-10), respectively. At 24 weeks, the median grade changed to 2 (range: 0-9) and 2 (range: 1-9) for 1450-nm diode laser and control, respectively.			⊕⊕○○ Low	CRITICAL	

Number of lesions, Inflammatory at 4 weeks (median)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1450 nm diode laser	Control	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	32 patients were randomized to receive 1450-nm diode laser on half of the face and control on the other half. At baseline, the median number of inflammatory lesions for 1450-nm diode laser and control was 10 (range: 0-34) and 10 (range: 1-27), respectively. At 4 weeks, the median number of inflammatory lesions changed to 9 (range: 1-33) and 8.5 (range: 2-29) for 1450-nm diode laser and control, respectively.				⊕⊕○○ Low	CRITICAL

Number of lesions, Inflammatory at 8 weeks (median)

1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	At baseline, the median number of inflammatory lesions for 1450-nm diode laser and control was 10 (range: 0-34) and 10 (range: 1-27), respectively. At 8 weeks, the median number of inflammatory lesions changed to 6.5 (range: 1-19) and 6.5 (range: 1-24) for 1450-nm diode laser and control, respectively.				⊕⊕○○ Low	CRITICAL

Number of lesions, Inflammatory at 24 weeks (median)

1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	At baseline, the median number of inflammatory lesions for 1450-nm diode laser and control was 10 (range: 0-34) and 10 (range: 1-27), respectively. At 24 weeks, the median number of inflammatory lesions changed to 6 (range: 0-24) and 6.5 (range: 1-21) for 1450-nm diode laser and control, respectively.				⊕⊕○○ Low	CRITICAL

AE, Hyperpigmentation at 48 weeks

1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^{c,d}	none	0/23 (0.0%)	0/23 (0.0%)	not estimable		⊕⊕○○ Low	IMPORTANT

CI: Confidence interval

Explanations

- a. RCT, Split face
- b. Unblinded patients and risk of attrition bias (39% dropout)
- c. Small sample size
- d. Zero events in both groups

References

1. Darne, S., E.L. Hiscutt, and D.C. Seukeran, *Evaluation of the clinical efficacy of the 1,450 nm laser in acne vulgaris: a randomized split-face, investigator-blinded clinical trial.* Br J Dermatol, 2011. **165**(6): p. 1256-62.

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e-Table 102. GRADE Evidence Profile for 595 nm pulsed dye laser vs. control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	595 nm pulsed dye laser	Control	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Comprehensive Acne Severity Scale at 4 weeks (mean absolute change from baseline)												
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^{b,c}	none	30	30	-	MD 0.07 higher (0.12 lower to 0.26 higher)	⊕⊕⊕○ Moderate	CRITICAL
Acne severity, Comprehensive Acne Severity Scale at 8 weeks (mean absolute change from baseline)												
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^{b,c}	none	30	30	-	MD 0.01 higher (0.18 lower to 0.2 higher)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Inflammatory, Nodules at 4 weeks (mean absolute change from baseline)												
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^{b,c}	none	30	30	-	MD 0.23 nodules lower (0.48 lower to 0.02 higher)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Inflammatory, Nodules at 8 weeks (mean absolute change from baseline)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	595 nm pulsed dye laser	Control	Relative (95% CI)	Absolute (95% CI)		
11,a	randomised trials	not serious	not serious	not serious	serious ^b	none	30	30	-	MD 0.5 nodules lower (0.86 lower to 0.14 lower)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Papules at 4 weeks (mean absolute change from baseline)

11,a	randomised trials	not serious	not serious	not serious	serious ^b	none	30	30	-	MD 1.93 papules lower (3.01 lower to 0.86 lower)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Papules at 8 weeks (mean absolute change from baseline)

11,a	randomised trials	not serious	not serious	not serious	serious ^{b,c}	none	30	30	-	MD 0.43 papules lower (1.75 lower to 0.89 higher)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Pustules at 4 weeks (mean absolute change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	595 nm pulsed dye laser	Control	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^{b,c}	none	30	30	-	MD 0.93 pustules higher (0.2 lower to 2.06 higher)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Pustules at 8 weeks (mean absolute change from baseline)

1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^{b,c}	none	30	30	-	MD 1.54 pustules higher (0.24 higher to 2.84 higher)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks (mean absolute change from baseline)

1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^{b,c}	none	30	30	-	MD 3.27 lesions lower (12.29 lower to 5.75 higher)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (mean absolute change from baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	595 nm pulsed dye laser	Control	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^{b,c}	none	30	30	-	MD 5.39 lesions lower (13.25 lower to 2.47 higher)	⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; MD: Mean difference

Explanations

- a. RCT, Split face
- b. Small sample size
- c. CI includes appreciable benefits and harm

References

1. Lekwuttikarn, R., et al., *Randomized, controlled trial split-faced study of 595-nm pulsed dye laser in the treatment of acne vulgaris and acne erythema in adolescents and early adulthood*. International Journal of Dermatology, 2017. **56(8)**: p. 884-888.

e-Table 103. GRADE Evidence Profile for 635-670 nm red light vs. control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	635-670 nm red light	Control	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any at 4 weeks (mean percent change from baseline)												
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	30 patients were randomized to receive 635-670-nm red light on half of the face and the other half was used as control. The mean percentage changes from baseline for 635-670-nm red light and control sides were -49.82% and 11.19%, respectively. The difference between the two treatment sides was significant (p < 0.005).			⊕⊕○○ Low	CRITICAL	
Number of lesions, Any at 8 weeks (mean percent change from baseline)												
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage changes from baseline for 635-670-nm red light and control sides were -55% and 19%, respectively. The difference between the two treatment sides was significant (p < 0.005).			⊕⊕○○ Low	CRITICAL	
Number of lesions, Inflammatory at 4 weeks (mean percent change from baseline)												
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage changes from baseline for 635-670-nm red light and control sides were -44.26% and 32.34%, respectively. The difference between the two treatment sides was not significant.			⊕⊕○○ Low	CRITICAL	
Number of lesions, Inflammatory at 8 weeks (mean percent change from baseline)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	635-670 nm red light	Control	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage changes from baseline for 635-670-nm red light and control sides were -66% and 74%, respectively. The difference between the two treatment sides was significant (p < 0.005).			⊕⊕○○ Low	CRITICAL	

Number of lesions, Non-inflammatory at 4 weeks (mean percent change from baseline)

11,a	randomised trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage changes from baseline for 635-670-nm red light and control sides were -50.19% and 4.47%, respectively. The difference between the two treatment sides was significant (p < 0.005).			⊕⊕○○ Low	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (mean percent change from baseline)

11,a	randomised trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage changes from baseline for 635-670-nm red light and control sides were -59% and 3%, respectively. The difference between the two treatment sides was significant (p < 0.005).			⊕⊕○○ Low	CRITICAL

Patient assessment of improvement, VAS (0-5) at 4 weeks (mean)

11,a	randomised trials	serious ^b	not serious	not serious	serious ^c	none	At baseline, the mean value for both 635-670-nm red light and control sides was 3.9. At 4 weeks, the mean values changed to 2.49 and 2.72 for 635-670-nm red light and control sides, respectively. The difference between the two treatment groups was not significant.			⊕⊕○○ Low	CRITICAL

Patient assessment of improvement, VAS (0-5) at 8 weeks (mean)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	635-670 nm red light	Control	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	At baseline, the mean value for both 635-670-nm red light and control sides was 3.9. At 4 weeks, the mean values changed to 1.8 and 2.9 for 635-670-nm red light and control sides, respectively. The difference between the two treatment groups was significant ($p < 0.005$).				⊕⊕○○ Low	CRITICAL

CI: Confidence interval

Explanations

- a. RCT, Split face
- b. Limited methods reporting and unblinded patients
- c. Small sample size

References

1. Na, J.I. and D.H. Suh, *Red light phototherapy alone is effective for acne vulgaris: randomized, single-blinded clinical trial*. Dermatol Surg, 2007. **33**(10): p. 1228-33; discussion 1233.

e-Table 104. GRADE Evidence Profile for Nd:YAG laser vs. control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nd:YAG laser	Control	Relative (95% CI)	Absolute (95% CI)		
Investigator Global Assessment at 12 weeks (mean percent improvement from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	A total of 20 patients were randomized to receive either 1064 nm Nd:YAG laser or sham treatment. The laser-treated group showed an Investigator's Global Assessment Scale (IGA) improvement of 26% compared with 7% for the sham group (a 271% improvement over the sham treatment group).			⊕⊕⊕○ Moderate	CRITICAL	
Acne severity, Leeds at 14 weeks (mean absolute change from baseline)												
1 ^{2,b}	randomised trials	not serious	not serious	not serious	serious ^{c,d}	none	32	32	-	MD 0.03 lower (0.42 lower to 0.36 higher)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Inflammatory, Cysts at 14 weeks (mean absolute change from baseline)												
1 ^{2,b}	randomised trials	not serious	not serious	not serious	serious ^c	none	32	32	-	MD 0.43 lesions lower (0.72 lower to 0.14 lower)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Inflammatory, Papules at 14 weeks (mean absolute change from baseline)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nd:YAG laser	Control	Relative (95% CI)	Absolute (95% CI)		
12,b	randomised trials	not serious	not serious	not serious	serious ^{c,d}	none	32	32	-	MD 0.54 lesions lower (2.84 lower to 1.76 higher)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Pustules at 14 weeks (mean absolute change from baseline)

12,b	randomised trials	not serious	not serious	not serious	serious ^{c,d}	none	32	32	-	MD 0.68 lesions lower (3.28 lower to 1.92 higher)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, Closed comedones at 14 weeks (mean absolute change from baseline)

12,b	randomised trials	not serious	not serious	not serious	serious ^{c,d}	none	32	32	-	MD 6.95 lesions lower (19.6 lower to 5.7 higher)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory, Open comedones at 14 weeks (mean absolute change from baseline)

12,b	randomised trials	not serious	not serious	not serious	serious ^{c,d}	none	32	32	-	MD 2.92 lesions lower (6.61 lower to 0.77 higher)	⊕⊕⊕○ Moderate	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nd:YAG laser	Control	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Inflammatory at 12 weeks (mean percent reduction from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	A total of 20 patients were randomized to receive either 1064-nm Nd:YAG laser or sham treatment. At 12 weeks, the treatment group showed a decrease in the number of inflammatory lesions of 42% compared with 26% in the sham group from baseline (a 62% improvement over sham).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean percent reduction from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	A total of 20 patients were randomized to receive either 1064 nm Nd:YAG laser or sham treatment. At 12 weeks, the treatment group showed a decrease in the number of non-inflammatory lesions of 26% compared with 27% in the sham group from baseline.				⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; MD: Mean difference

Explanations

- a. Small sample size and no CIs or p-values provided
- b. RCT, Split face
- c. Small sample size
- d. CI includes appreciable benefits and harm

References

1. Kesty, K. and D.J. Goldberg, 650 usec 1064nm Nd:YAG laser treatment of acne: A double-blind randomized control study. *Journal of Cosmetic Dermatology*, 2020. **19(9)**: p. 2295-2300.
2. Orringer, J.S., et al., A randomized, controlled, split-face clinical trial of 1320-nm Nd:YAG laser therapy in the treatment of acne vulgaris. *J Am Acad Dermatol*, 2007. **56(3)**: p. 432-8.

e-Table 105. GRADE Evidence Profile for 532 nm KTP laser vs. control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	532 nm KTP laser (4 weeks)	Control	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Michaëlsson at 4 weeks (mean percent change from baseline)												
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	Forty-four patients were randomly divided into two groups. Group 1 was treated once weekly for 4 weeks, and Group 2 was treated twice weekly for 2 weeks. Laser treatment was applied to half of the face, and the other half remained as untreated. In Group 1, the mean percentage changes from baseline for 532-nm KTP laser and control sides were -21% and -2%, respectively. In Group 2, the mean percentage changes from baseline for 532-nm KTP laser and control sides were -26% and -12%, respectively. The difference between the two treatments was significant (p = 0.004).				⊕⊕○○ Low	CRITICAL

CI: Confidence interval

Explanations

- a. RCT, Split face
b. Limited methods reporting and open label study
c. Small sample size

References

1. Yilmaz, O., et al., *Evaluation of 532-nm KTP laser treatment efficacy on acne vulgaris with once and twice weekly applications*. J Cosmet Laser Ther, 2011. **13**(6): p. 303-7.

25. Photodynamic therapy with ALA vs. Control*

e-Table 106. GRADE Evidence Profile for photodynamic therapy with ALA vs. control*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA	Control	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Leeds at 16 weeks (mean absolute change from baseline)												
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	29	29	-	MD 0.55 lower (0.66 lower to 0.44 lower)	⊕⊕○○ Low	CRITICAL
Number of lesions, Inflammatory at 4 weeks (mean)												
1 ^{2,a}	randomised trials	serious ^d	not serious	not serious	serious ^c	none	180	180	-	MD 2.6 higher (3.2 lower to 2 lower)	⊕⊕○○ Low	CRITICAL
Number of lesions, Inflammatory at 12 weeks (mean)												
1 ^{2,a}	randomised trials	serious ^d	not serious	not serious	serious ^c	none	180	180	-	MD 0.67 lower (1.27 lower to 0.07 lower)	⊕⊕○○ Low	CRITICAL
Number of lesions, Inflammatory, Cysts at 16 weeks (mean absolute change from baseline)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA	Control	Relative (95% CI)	Absolute (95% CI)		
11, ^a	randomised trials	serious ^b	not serious	not serious	serious ^c	none	29	29	-	MD 0.14 lesions higher (0.03 higher to 0.25 higher)	⊕⊕○○ Low	CRITICAL

Number of lesions, Inflammatory, Papules at 16 weeks (mean absolute change from baseline)

11, ^a	randomised trials	serious ^b	not serious	not serious	serious ^c	none	29	29	-	MD 0.82 lesions lower (1.53 lower to 0.11 lower)	⊕⊕○○ Low	CRITICAL

Number of lesions, Inflammatory, Pustules at 16 weeks (mean absolute change from baseline)

11, ^a	randomised trials	serious ^b	not serious	not serious	serious ^{c,e}	none	29	29	-	MD 0.1 lesions lower (0.8 lower to 0.6 higher)	⊕⊕○○ Low	CRITICAL

Number of lesions, Inflammatory at 24 weeks (mean)

12, ^a	randomised trials	serious ^d	not serious	not serious	serious ^c	none	180	180	-	MD 2.91 higher (3.51 lower to 2.31 lower)	⊕⊕○○ Low	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA	Control	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Non-inflammatory at 4 weeks (mean)

12.a	randomised trials	serious ^d	not serious	not serious	serious ^c	none	180	180	-	MD 1.91 lower (2.51 lower to 1.31 lower)	⊕⊕○○ Low	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean)

12.a	randomised trials	serious ^d	not serious	not serious	serious ^c	none	180	180	-	MD 2.4 lower (3 lower to 1.8 lower)	⊕⊕○○ Low	CRITICAL

Number of lesions, Non-inflammatory, Closed comedones at 16 weeks (mean absolute change from baseline)

11.a	randomised trials	serious ^b	not serious	not serious	serious ^c	none	29	29	-	MD 2.9 % lower (3.98 lower to 1.82 lower)	⊕⊕○○ Low	CRITICAL

Number of lesions, Non-inflammatory, Open comedones at 16 weeks (mean absolute change from baseline)

11.a	randomised trials	serious ^b	not serious	not serious	serious ^c	none	29	29	-	MD 2 lesions higher (0.71 higher to 3.29 higher)	⊕⊕○○ Low	CRITICAL

Number of lesions, Non-inflammatory at 24 weeks (mean)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA	Control	Relative (95% CI)	Absolute (95% CI)		
12,a	randomised trials	serious ^d	not serious	not serious	serious ^c	none	180	180	-	MD 3.54 lower (4.14 lower to 2.94 lower)	⊕⊕○○ Low	CRITICAL

CI: Confidence interval; MD: mean difference

Explanations

- a. RCT, Split face
- b. Unclear allocation concealment, unblinded patients, and risk of attrition bias (34% dropout)
- c. Small sample size
- d. Limited methods reporting and unblinded patients
- e. CI includes appreciable benefits and harm

* Orringer 2010¹: 44 patients with facial acne were randomized to receive a total of up to three pulsed dye laser treatments (at approximately 2 weeks interval) to one side of the face after a 60–90 min ALA application time, while the contralateral side remained untreated and served as a control. Laser therapy was performed using a pulsed dye laser (VBeam, Candela Corporation, Wayland, MA, USA) using the following treatment parameters: 10-mm spot size, 10-ms pulse duration, and 6.5–7.5 J/cm². (Patients with Fitzpatrick types I–IV skin were treated at 7.5 J/cm², while those of darker skin types were treated at lower fluences because of their relatively increased risk of postinflammatory hyperpigmentation.) A single pass of minimally overlapping pulses was applied to one side of the face.

Yin 2010²: One hundred and eighty patients with moderate to severe facial acne were recruited and randomly divided into four groups. Each group was treated with a different concentration (5%, 10%, 15% and 20%) of ALA under occlusion with plastic film for 1.5 hours followed by 126 J cm⁻² red light (Omnilux Revive, wavelength 633 ± 3 nm; Photo Therapeutics, Carlsbad, CA, U.S.A.) for 20 min to the facial lesions on the right side and placebo agent on the left side as control. Each patient was treated once every 10 days for four sessions.

References

- Orringer, J.S., et al., *Photodynamic therapy for acne vulgaris: a randomized, controlled, split-face clinical trial of topical aminolevulinic acid and pulsed dye laser therapy*. Journal of Cosmetic Dermatology, 2010. **9**(1): p. 28-34.
- Yin, R., et al., *Investigation of optimal aminolaevulinic acid concentration applied in topical aminolaevulinic acid-photodynamic therapy for treatment of moderate to severe acne: a pilot study in Chinese subjects*. Br J Dermatol, 2010. **163**(5): p. 1064-71.

27. Combined 589 nm and 1319 nm laser vs. Control

e-Table 107. GRADE Evidence Profile for combined 589 nm and 1319 nm laser vs. control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 589 nm and 1319 nm laser	Control	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Inflammatory at 8-12 weeks (mean percent reduction from baseline)												
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	Nine patients were randomized to receive one pass with the 1,319-nm laser followed by one pass with the 589-nm laser only to one side of the face. At 8-12 weeks, inflammatory acne lesions were reduced by 2.5 (-23.1%) on the treatment side and increased by 1.1 (+11.1%) on the control side.			⊕⊕○○ Low	CRITICAL	

CI: Confidence interval

Explanations

a. RCT, Split face

b. Limited methods reporting and unblinded patients

c. Small sample size and no CIs or p-values reported

References

1. Kang, A., et al., *Treatment of moderate-to-severe facial acne vulgaris with solid-state fractional 589/1,319-nm laser*. Journal of Clinical and Aesthetic Dermatology, 2019. **12(3)**: p. 28-31.

28. Combined 420 nm blue light and 660 nm red light vs. Control

e-Table 108. GRADE Evidence Profile for combined 420 nm blue light and 660 nm red light vs. control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 420 nm blue light and 660 nm red light	Control	Relative (95% CI)	Absolute (95% CI)		
Investigator Global Assessment, 0 at 4 weeks												
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	2/18 (11.1%)	0/17 (0.0%)	RR 4.74 (0.24 to 92.07)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	CRITICAL
Investigator Global Assessment, 0 at 8 weeks												
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	3/18 (16.7%)	0/17 (0.0%)	RR 6.63 (0.37 to 119.59)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	CRITICAL
Investigator Global Assessment, 0 at 12 weeks												
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	5/18 (27.8%)	0/17 (0.0%)	RR 10.42 (0.62 to 175.25)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	CRITICAL

Investigator Global Assessment, 1 at 4 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 420 nm blue light and 660 nm red light	Control	Relative (95% CI)	Absolute (95% CI)		
11.a	randomised trials	not serious	not serious	not serious	serious ^b	none	3/18 (16.7%)	1/17 (5.9%)	RR 2.83 (0.33 to 24.66)	108 more per 1,000 (from 39 fewer to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL

Investigator Global Assessment, 1 at 8 weeks

11.a	randomised trials	not serious	not serious	not serious	serious ^b	none	4/18 (22.2%)	1/17 (5.9%)	RR 3.78 (0.47 to 30.50)	164 more per 1,000 (from 31 fewer to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL

Investigator Global Assessment, 1 at 12 weeks

11.a	randomised trials	not serious	not serious	not serious	serious ^b	none	9/18 (50.0%)	2/17 (11.8%)	RR 4.25 (1.07 to 16.92)	382 more per 1,000 (from 8 more to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL

Investigator Global Assessment, 2 at 4 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 420 nm blue light and 660 nm red light	Control	Relative (95% CI)	Absolute (95% CI)		
11.a	randomised trials	not serious	not serious	not serious	serious ^b	none	12/18 (66.7%)	3/17 (17.6%)	RR 3.78 (1.29 to 11.10)	491 more per 1,000 (from 51 more to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL

Investigator Global Assessment, 2 at 8 weeks

11.a	randomised trials	not serious	not serious	not serious	serious ^b	none	10/18 (55.6%)	2/17 (11.8%)	RR 4.72 (1.20 to 18.51)	438 more per 1,000 (from 24 more to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL

Investigator Global Assessment, 2 at 12 weeks

11.a	randomised trials	not serious	not serious	not serious	serious ^b	none	4/18 (22.2%)	1/17 (5.9%)	RR 3.78 (0.47 to 30.50)	164 more per 1,000 (from 31 fewer to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL

Investigator Global Assessment, 3 at 4 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 420 nm blue light and 660 nm red light	Control	Relative (95% CI)	Absolute (95% CI)		
11,a	randomised trials	not serious	not serious	not serious	serious ^b	none	9/17 (52.9%)	1/18 (5.6%)	RR 0.10 (0.01 to 0.74)	50 fewer per 1,000 (from 55 fewer to 14 fewer)	⊕⊕⊕○ Moderate	CRITICAL

Investigator Global Assessment, 3 at 8 weeks

11,a	randomised trials	not serious	not serious	not serious	serious ^b	none	1/18 (5.6%)	12/17 (70.6%)	RR 0.08 (0.01 to 0.54)	649 fewer per 1,000 (from 699 fewer to 325 fewer)	⊕⊕⊕○ Moderate	CRITICAL

Investigator Global Assessment, 3 at 12 weeks

1a,c	randomised trials	not serious	not serious	not serious	serious ^d	none	0/18 (0.0%)	10/17 (58.8%)	RR 0.05 (0.00 to 0.71)	559 fewer per 1,000 (from 171 fewer to -)	⊕⊕⊕○ Moderate	CRITICAL

Investigator Global Assessment, 4 at 4 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 420 nm blue light and 660 nm red light	Control	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a,c}	randomised trials	not serious	not serious	not serious	serious ^d	none	0/18 (0.0%)	4/17 (23.5%)	RR 0.11 (0.01 to 1.82)	209 fewer per 1,000 (from 233 fewer to 193 more)	⊕⊕⊕○ Moderate	CRITICAL

Investigator Global Assessment, 4 at 8 weeks

1 ^{1,a,c}	randomised trials	not serious	not serious	not serious	serious ^d	none	0/18 (0.0%)	2/17 (11.8%)	RR 0.19 (0.01 to 3.68)	95 fewer per 1,000 (from 116 fewer to 315 more)	⊕⊕⊕○ Moderate	CRITICAL

Investigator Global Assessment, 4 at 12 weeks

1 ^{1,a,c}	randomised trials	not serious	not serious	not serious	serious ^d	none	0/18 (0.0%)	4/17 (23.5%)	RR 0.11 (0.01 to 1.82)	209 fewer per 1,000 (from 233 fewer to 193 more)	⊕⊕⊕○ Moderate	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 420 nm blue light and 660 nm red light	Control	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Inflammatory at 4 weeks (mean percent of baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	The mean percent of baseline of inflammatory lesions in the control and combined 420-nm blue light and 660-nm red light groups was 99.97% and 43.98%, respectively. The difference between the two treatment groups was significant (p <0.05).		⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 8 weeks (mean percent of baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	The mean percent of baseline of inflammatory lesions in the control and combined 420-nm blue light and 660-nm red light groups was 107.03% and 38.37%, respectively. The difference between the two treatment groups was significant (p <0.05).		⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (mean percent of baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	The mean percent of baseline of inflammatory lesions in the control and combined 420-nm blue light and 660-nm red light groups was 75.43% and 22.09%, respectively. The difference between the two treatment groups was significant (p <0.05).		⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks (mean percent of baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 420 nm blue light and 660 nm red light	Control	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	The mean percent of baseline of non-inflammatory lesions in the control and combined 420-nm blue light and 660-nm red light groups was 99.38% and 63.75%, respectively. The difference between the two treatment groups was significant (p <0.05).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (mean percent of baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	The mean percent of baseline of non-inflammatory lesions in the control and combined 420-nm blue light and 660-nm red light groups was 96.88% and 56.25%, respectively. The difference between the two treatment groups was significant (p <0.05).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean percent of baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	The mean percent of baseline of non-inflammatory lesions in the control and combined 420-nm blue light and 660-nm red light groups was 104.38% and 46.88%, respectively. The difference between the two treatment groups was significant (p <0.05).				⊕⊕⊕○ Moderate	CRITICAL

Patient assessment of improvement, Global, VAS at 4 weeks (mean)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 420 nm blue light and 660 nm red light	Control	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	At baseline, the mean value for control and combined 420-nm blue light and 660-nm red light groups was 10.01. At 4 weeks, the mean value changed to 10.4 and 6.17 for control and combined 420-nm blue light and 660-nm red light groups, respectively. The difference between the two treatment groups was significant (P <0.05).			⊕⊕⊕○ Moderate	CRITICAL	

Patient assessment of improvement, Global, VAS at 8 weeks (mean)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	At baseline, the mean value for control and combined 420-nm blue light and 660-nm red light groups was 10.01. At 8 weeks, the mean value changed to 9.03 and 6.39 for control and combined 420-nm blue light and 660-nm red light groups, respectively. The difference between the two treatment groups was significant (P <0.05).			⊕⊕⊕○ Moderate	CRITICAL

Patient assessment of improvement, Global, VAS at 12 weeks (mean)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	At baseline, the mean value for control and combined 420-nm blue light and 660-nm red light groups was 10.01. At 12 weeks, the mean value changed to 10.84 and 4.3 for control and combined 420-nm blue light and 660-nm red light groups, respectively. The difference between the two treatment groups was significant (P <0.05).			⊕⊕⊕○ Moderate	CRITICAL

AE, Any, Serious at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 420 nm blue light and 660 nm red light	Control	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	0/17 (0.0%)	0/18 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

- a. 0 Clear skin with no inflammatory or noninflammatory lesions 1 Almost clear, rare noninflammatory lesions with no more than one small inflammatory lesion 2 Mild severity; greater than Grade 1; some noninflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions) 3 Moderate severity; greater than Grade 2; up to many noninflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion 4 Severe, greater than Grade 3; up to many noninflammatory and inflammatory lesions, but no more than a few nodular lesions
- b. Small sample size resulting in a wide CI that include appreciable benefits and harm
- c. The difference between the two treatment groups was significant ($p < 0.05$)
- d. Small sample size

References

1. Kwon, H.H., et al., *The clinical and histological effect of home-use, combination blue-red LED phototherapy for mild-to-moderate acne vulgaris in Korean patients: a double-blind, randomized controlled trial*. Br J Dermatol, 2013. **168**(5): p. 1088-94.

e-Table 109. GRADE Evidence Profile for photodynamic therapy with ALA 20% vs. ALA 20%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 20%	635 nm light	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Inflammatory at 4 weeks (mean)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	10 patients with acne on their back were recruited. Each patient's back was marked with four areas. Each site was then randomly allocated to either ALA-PDT treatment, light alone, ALA alone, or untreated control. At baseline, the average number of inflammatory lesions for photodynamic therapy with ALA 20% and ALA 20% alone were 11.6 and 6.6, respectively. At 4 weeks, the average inflammatory lesion counts decreased to 3.6 and 4.6 for photodynamic therapy with ALA 20% and ALA 20% alone sides, respectively. There was a statistically significant reduction from baseline in inflammatory acne lesion counts only at the ALA-PDT treated site (p < 0.005).				⊕⊕○○ Low	CRITICAL

CI: Confidence interval

Explanations

a. RCT, Split back

b. Limited methods reporting and unblinded patients

c. Small sample size

References

1. Pollock, B., et al., *Topical aminolaevulinic acid-photodynamic therapy for the treatment of acne vulgaris: a study of clinical efficacy and mechanism of action*. Br J Dermatol, 2004. **151**(3): p. 616-22.

e-Table 110. GRADE Evidence Profile for 633 nm red LED light + erythromycin vs. erythromycin

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	633 nm red LED light + Erythromycin	Erythromycin	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any, <10% reduction at 4 weeks												
1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	1/15 (6.7%)	6/15 (40.0%)	RR 0.17 (0.02 to 1.22)	332 fewer per 1,000 (from 392 fewer to 88 more)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, <10% reduction at 8 weeks												
1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	1/15 (6.7%)	4/15 (26.7%)	RR 0.25 (0.03 to 2.00)	200 fewer per 1,000 (from 259 fewer to 267 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, ~25% reduction at 4 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	633 nm red LED light + Erythromycin	Erythromycin	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	12/15 (80.0%)	9/15 (60.0%)	RR 1.33 (0.82 to 2.17)	198 more per 1,000 (from 108 fewer to 702 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, ~25% reduction at 8 weeks

1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	8/15 (53.3%)	11/15 (73.3%)	RR 0.72 (0.41 to 1.28)	205 fewer per 1,000 (from 433 fewer to 205 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, ~50% reduction at 4 weeks

1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	1/15 (6.7%)	0/15 (0.0%)	RR 3.03 (0.13 to 100.00)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, ~50% reduction at 8 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	633 nm red LED light + Erythromycin	Erythromycin	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	5/15 (33.3%)	0/15 (0.0%)	RR 11.11 (0.66 to 100.00)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, ~75% reduction at 8 weeks

1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	1/15 (6.7%)	0/15 (0.0%)	RR 3.03 (0.13 to 100.00)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; RR: Risk ratio

Explanations

Small sample size and wide CI including appreciable benefits and harm

References

- Eid, M.M., et al., *Narrow Band Ultraviolet B Versus Red Light-Emitting Diodes in the Treatment of Facial Acne Vulgaris: A Randomized Controlled Trial*. Photobiomodulation, photomedicine, and laser surgery, 2021. **39(6)**: p. 418-424.

31. Narrow band ultraviolet B + Erythromycin vs. Erythromycin

e-Table 111. GRADE Evidence Profile for narrow band ultraviolet b + erythromycin vs. erythromycin

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Narrow band ultraviolet B + Erythromycin	Erythromycin	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any, <10% reduction at 4 weeks												
1 ¹	randomized trials	not serious	not serious	not serious	serious ^{a,c}	none	1/15 (6.7%)	6/15 (40.0%)	RR 0.17 (0.02 to 1.22)	332 fewer per 1,000 (from 392 fewer to 88 more)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, <10% reduction at 8 weeks												
1 ¹	randomized trials	not serious	not serious	not serious	serious ^{a,c}	none	0/15 (0.0%)	4/15 (26.7%)	RR 0.11 (0.01 to 1.90)	237 fewer per 1,000 (from 264 fewer to 240 more)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, ~25% reduction at 4 weeks												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Narrow band ultraviolet B + Erythromycin	Erythromycin	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,b}	randomized trials	not serious	not serious	not serious	serious ^{a,c}	none	11/15 (73.3%)	9/15 (60.0%)	RR 1.22 (0.73 to 2.04)	132 more per 1,000 (from 162 fewer to 624 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, ~25% reduction at 8 weeks

1 ^{1,b}	randomized trials	not serious	not serious	not serious	serious ^a	none	1/15 (6.7%)	11/15 (73.3%)	RR 0.09 (0.01 to 0.62)	667 fewer per 1,000 (from 726 fewer to 279 fewer)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, ~50% reduction at 4 weeks

1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	3/15 (20.0%)	0/15 (0.0%)	not estimable		⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, ~50% reduction at 8 weeks

1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	6/15 (40.0%)	0/15 (0.0%)	not estimable		⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, ~75% reduction at 8 weeks

1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	8/15 (53.3%)	0/15 (0.0%)	not estimable		⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; RR: Risk ratio

Explanations

- a. Small sample size
- b. Mild improvement
- c. CI include appreciable benefits and harm

References

1. Eid, M.M., et al., *Narrow Band Ultraviolet B Versus Red Light-Emitting Diodes in the Treatment of Facial Acne Vulgaris: A Randomized Controlled Trial*. Photobiomodulation, photomedicine, and laser surgery, 2021. **39(6)**: p. 418-424.

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32. Photodynamic therapy with ALA 5% + Minocycline vs. Minocycline

e-Table 112. GRADE Evidence Profile for photodynamic therapy with ala 5% + minocycline vs. minocycline

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 5% + Minocycline	Minocycline	Relative (95% CI)	Absolute (95% CI)		
Investigator Global Assessment, <2 at 4 weeks												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^{b,c}	none	22/48 (45.8%)	16/47 (34.0%)	RR 1.35 (0.81 to 2.23)	119 more per 1,000 (from 65 fewer to 419 more)	⊕⊕○○ Low	CRITICAL
Investigator Global Assessment, <2 at 8 weeks												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^{b,c}	none	30/48 (62.5%)	20/47 (42.6%)	RR 1.47 (0.99 to 2.19)	200 more per 1,000 (from 4 fewer to 506 more)	⊕⊕○○ Low	CRITICAL
Number of lesions, Inflammatory at 4 weeks (mean percent change from baseline)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	The mean percentage changes from baseline for photodynamic therapy with ALA 5% + minocycline and minocycline groups were -60.98% and -45.37%, respectively. The difference between the two treatment groups was significant (p < 0.001).				⊕⊕○○ Low	CRITICAL
Number of lesions, Inflammatory at 8 weeks (mean percent change from baseline)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 5% + Minocycline	Minocycline	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	The mean percentage changes from baseline for photodynamic therapy with ALA 5% + minocycline and minocycline groups were -74.4% and -53.3%, respectively. The difference between the two treatment groups was significant (p < 0.001).				⊕⊕○○ Low	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks (mean percent change from baseline)

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	The mean percentage changes from baseline for photodynamic therapy with ALA 5% + minocycline and minocycline groups were -52.43% and -37.38%, respectively. The difference between the two treatment groups was significant (p < 0.001).				⊕⊕○○ Low	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (mean percent change from baseline)

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	The mean percentage changes from baseline for photodynamic therapy with ALA 5% + minocycline and minocycline groups were -61.7% and -42.4%, respectively. The difference between the two treatment groups was significant (p < 0.001).				⊕⊕○○ Low	CRITICAL

AE, Hyperpigmentation at 8 weeks

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	1/48 (2.1%)	0/47 (0.0%)	not estimable		⊕⊕○○ Low	IMPORTANT

Quality of life, Dermatology Life Quality Index at 4 weeks (mean)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 5% + Minocycline	Minocycline	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	At baseline, the mean values of DLQI for photodynamic therapy with ALA 5% + minocycline and minocycline groups were 11.8 (SD: 4.7) and 11.7 (SD: 4.5), respectively. At 4 weeks, the mean values changed to 7.01 and 7.68 for photodynamic therapy with ALA 5% + minocycline and minocycline groups, respectively. The difference between the two treatment groups was not significant. ^d				⊕⊕○○ Low	IMPORTANT

Quality of life, Dermatology Life Quality Index at 8 weeks (mean)

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	At baseline, the mean values of DLQI for photodynamic therapy with ALA 5% + minocycline and minocycline groups were 11.8 (SD: 4.7) and 11.7 (SD: 4.5), respectively. At 8 weeks, the mean values changed to 4.4 and 6.3 for photodynamic therapy with ALA 5% + minocycline and minocycline groups, respectively. The difference between the two treatment groups was significant (p < 0.001). ^e				⊕⊕○○ Low	IMPORTANT

AE, Any, Local event at 8 weeks

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	16/48 (33.3%)	6/47 (12.8%)	RR 2.61 (1.12 to 6.09)	206 more per 1,000 (from 15 more to 650 more)	⊕⊕○○ Low	IMPORTANT

AE, Burning and irritation at 8 weeks

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	7/48 (14.6%)	0/47 (0.0%)	not estimable		⊕⊕○○ Low	IMPORTANT

AE, Erythema at 8 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 5% + Minocycline	Minocycline	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	4/48 (8.3%)	0/47 (0.0%)	not estimable		⊕⊕○○ Low	IMPORTANT

AE, Pain at 8 weeks

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	8/48 (16.7%)	0/47 (0.0%)	not estimable		⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; MD: Mean difference

Explanations

- a. Unclear allocation concealment and open label study
- b. Small sample size
- c. CI includes appreciable benefits and harm
- d. SDs are not provided at 4 weeks.
- e. SDs are not provided at 8 weeks.

References

1. Xu, X., et al., *Efficacy of photodynamic therapy combined with minocycline for treatment of moderate to severe facial acne vulgaris and influence on quality of life*. *Medicine*, 2017. **96**(51): p. e9366.

33. Clindamycin 1% + Benzoyl peroxide 5% + 585 nm pulsed dye laser vs. Clindamycin 1% + Benzoyl peroxide 5%

e-Table 113. GRADE Evidence Profile for clindamycin 1% + benzoyl peroxide 5% + 585 nm pulsed dye laser vs. clindamycin 1% + benzoyl peroxide 5%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clindamycin 1% + Benzoyl peroxide 5% + 585 nm pulsed dye laser	Clindamycin 1% + Benzoyl peroxide 5%	Relative (95% CI)	Absolute (95% CI)		
Investigator Global Assessment at 4 weeks (mean percent reduction from baseline)												
1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	The mean percentage reductions from baseline for clindamycin 1% + benzoyl peroxide 5% + 585-nm pulsed dye laser and clindamycin 1% + benzoyl peroxide 5% groups were 24.6% and 27.1%, respectively. The difference between the two treatment groups was not significant.				⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any at 4 weeks (mean percent reduction from baseline)												
1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	The mean percentage reductions from baseline for clindamycin 1% + benzoyl peroxide 5% + 585-nm pulsed dye laser and clindamycin 1% + benzoyl peroxide 5% groups were 9% and 9.2%, respectively. The difference between the two treatment groups was not significant.				⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Inflammatory at 4 weeks (mean percent reduction from baseline)												
1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	The mean percentage reductions from baseline for clindamycin 1% + benzoyl peroxide 5% + 585-nm pulsed dye laser and clindamycin 1% + benzoyl peroxide 5% groups were 36.9% and 36.3%, respectively. The difference between the two treatment groups was not significant.				⊕⊕⊕○ Moderate	CRITICAL

Quality of life, Dermatology Life Quality Index at 4 weeks (mean percent change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clindamycin 1% + Benzoyl peroxide 5% + 585 nm pulsed dye laser	Clindamycin 1% + Benzoyl peroxide 5%	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for clindamycin 1% + benzoyl peroxide 5% + 585-nm pulsed dye laser and clindamycin 1% + benzoyl peroxide 5% groups were -42.5% and -54.5%, respectively. The difference between the two treatment groups was not significant.				⊕⊕⊕○ Moderate	IMPORTANT

AE, Any at 4 weeks

1 ¹	randomized trials	not serious	not serious	not serious	serious ^b	none	1/80 (1.3%)	0/80 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Purpura, Mild at 4 weeks

1 ¹	randomized trials	not serious	not serious	not serious	serious ^b	none	1/80 (1.3%)	0/80 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

CI: Confidence interval

Explanations

- a. Small sample size and no CIs or p-values reported
- b. Small sample size

References

1. Karsai, S., L. Schmitt, and C. Raulin, *The pulsed-dye laser as an adjuvant treatment modality in acne vulgaris: a randomized controlled single-blinded trial*. Br J Dermatol, 2010. **163**(2): p. 395-401.

34. Topical approaches* vs. 905 nm laser + Topical approaches*

e-Table 114. GRADE Evidence Profile for topical approaches* vs. 905 nm laser + topical approaches*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical approaches	905 nm laser + Topical approaches	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any at 4 weeks (mean percent change from baseline)												
1 1,a	randomized trials	not serious	not serious	not serious	serious ^b	none	20	15	-	MD 40.3 % higher (33.35 higher to 47.25 higher)	⊕⊕⊕⊕ High	CRITICAL

CI: Confidence interval; MD: Mean difference

*Topical approaches included antibiotic cream, medicated soap, talcum powder, and personal hygiene.

Explanations

a. Clearance of acne

b. Small sample size

References

1. Anyachukwu, C.C. and O.K.K. Onyeso, *Efficacy of adjunct (laser) therapy to topical agents among Southern Nigerian acne vulgaris patients*. Acupuncture and Related Therapies, 2014. **2(4)**: p. 66-70.

e-Table 115. GRADE Evidence Profile for 1,550nm nonablative fractional laser treatment* plus isotretinoin vs. isotretinoin

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1550 nm Nonablative fractional lasers plus isotretinoin	isotretinoin	Relative (95% CI)	Absolute (95% CI)		
Leeds Acne Score at 6 months												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	Eighteen patients who received 10 mg oral isotretinoin per day completed 3 sessions of NAFL treatment at monthly intervals on one half of the face. Average Leeds acne-grading scores decreased from 10.6 to 5.8 on the control side of the face and from 10.4 to 3.5 on the treated side of the face. The change in Leeds scores differed significantly between sides (p < .05)		⊕⊕○○ Low		CRITICAL	
Inflammatory lesions at 6 months												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	Eighteen patients who received 10 mg oral isotretinoin per day completed 3 sessions of NAFL treatment at monthly intervals on one half of the face. The number of papules and nodules did not differ significantly between sides.		⊕⊕○○ Low		CRITICAL	
Noninflammatory lesions at 6 months												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	Eighteen patients who received 10 mg oral isotretinoin per day completed 3 sessions of NAFL treatment at monthly intervals on one half of the face. Comedone number decreased more on laser side as compared to control side.		⊕⊕○○ Low		CRITICAL	
Self-assessed participant satisfaction after last treatment												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	2 patients were very satisfied, 12 were satisfied, and 4 were neutral after the last laser treatment.		⊕⊕○○ Low		IMPORTANT	

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1550 nm Nonablative fractional lasers plus isotretinoin	isotretinoin	Relative (95% CI)	Absolute (95% CI)		

Pain

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	18/18 (100.0%)	0/18 (0.0%)	RR 37.00 (2.40 to 570.78)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ Low	IMPORTANT

Erythema

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	17/18 (94.4%)	0/18 (0.0%)	RR 35.00 (2.26 to 541.10)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ Low	IMPORTANT

Edema

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	16/18 (88.9%)	0/18 (0.0%)	RR 33.00 (2.13 to 511.42)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; RR: Risk ratio

* Treatment was delivered in a single pass using a 1,550-nm Er:glass fractional laser (Sellas, Korea). Three treatments were administered at monthly intervals using the mid-dermis model. The laser was used in low-energy mode (20 mJ/cm² and 100–169 points per area) to reduce the potential risks of keloid and hypertrophic scar development. Laser treated side was cooled with ice packs for 30 minutes. Patients also received antibiotics and a collagen mask (Trauer Biotechnology, Guangzhou, China) to be used on the entire face for 1–2 weeks to promote skin repair.

Explanations

- a. Limited methods reporting. Split-face RCT. Patients were aware of treatment assignments. Only 75% completed the treatments.
- b. Small sample size.

References

1. Xia, J., et al., *Concomitant Use of 1,550-nm Nonablative Fractional Laser With Low-Dose Isotretinoin for the Treatment of Acne Vulgaris in Asian Patients: A Randomized Split-Face Controlled Study*. *Dermatol Surg*, 2018. **44**(9): p. 1201-1208.

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e-Table 116. GRADE Evidence Profile for 1,550nm nonablative fractional laser treatment* plus isotretinoin vs. isotretinoin

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPL plus isotretinoin	isotretinoin	Relative (95% CI)	Absolute (95% CI)		
Physician global assessment, at 12 weeks												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	24	23	-	MD 0.5 lower (0.86 lower to 0.14 lower)	⊕⊕○○ Low	CRITICAL
Total lesion at 12 weeks												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	24	23	-	MD 9 lower (17.28 lower to 0.72 lower)	⊕⊕○○ Low	CRITICAL
Total lesion, percentage change from baseline, at 12 weeks												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	24	23	-	MD 23.6 lower (38.27 lower to 8.93 lower)	⊕⊕○○ Low	CRITICAL
Inflammatory lesion at 12 weeks												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPL plus isotretinoin	isotretinoin	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	24	23	-	MD 8 lower (15.04 lower to 0.96 lower)	⊕⊕○○ Low	CRITICAL

Inflammatory lesion, percentage change from baseline, at 12 weeks

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	24	23	-	MD 28 lower (42.69 lower to 13.31 lower)	⊕⊕○○ Low	CRITICAL

Inflammatory lesion, at 12 weeks

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^{b,c}	none	24	23	-	MD 1 lower (3.35 lower to 1.35 higher)	⊕⊕○○ Low	CRITICAL

Inflammatory lesion, percentage change from baseline, at 12 weeks

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^{b,c}	none	24	23	-	MD 2.1 lower (20.39 lower to 16.19 higher)	⊕⊕○○ Low	CRITICAL

Serious AE

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	0/24 (0.0%)	0/23 (0.0%)	not estimable		⊕⊕○○ Low	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPL plus isotretinoin	isotretinoin	Relative (95% CI)	Absolute (95% CI)		

Quality of life, DLQI, at 12 weeks

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	24	23	-	MD 1.6 lower (2.77 lower to 0.43 lower)	⊕⊕○○ Low	IMPORTANT

Patient satisfaction, VAS, at 12 weeks

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	24	23	-	MD 1.6 higher (1 higher to 2.2 higher)	⊕⊕○○ Low	IMPORTANT

Recurrence at 2 months after the completion

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	5/24 (20.8%)	12/23 (52.2%)	RR 0.40 (0.17 to 0.96)	313 fewer per 1,000 (from 433 fewer to 21 fewer)	⊕⊕○○ Low	IMPORTANT

Blister sized 1 cm in diameter

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	1/24 (4.2%)	0/23 (0.0%)	RR 2.88 (0.12 to 67.29)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ Low	IMPORTANT

Mild to moderate pain

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPL plus isotretinoin	isotretinoin	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	15/24 (62.5%)	0/23 (0.0%)	RR 29.76 (1.88 to 470.16)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ Low	IMPORTANT

Abnormal serum lipids

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	0/24 (0.0%)	0/23 (0.0%)	not estimable		⊕⊕○○ Low	IMPORTANT

Abnormal liver enzyme

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	0/24 (0.0%)	0/23 (0.0%)	not estimable		⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

*A biweekly IPL treatment with a 420-nm cutoff filter (Alma Lovely II Modular Skin Quadripartite lasers, Alma lasers, Caesarea, Israel) for 4 weeks (totally 8 sessions), starting from week 0. Cooling gel was applied before IPL treatment. Parameters were as follows: spot size 10 mm × 20 mm, pulse duration 30 ms or 40 ms, and fluence 10–15 J/cm². Adjustments were made according to each patient's skin phototype, acne lesion severity, degree of pain, and skin reaction during the treatment. 0.5–0.75 mg/kg/day isotretinoin capsules (Donghai Pharmaceutical., Shanghai, China) were given for 8 weeks. Dose of isotretinoin was adjusted according to adverse events (e.g., skin irritation). Topical agents for both groups included adapalene 0.1% gel (Laboratoires Galderma, Lausanne, Switzerland) p.n. and fusidic acid 2% cream (Bright Future Pharmaceutical., Hong Kong, China) once daily.

Explanations

- a. Limited methods reporting.
- b. Small sample size.
- c. CI includes appreciable benefits and harm

References

1. Li, Y., et al., *Isotretinoin plus 420 nm intense pulsed light versus isotretinoin alone for the treatment of acne vulgaris: a randomized, controlled study of efficacy, safety, and patient satisfaction in Chinese subjects*. *Lasers Med Sci*, 2020.

37. PDL plus isotretinoin vs isotretinoin*

e-Table 117. GRADE Evidence Profile for PDL plus isotretinoin vs isotretinoin*

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PDL plus isotretinoin	Isotretinoin	Relative (95% CI)	Absolute (95% CI)		
Physician global assessment, Global acne grading system (38 point system) at 6 months												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	23	23	-	MD 5.57 lower (10.4 lower to 0.74 lower)	⊕⊕⊕○ Moderate	CRITICAL
Acne severity improvement at 6 months												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	23	23	-	MD 8.26 higher (0.78 higher to 15.74 higher)	⊕⊕⊕○ Moderate	CRITICAL
Quality of life, DLQI at 6 months												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	23	23	-	MD 1.04 lower (1.83 lower to 0.25 lower)	⊕⊕⊕○ Moderate	IMPORTANT

Erythema at 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PDL plus isotretinoin	Isotretinoin	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	23	23	-	MD 0.43 lower (0.81 lower to 0.05 lower)	⊕⊕⊕○ Moderate	IMPORTANT

Other safety outcomes

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mild pain during the sessions was tolerated by all patients. Erythema subsided within a few days. No hyperpigmentation or scarring was reported by any of the study subjects.				⊕⊕⊕○ Moderate	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

* The combination group was treated with oral isotretinoin (0.25 mg/kg/day) over a period of 6 months and five sessions of PDL (Vbeam; Candela, Massachusetts, United States) using 4.5–5.5 J/cm², 3 milliseconds pulse duration, and 10 mm spot size, at 2 weeks' interval. Treatment was delivered as one pass over the lesions. The second group (ISO) was treated with oral isotretinoin (0.5 mg/kg/day) as monotherapy (Isotretinoin, Sun pharmaceutical industries limited, Paonta Sahib, India) over a period of 6 months. Concerning the cumulative dose of isotretinoin, the ISO and PDL group received significantly less dosage (40–60 mg/kg, 48.7 ± 5.7 mg/kg) in comparison with the ISO group (90–110 mg/kg, 100.4 ± 3.1 mg/kg) (P < 0.05).

Explanations

a. Small sample size

References

1. Ibrahim, S.M., et al., *Combined Low-Dose Isotretinoin and Pulsed Dye Laser Versus standard-Dose Isotretinoin in the Treatment of Inflammatory Acne*. Lasers Surg Med, 2020.

38. Photodynamic therapy with vehicle vs. Photodynamic therapy with ALA

e-Table 118. GRADE Evidence Profile for photodynamic therapy with vehicle vs. photodynamic therapy with ALA

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with vehicle	Photodynamic therapy with ALA	Relative (95% CI)	Absolute (95% CI)		
Investigator Global Assessment at 4 weeks (mean)												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	At baseline, the mean values for photodynamic therapy with vehicle and photodynamic therapy with ALA were 2.97 and 2.97, respectively. At 4 weeks, the mean decreased to 2.9 and 2.3 for photodynamic therapy with vehicle and photodynamic therapy with ALA, respectively. The difference between the two treatments was significant (p <0.05).			⊕⊕⊕○ Moderate	CRITICAL	
Investigator Global Assessment at 8 weeks (mean)												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	At baseline, the mean values for photodynamic therapy with vehicle and photodynamic therapy with ALA were 2.97 and 2.97, respectively. At 8 weeks, the mean decreased to 2.84 and 2.08 for photodynamic therapy with vehicle and photodynamic therapy with ALA, respectively. The difference between the two treatments was significant (p <0.05).			⊕⊕⊕○ Moderate	CRITICAL	
Investigator Global Assessment at 12 weeks (mean)												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	At baseline, the mean values for photodynamic therapy with vehicle and photodynamic therapy with ALA were 2.97 and 2.97, respectively. At 12 weeks, the mean decreased to 2.7 and 1.7 for photodynamic therapy with vehicle and photodynamic therapy with ALA, respectively. The difference between the two treatments was significant (p <0.05).			⊕⊕⊕○ Moderate	CRITICAL	

Number of lesions, Inflammatory at 4 weeks (mean percent of baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with vehicle	Photodynamic therapy with ALA	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of inflammatory lesions in the photodynamic therapy with vehicle and photodynamic therapy with ALA groups was 94.04% and 72.83%, respectively. The difference between the two treatments was significant (p <0.05).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 8 weeks (mean percent of baseline)

1 ¹	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of inflammatory lesions in the photodynamic therapy with vehicle and photodynamic therapy with ALA groups was 93.33% and 54.44%, respectively. The difference between the two treatments was significant (p <0.05).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (mean percent of baseline)

1 ¹	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of inflammatory lesions in the photodynamic therapy with vehicle and photodynamic therapy with ALA groups was 91.57% and 47.02%, respectively. The difference between the two treatments was significant (p <0.05).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks (mean percent of baseline)

1 ¹	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of non-inflammatory lesions in the photodynamic therapy with vehicle and photodynamic therapy with ALA groups was 95.7% and 88.73%, respectively. The difference between the two treatments was not significant.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (mean percent of baseline)

1 ¹	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of non-inflammatory lesions in the photodynamic therapy with vehicle and photodynamic therapy with ALA groups was 93.79% and 73.94%, respectively. The difference between the two treatments was significant (p <0.05).				⊕⊕⊕○ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with vehicle	Photodynamic therapy with ALA	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Non-inflammatory at 12 weeks (mean percent of baseline)

1 ¹	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of non-inflammatory lesions in the photodynamic therapy with vehicle and photodynamic therapy with ALA groups was 94.32% and 65.07%, respectively. The difference between the two treatments was significant (p <0.05).				⊕⊕⊕○ Moderate	CRITICAL

AE, Dry skin, Mild at 12 weeks

1 ¹	randomized trials	not serious	not serious	not serious	serious ^b	none	0/24 (0.0%)	5/24 (20.8%)	RR 0.09 (0.01 to 1.56)	190 fewer per 1,000 (from 206 fewer to 117 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema, Mild at 12 weeks

1 ¹	randomized trials	not serious	not serious	not serious	serious ^b	none	0/24 (0.0%)	5/24 (20.8%)	RR 0.09 (0.01 to 1.56)	190 fewer per 1,000 (from 206 fewer to 117 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pain, Mild at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with vehicle	Photodynamic therapy with ALA	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	not serious	not serious	not serious	serious ^b	none	0/24 (0.0%)	5/24 (20.8%)	RR 0.09 (0.01 to 1.56)	190 fewer per 1,000 (from 206 fewer to 117 more)	⊕⊕⊕○ Moderate	IMPORTANT

CI: Confidence interval; RR: risk ratio

Explanations

a. 0 Clear skin with no inflammatory or non-inflammatory lesions 1 Almost clear, rare non-inflammatory lesions with no more than one small inflammatory lesion 2 Mild severity; greater than grade 1; some noninflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions) 3 Moderate severity; greater than grade 2; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion. 4 Severe, greater than grade 3; up to many noninflammatory and inflammatory lesions, but no more than a few nodular lesions. 5 Very severe; greater than grade 4; highly inflammatory acne covering the face; with nodules and cysts present

b. Small sample size

References

1. Kwon, H.H., et al., *Daylight photodynamic therapy with 1.5% 3-butenyl 5-aminolevulinate gel as a convenient, effective and safe therapy in acne treatment: A double-blind randomized controlled trial*. Journal of Dermatology, 2016. **43**(5): p. 515-521.

39. Photodynamic therapy (635 nm light) with ALA 20% vs. 635 nm light

e-Table 119. GRADE Evidence Profile for photodynamic therapy (635 nm light) with ALA 20% vs. 635 nm light

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 20%	635 nm light	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Inflammatory at 4 weeks (mean)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	10 patients with acne on their back were recruited. Each patient's back was marked with four areas. Each site was then randomly allocated to either ALA-PDT treatment, light alone, ALA alone, or untreated control. At baseline, the average number of inflammatory lesions for photodynamic therapy with ALA 20% and 635-nm light were 11.6 and 8.3, respectively. At 4 weeks, the average inflammatory lesion counts decreased to 3.6 and 6.1 for photodynamic therapy with ALA 20% and 635-nm light sides, respectively. There was a statistically significant reduction from baseline in inflammatory acne lesion counts only at the ALA-PDT treated site (p < 0.005).				⊕⊕○○ Low	CRITICAL

CI: Confidence interval

Explanations

- a. RCT, Split back
- b. Limited methods reporting and unblinded patients
- c. Small sample size

References

1. Pollock, B., et al., *Topical aminolaevulinic acid-photodynamic therapy for the treatment of acne vulgaris: a study of clinical efficacy and mechanism of action*. Br J Dermatol, 2004. **151**(3): p. 616-22.

e-Table 120. GRADE Evidence Profile for photodynamic therapy (532 nm KTP laser) with ALA vs. 532 nm KTP laser

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA	532 nm KTP laser	Relative (95% CI)	Absolute (95% CI)		
Investigator Global Assessment at 6 weeks (mean percent change from baseline)												
1 ^{1,a,b}	randomized trials	serious ^c	not serious	not serious	serious ^d	none	10 patients were randomized to receive photodynamic therapy with ALA on half of the face and 532-nm KTP laser on the other half. The mean percentage changes from baseline for photodynamic therapy with ALA and 532-nm KTP laser sides were -39% and -34%, respectively.		⊕⊕○○ Low		CRITICAL	

CI: Confidence interval

Explanations

a. RCT, Split face

b. Grade 0 – clear skin, no inflammatory lesions Grade 1 – Almost clear, rare non-inflammatory lesions, few small inflammatory lesions Grade 2 – Mild severity, some non-inflammatory lesions, some inflammatory lesions (papules, pustules, no nodular lesions) Grade 3 – Moderate severity, many non-inflammatory and moderate inflammatory, no more than one nodular lesion Grade 4 – Severe, many non-inflammatory and inflammatory lesions, nodular lesions are present

c. Limited methods reporting, open label study, and risk of attrition bias (Data were available from only 80% of the patients)

d. Small sample size and no CIs or p-values reported

References

1. Sadick, N., *An open-label, split-face study comparing the safety and efficacy of levulan kerastick (aminolevulonic acid) plus a 532 nm KTP laser to a 532 nm KTP laser alone for the treatment of moderate facial acne.* J Drugs Dermatol, 2010. 9(3): p. 229-33.

41. Photodynamic therapy (IPL) with ALA vs. Intense pulsed light

e-Table 121. GRADE Evidence Profile for photodynamic therapy (IPL) with ALA vs. intense pulsed light

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA	Intense pulsed light	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any at 4 weeks (mean percent change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	Forty-one patients with moderate to severe facial acne were randomly assigned to receive a total of four sessions of ALA-IPL-PDT (n=21) or IPL alone (n=20) at 1 week interval. The mean percentage changes from baseline for photodynamic therapy with ALA and intense pulsed light groups were - 57.53% and -40.94%, respectively. The difference between the two treatment groups was significant (p < 0.05).			⊕⊕⊕○ Moderate	CRITICAL	
Number of lesions, Any at 8 weeks (mean percent change from baseline)												
2 ^{1,2}	randomised trials	not serious	not serious	not serious	serious ^a	none	Forty-one patients with moderate to severe facial acne were randomly assigned to receive a total of four sessions of ALA-IPL-PDT (n=21) or IPL alone (n=20) at 1 week interval. The mean percentage changes from baseline for photodynamic therapy with ALA and intense pulsed light groups were - 64.67% and -46.30%, respectively. The difference between the two treatment groups was significant (p < 0.05). ¹ 25 patients were randomized to receive two sessions (at 2 week interval) of ALA-PDT using IPL (n=15) or IPL only (n=10). The mean percentage changes from baseline for photodynamic therapy with ALA and intense pulsed light groups were - 45.6% and -27.8%, respectively. The difference between the two treatment groups was not significant (p = 0.202). ²			⊕⊕⊕○ Moderate	CRITICAL	

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA	Intense pulsed light	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Any at 12 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	Forty-one patients with moderate to severe facial acne were randomly assigned to receive a total of four sessions of ALA-IPL-PDT (n=21) or IPL alone (n=20) at 1 week interval. The mean percentage changes from baseline for photodynamic therapy with ALA and intense pulsed light groups were -70.53% and -48.95%, respectively. The difference between the two treatment groups was significant (p < 0.05).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 4 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	21	20	-	MD 12.8 lower (23.89 lower to 1.71 lower)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 8 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	21	20	-	MD 11.4 lower (22.22 lower to 0.58 lower)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 8 weeks (mean percent change from baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA	Intense pulsed light	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	serious ^a	none	25 patients were randomized to receive two sessions (at 2 week interval) of ALA-PDT using IPL (n=15) or IPL only (n=10). The mean percentage changes from baseline for photodynamic therapy with ALA and intense pulsed light groups were -73.4% and -18.9%, respectively. The difference between the two treatment groups was significant (p = 0.012).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	21	20	-	MD 13.2 lower (25.68 lower to 0.72 lower)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^{a,d}	none	21	20	-	MD 6.5 lower (18.15 lower to 5.15 higher)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	21	20	-	MD 15.6 lower (30.58 lower to 0.62 lower)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (mean percent change from baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA	Intense pulsed light	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	serious ^a	none	25 patients were randomized to receive two sessions (at 2 week interval) of ALA-PDT using IPL (n=15) or IPL only (n=10). The mean percentage changes from baseline for photodynamic therapy with ALA and intense pulsed light groups were -33.6% and -29.8%, respectively. The difference between the two treatment groups was not significant (p = 0.739).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks after the first treatment (mean percent change from baseline)

1 ^{3,b}	randomised trials	serious ^c	not serious	not serious	serious ^a	none	20 patients were assigned to three sessions (at 1 month interval) of short ALA incubation (30 minutes) with APL (n=9) or long ALA incubation (3 hour) with IPL (n=11) on half of the face by randomization, and the other half was treated with IPL only. The mean percentage changes from baseline at 4 weeks after the first treatment for ALA 20% (3-hour incubation), APL-ALA 20% (30-minute incubation), and intense pulsed light sides were -52.44%, -46.34%, and -32.32%, respectively. The difference between the treatments was not significant.				⊕⊕○○ Low	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks after the second treatment (mean percent change from baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA	Intense pulsed light	Relative (95% CI)	Absolute (95% CI)		
13,b	randomised trials	serious ^c	not serious	not serious	serious ^a	none	20 patients were assigned to three sessions (at 1 month interval) of short ALA incubation (30 minutes) with APL (n=9) or long ALA incubation (3 hour) with IPL (n=11) on half of the face by randomization, and the other half was treated with IPL only. The mean percentage changes from baseline at 4 weeks after the second treatment for ALA 20% (3-hour incubation), APL-ALA 20% (30-minute incubation), and intense pulsed light sides were -70.12%, -59.76% and -53.66%, respectively. The difference between the treatments was not significant.				⊕⊕○○ Low	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	21	20	-	MD 19.2 lower (37.63 lower to 0.77 lower)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks after the third treatment (mean percent change from baseline)

13,b	randomised trials	serious ^c	not serious	not serious	serious ^a	none	20 patients were assigned to three sessions (at 1 month interval) of short ALA incubation (30 minutes) with APL (n=9) or long ALA incubation (3 hour) with IPL (n=11) on half of the face by randomization, and the other half was treated with IPL only. The mean percentage changes from baseline at 4 weeks after the third treatment for ALA 20% (3-hour incubation), APL-ALA 20% (30-minute incubation), and intense pulsed light sides were -84.4%, -72.6% and -65.9%, respectively. The difference between the treatments was not significant.				⊕⊕○○ Low	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA	Intense pulsed light	Relative (95% CI)	Absolute (95% CI)		

Patient assessment of improvement, Global, None at 8 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^{a,d}	none	0/15 (0.0%)	2/10 (20.0%)	RR 0.14 (0.01 to 2.60)	172 fewer per 1,000 (from 198 fewer to 320 more)	⊕⊕⊕○ Moderate	CRITICAL

Patient assessment of improvement, Global, Slight at 8 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^{a,d}	none	0/15 (0.0%)	1/10 (10.0%)	RR 0.23 (0.01 to 5.12)	77 fewer per 1,000 (from 99 fewer to 412 more)	⊕⊕⊕○ Moderate	CRITICAL

Patient assessment of improvement, Global, Moderate at 8 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^{a,d}	none	5/15 (33.3%)	4/10 (40.0%)	RR 0.83 (0.29 to 2.37)	68 fewer per 1,000 (from 284 fewer to 548 more)	⊕⊕⊕○ Moderate	CRITICAL

Patient assessment of improvement, Global, Marked at 8 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA	Intense pulsed light	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	serious ^{a,d}	none	10/15 (66.7%)	3/10 (30.0%)	RR 2.22 (0.81 to 6.11)	366 more per 1,000 (from 57 fewer to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL

AE, Hyperpigmentation at 8 weeks

2 ^{2,3}	randomised trials	not serious	not serious	not serious	serious ^{a,d}	none	5/35 (14.3%)	1/30 (3.3%)	RR 2.67 (0.35 to 20.51)	56 more per 1,000 (from 22 fewer to 650 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Exfoliation at 8 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^{a,d}	none	10/15 (66.7%)	2/10 (20.0%)	RR 3.33 (0.92 to 12.11)	466 more per 1,000 (from 16 fewer to 1,000 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Pain,

1 ²	randomised trials	not serious	not serious	not serious	serious ^a	none	15/15 (100.0%)	10/10 (100.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

AE, Erythema at 8 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA	Intense pulsed light	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	serious ^{a,d}	none	14/15 (93.3%)	8/10 (80.0%)	RR 1.17 (0.83 to 1.64)	136 more per 1,000 (from 136 fewer to 512 more)	⊕⊕⊕○ Moderate	IMPORTANT

AE, Acneiform eruption at 8 weeks

1 ^{3,b}	randomised trials	serious ^c	not serious	not serious	serious ^a	none	1/20 (5.0%)	0/20 (0.0%)	not estimable		⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

- a. Small sample size
- b. RCT, Split face
- c. Limited methods reporting and unblinded patients
- d. CI includes appreciable benefits and harm

References

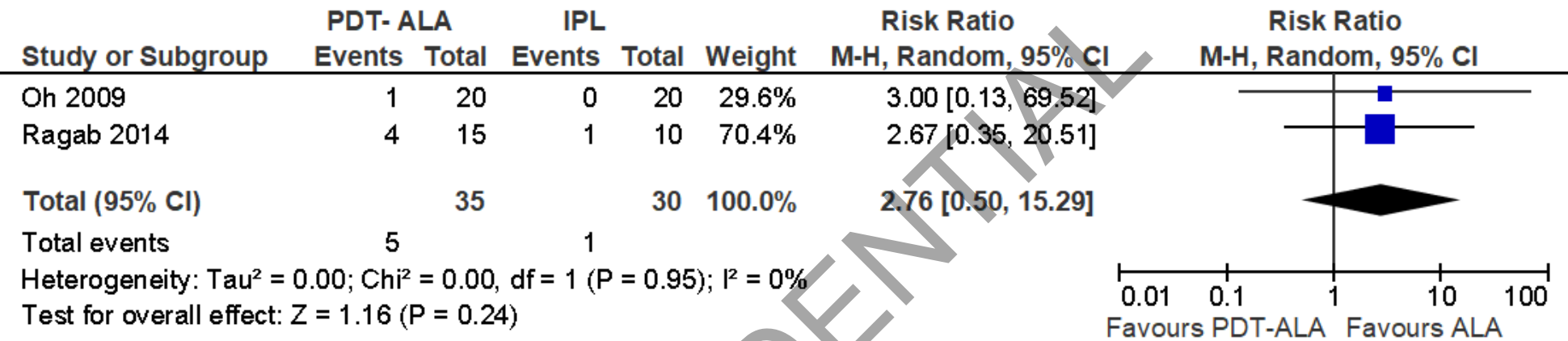
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- Oh, S.H., et al., *A comparative study of topical 5-aminolevulinic acid incubation times in photodynamic therapy with intense pulsed light for the treatment of inflammatory acne*. Dermatol Surg, 2009. **35**(12): p. 1918-26.

Forest Plot

e-Figure 178. Hyperpigmentation, photodynamic therapy (IPL) with ALA vs. intense pulsed light

1 PDT-ALA versus Intense pulse light

1.1 Hyperpigmentation



42. Photodynamic therapy with ALA 20% (30 minute incubation) vs. Photodynamic therapy with ALA 20% (3 hour incubation)

e-Table 122. GRADE Evidence Profile for photodynamic therapy with ALA 20% (30 minute incubation) vs. photodynamic therapy with ALA 20% (3 hour incubation)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 20% (30 minute incubation)	Photodynamic therapy with ALA 20% (3 hour incubation)	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Non-inflammatory at 4 weeks (Mean percent change from baseline)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage changes from baseline for photodynamic therapy with ALA 20% (30-minute incubation) and photodynamic therapy with ALA 20% (3-hour incubation) sides were -46.34% and -52.44%, respectively. The difference between the two treatments was not significant (p = 0.11).		⊕⊕○ ○ Low		CRITICAL	
Number of lesions, Non-inflammatory at 8 weeks (Mean percent change from baseline)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage changes from baseline for photodynamic therapy with ALA 20% (30-minute incubation) and photodynamic therapy with ALA 20% (3-hour incubation) sides were -59.76% and -70.12%, respectively. The difference between the two treatments was not significant (p = 0.11).		⊕⊕○ ○ Low		CRITICAL	
Number of lesions, Non-inflammatory at 12 weeks (Mean percent change from baseline)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage changes from baseline for photodynamic therapy with ALA 20% (30-minute incubation) and photodynamic therapy with ALA 20% (3-hour incubation) sides were -72.6% and -84.4%, respectively. The difference between the two treatments was not significant (p = 0.11).		⊕⊕○ ○ Low		CRITICAL	

AE, Hyperpigmentation at 8 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 20% (30 minute incubation)	Photodynamic therapy with ALA 20% (3 hour incubation)	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	1/9 (11.1%)	0/11 (0.0%)	not estimable		⊕⊕○ ○ Low	IMPORTANT

AE, Acneiform eruption at 8 weeks

1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	1/9 (11.1%)	0/11 (0.0%)	not estimable		⊕⊕○ ○ Low	IMPORTANT

CI: Confidence interval

Explanations

- a. RCT, Split face
- b. Limited methods reporting and unblinded patients
- c. Small sample size

References

1. Oh, S.H., et al., *A comparative study of topical 5-aminolevulinic acid incubation times in photodynamic therapy with intense pulsed light for the treatment of inflammatory acne*. *Dermatol Surg*, 2009. **35**(12): p. 1918-26.

43. Photodynamic therapy with riboflavin-tryptophan gel vs. Photodynamic therapy with ALA

e-Table 123. GRADE Evidence Profile for photodynamic therapy with riboflavin-tryptophan gel vs. photodynamic therapy with ALA

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with riboflavin-Tryptophan gel	Photodynamic therapy with ALA	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Global Acne Assessment Score, 0 or 1 at 5 weeks												
1 1.a	randomised trials	not serious	not serious	not serious	serious ^{b,c}	none	10/37 (27.0%)	7/37 (18.9%)	OR 1.59 (0.21 to 11.87)	81 more per 1,000 (from 142 fewer to 546 more)	⊕⊕⊕○ Moderate	CRITICAL
Acne severity, Global Acne Assessment Score, 0 or 1 at 7 weeks												
1 1.a	randomised trials	not serious	not serious	not serious	serious ^{b,c}	none	9/37 (24.3%)	7/37 (18.9%)	OR 1.38 (0.18 to 10.40)	54 more per 1,000 (from 149 fewer to 519 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Papules at 5 weeks (mean)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with riboflavin-Tryptophan gel	Photodynamic therapy with ALA	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	At baseline, the average number of lesions for riboflavin-tryptophan gel and photodynamic therapy with ALA was 2.16 and 2.24, respectively. At 5 weeks, the average inflammatory lesion counts decreased to 1.37 and 1.3 for riboflavin-tryptophan gel and photodynamic therapy with ALA sides, respectively. The difference between the two treatments was not significant.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory, Papules at 7 weeks (mean)

1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	At baseline, the average number of lesions for riboflavin-tryptophan gel and photodynamic therapy with ALA was 2.16 and 2.24, respectively. At 7 weeks, the average inflammatory lesion counts decreased to 1.53 and 1.3 for riboflavin-tryptophan gel and photodynamic therapy with ALA sides, respectively. The difference between the two treatments was not significant.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 5 weeks (mean)

1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	At baseline, the average number of lesions for riboflavin-tryptophan gel and photodynamic therapy with ALA was 21.67 and 23.14, respectively. At 5 weeks, the average inflammatory lesion counts decreased to 14.9 and 16.96 for riboflavin-tryptophan gel and photodynamic therapy with ALA sides, respectively. The difference between the two treatments was not significant.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 7 weeks (mean)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with riboflavin-Tryptophan gel	Photodynamic therapy with ALA	Relative (95% CI)	Absolute (95% CI)		
1 ^a	randomised trials	not serious	not serious	not serious	serious ^b	none	At baseline, the average number of lesions for riboflavin-tryptophan gel and photodynamic therapy with ALA was 21.67 and 23.14, respectively. At 7 weeks, the average inflammatory lesion counts decreased to 14.39 and 15.07 for riboflavin-tryptophan gel and photodynamic therapy with ALA sides, respectively. The difference between the two treatments was not significant.				⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; OR: Odds ratio

Explanations

- a. RCT, Split face
- b. Small sample size
- c. CI includes appreciable benefits and harm

References

1. Wangsuwan, S. and J. Meephansan, *Comparative study of photodynamic therapy with riboflavin-tryptophan gel and 13% 5-aminolevulinic acid in the treatment of mild to moderate acne vulgaris*. Clinical, Cosmetic and Investigational Dermatology, 2019. **12**: p. 805-814.

44. Extraction + Photodynamic therapy with ALA 5% vs. Extraction + Photodynamic therapy with ALA 10%

e-Table 124. GRADE Evidence Profile for extraction + photodynamic therapy with ala 5% vs. extraction + photodynamic therapy with ala 10%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Extraction + Photodynamic therapy with ALA 5%	Extraction + Photodynamic therapy with ALA 10%	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any, <20% reduction at 12 weeks												
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	0/23 (0.0%)	0/23 (0.0%)	not estimable		⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, 20-59% reduction at 12 weeks												
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^{b,c}	none	5/23 (21.7%)	1/23 (4.3%)	OR 6.11 (0.37 to 100.55)	174 more per 1,000 (from 27 fewer to 777 more)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, 60-89% reduction at 12 weeks												
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^{b,c}	none	15/23 (65.2%)	21/23 (91.3%)	OR 0.18 (0.02 to 1.94)	259 fewer per 1,000 (from 739 fewer to 40 more)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, >=90% reduction at 12 weeks												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Extraction + Photodynamic therapy with ALA 5%	Extraction + Photodynamic therapy with ALA 10%	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^{b,c}	none	1/23 (4.3%)	1/23 (4.3%)	OR 1.00 (0.04 to 27.06)	0 fewer per 1,000 (from 42 fewer to 508 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 4 weeks (median percent reduction from baseline)

1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	The median percentage reductions from baseline for extraction + photodynamic therapy with ALA 5% and extraction + photodynamic therapy with ALA 10% were 62.5% (58.3-72.4%) and 79.2% (70.6-85%), respectively. The difference between the two treatments was significant (p = 0.009). ^d				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (median percent reduction from baseline)

1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	The median percentage reductions from baseline for extraction + photodynamic therapy with ALA 5% and extraction + photodynamic therapy with ALA 10% were 78.3% (67.6-93.1%) and 88.5% (85-92.5%), respectively. The difference between the two treatments was significant (p = 0.018). ^d				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks (median percent reduction from baseline)

1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	The median percentage reductions from baseline for extraction + photodynamic therapy with ALA 5% and extraction + photodynamic therapy with ALA 10% sides were 58.5% (53.9-66.7%) and 54.8% (50-71.4%), respectively. The difference between the two treatments was not significant (p = 0.758). ^d				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (median percent reduction from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Extraction + Photodynamic therapy with ALA 5%	Extraction + Photodynamic therapy with ALA 10%	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	The median percentage reductions from baseline for extraction + photodynamic therapy with ALA 5% and extraction + photodynamic therapy with ALA 10% sides were 60.5% (52.6-71.4%) and 56.3% (50-72.6%), respectively. The difference between the two treatments was not significant (p = 0.357). ^d				⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; OR: Odds ratio

Explanations

- a. RCT, Split face
- b. Small sample size
- c. CI includes appreciable benefits and harm
- d. Percentage of reductions were expressed as median with 25%-75% percentiles in parentheses.

References

1. Zhang, J., et al., *Photodynamic therapy for severe facial acne vulgaris with 5% 5-aminolevulinic acid vs 10% 5-aminolevulinic acid: A split-face randomized controlled study.* Journal of Cosmetic Dermatology, 2020. **19**(2): p. 368-374.

Comparing Different Laser/Light/Photodynamic Therapies

45. 1064 nm Nd:YAG laser vs. 595 nm pulsed dye laser

e-Table 125. GRADE Evidence Profile for 1064 nm Nd:YAG laser vs. 595 nm pulsed dye laser

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1064 nm Nd:YAG laser	595 nm pulsed dye laser	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Inflammatory at 4 weeks (mean)												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	34	34	-	MD 0.06 lesions higher (0.86 lower to 0.98 higher)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Inflammatory at 8 weeks (mean)												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	34	34	-	MD 1.15 lesions higher (0.17 lower to 2.47 higher)	⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; MD: Mean difference

Explanations

a. RCT, Split face

b. Small sample size and CI including both appreciable benefits and harm

References

1. Chalermasuwiwattanakan, N., et al., *The comparative study of efficacy between 1064-nm long-pulsed Nd:YAG laser and 595-nm pulsed dye laser for the treatment of acne vulgaris*. Journal of Cosmetic Dermatology, 2021. **20**(7): p. 2108-2115.

e-Table 126. GRADE Evidence Profile for intense pulsed light vs. 585 nm pulsed dye laser

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intense pulsed light	585 nm pulsed dye laser	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Inflammatory at 4 weeks (mean percent of baseline)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	20 patients were randomized to receive intense pulsed light on half of the face and 585-nm pulsed dye laser on the other half. The mean percent of baseline of inflammatory lesions in the intense pulsed light and 585-nm pulsed dye laser sides was 34% and 38%, respectively. The difference between the two treatment groups was significant (p <0.05).		⊕⊕○○ Low		CRITICAL	
Number of lesions, Inflammatory at 8 weeks (mean percent of baseline)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percent of baseline of inflammatory lesions in the intense pulsed light and 585-nm pulsed dye laser sides was 45% and 14%, respectively. The difference between the two treatment sides was significant (p <0.05).		⊕⊕○○ Low		CRITICAL	
Number of lesions, Non-inflammatory at 4 weeks (mean percent of baseline)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percent of baseline of non-inflammatory lesions in the intense pulsed light and 585-nm pulsed dye laser sides was 67% and 53%, respectively. The difference between the two treatment sides was not significant.		⊕⊕○○ Low		CRITICAL	

Number of lesions, Non-inflammatory at 8 weeks (mean percent of baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intense pulsed light	585 nm pulsed dye laser	Relative (95% CI)	Absolute (95% CI)		
1 1,a	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percent of baseline of non-inflammatory lesions in the intense pulsed light and 585-nm pulsed dye laser sides was 57% and 41%, respectively. The difference between the two treatment sides was significant ($p < 0.05$).				⊕⊕○○ Low	CRITICAL

AE, Any, Significant at 8 weeks

1 1,a	randomized trials	serious ^b	not serious	not serious	serious ^c	none	0/20 (0.0%)	0/20 (0.0%)	not estimable		⊕⊕○○ Low	IMPORTANT

CI: Confidence interval

Explanations

a. RCT, Split face

b. Limited methods reporting and unblinded patients

c. Small sample size and no CIs or p-values reported

References

- Choi, Y.S., et al., *Intense pulsed light vs. pulsed-dye laser in the treatment of facial acne: a randomized split-face trial*. J Eur Acad Dermatol Venereol, 2010. **24**(7): p. 773-80.

e-Table 127. GRADE Evidence Profile for 530-750 nm red light vs. intense pulsed light

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	530-750 nm red light	Intense pulsed light	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Leeds at 4 weeks (mean)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	At baseline, the mean values of acne severity for 530-750-nm red light and intense pulsed light sides were 3.49 and 3.68, respectively. At 4 weeks, the mean values changed to 2.29 and 2.53 for 530-750-nm red light and intense pulsed light sides, respectively. The difference between the two treatments was not significant.		⊕⊕○○ Low		CRITICAL	
Number of lesions, Any at 4 weeks (mean percent change from baseline)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	22 patients were randomized to receive 530-750-nm red light on half of the face and intense pulsed light on the other half. The mean percentage changes from baseline for 530-750-nm red light and intense pulsed light sides were -28.6% and -30.3%, respectively.		⊕⊕○○ Low		CRITICAL	
Number of lesions, Any at 8 weeks (mean percent change from baseline)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage changes from baseline for 530-750-nm red light and intense pulsed light sides were -48.7% and -52.5%, respectively. The difference between the two treatments was not significant.		⊕⊕○○ Low		CRITICAL	

Number of lesions, Non-inflammatory at 4 weeks (mean percent change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	530-750 nm red light	Intense pulsed light	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage changes from baseline for 530-750-nm red light and intense pulsed light sides were -27.48% and -26.12%, respectively. The difference between the two treatments was not significant.				⊕⊕○○ Low	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (mean percent change from baseline)

11.a	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage changes from baseline for 530-750-nm red light and intense pulsed light sides were -43.4% and -46.3%, respectively. The difference between the two treatments was not significant.			⊕⊕○○ Low	CRITICAL

Number of lesions, Inflammatory at 4 weeks (mean percent change from baseline)

11.a	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage changes from baseline for 530-750-nm red light and intense pulsed light sides were -35.12% and -44.35%, respectively. The difference between the two treatments was not significant.			⊕⊕○○ Low	CRITICAL

Number of lesions, Inflammatory at 8 weeks (mean percent change from baseline)

11.a	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage changes from baseline for 530-750-nm red light and intense pulsed light sides were -69.5% and -72%, respectively. The difference between the two treatments was not significant.			⊕⊕○○ Low	CRITICAL

Patient assessment of improvement, VAS (0-10) at 8 weeks (mean)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	530-750 nm red light	Intense pulsed light	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	At baseline, the mean values for 530-750-nm red light and intense pulsed light sides were 10 and 10, respectively. At 8 weeks, the mean values decreased to 5 and 4.9 for 530-750-nm red light and intense pulsed light sides, respectively. The difference between the two treatments was not significant.				⊕⊕○○ Low	CRITICAL

AE, Erythema at 4 weeks

1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	1/20 (5.0%)	0/20 (0.0%)	OR 0.32 (0.01 to 12.45)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; OR: Odds ratio

Explanations

- a. RCT, Split face
- b. Limited methods reporting and unblinded patients
- c. Small sample size

References

1. Hong, J.S., et al., *Acne treatment by methyl aminolevulinate photodynamic therapy with red light vs. intense pulsed light*. Int J Dermatol, 2013. **52**(5): p. 614-9.

48. Photodynamic therapy (633nm red light) with ALA vs. Intense pulsed light

e-Table 128. GRADE Evidence Profile for photodynamic therapy (633nm red light) with ALA vs. intense pulsed light

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 5%	Intense pulsed light	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any, <20% reduction at 4 weeks												
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	0/50 (0.0%)	0/50 (0.0%)	not estimable		⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, 20-59% reduction at 4 weeks												
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	4/50 (8.0%)	21/50 (42.0%)	OR 0.12 (0.02 to 0.93)	340 fewer per 1,000 (from 406 fewer to 18 fewer)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, 60-89% reduction at 4 weeks												
1 ^{1,a}	randomised trials	not serious	not serious	not serious	serious ^b	none	16/50 (32.0%)	13/50 (26.0%)	OR 1.34 (0.20 to 8.93)	60 more per 1,000 (from 194 fewer to 498 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, ≥90% reduction at 4 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 5%	Intense pulsed light	Relative (95% CI)	Absolute (95% CI)		
11 ^a	randomised trials	not serious	not serious	not serious	serious ^b	none	30/50 (60.0%)	16/50 (32.0%)	OR 3.19 (0.49 to 20.80)	280 more per 1,000 (from 133 fewer to 587 more)	⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; OR: Odds ratio

Explanations

- a. RCT, Split face
- b. Small sample size

References

1. Liu, L.H., et al., *Randomized trial of three phototherapy methods for the treatment of acne vulgaris in Chinese patients*. Photodermatol Photoimmunol Photomed, 2014. **30**(5): p. 246-53.

e-Table 129. GRADE Evidence Profile for pulsed dye laser vs. combined 585 nm and 1064 nm laser

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulsed dye laser	Combined 585 nm and 1064 nm laser	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Leeds at 4 weeks (mean)												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	At baseline, the mean values of acne severity for pulsed dye laser and combined 585-nm and 1064-nm laser sides were 2.43 and 2.19, respectively. At 4 weeks, the mean values decreased to 1.54 and 1.44 for pulsed dye laser and combined 585-nm and 1064-nm laser sides, respectively (p < 0.05 compared with baseline for both treatments).			⊕⊕⊕○ Moderate	CRITICAL	
Acne severity, Leeds at 8 weeks (mean)												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	At baseline, the mean values of acne severity for pulsed dye laser and combined 585-nm and 1064-nm laser sides were 2.43 and 2.19, respectively. At 8 weeks, the mean values decreased to 1.09 and 1.05 for pulsed dye laser and combined 585-nm and 1064-nm laser sides, respectively (p < 0.05 compared with baseline for both treatments).			⊕⊕⊕○ Moderate	CRITICAL	
Acne severity, Leeds at 12 weeks (mean)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulsed dye laser	Combined 585 nm and 1064 nm laser	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	At baseline, the mean values of acne severity for pulsed dye laser and combined 585-nm and 1064-nm laser sides were 2.43 and 2.19, respectively. At 12 weeks, the mean values decreased to 0.77 and 0.91 for pulsed dye laser and combined 585-nm and 1064-nm laser sides, respectively (p < 0.05 compared with baseline for both treatments).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks (mean percent of baseline)

1 ^{1.a}	randomized trials	not serious	not serious	not serious	serious ^b	none	16 patients were randomized to receive pulsed dye laser on half of the face and combined 585/1,064-nm laser on the other half. At 4 weeks, the mean percent of baseline of non-inflammatory lesions in the pulsed dye laser and combined 585-nm and 1064-nm laser sides was 59.57% and 52.17%, respectively. The difference between the two treatments was not significant.			⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (mean percent of baseline)

1 ^{1.a}	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of non-inflammatory lesions in the pulsed dye laser and combined 585-nm and 1064-nm laser sides was 37% and 26%, respectively. The difference between the two treatments was significant ($p < 0.05$).			⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean percent of baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulsed dye laser	Combined 585 nm and 1064 nm laser	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of non-inflammatory lesions in the pulsed dye laser and combined 585-nm and 1064-nm laser sides was 31% and 26%, respectively. The difference between the two treatments was not significant.			⊕⊕⊕○ Moderate	CRITICAL	

Number of lesions, Inflammatory at 4 weeks (mean percent of baseline)

1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of inflammatory lesions in the pulsed dye laser and combined 585-nm and 1064-nm laser sides was 27.55% and 18.11%, respectively. The difference between the two treatments was not significant.			⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (mean percent of baseline)

1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of inflammatory lesions in the pulsed dye laser and combined 585-nm and 1064-nm laser sides was 14% and 11%, respectively. The difference between the two treatments was not significant.			⊕⊕⊕○ Moderate	CRITICAL

Patient assessment of improvement, Global, VAS (0-10) at 4 weeks (mean)

1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	At baseline, the mean values for pulsed dye laser and combined 585-nm and 1064-nm laser sides were 3.3 and 3.7, respectively. At 4 weeks, the mean values increased to 5.66 and 5.56 for pulsed dye laser and combined 585-nm and 1064-nm laser sides, respectively (p < 0.05 compared with baseline for both treatments).			⊕⊕⊕○ Moderate	CRITICAL

Patient assessment of improvement, Global, VAS (0-10) at 8 weeks (mean)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulsed dye laser	Combined 585 nm and 1064 nm laser	Relative (95% CI)	Absolute (95% CI)		
11.a	randomized trials	not serious	not serious	not serious	serious ^b	none	At baseline, the mean values for pulsed dye laser and combined 585-nm and 1064-nm laser sides were 3.3 and 3.7, respectively. At 8 weeks, the mean values increased to 6.63 and 6.6 for pulsed dye laser and combined 585-nm and 1064-nm laser sides, respectively (p < 0.05 compared with baseline for both treatments).				⊕⊕⊕○ Moderate	CRITICAL

Patient assessment of improvement, Global, VAS (0-10) at 12 weeks (mean)

1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	At baseline, the mean values for pulsed dye laser and combined 585-nm and 1064-nm laser sides were 3.3 and 3.7, respectively. At 8 weeks, the mean values increased to 6.13 and 6.13 for pulsed dye laser and combined 585-nm and 1064-nm laser sides, respectively (p < 0.05 compared with baseline for both treatments).			⊕⊕⊕○ Moderate	CRITICAL

AE, Erythema, Mild at 12 weeks

1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	16/16 (100.0%)	16/16 (100.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

CI: Confidence interval

Explanations

a. RCT, Split face

b. Small sample size.

References

1. Jung, J.Y., et al., *Comparison of a pulsed dye laser and a combined 585/1,064-nm laser in the treatment of acne vulgaris*. *Dermatol Surg*, 2009. **35**(8): p. 1181-7.

e-Table 130. GRADE Evidence Profile for photopneumatic therapy + intense pulsed light vs. intense pulsed light

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photopneumatic therapy + Intense pulsed light	Intense pulsed light	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Inflammatory at 10 weeks (mean percent reduction from baseline)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	50 patients were randomized to receive photopneumatic therapy + intense pulsed light therapy on one side of the face, and intense pulsed light on the other side of the face. At 10 weeks, inflammatory lesions decreased by 61.24% and by 46.34%, from baseline for photopneumatic therapy + intense pulsed light therapy and intense pulsed light sides, respectively which was a significant difference between the two treatments (P < 0.01).				⊕⊕○○ Low	CRITICAL
Number of lesions, Non-inflammatory at 10 weeks (mean percent reduction from baseline)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	At 10 weeks, non-inflammatory lesions decreased by 40.61% and by 29.85%, from baseline for photopneumatic therapy + intense pulsed light therapy and intense pulsed light sides, respectively which was a significant difference between the two treatments (P < 0.05).				⊕⊕○○ Low	CRITICAL

CI: Confidence interval

Explanations

a. RCT, Split face

b. Limited methods reporting and unblinded patients

c. Small sample size

References

1. Kim, J.E., et al., *A split-face comparative trial of photopneumatic therapy versus intense pulsed light for the treatment of acne vulgaris*. Journal of Cosmetic and Laser Therapy, 2020. **22(4-5)**: p. 185-189.

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51. Blue light vs. 1450 nm diode laser + Blue light

e-Table 131. GRADE Evidence Profile for blue light vs. 1450 nm diode laser + blue light

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Blue light	1450 nm diode laser + Blue light	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Leeds at 4 weeks (mean)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	At baseline, the mean values of Leeds revised acne grade for blue light and 1450-nm diode laser + blue light groups were 4.3 and 4.5, respectively. At 4 weeks, the mean decreased to 4.09 and 3.48 for blue light and 1450-nm diode laser + blue light sides, respectively. The difference between the two treatments was significant (p <0.05).			⊕⊕○○ Low	CRITICAL	
Acne severity, Leeds at 8 weeks (mean)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	At baseline, the mean values of Leeds revised acne grade for blue light and 1450-nm diode laser + blue light groups were 4.3 and 4.5, respectively. At 8 weeks, the mean decreased to 3.4 and 2.7 for blue light and 1450-nm diode laser + blue light groups, respectively. The difference between the two treatments was significant (p <0.05).			⊕⊕○○ Low	CRITICAL	
Acne severity, Leeds at 12 weeks (mean)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Blue light	1450 nm diode laser + Blue light	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	At baseline, the mean values of Leeds revised acne grade for blue light and 1450-nm diode laser + blue light groups were 4.3 and 4.5, respectively. At 8 weeks, the mean decreased to 2.9 and 2.06 for blue light and 1450 nm diode laser + blue light groups, respectively. The difference between the two treatments was significant (p <0.05).				⊕⊕○○ Low	CRITICAL

Acne severity, Leeds at 24 weeks (mean)

1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	At baseline, the mean values of Leeds revised acne grade for Blue light and 1450 nm diode laser + Blue light groups were 4.3 and 4.5, respectively. At 8 weeks, the mean decreased to 3.16 and 1.84 for Blue light and 1450 nm diode laser + Blue light groups, respectively. The difference between the two treatments was significant (p <0.05).			⊕⊕○○ Low	CRITICAL

Number of lesions, Inflammatory at 4 weeks (mean percent of baseline)

1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percent of baseline of inflammatory lesions in the blue light and 1450-nm diode laser + blue light groups was 92.4% and 78.21%, respectively. The difference between the two treatments was significant (p <0.05).			⊕⊕○○ Low	CRITICAL

Number of lesions, Inflammatory at 8 weeks (mean percent of baseline)

1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percent of baseline of inflammatory lesions in the blue light and 1450-nm diode laser + blue light groups was 75.91% and 59.42%, respectively. The difference between the two treatments was significant (p <0.05).			⊕⊕○○ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Blue light	1450 nm diode laser + Blue light	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Inflammatory at 12 weeks (mean percent of baseline)

11.a	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percent of baseline of inflammatory lesions in the blue light and 1450-nm diode laser + blue light groups was 62.49% and 41.792%, respectively. The difference between the two treatments was significant (p <0.05).			⊕⊕○○ Low	CRITICAL

Number of lesions, Inflammatory at 24 weeks (mean percent of baseline)

11.a	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percent of baseline of inflammatory lesions in the blue light and 1450-nm diode laser + blue light groups was 65.56% and 37.57%, respectively. The difference between the two treatments was significant (p <0.05).			⊕⊕○○ Low	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks (mean percent of baseline)

11.a	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percent of baseline of non-inflammatory lesions in the blue light and 1450-nm diode laser + blue light groups was 96.52% and 92.18%, respectively. The difference between the two treatments was significant (p <0.05).			⊕⊕○○ Low	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (mean percent of baseline)

11.a	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percent of baseline of non-inflammatory lesions in the blue light and 1450-nm diode laser + blue light groups was 94.42% and 75.47%, respectively. The difference between the two treatments was significant (p <0.05).			⊕⊕○○ Low	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean percent of baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Blue light	1450 nm diode laser + Blue light	Relative (95% CI)	Absolute (95% CI)		
11 ^a	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percent of baseline of non-inflammatory lesions in the blue light and 1450-nm diode laser + blue light groups was 102.58% and 65.08%, respectively. The difference between the two treatments was significant (p <0.05).				⊕⊕○○ Low	CRITICAL

Number of lesions, Non-inflammatory at 24 weeks (mean percent of baseline)

1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percent of baseline of non-inflammatory lesions in the blue light and 1450-nm diode laser + blue light groups was 92.19% and 55.47%, respectively. The difference between the two treatments was significant (p <0.05).			⊕⊕○○ Low	CRITICAL

AE, Hyperpigmentation at 12 weeks

1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^{c,d}	none	0/12 (0.0%)	1/12 (8.3%)	OR 0.31 (0.01 to 12.47)	56 fewer per 1,000 (from 82 fewer to 448 more)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; OR: Odds ratio

Explanations

- a. RCT, Split face
- b. Unclear allocation concealment and open label study
- c. Small sample size
- d. CI includes appreciable benefits and harm

References

1. Kwon, H.H., et al., *A Novel Combined Light-Based Treatment of Acne Vulgaris With 1,450-nm Diode Laser and 450-nm Blue Light*. *Dermatologic Surgery*, 2019. **45**(9): p. 1147-1154.

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e-Table 132. GRADE Evidence Profile for 1450 nm diode laser (stamp only) vs. 1450 nm diode laser (dual mode)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1450 nm diode laser (stamp only)	1450 nm diode laser (dual mode)	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Leeds at 4 weeks (mean)												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	At baseline, the mean values of Leeds revised acne grade for 1450-nm diode laser (stamp only) and 1450-nm diode laser (dual mode) sides were 3.8 and 4.0, respectively. At 4 weeks, the mean decreased to 3.7 and 3.6 for 1450 nm diode laser (stamp only) and 1450-nm diode laser (dual mode) sides, respectively.			⊕⊕⊕○ Moderate	CRITICAL	
Acne severity, Leeds at 8 weeks (mean)												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	At baseline, the mean values of Leeds revised acne grade for 1450-nm diode laser (stamp only) and 1450-nm diode laser (dual mode) sides were 3.8 and 4.0, respectively. At 8 weeks, the mean decreased to 3.3 and 3.11 for 1450 nm diode laser (stamp only) and 1450-nm diode laser (dual mode) sides, respectively.			⊕⊕⊕○ Moderate	CRITICAL	
Acne severity, Leeds at 12 weeks (mean)												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	At baseline, the mean values of Leeds revised acne grade for 1450-nm diode laser (stamp only) and 1450-nm diode laser (dual mode) sides were 3.8 and 4.0, respectively. At 12 weeks, the mean decreased to 2.48 and 2.18 for 1450 nm diode laser (stamp only) and 1450-nm diode laser (dual mode) sides, respectively.			⊕⊕⊕○ Moderate	CRITICAL	

Acne severity, Leeds at 24 weeks (mean)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1450 nm diode laser (stamp only)	1450 nm diode laser (dual mode)	Relative (95% CI)	Absolute (95% CI)		
11. ^a	randomized trials	not serious	not serious	not serious	serious ^b	none	At baseline, the mean values of Leeds revised acne grade for 1450-nm diode laser (stamp only) and 1450-nm diode laser (dual mode) sides were 3.8 and 4.0, respectively. At 24 weeks, the mean decreased to 2.74 and 1.9 for 1450-nm diode laser (stamp only) and 1450 nm diode laser (dual mode) sides, respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 4 weeks (mean percent of baseline)

1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of inflammatory lesions in the 1450-nm diode laser (stamp only) and 1450-nm diode laser (dual mode) sides was 87.54% and 83.92%, respectively.			⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 8 weeks (mean percent of baseline)

1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of inflammatory lesions in the 1450-nm diode laser (stamp only) and 1450-nm diode laser (dual mode) groups was 69.64% and 61.73%, respectively.			⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (mean percent of baseline)

1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of inflammatory lesions in the 1450-nm diode laser (stamp only) and 1450-nm diode laser (dual mode) sides was 53.38% and 45.15%, respectively.			⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 24 weeks (mean percent of baseline)

1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of inflammatory lesions in the 1450-nm diode laser (stamp only) and 1450-nm diode laser (dual mode) sides was 60.21% and 36.14%, respectively.			⊕⊕⊕○ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1450 nm diode laser (stamp only)	1450 nm diode laser (dual mode)	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Non-inflammatory at 4 weeks (mean percent of baseline)

11,a	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of non-inflammatory lesions in the 1450 nm diode laser (stamp only) and 1450-nm diode laser (dual mode) sides was 95.79% and 91.84%, respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (mean percent of baseline)

11,a	randomized trials	not serious	not serious	not serious	serious ^c	none	The mean percent of baseline of non-inflammatory lesions in the 1450-nm diode laser (stamp only) and 1450-nm diode laser (dual mode) groups was 94.48% and 74.37%, respectively. The difference between the two treatments was significant (p <0.05).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean percent of baseline)

11,a	randomized trials	not serious	not serious	not serious	serious ^c	none	The mean percent of baseline of non-inflammatory lesions in the 1450-nm diode laser (stamp only) and 1450-nm diode laser (dual mode) groups was 77.68% and 61.85%, respectively. The difference between the two treatments was significant (p <0.05).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 24 weeks (mean percent of baseline)

11,a	randomized trials	not serious	not serious	not serious	serious ^c	none	The mean percent of baseline of non-inflammatory lesions in the 1450-nm diode laser (stamp only) and 1450-nm diode laser (dual mode) sides was 84.94% and 54.94%, respectively. The difference between the two treatments was significant (p <0.05).				⊕⊕⊕○ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1450 nm diode laser (stamp only)	1450 nm diode laser (dual mode)	Relative (95% CI)	Absolute (95% CI)		

Patient assessment of improvement, Global, 0-4 (mean)

1 ^{1,a,d}	randomized trials	not serious	not serious	not serious	serious ^c	none	24	24	-	MD 0.7 lower (0.99 lower to 0.41 lower)	⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. RCT, Split face

b. Small sample size and no CIs or p-values provided

c. Small sample size

d. The improvements of acne, seborrhea, and skin texture were evaluated using a 5-point scale (0 = none, 1 = slight improvement, 2 = moderate improvement, 3 = good improvement, and 4 = excellent improvement).

References

1. Kwon, H.H., et al., *Comparison of novel dual mode vs conventional single pass of a 1450-nm diode laser in the treatment of acne vulgaris for Korean patients: A 20-week prospective, randomized, split-face study*. Journal of Cosmetic Dermatology, 2018. **17**(6): p. 1063-1068.

e-Table 133. GRADE Evidence Profile for intense pulsed light vs. combined 420 nm blue light and 660 nm red light

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intense pulsed light	Combined 420 nm blue light and 660 nm red light	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any, <20% reduction at 4 weeks												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	0/50 (0.0%)	0/50 (0.0%)	not estimable		⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, 20-59% reduction at 4 weeks												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^c	none	21/50 (42.0%)	28/50 (56.0%)	OR 0.57 (0.09 to 3.67)	140 fewer per 1,000 (from 457 fewer to 264 more)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, 60-89% reduction at 4 weeks												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^c	none	13/50 (26.0%)	12/50 (24.0%)	OR 1.11 (0.16 to 7.55)	20 more per 1,000 (from 192 fewer to 465 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, ≥90% reduction at 4 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intense pulsed light	Combined 420 nm blue light and 660 nm red light	Relative (95% CI)	Absolute (95% CI)		
11. ^a	randomized trials	not serious	not serious	not serious	serious ^c	none	16/50 (32.0%)	10/50 (20.0%)	OR 1.88 (0.28 to 12.81)	120 more per 1,000 (from 135 fewer to 562 more)	⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; OR: Odds ratio

Explanations

- a. RCT, Split face
- b. Small sample size
- c. Small sample size and CI including appreciable benefits and harm

References

1. Liu, L.H., et al., *Randomized trial of three phototherapy methods for the treatment of acne vulgaris in Chinese patients*. Photodermatol Photoimmunol Photomed, 2014. **30**(5): p. 246-53.

54. Intense pulsed light vs. 1064 nm Nd:YAG laser

e-Table 134. GRADE Evidence Profile for intense pulsed light vs. 1064 nm Nd:YAG laser

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intense pulsed light	1064 nm Nd:YAG laser	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Leeds at 12 weeks (mean)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	74	74	-	MD 0.3 higher (0.26 higher to 0.34 higher)	⊕⊕○○ Low	CRITICAL
Number of lesions, Any at 4 weeks (mean reduction from baseline)												
1 ²	randomized trials	serious ^b	not serious	not serious	serious ^c	none	15	15	-	MD 25.9 lesions higher (13.9 higher to 37.9 higher)	⊕⊕○○ Low	CRITICAL
Number of lesions, Any at 8 weeks (mean reduction from baseline)												
1 ²	randomized trials	serious ^b	not serious	not serious	serious ^{c,d}	none	15	15	-	MD 3.3 lesions higher (13.73 lower to 20.33 higher)	⊕⊕○○ Low	CRITICAL
Number of lesions, Inflammatory at 8 weeks (mean reduction from baseline)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intense pulsed light	1064 nm Nd:YAG laser	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomized trials	serious ^b	not serious	not serious	serious ^{c,d}	none	15	15	-	MD 9 lesions lower (32.47 lower to 14.47 higher)	⊕⊕○○ Low	CRITICAL

Number of lesions, Inflammatory, Cysts at 12 weeks (mean percent change from baseline)

1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	74 patients were randomized to receive intense pulsed light on half of the face and 1064-nm Nd:YAG laser on the other half. The mean percentage change from baseline for both intense pulsed light and 1064-nm Nd:YAG laser groups was -100%.				⊕⊕○○ Low	CRITICAL

Number of lesions, Inflammatory, Nodules at 12 weeks (mean percent change from baseline)

1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage changes from baseline for intense pulsed light and 1064-nm Nd:YAG laser groups were -85.7% and -88.1%, respectively. The difference between the two treatment groups was not significant (p > 0.05).				⊕⊕○○ Low	CRITICAL

Number of lesions, Inflammatory, Papules at 12 weeks (mean percent change from baseline)

1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage changes from baseline for intense pulsed light and 1064-nm Nd:YAG laser groups were -75.5% and -78.0%, respectively. The difference between the two treatment groups was not significant (p > 0.05).				⊕⊕○○ Low	CRITICAL

Number of lesions, Inflammatory, Pustules at 12 weeks (mean percent change from baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intense pulsed light	1064 nm Nd:YAG laser	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage changes from baseline for intense pulsed light and 1064-nm Nd:YAG laser groups were -83.7% and -84.9%, respectively. The difference between the two treatment groups was not significant (p > 0.05).				⊕⊕○○ Low	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (mean reduction from baseline)

1 ²	randomized trials	serious ^b	not serious	not serious	serious ^c	none	15	15	-	MD 34.9 lesions lower (61.44 lower to 8.36 lower)	⊕⊕○○ Low	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean percent change from baseline)

1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage changes from baseline for intense pulsed light and 1064-nm Nd:YAG laser groups were -18.3% and -19.3%, respectively. The difference between the two treatment groups was not significant (p > 0.05).				⊕⊕○○ Low	CRITICAL

AE, Scarring at 4 weeks

1 ²	randomized trials	serious ^b	not serious	not serious	serious ^{c,d}	none	0/15 (0.0%)	2/15 (13.3%)	RR 0.20 (0.01 to 3.85)	107 fewer per 1,000 (from 132 fewer to 380 more)	⊕⊕○○ Low	CRITICAL

AE, Hyperpigmentation at 4 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intense pulsed light	1064 nm Nd:YAG laser	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomized trials	serious ^b	not serious	not serious	serious ^c	none	0/15 (0.0%)	12/15 (80.0%)	RR 0.04 (0.00 to 0.62)	768 fewer per 1,000 (from 304 fewer to -)	⊕⊕○○ Low	IMPORTANT

AE, Edema at 4 weeks

1 ²	randomized trials	serious ^b	not serious	not serious	serious ^{c,d}	none	0/15 (0.0%)	5/15 (33.3%)	RR 0.09 (0.01 to 1.51)	303 fewer per 1,000 (from 330 fewer to 170 more)	⊕⊕○○ Low	IMPORTANT

AE, Erythema at 4 weeks

1 ²	randomized trials	serious ^b	not serious	not serious	serious ^c	none	1/15 (6.7%)	15/15 (100.0%)	RR 0.10 (0.02 to 0.45)	900 fewer per 1,000 (from 980 fewer to 550 fewer)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: risk ratio

Explanations

a. RCT, Split face

b. Limited methods reporting and unblinded patients

c. Small sample size

d. CI includes appreciable benefits and harm

References

1. Mohamed, E.E., K. Tawfik, and M. Elsaie, *Intense pulsed light versus 1,064 long-pulsed neodymium: Yttrium-aluminum- Garnet laser in the treatment of facial ACNE vulgaris*. Journal of Clinical and Diagnostic Research, 2016. **10(7)**: p. WC01-WC03.
2. Monib, K.M.E. and M.S. Hussein, *Nd:YAG laser vs IPL in inflammatory and noninflammatory acne lesion treatment*. Journal of Cosmetic Dermatology, 2020. **19(9)**: p. 2325-2332.

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55. Photodynamic therapy with ALA 5% vs. Combined 420 nm blue light and 660 nm red light

e-Table 135. GRADE Evidence Profile for photodynamic therapy with ALA 5% vs. combined 420 nm blue light and 660 nm red light

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 5%	Combined 420 nm blue light and 660 nm red light	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any, <20% reduction at 4 weeks												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	0/50 (0.0%)	0/50 (0.0%)	not estimable		⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, 20-59% reduction at 4 weeks												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	4/50 (8.0%)	28/50 (56.0%)	OR 0.07 (0.01 to 0.53)	478 fewer per 1,000 (from 547 fewer to 157 fewer)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, 60-89% reduction at 4 weeks												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^{b,c}	none	16/50 (32.0%)	12/50 (24.0%)	OR 1.49 (0.22 to 9.99)	80 more per 1,000 (from 175 fewer to 519 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, ≥90% reduction at 4 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 5%	Combined 420 nm blue light and 660 nm red light	Relative (95% CI)	Absolute (95% CI)		
11. ^a	randomized trials	not serious	not serious	not serious	serious ^{b,c}	none	30/50 (60.0%)	10/50 (20.0%)	OR 6.00 (0.89 to 40.49)	400 more per 1,000 (from 18 fewer to 710 more)	⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; OR: Odds ratio

Explanations

- a. RCT, Split face
- b. Small sample size
- c. CI includes appreciable benefits and harm

References

1. Liu, L.H., et al., *Randomized trial of three phototherapy methods for the treatment of acne vulgaris in Chinese patients*. Photodermatol Photoimmunol Photomed, 2014. **30**(5): p. 246-53.

e-Table 136. GRADE Evidence Profile for fractional microneedle radiofrequency vs. bipolar radiofrequency

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fractional microneedle radiofrequency	Bipolar radiofrequency	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Leeds, Grade 1 at 12 weeks												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	18/20 (90.0%)	5/20 (25.0%)	OR 27.00 (2.33 to 312.98)	650 more per 1,000 (from 187 more to 741 more)	⊕⊕⊕○ Moderate	CRITICAL
Acne severity, Leeds at 4 weeks (mean)												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^c	none	20 patients were randomized to receive fractional microneedle radiofrequency on half of the face and bipolar radiofrequency on the other half. At baseline, the mean values of acne severity for fractional microneedle radiofrequency and bipolar radiofrequency groups were 2.80 and 2.81, respectively. At 4 weeks, the mean values decreased to 1.90 and 2.38 for fractional microneedle radiofrequency and bipolar radiofrequency groups, respectively. The difference between the two treatment groups was significant (p <0.05).			⊕⊕⊕○ Moderate	CRITICAL	

Acne severity, Leeds at 8 weeks (mean)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fractional microneedle radiofrequency	Bipolar radiofrequency	Relative (95% CI)	Absolute (95% CI)		
11,a	randomized trials	not serious	not serious	not serious	serious ^c	none	At baseline, the mean values of acne severity for fractional microneedle radiofrequency and bipolar radiofrequency groups were 2.80 and 2.81, respectively. At 8 weeks, the mean values decreased to 1.28 and 2.03 for fractional microneedle radiofrequency and bipolar radiofrequency groups, respectively. The difference between the two treatment groups was significant (p <0.05).				⊕⊕⊕○ Moderate	CRITICAL

Acne severity, Leeds at 12 weeks (mean)

11,a	randomized trials	not serious	not serious	not serious	serious ^c	none	At baseline, the mean values of acne severity for fractional microneedle radiofrequency and bipolar radiofrequency groups were 2.80 and 2.81, respectively. At 12 weeks, the mean values decreased to 1.09 and 1.76 for fractional microneedle radiofrequency and bipolar radiofrequency groups, respectively. The difference between the two treatment groups was significant (p <0.05).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 4 weeks (mean percent of baseline)

11,a	randomized trials	not serious	not serious	not serious	serious ^c	none	The mean percent of baseline of inflammatory lesions in the fractional microneedle radiofrequency and bipolar radiofrequency groups was 59.67% and 126.24%, respectively. The difference between the two treatment groups was significant (p <0.05).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 8 weeks (mean percent of baseline)

11,a	randomized trials	not serious	not serious	not serious	serious ^c	none	The mean percent of baseline of inflammatory lesions in the fractional microneedle radiofrequency and bipolar radiofrequency groups was 24.2% and 93.55%, respectively. The difference between the two treatment groups was significant (p <0.05).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (mean percent of baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fractional microneedle radiofrequency	Bipolar radiofrequency	Relative (95% CI)	Absolute (95% CI)		
11,a	randomized trials	not serious	not serious	not serious	serious ^c	none	The mean percent of baseline of inflammatory lesions in the fractional microneedle radiofrequency and bipolar radiofrequency groups was 19.67% and 84.58%, respectively. The difference between the two treatment groups was significant (p <0.05).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks (mean percent of baseline)

11,a	randomized trials	not serious	not serious	not serious	serious ^c	none	The mean percent of baseline of non-inflammatory lesions in the fractional microneedle radiofrequency and bipolar radiofrequency groups was 79.4% and 126.55%, respectively. The difference between the two treatment groups was significant (p <0.05).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (mean percent of baseline)

11,a	randomized trials	not serious	not serious	not serious	serious ^c	none	The mean percent of baseline of non-inflammatory lesions in the fractional microneedle radiofrequency and bipolar radiofrequency groups was 38.29% and 106.98%, respectively. The difference between the two treatment groups was significant (p <0.05).				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean percent of baseline)

11,a	randomized trials	not serious	not serious	not serious	serious ^c	none	The mean percent of baseline of non-inflammatory lesions in the fractional microneedle radiofrequency and bipolar radiofrequency groups was 34.86% and 115.38%, respectively. The difference between the two treatment groups was significant (p <0.05).				⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; OR: Odds ratio

Explanations

a. RCT, Split face

b. Small sample size resulting in a wide CI

c. Small sample size

References

1. Min, S., et al., *Comparison of fractional microneedling radiofrequency and bipolar radiofrequency on acne and acne scar and investigation of mechanism: comparative randomized controlled clinical trial*. Arch Dermatol Res, 2015. **307**(10): p. 897-904.

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57. Daylight photodynamic therapy with ALA 5% vs. Conventional photodynamic (LED red light, 630 nm) therapy with ALA 5%

e-Table 137. GRADE Evidence Profile for daylight photodynamic therapy with ALA 5% vs. conventional photodynamic (LED red light, 630 nm) therapy with ALA 5%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 5% (Daylight)	Photodynamic therapy with ALA	Relative (95% CI)	Absolute (95% CI)		
Investigator assessment of improvement, Poor (20-59%) at 4 weeks												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	4/40 (10.0%)	6/40 (15.0%)	RR 0.67 (0.20 to 2.18)	49 fewer per 1,000 (from 120 fewer to 177 more)	⊕⊕○ ○ Low	CRITICAL
Investigator assessment of improvement, Good (60-89%) at 4 weeks												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	23/40 (57.5%)	24/40 (60.0%)	RR 0.96 (0.66 to 1.38)	24 fewer per 1,000 (from 204 fewer to 228 more)	⊕⊕○ ○ Low	CRITICAL
Investigator assessment of improvement, None at 4 weeks												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	0/40 (0.0%)	0/40 (0.0%)	not estimable		⊕⊕○ ○ Low	CRITICAL

Objective response rate at 4 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 5% (Daylight)	Photodynamic therapy with ALA	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,d}	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	36/40 (90.0%)	34/40 (85.0%)	RR 1.06 (0.90 to 1.25)	51 more per 1,000 (from 85 fewer to 213 more)	⊕⊕○○ Low	CRITICAL

AE, Pigmentation at 4 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	3/40 (7.5%)	2/40 (5.0%)	RR 1.50 (0.26 to 8.50)	25 more per 1,000 (from 37 fewer to 375 more)	⊕⊕○○ Low	IMPORTANT

Acne reoccurrence at 8 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	10/40 (25.0%)	9/40 (22.5%)	RR 1.11 (0.51 to 2.44)	25 more per 1,000 (from 110 fewer to 324 more)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

a. Limited methods reporting and open label study

- b. Small sample size
- c. CI includes appreciable benefits and harm
- d. The objective response rate: (number of cases of excellent and good response)/(total number of cases) x 100%

References

1. Zhang, L., et al., *Conventional versus daylight photodynamic therapy for acne vulgaris: A randomized and prospective clinical study in China*. Photodiagnosis & Photodynamic Therapy, 2020. **31**: p. 101796.

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e-Table 138. GRADE Evidence Profile for pulsed dye laser vs. intense pulsed light

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulsed dye laser	Intense pulsed light	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any at 4 weeks (mean percent change from baseline)												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	15 and 15 patients were randomized to receive pulsed dye laser or intense pulsed light, respectively. The mean percentage changes from baseline for pulsed dye laser and intense pulsed light groups were -73.75% and -41.68%, respectively.			⊕⊕○○ Low	CRITICAL	

CI: Confidence interval

Explanations

- a. Limited methods reporting and unblinded patients
- b. Small sample size and no CIs or p-values reported

References

1. Sami, N.A., A.T. Attia, and A.M. Badawi, *Phototherapy in the treatment of acne vulgaris*. J Drugs Dermatol, 2008. 7(7): p. 627-32.

e-Table 139. GRADE Evidence Profile for intense pulsed light vs. combined 470 nm blue light and 623 nm red light

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intense pulsed light	Combined 470 nm blue light and 623 nm red light	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any at 4 weeks (mean percent change from baseline)												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	15 and 15 patients were randomized to receive intense pulsed light or combined 470-nm blue light and 623-nm red light, respectively. The mean percentage changes from baseline for intense pulsed light and combined 470-nm blue light and 623-nm red light groups were -41.68% and -35.64%, respectively.			⊕⊕○○ Low		

CI: Confidence interval

Explanations

- a. Limited methods reporting and unblinded patients
- b. Small sample size and no CIs or p-values reported

References

1. Sami, N.A., A.T. Attia, and A.M. Badawi, *Phototherapy in the treatment of acne vulgaris*. J Drugs Dermatol, 2008. 7(7): p. 627-32.

e-Table 140. GRADE Evidence Profile for pulsed dye laser vs. combined 470 nm blue light and 623 nm red light

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pulsed dye laser	combined 470 nm blue light and 623 nm red light	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any at 4 weeks (mean percent change from baseline)												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	15 and 15 patients were randomized to receive pulsed dye laser or combined 470-nm blue light and 623-nm red light, respectively. The mean percentage changes from baseline for pulsed dye laser and combined 470-nm blue light and 623-nm red light groups were -73.75% and -35.64%, respectively.				⊕⊕○○ Low	CRITICAL

CI: Confidence interval

Explanations

- a. Limited methods reporting and unblinded patients
- b. Small sample size and no CIs or p-values reported

References

1. Sami, N.A., A.T. Attia, and A.M. Badawi, *Phototherapy in the treatment of acne vulgaris*. J Drugs Dermatol, 2008. 7(7): p. 627-32.

61. Alternating 470 nm blue light and 640 nm red light (twice weekly) vs. Alternating 470 nm blue light and 640 nm red light (once weekly)

e-Table 141. GRADE Evidence Profile for alternating 470 nm blue light and 640 nm red light (twice weekly) vs. alternating 470 nm blue light and 640 nm red light (once weekly)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alternating 470 nm blue light and 640 nm red light (twice weekly)	Alternating 470 nm blue light and 640 nm red light (once weekly)	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Inflammatory at 5 weeks (mean percent improvement from baseline)												
1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	The mean percentage improvements from baseline for alternating 470 nm blue light and 640 nm red light (twice weekly) and alternating 470 nm blue light and 640 nm red light (once weekly) groups were 53.53% and 50.32%, respectively. The difference between the two treatment groups was not significant (p = 0.266).			⊕⊕⊕○ Moderate	CRITICAL	
Number of lesions, Inflammatory at 8 weeks (mean percent improvement from baseline)												
1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	The mean percentage improvements from baseline for alternating 470 nm blue light and 640 nm red light (twice weekly) and alternating 470 nm blue light and 640 nm red light (once weekly) groups were 43.74% and 44.61%, respectively. The difference between the two treatment groups was not significant (p = 0.266).			⊕⊕⊕○ Moderate	CRITICAL	

Number of lesions, Inflammatory at 12 weeks (mean percent improvement from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Alternating 470 nm blue light and 640 nm red light (twice weekly)	Alternating 470 nm blue light and 640 nm red light (once weekly)	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	The mean percentage improvements from baseline for alternating 470 nm blue light and 640 nm red light (twice weekly) and alternating 470 nm blue light and 640 nm red light (once weekly) groups were 55.25% and 51.03%, respectively. The difference between the two treatment groups was not significant (p = 0.266).				⊕⊕⊕○ Moderate	CRITICAL

Patient assessment of improvement, Global, >25% at 4 weeks

1 ¹	randomized trials	not serious	not serious	not serious	serious ^{a,b}	none	6/15 (40.0%)	5/15 (33.3%)	RR 1.20 (0.47 to 3.09)	67 more per 1,000 (from 177 fewer to 697 more)	⊕⊕⊕○ Moderate	CRITICAL

Patient assessment of improvement, Global, >50% at 8 weeks

1 ¹	randomized trials	not serious	not serious	not serious	serious ^{a,b}	none	3/15 (20.0%)	3/15 (20.0%)	RR 1.00 (0.24 to 4.18)	0 fewer per 1,000 (from 152 fewer to 636 more)	⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; RR: Risk ratio

Explanations

- a. Small sample size
- b. CI includes appreciable benefits and harm

References

1. Nitayavardhana, S., et al., *A Comparative Study Between Once-Weekly and Alternating Twice-Weekly Regimen Using Blue (470 nm) and Red (640 nm) Light Combination LED Phototherapy for Moderate-to-Severe Acne Vulgaris*. *Lasers in Surgery & Medicine*, 2021. **53**(8): p. 1080-1085.

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62. Photodynamic therapy with ALA (IPL) vs. Photodynamic therapy with ALA plus radiofrequency (IPL+RF)

e-Table 142. GRADE Evidence Profile for photodynamic therapy with ALA (IPL) vs. photodynamic therapy with ALA plus radiofrequency (IPL+RF)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA (IPL)	Photodynamic therapy with ALA (IPL + RF)	Relative (95% CI)	Absolute (95% CI)		
Investigator assessment of improvement, Percentage improvement at 4 weeks												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	The median percent improvements from baseline for photodynamic therapy with ALA (IPL) and photodynamic therapy with ALA (IPL + RF) groups were 56.25% (96.9% CI: 27.5-85.0) and 23.75% (96.9% CI: 2.5-85.0), respectively. The difference between the two treatment groups was not significant.			⊕⊕○○ Low	CRITICAL	
Investigator assessment of improvement, Percentage improvement at 12 weeks												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	The median percent improvements from baseline for photodynamic therapy with ALA (IPL) and photodynamic therapy with ALA (IPL + RF) groups were 70% (range: 35) and 50% (range: 47.5), respectively. The difference between the two treatment groups reached borderline statistical significance (p = 0.0498).			⊕⊕○○ Low	CRITICAL	
Acne severity, Bespoke, 1-4 at 4 weeks (median)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	At baseline, the median acne grades for photodynamic therapy with ALA (IPL) and photodynamic therapy with ALA (IPL + RF) groups were 2.75 (96.9% CI: 2.5-4) and 2.5 (96.9% CI: 2.0-4.0), respectively. At 4 weeks, the median acne grades changed to 1.5 (96.9% CI: 1.0-2.5) and 2.25 (96.9% CI: 1.5-3.5) for photodynamic therapy with ALA (IPL) and photodynamic therapy with ALA (IPL + RF) groups, respectively.			⊕⊕○○ Low	CRITICAL	

Acne severity, Bespoke, 1-4 at 12 weeks (median)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA (IPL)	Photodynamic therapy with ALA (IPL + RF)	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	At baseline, the median acne grades for photodynamic therapy with ALA (IPL) and photodynamic therapy with ALA (IPL + RF) groups were 2.75 (96.9% CI: 2.5-4) and 2.5 (96.9% CI: 2.0-4.0), respectively. At 12 weeks, the median acne grades changed to 1.75 (range: 1.5) and 1.5 (range: 2) for photodynamic therapy with ALA (IPL) and photodynamic therapy with ALA (IPL + RF) groups, respectively.				⊕⊕○○ Low	CRITICAL

Number of lesions, Any at 4 weeks (median percent reduction from baseline)

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	A total of 22 patients were randomly divided between three treatment groups, however, the number of patients per treatment arm was not reported. The median percent reductions from baseline for photodynamic therapy with ALA (IPL) and photodynamic therapy with ALA (IPL + RF) groups were 76.8% (96.9% CI: 12.5-86.4) and 47% (96.9% CI: 8.3-82.2), respectively. The difference between the two treatment groups was not significant (p = 0.3114).				⊕⊕○○ Low	CRITICAL

Number of lesions, Any at 12 weeks (median percent reduction from baseline)

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	The median percent reduction from baseline for photodynamic therapy with ALA (IPL) and photodynamic therapy with ALA (IPL + RF) groups were 73.2% (range: 72.4) and 41.65% (range: 167.5), respectively.				⊕⊕○○ Low	CRITICAL

Patient assessment of improvement, Global, Percentage improvement at 4 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA (IPL)	Photodynamic therapy with ALA (IPL + RF)	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	The median percent improvements from baseline for photodynamic therapy with ALA (IPL) and photodynamic therapy with ALA (IPL + RF) groups were 58.75% (96.9% CI: 5.0-70.0%) and 20% (96.9% CI: 0-80), respectively. The difference between the two treatment groups was not significant (p = 0.3210).				⊕⊕○○ Low	CRITICAL

CI: Confidence interval

Explanations

- a. Limited methods reporting, open label study, and risk of attrition bias (40% dropout)
b. Small sample size

References

1. Taub, A.F., *A comparison of intense pulsed light, combination radiofrequency and intense pulsed light, and blue light in photodynamic therapy for acne vulgaris*. J Drugs Dermatol, 2007. 6(10): p. 1010-6.

63. Photodynamic therapy (Blue light) with ALA vs. Photodynamic therapy with ALA plus radiofrequency(IPL + RF)

e-Table 143. GRADE Evidence Profile for photodynamic therapy (Blue light) with ALA vs. photodynamic therapy with ALA plus radiofrequency(IPL + RF)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy (blue light) with ALA	Photodynamic therapy(IPL) with ALA (IPL + RF)	Relative (95% CI)	Absolute (95% CI)		
Investigator assessment of improvement, Percentage improvement at 4 weeks												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	A total of 22 patients were randomly divided between three treatment groups, however, the number of patients per treatment arm was not reported. The median percent improvements from baseline for blue light-ALA and IPL-ALA + RF groups were 20% (96.9% CI: 0-62.5) and 23.75% (96.9% CI: 2.5-85.0), respectively. The difference between the two treatment groups was not significant.			⊕⊕○○ Low	CRITICAL	
Investigator assessment of improvement, Percentage improvement at 12 weeks												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	The median percent improvements from baseline for blue light-ALA and IPL-ALA + RF groups were 25% (range: 40) and 50% (range: 47.5), respectively. The difference between the two treatment groups reached borderline statistical significance (p = 0.0498).			⊕⊕○○ Low	CRITICAL	
Acne severity, Bespoke, 1-4 at 4 weeks (median)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	At baseline, the median acne grades for blue light-ALA and IPL-ALA + RF groups were 3.25 (96.9% CI: 2.5-3.5) and 2.5 (96.9% CI: 2.0-4.0), respectively. At 4 weeks, the median acne grades changed to 1.5 (96.9% CI: 1.0-3.5) and 2.25 (96.9% CI: 1.5-3.5) for blue light-ALA and IPL-ALA + RF groups, respectively.			⊕⊕○○ Low	CRITICAL	
Acne severity, Bespoke, 1-4 at 12 weeks (median)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy (blue light) with ALA	Photodynamic therapy(IPL) with ALA (IPL + RF)	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	At baseline, the median acne grades for blue light-ALA and IPL-ALA + RF groups were 3.25 (96.9% CI: 2.5-3.5) and 2.5 (96.9% CI: 2.0-4.0), respectively. At 12 weeks, the median acne grades changed to 2.00 (range: 1) and 1.5 (range: 2) for photodynamic therapy with unknown photosensitizer (blue light) and photodynamic therapy with ALA (IPL + RF) groups, respectively.				⊕⊕○○ Low	CRITICAL

Number of lesions, Any at 4 weeks (median percent reduction from baseline)

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	The median percent reductions from baseline for blue light-ALA and IPL-ALA + RF groups were 52.8% (96.9% CI: -88.9-66.7) and 47% (96.9% CI: 8.3-82.2), respectively. The difference between the two treatment groups was not significant (p = 0.3114).				⊕⊕○○ Low	CRITICAL

Number of lesions, Any at 12 weeks (median percent reduction from baseline)

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	The median percent reductions from baseline for blue light-ALA and IPL-ALA + RF groups were -88.9% (range: 123.3) and 41.65% (range: 167.5), respectively.				⊕⊕○○ Low	CRITICAL

Patient assessment of improvement, Global, Percentage improvement at 4 weeks

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	The median percent improvements from baseline for blue light-ALA and IPL-ALA + RF groups were 15% (96.9% CI: 0-87.5%) and 20% (96.9% CI: 0-80), respectively. The difference between the two treatment groups was not significant (p = 0.3210).				⊕⊕○○ Low	CRITICAL

CI: Confidence interval

Explanations

a. Limited methods reporting, open label study, and risk of attrition bias (40% dropout)

b. Small sample size

References

1. Taub, A.F., *A comparison of intense pulsed light, combination radiofrequency and intense pulsed light, and blue light in photodynamic therapy for acne vulgaris*. J Drugs Dermatol, 2007. **6**(10): p. 1010-6.

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64. Photodynamic therapy with ALA (Blue Light-ALA) vs. Photodynamic therapy with ALA (IPL-ALA)

e-Table 144. GRADE Evidence Profile for photodynamic therapy with ALA (Blue Light-ALA) vs. photodynamic therapy with ALA (IPL-ALA)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy (blue light) with ALA	Photodynamic therapy with ALA (IPL)	Relative (95% CI)	Absolute (95% CI)		
Investigator assessment of improvement, Percentage improvement at 4 weeks												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	The median percent improvements from baseline for photodynamic therapy with ALA (blue light) and photodynamic therapy with ALA (IPL) groups were 20% (96.9% CI: 0-62.5) and 56.25% (96.9% CI: 27.5-85.0), respectively. The difference between the two treatment groups was not significant.			⊕⊕○○ Low	CRITICAL	
Investigator assessment of improvement, Percentage improvement at 12 weeks												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	The median percent improvements from baseline for photodynamic therapy with ALA (blue light) and photodynamic therapy with ALA (IPL) groups were 25% (range: 40%) and 70% (range: 35%), respectively. The difference between the two treatment groups reached borderline statistical significance (p = 0.0498).			⊕⊕○○ Low	CRITICAL	
Acne severity, Bespoke, 1-4 at 4 weeks (median)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	At baseline, the median acne for photodynamic therapy with ALA (blue light) and photodynamic therapy with ALA (IPL) groups were 3.25 (96.9% CI: 2.5-3.5) and 2.75 (96.9% CI: 2.5-4.0), respectively. At 4 weeks, the median acne grades changed to 1.5 (96.9% CI: 1.0-3.5) and 1.5 (96.9% CI: 1.0-2.5) for photodynamic therapy with ALA (blue light) and photodynamic therapy with ALA (IPL) groups, respectively.			⊕⊕○○ Low	CRITICAL	

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy (blue light) with ALA	Photodynamic therapy with ALA (IPL)	Relative (95% CI)	Absolute (95% CI)		

Acne severity, Bespoke, 1-4 at 12 weeks (median)

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	At baseline, the median acne grades for photodynamic therapy with ALA (blue light) and photodynamic therapy with ALA (IPL) groups were 3.25 (96.9% CI: 2.5-3.5) and 2.75 (96.9% CI: 2.5-4.0), respectively. At 12 weeks, the median acne grades changed to 2.00 (range: 1) and 1.75 (range: 1.5) for photodynamic therapy with ALA (blue light) and photodynamic therapy with ALA (IPL) groups, respectively.			⊕⊕○○ Low	CRITICAL

Number of lesions, Any at 4 weeks (median percent reduction from baseline)

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	A total of 22 patients were randomly divided between three treatment groups, however, the number of patients per treatment arm was not reported. The median percent reductions from baseline for photodynamic therapy with unknown photosensitizer (blue light) and photodynamic therapy with ALA (IPL) groups were 52.8% (96.9% CI: -88.9-66.7) and 76.8% (96.9% CI: 12.5-86.4), respectively. The difference between the two treatment groups was not significant (p = 0.3114).			⊕⊕○○ Low	CRITICAL

Number of lesions, Any at 12 weeks (median percent reduction from baseline)

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	The median percent changes from baseline for photodynamic therapy with ALA (blue light) and photodynamic therapy with ALA (IPL) groups were - 88.9% (range: 123.3) and 73.2% (range: 72.4), respectively.			⊕⊕○○ Low	CRITICAL

Patient assessment of improvement, Global, Percentage improvement at 4 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy (blue light) with ALA	Photodynamic therapy with ALA (IPL)	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	The median percent improvements from baseline for photodynamic therapy with ALA (blue light) and photodynamic therapy with ALA (IPL) groups were 15% (96.9% CI: 0-87.5%) and 58.75% (96.9% CI: 5.0-70.0%), respectively. The difference between the two treatment groups was not significant (p = 0.3210).				⊕⊕○○ Low	CRITICAL

CI: Confidence interval

Explanations

a. Limited methods reporting, open label study, and risk of attrition bias (40% dropout)

b. Small sample size

References

1. Taub, A.F., *A comparison of intense pulsed light, combination radiofrequency and intense pulsed light, and blue light in photodynamic therapy for acne vulgaris*. J Drugs Dermatol, 2007. 6(10): p. 1010-6.

65. Combined 445 nm blue light and 630 nm red light + Salicylic acid 1% with retinol vs. Combined 445 nm blue light and 630 nm red light

e-Table 145. GRADE Evidence Profile for combined 445 nm blue light and 630 nm red light + salicylic acid 1% with retinol vs. combined 445 nm blue light and 630 nm red light

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 445 nm blue light and 630 nm red light + Salicylic acid 1% with retinol	Combined 445 nm blue light and 630 nm red light	Relative (95% CI)	Absolute (95% CI)		

Investigator Global Assessment at 4 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and combined 445-nm blue light and 630-nm red light groups were -7.3% (p = 0.05) and -3.8%, respectively.	⊕⊕⊕○ Moderate	CRITICAL

Investigator Global Assessment at 8 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and combined 445-nm blue light and 630-nm red light groups were -7.2% and -12.4% (p = 0.01), respectively.	⊕⊕⊕○ Moderate	CRITICAL

Investigator Global Assessment at 12 weeks (mean percent change from baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 445 nm blue light and 630 nm red light + Salicylic acid 1% with retinol	Combined 445 nm blue light and 630 nm red light	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and combined 445-nm blue light and 630-nm red light groups were -13.9% (p = 0.01) and -19.0% (p = 0.001), respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any at 4 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and combined 445-nm blue light and 630-nm red light groups were -10.2% and -13.5% (p = 0.01), respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any at 8 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and combined 445-nm blue light and 630-nm red light groups were -12.7% and -19.5% (p = 0.001), respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any at 12 weeks (mean percent change from baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 445 nm blue light and 630 nm red light + Salicylic acid 1% with retinol	Combined 445 nm blue light and 630 nm red light	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and combined 445-nm blue light and 630-nm red light groups were -15.3% and -22.8% (p = 0.01), respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 4 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and combined 445-nm blue light and 630-nm red light groups were -19.5% (p = 0.001) and -15.1% (p = 0.01), respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 8 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and combined 445-nm blue light and 630-nm red light groups were -14.6% (p = 0.05) and -23.9% (p = 0.001), respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 445 nm blue light and 630 nm red light + Salicylic acid 1% with retinol	Combined 445 nm blue light and 630 nm red light	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and combined 445-nm blue light and 630-nm red light groups were -22.7% (p = 0.01) and -24.4% (p = 0.01), respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and combined 445-nm blue light and 630-nm red light groups were -1.9% and -10.9%, respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and combined 445-nm blue light and 630-nm red light groups were -7.8% and -14.6%, respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean percent change from baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 445 nm blue light and 630 nm red light + Salicylic acid 1% with retinol	Combined 445 nm blue light and 630 nm red light	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and combined 445-nm blue light and 630-nm red light groups were -4.8% and -19.5% (p = 0.001), respectively.				⊕⊕⊕○ Moderate	CRITICAL

AE, Any at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	0/35 (0.0%)	0/35 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

CI: Confidence interval

Explanations

a. Small sample size

References

1. Nestor, M.S., et al., *Efficacy and tolerability of a combined 445nm and 630nm over-the-counter light therapy mask with and without topical salicylic acid versus topical benzoyl peroxide for the treatment of mild-to-moderate acne vulgaris*. Journal of Clinical and Aesthetic Dermatology, 2016. **9**(3): p. 25-35.

e-Table 146. GRADE Evidence Profile for narrow band ultraviolet b + erythromycin vs. 633 nm red led light + erythromycin

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Narrow band ultraviolet B + Erythromycin	633 nm red LED light + Erythromycin	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any, <10% reduction at 4 weeks												
1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	1/15 (6.7%)	1/15 (6.7%)	RR 1.00 (0.07 to 14.55)	0 fewer per 1,000 (from 62 fewer to 903 more)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, <10% reduction at 8 weeks												
1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	0/15 (0.0%)	1/15 (6.7%)	RR 0.33 (0.01 to 7.58)	45 fewer per 1,000 (from 66 fewer to 439 more)	⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any, ~25% reduction at 4 weeks												
1 ^{1,b}	randomized trials	not serious	not serious	not serious	serious ^a	none	11/15 (73.3%)	12/15 (80.0%)	RR 0.92 (0.62 to 1.36)	64 fewer per 1,000 (from 304 fewer to 288 more)	⊕⊕⊕○ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Narrow band ultraviolet B + Erythromycin	633 nm red LED light + Erythromycin	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,b}	randomized trials	not serious	not serious	not serious	serious ^a	none	1/15 (6.7%)	8/15 (53.3%)	RR 0.12 (0.02 to 0.88)	469 fewer per 1,000 (from 523 fewer to 64 fewer)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, ~50% reduction at 4 weeks

1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	3/15 (20.0%)	1/15 (6.7%)	RR 3.00 (0.35 to 25.68)	133 more per 1,000 (from 43 fewer to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, ~50% reduction at 8 weeks

1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	6/15 (40.0%)	5/15 (33.3%)	RR 1.20 (0.47 to 3.09)	67 more per 1,000 (from 177 fewer to 697 more)	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any, ~75% reduction at 8 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Narrow band ultraviolet B + Erythromycin	633 nm red LED light + Erythromycin	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	8/15 (53.3%)	1/15 (6.7%)	RR 8.00 (1.14 to 56.33)	467 more per 1,000 (from 9 more to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; RR: Risk ratio

Explanations

- a. Small sample size resulting in a CI that include appreciable benefits and harm
- b. Mild improvement

References

1. Eid, M.M., et al., *Narrow Band Ultraviolet B Versus Red Light-Emitting Diodes in the Treatment of Facial Acne Vulgaris: A Randomized Controlled Trial*. Photobiomodulation, photomedicine, and laser surgery, 2021. **39(6)**: p. 418-424.

Laser/Light/Photodynamic Therapy vs. Other Acne Treatment (Oral or Topical)

67. 407-420 nm blue light vs. Benzoyl peroxide 4%

e-Table 147. GRADE Evidence Profile for 407-420 nm blue light vs. benzoyl peroxide 4%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	407-420 nm blue light	Benzoyl peroxide 4%	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any at 4 weeks (mean)												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	62	62	-	MD 1.24 lesions higher (2.21 lower to 4.69 higher)	⊕⊕○○ Low	CRITICAL
Number of lesions, Any at 8 weeks (mean)												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^c	none	62	62	-	MD 4.01 lesions lower (6.67 lower to 1.35 lower)	⊕⊕○○ Low	CRITICAL
Number of lesions, Any at 12 weeks (mean)												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^c	none	62	62	-	MD 4.89 lesions lower (7.69 lower to 2.09 lower)	⊕⊕⊕○ Low	CRITICAL

AE, Burning and irritation at 4 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	407-420 nm blue light	Benzoyl peroxide 4%	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^c	none	0/62 (0.0%)	34/62 (54.8%)	RR 0.01 (0.00 to 0.23)	543 fewer per 1,000 (from 422 fewer to -)	⊕⊕○○ Low	IMPORTANT

AE, Burning and irritation at 8 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^c	none	0/62 (0.0%)	6/62 (9.7%)	RR 0.08 (0.00 to 1.34)	89 fewer per 1,000 (from – to 33 more)	⊕⊕○○ Low	IMPORTANT

AE, Burning and irritation at 12 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^c	none	0/62 (0.0%)	0/62 (0.0%)	not estimable		⊕⊕○○ Low	IMPORTANT

AE, Erythema at 4 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^c	none	5/62 (8.1%)	27/62 (43.5%)	RR 0.19 (0.08 to 0.45)	353 fewer per 1,000 (from 401 fewer to 240 fewer)	⊕⊕○○ Low	IMPORTANT

AE, Erythema at 8 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	407-420 nm blue light	Benzoyl peroxide 4%	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^c	none	0/62 (0.0%)	11/62 (17.7%)	RR 0.04 (0.00 to 0.72)	170 fewer per 1,000 (from 50 fewer to -)	⊕⊕○○ Low	IMPORTANT

AE, Erythema at 12 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	0/62 (0.0%)	5/62 (8.1%)	RR 0.09 (0.01 to 1.61)	73 fewer per 1,000 (from 80 fewer to 49 more)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; MD: mean difference; RR: Risk ratio

Explanations

a. Limited methods reporting and unblinded patients

b. CI includes both appreciable benefits and harm

c. Small sample size

References

- Cheema, A.N., et al., *Efficacy and safety of blue light versus 4% topical benzoyl peroxide in mild to moderate acne*. Journal of Pakistan Association of Dermatologists, 2018. **28(1)**: p. 79-84.

e-Table 148. GRADE Evidence Profile for intense pulsed light vs. benzoyl peroxide 5%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intense pulsed light	Benzoyl peroxide 5%	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Hayashi, No acne at 5 weeks (Mild acne subgroup)												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	1/3 (33.3%)	1/3 (33.3%)	RR 1.00 (0.10 to 9.61)	0 fewer per 1,000 (from 300 fewer to 1,000 more)	⊕⊕○○ Low	CRITICAL
Acne severity, Hayashi, Mild acne at 5 weeks (Mild acne subgroup)												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	2/3 (66.7%)	2/3 (66.7%)	RR 1.00 (0.32 to 3.10)	0 fewer per 1,000 (from 453 fewer to 1,000 more)	⊕⊕○○ Low	CRITICAL
Acne severity, Hayashi, Moderate acne at 5 weeks (Mild acne subgroup)												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	0/3 (0.0%)	0/3 (0.0%)	not estimable		⊕⊕○○ Low	CRITICAL
Acne severity, Hayashi, Severe acne at 5 weeks (Mild acne subgroup)												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	0/3 (0.0%)	0/3 (0.0%)	not estimable		⊕⊕○○ Low	CRITICAL
Acne severity, Hayashi, No acne at 5 weeks (Moderate acne subgroup)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intense pulsed light	Benzoyl peroxide 5%	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	0/16 (0.0%)	0/16 (0.0%)	not estimable		⊕⊕○○ Low	CRITICAL

Acne severity, Hayashi, Mild acne at 5 weeks (Moderate acne subgroup)

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	10/16 (62.5%)	16/16 (100.0%)	not estimable		⊕⊕○○ Low	CRITICAL

Acne severity, Hayashi, Moderate acne at 5 weeks (Moderate acne subgroup)

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	5/16 (31.3%)	0/16 (0.0%)	not estimable		⊕⊕○○ Low	CRITICAL

Acne severity, Hayashi, Severe acne at 5 weeks (Moderate acne subgroup)

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	1/16 (6.3%)	0/16 (0.0%)	not estimable		⊕⊕○○ Low	CRITICAL

Acne severity, Hayashi, No acne at 5 weeks (Severe acne subgroup)

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	0/6 (0.0%)	0/6 (0.0%)	not estimable		⊕⊕○○ Low	CRITICAL

Acne severity, Hayashi, Mild acne at 5 weeks (Severe acne subgroup)

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	3/6 (50.0%)	5/6 (83.3%)	RR 0.60 (0.25 to 1.44)	333 fewer per 1,000 (from 625 fewer to 367 more)	⊕⊕○○ Low	CRITICAL

Acne severity, Hayashi, Moderate acne at 5 weeks (Severe acne subgroup)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intense pulsed light	Benzoyl peroxide 5%	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	3/6 (50.0%)	1/6 (16.7%)	RR 3.00 (0.42 to 21.30)	333 more per 1,000 (from 97 fewer to 1,000 more)	⊕⊕○○ Low	CRITICAL

Acne severity, Hayashi, Severe acne at 5 weeks (Severe acne subgroup)

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	0/6 (0.0%)	0/6 (0.0%)	not estimable		⊕⊕○○ Low	CRITICAL

Number of lesions, Any at 5 weeks (mean percent change from baseline)

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	25	25	-	MD 7.84 % lower (21.32 lower to 5.64 higher)	⊕⊕○○ Low	CRITICAL

Patient assessment of improvement, Global, None at 5 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	1/25 (4.0%)	0/25 (0.0%)	not estimable		⊕⊕○○ Low	CRITICAL

Patient assessment of improvement, Global, Fair at 5 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	6/25 (24.0%)	3/25 (12.0%)	RR 2.00 (0.56 to 7.12)	120 more per 1,000 (from 53 fewer to 734 more)	⊕⊕○○ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intense pulsed light	Benzoyl peroxide 5%	Relative (95% CI)	Absolute (95% CI)		

Patient assessment of improvement, Global, Good at 5 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	24/25 (96.0%)	13/25 (52.0%)	RR 1.85 (1.26 to 2.71)	442 more per 1,000 (from 135 more to 889 more)	⊕⊕○○ Low	CRITICAL

Patient assessment of improvement, Global, Excellent at 5 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	17/25 (68.0%)	9/25 (36.0%)	RR 1.89 (1.05 to 3.40)	320 more per 1,000 (from 18 more to 864 more)	⊕⊕○○ Low	CRITICAL

Patient assessment of improvement, Global, Worse at 5 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	2/25 (8.0%)	0/25 (0.0%)	not estimable		⊕⊕○○ Low	CRITICAL

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

- a. Limited methods reporting and open label study
- b. Small sample size
- c. CI includes appreciable benefits and harm

References

1. El-Latif, A.A., et al., *Intense pulsed light versus benzoyl peroxide 5% gel in treatment of acne vulgaris*. Lasers in Medical Science, 2014. **29**(3): p. 1009-15.

e-Table 149. GRADE Evidence Profile for isotretinoin vs. 405-420 nm blue light

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isotretinoin	405-420 nm blue light	Relative (95% CI)	Absolute (95% CI)		
Investigator assessment of improvement, Bespoke, No change at 24 weeks (5-point scale)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^{c,d}	none	2/30 (6.7%)	2/30 (6.7%)	RR 1.00 (0.15 to 6.64)	0 fewer per 1,000 (from 57 fewer to 376 more)	⊕⊕○○ Low	CRITICAL
Investigator assessment of improvement, Bespoke, Resolved at 24 weeks (5-point scale)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^{c,d}	none	6/30 (20.0%)	4/30 (13.3%)	RR 1.50 (0.47 to 4.78)	67 more per 1,000 (from 71 fewer to 504 more)	⊕⊕○○ Low	CRITICAL
Investigator assessment of improvement, Bespoke, Improvement at 24 weeks (5-point scale)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^{c,d}	none	3/30 (10.0%)	5/30 (16.7%)	RR 0.60 (0.16 to 2.29)	67 fewer per 1,000 (from 140 fewer to 215 more)	⊕⊕○○ Low	CRITICAL

Investigator assessment of improvement, Bespoke, Marked at 24 weeks (5-point scale)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isotretinoin	405-420 nm blue light	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^{c,d}	none	14/30 (46.7%)	16/30 (53.3%)	RR 0.88 (0.53 to 1.45)	64 fewer per 1,000 (from 251 fewer to 240 more)	⊕⊕○○ Low	CRITICAL

CI: Confidence interval; RR: Risk ratio

Explanations

- a. Investigator's global improvement rating on a five-point scale (-1=worsened, 0=unchanged, 1=improved, 2=markedly improved, and 3=resolved). On the IGA scale.
b. Limited methods reporting and open label study
c. Small sample size
d. CI includes both appreciable benefits and harm

References

1. Elgendy, A., et al., *Blue light therapy versus low dose isotretinoin in mild to moderate acne*. Global Dermatology, 2015. 2(3).

e-Table 150. GRADE Evidence Profile for tretinoin 0.1% + benzoyl peroxide 5% vs. pulsed dye laser

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tretinoin 0.1% + Benzoyl peroxide 5%	Pulsed dye laser	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Leeds at 12 weeks (mean)												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	At baseline, the mean values of acne severity score for tretinoin 0.1% + benzoyl peroxide 5% and pulsed dye laser groups were 2.02 (SD: 1.01) and 1.67 (SD: 0.93), respectively. At 12 weeks, the mean values decreased to 0.65 (SD: 0.47) and 0.56 (SD: 0.57) for tretinoin 0.1% + benzoyl peroxide 5% and pulsed dye laser groups, respectively. The difference between the two treatment groups was not significant.			⊕⊕○○ Low	CRITICAL	
Number of lesions, Any, >75% reduction at 12 weeks												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	5/13 (38.5%)	6/13 (46.2%)	RR 0.83 (0.34 to 2.06)	78 fewer per 1,000 (from 305 fewer to 489 more)	⊕⊕○○ Low	CRITICAL

Number of lesions, Any, 50-75% reduction at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tretinoin 0.1% + Benzoyl peroxide 5%	Pulsed dye laser	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	8/13 (61.5%)	7/13 (53.8%)	RR 1.14 (0.59 to 2.22)	75 more per 1,000 (from 221 fewer to 657 more)	⊕⊕○○ Low	CRITICAL

AE, Any, Mild at 12 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	6/13 (46.2%)	5/13 (38.5%)	RR 1.20 (0.49 to 2.96)	77 more per 1,000 (from 196 fewer to 754 more)	⊕⊕○○ Low	IMPORTANT

AE, Any, Moderate at 12 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	2/13 (15.4%)	3/13 (23.1%)	RR 0.67 (0.13 to 3.35)	76 fewer per 1,000 (from 201 fewer to 542 more)	⊕⊕○○ Low	IMPORTANT

AE, Any, Trace at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tretinoin 0.1% + Benzoyl peroxide 5%	Pulsed dye laser	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	5/13 (38.5%)	5/13 (38.5%)	RR 1.00 (0.38 to 2.64)	0 fewer per 1,000 (from 238 fewer to 631 more)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

a. Limited methods reporting and unblinded patients

b. Small sample size and wide CI including appreciable benefits and harm

References

1. Leheta, T.M., *Role of the 585-nm pulsed dye laser in the treatment of acne in comparison with other topical therapeutic modalities*. J Cosmet Laser Ther, 2009. **11**(2): p. 118-24.

e-Table 151. GRADE Evidence Profile for combined 445 nm blue light and 630 nm red light vs. benzoyl peroxide 2.5%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 445 nm blue light and 630 nm red light	Benzoyl peroxide 2.5%	Relative (95% CI)	Absolute (95% CI)		
Investigator Global Assessment at 4 weeks (mean percent change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light and benzoyl peroxide 2.5% groups were -3.8% and -3.4%, respectively.				⊕⊕⊕○ Moderate	CRITICAL
Investigator Global Assessment at 8 weeks (mean percent change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light and benzoyl peroxide 2.5% groups were -12.4% (p = 0.01) and -7.5% (p = 0.05), respectively.				⊕⊕⊕○ Moderate	CRITICAL
Investigator Global Assessment at 12 weeks (mean percent change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light and benzoyl peroxide 2.5% groups were -19.0% (p = 0.001) and -4.7%, respectively.				⊕⊕⊕○ Moderate	CRITICAL
Number of lesions, Any at 4 weeks (mean percent change from baseline)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light and benzoyl peroxide 2.5% groups were -13.5% (p = 0.01) and -9.8% (p = 0.01), respectively.				⊕⊕⊕○ Moderate	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 445 nm blue light and 630 nm red light	Benzoyl peroxide 2.5%	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Any at 8 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light and benzoyl peroxide 2.5% groups were -19.5% (p = 0.001) and -14.46% (p = 0.001), respectively.		⊕⊕⊕○ Moderate		CRITICAL

Number of lesions, Any at 12 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light and benzoyl peroxide 2.5% groups were -22.8% (p = 0.01) and -11.4% (p = 0.05), respectively.		⊕⊕⊕○ Moderate		CRITICAL

Number of lesions, Inflammatory at 4 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light and benzoyl peroxide 2.5% groups were -15.1% (p = 0.01) and -11%, respectively.		⊕⊕⊕○ Moderate		CRITICAL

Number of lesions, Inflammatory at 8 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light and benzoyl peroxide 2.5% groups were -23.9% (p = 0.001) and -19.1% (p = 0.01), respectively.		⊕⊕⊕○ Moderate		CRITICAL

Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 445 nm blue light and 630 nm red light	Benzoyl peroxide 2.5%	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light and benzoyl peroxide 2.5% groups were -24.4% (p = 0.01) and -17.2% (p = 0.05), respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light and benzoyl peroxide 2.5% groups were -10.9% and -4.3%, respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light and benzoyl peroxide 2.5% groups were -14.6% and -7.6%, respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light and benzoyl peroxide 2.5% groups were -19.5% (p = 0.001) and -6.3%, respectively.				⊕⊕⊕○ Moderate	CRITICAL

AE, Any at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	0/35 (0.0%)	0/35 (0.0%)	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

CI: Confidence interval

Explanations

a. Small sample size

References

1. Nestor, M.S., et al., *Efficacy and tolerability of a combined 445nm and 630nm over-the-counter light therapy mask with and without topical salicylic acid versus topical benzoyl peroxide for the treatment of mild-to-moderate acne vulgaris*. Journal of Clinical and Aesthetic Dermatology, 2016. **9(3)**: p. 25-35.

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72. Combined 445 nm blue light and 630 nm red light+ Salicylic acid 1% with retinol vs. Benzoyl peroxide 2.5%

e-Table 152. GRADE Evidence Profile for combined 445 nm blue light and 630 nm red light+ salicylic acid 1% with retinol vs. benzoyl peroxide 2.5%

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 445 nm blue light and 630 nm red light + Salicylic acid 1% with retinol	Benzoyl peroxide 2.5%	Relative (95% CI)	Absolute (95% CI)		

Investigator Global Assessment at 4 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and benzoyl peroxide 2.5% groups were -7.3% (p = 0.05) and -3.4%, respectively.	⊕⊕⊕○ Moderate	CRITICAL

Investigator Global Assessment at 8 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and benzoyl peroxide 2.5% groups were -7.2% and -7.5% (p = 0.05), respectively.	⊕⊕⊕○ Moderate	CRITICAL

Investigator Global Assessment at 12 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and benzoyl peroxide 2.5% groups were -13.9% (p = 0.01) and -4.7%, respectively.	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any at 4 weeks (mean percent change from baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 445 nm blue light and 630 nm red light + Salicylic acid 1% with retinol	Benzoyl peroxide 2.5%	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and benzoyl peroxide 2.5% groups were -10.2% and -9.8% (p = 0.01), respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any at 8 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and benzoyl peroxide 2.5% groups were -12.7% and -14.46% (p = 0.01), respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Any at 12 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and benzoyl peroxide 2.5% groups were -15.3% and -11.4% (p = 0.05), respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 4 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and benzoyl peroxide 2.5% groups were -19.5% (p = 0.001) and -11%, respectively.				⊕⊕⊕○ Moderate	CRITICAL

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 445 nm blue light and 630 nm red light + Salicylic acid 1% with retinol	Benzoyl peroxide 2.5%	Relative (95% CI)	Absolute (95% CI)		

Number of lesions, Inflammatory at 8 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and benzoyl peroxide 2.5% groups were -14.6% (p = 0.05) and -19.1% (p = 0.01), respectively.	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and benzoyl peroxide 2.5% groups were -22.7% (p = 0.01) and -17.2% (p = 0.05), respectively.	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and benzoyl peroxide 2.5% groups were -1.9% and -4.3%, respectively.	⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (mean percent change from baseline)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combined 445 nm blue light and 630 nm red light + Salicylic acid 1% with retinol	Benzoyl peroxide 2.5%	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and benzoyl peroxide 2.5% groups were -7.8% and -7.6%, respectively.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean percent change from baseline)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	The mean percentage changes from baseline for combined 445-nm blue light and 630 -nm red light + salicylic acid 1% with retinol and benzoyl peroxide 2.5% groups were -4.8% and -6.3%, respectively.				⊕⊕⊕○ Moderate	CRITICAL

AE, Any at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	0/35 (0.0%)	0/35 (0.0%)	not estimable		⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval

Explanations

a. Small sample size

References

1. Nestor, M.S., et al., *Efficacy and tolerability of a combined 445nm and 630nm over-the-counter light therapy mask with and without topical salicylic acid versus topical benzoyl peroxide for the treatment of mild-to-moderate acne vulgaris*. Journal of Clinical and Aesthetic Dermatology, 2016. **9(3)**: p. 25-35.

Extraction vs. Other Acne Agent

73. Acne lesion extraction vs. Doxycycline

e-Table 153. GRADE Evidence Profile for acne lesion extraction vs. doxycycline

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acne lesion extraction	Doxycycline	Relative (95% CI)	Absolute (95% CI)		
Improvement of acne lesions at 4 weeks												
1 ¹	randomized trials	not serious	not serious	not serious	serious ^a	none	70 and 70 patients were randomized to receive acne lesion extraction or doxycycline, respectively. At 4 weeks, the improvement of acne lesions for acne lesion extraction and doxycycline groups was reported in 34% and 48% of patients, respectively. The difference between the two treatments was not significant (p = 0.063).				⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval

Explanations

Small sample size

References

1. Sitohang, I.B.S., R.W. Soebaryo, and M. Kanoko, *Acne Lesion Extraction versus Oral Doxycycline for Moderate Acne Vulgaris: A Randomized Clinical Trial*. J Clin Aesthet Dermatol, 2021. **14**(6): p. E61-E65.

Others

74. Glycolic acid 70% + Salicylic acid 20% + Doxycycline vs. Glycolic acid 70% + Salicylic acid 20%

e-Table 154. GRADE Evidence Profile for glycolic acid 70% + salicylic acid 20% + doxycycline vs. glycolic acid 70% + salicylic acid 20%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glycolic acid 70% + Salicylic acid 20% + Doxycycline	Glycolic acid 70% + Salicylic acid 20%	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Bespoke, Unknown scale at 12 weeks (median)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	15 and 15 patients were randomized to receive glycolic acid 70% + salicylic acid 20% + doxycycline and glycolic acid 70% + salicylic acid 20%, respectively. At baseline, the median values of acne severity for glycolic acid 70% + salicylic acid 20% and doxycycline groups were 2 (range: 2-4) and 2 (range: 2-4), respectively. At 12 weeks, the median values changed to 2 (range: 0-2, n: 13) and 2 (range: 0-2, n: 14) for glycolic acid 70% + salicylic acid 20% + doxycycline and glycolic acid 70% + salicylic acid 20% groups, respectively. The difference between the two treatment groups was not significant. ^b			⊕⊕⊕○ Moderate	CRITICAL	

Number of lesions, Any at 12 weeks (median)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glycolic acid 70% + Salicylic acid 20% + Doxycycline	Glycolic acid 70% + Salicylic acid 20%	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	At baseline, the median number of lesions for glycolic acid 70% + salicylic acid 20% + doxycycline and glycolic acid 70% + salicylic acid 20% groups was 23 (range: 8-40) and 17 (range: 10-38), respectively. At 12 weeks, the median values changed to 2 (range: 0-7, n: 13) and 2 (range: 0-6, n: 14) for glycolic acid 70% + salicylic acid 20% + doxycycline and glycolic acid 70% + salicylic acid 20% groups, respectively. The difference between the two treatment groups was not significant.				⊕⊕⊕○ Moderate	CRITICAL

Patient assessment of improvement, Global, VAS (1-4) at 12 weeks (median)

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	At baseline, the median values of patient satisfaction for glycolic acid 70% + salicylic acid 20% + doxycycline and glycolic acid 70% + salicylic acid 20% groups were 2 (range: 1-3) and 2 (range: 1-3), respectively. At 12 weeks, the median values changed to 4 (range: 3-4, n: 13) and 4 (range: 3-4, n: 14) for glycolic acid 70% + salicylic acid 20% + doxycycline and glycolic acid 70% + salicylic acid 20% groups, respectively.			⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval

Explanations

a. Small sample size

b. n: number of patients at the follow-up.

References

1. Zayed, A.A., et al., *Sequential peeling as a monotherapy for treatment of milder forms of acne vulgaris*. Journal of Cosmetic Dermatology, 2020. **19**(6): p. 1381-1387.

e-Table 155. GRADE Evidence Profile for fractional microneedle radiofrequency vs. 1450 nm diode laser

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fractional microneedle radiofrequency	1450 nm diode laser	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Leeds at 4 weeks (mean)												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	At baseline, the mean values of Leeds revised acne grade for fractional microneedle radiofrequency and 1450-nm diode laser sides were 4.5 and 4.3, respectively. At 4 weeks, the mean decreased to 3.89 and 4.09 for fractional microneedle radiofrequency and 1450-nm diode laser sides, respectively. The difference between the two treatment groups was not significant.			⊕⊕⊕○ Moderate	CRITICAL	
Acne severity, Leeds at 8 weeks (mean)												
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	At baseline, the mean values of Leeds revised acne grade for fractional microneedle radiofrequency and 1450-nm diode laser sides were 4.5 and 4.3, respectively. At 8 weeks, the mean decreased to 2.88 and 3.19 for fractional microneedle radiofrequency and 1450-nm diode laser sides, respectively. The difference between the two treatment groups was not significant.			⊕⊕⊕○ Moderate	CRITICAL	

Acne severity, Leeds at 12 weeks (mean)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fractional microneedle radiofrequency	1450 nm diode laser	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	At baseline, the mean values of Leeds revised acne grade for fractional microneedle radiofrequency and 1450-nm diode laser sides were 4.5 and 4.3, respectively. At 8 weeks, the mean decreased to 2.29 and 2.61 for fractional microneedle radiofrequency and 1450-nm diode laser sides, respectively. The difference between the two treatment groups was not significant.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 4 weeks (mean percent of baseline)

1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of inflammatory lesions in the fractional microneedle radiofrequency and 1450-nm diode laser sides was 84.16% and 88.06%, respectively. The difference between the two treatment groups was not significant.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 8 weeks (mean percent of baseline)

1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of inflammatory lesions in the fractional microneedle radiofrequency and 1450-nm diode laser sides was 61.89% and 69.69%, respectively. The difference between the two treatment groups was not significant.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Inflammatory at 12 weeks (mean percent of baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fractional microneedle radiofrequency	1450 nm diode laser	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of inflammatory lesions in the fractional microneedle radiofrequency and 1450-nm diode laser sides was 46.44% and 53.76%, respectively. The difference between the two treatment groups was not significant.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 4 weeks (mean percent of baseline)

1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of inflammatory lesions in the fractional microneedle radiofrequency and 1450-nm diode laser sides was 92.13% and 96.85%, respectively. The difference between the two treatment groups was not significant.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 8 weeks (mean percent of baseline)

1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of inflammatory lesions in the fractional microneedle radiofrequency and 1450-nm diode laser sides was 75.12% and 79.84%, respectively. The difference between the two treatment groups was not significant.				⊕⊕⊕○ Moderate	CRITICAL

Number of lesions, Non-inflammatory at 12 weeks (mean percent of baseline)

1 ^{1,a}	randomized trials	not serious	not serious	not serious	serious ^b	none	The mean percent of baseline of inflammatory lesions in the fractional microneedle radiofrequency and 1450-nm diode laser sides was 66.61% and 72.76%, respectively. The difference between the two treatment groups was not significant.				⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval

Explanations

- a. RCT, Split face
- b. Small sample size and no CIs or p-values provided

References

1. Kwon, H.H., et al., *Novel device-based acne treatments: comparison of a 1450-nm diode laser and microneedling radiofrequency on mild-to-moderate acne vulgaris and seborrhoea in Korean patients through a 20-week prospective, randomized, split-face study*. Journal of the European Academy of Dermatology and Venereology, 2018. **32(4)**: p. 639-644.

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e-Table 156. GRADE Evidence Profile for fractional microneedle radiofrequency vs. 10600 nm CO2 fractional laser

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fractional microneedle radiofrequency	10600 nm CO2 fractional laser	Relative (95% CI)	Absolute (95% CI)		
Investigator assessment of improvement, Bespoke, 0-4 (3 months after the last operation)												
1 1,a	randomized trials	serious ^b	not serious	not serious	serious ^c	none	20	20	-	MD 0.43 higher (0.13 higher to 0.73 higher)	⊕⊕○○ Low	CRITICAL
Number of lesions, Inflammatory, Papules (3 months after the last operation, mean percent reduction from baseline)												
1 1,a	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage reduction from baseline for fractional microneedle radiofrequency and 10600-nm CO2 fractional laser sides were 49% and 54%, respectively. The difference between the two treatments was not significant.				⊕⊕○○ Low	CRITICAL
Number of lesions, Inflammatory, Pustules (3 months after the last operation, mean percent reduction from baseline)												
1 1,a	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage reduction from baseline for fractional microneedle radiofrequency and 10600-nm CO2 fractional laser sides were 36% and 41%, respectively. The difference between the two treatments was not significant.				⊕⊕○○ Low	CRITICAL

AE, Hyperpigmentation (3 months after the last operation)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fractional microneedle radiofrequency	10600 nm CO2 fractional laser	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^{c,d}	none	0/20 (0.0%)	2/20 (10.0%)	OR 0.18 (0.01 to 6.16)	80 fewer per 1,000 (from 99 fewer to 306 more)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

Explanations

- a. RCT, Split face
- b. Limited methods reporting and unblinded patients
- c. Small sample size
- d. CI includes appreciable benefits and harm

References

1. Shin, J.U., et al., *A split-face comparison of a fractional microneedle radiofrequency device and fractional carbon dioxide laser therapy in acne patients*. J Cosmet Laser Ther, 2012. **14**(5): p. 212-7.

e-Table 157. GRADE Evidence Profile for 1450 nm diode laser + dermabrasion vs. 1450 nm diode laser

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1450 nm diode laser + dermabrasion	1450 nm diode laser	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any at 3 weeks (mean percent change from baseline)												
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	20 patients were randomized to receive 1450-nm diode laser + dermabrasion on half of the face and 1450-nm diode laser on the other half. The mean percentage changes from baseline for 1450-nm diode laser + dermabrasion and 1450-nm diode laser sides were -55.6% and -53.5%, respectively. The difference between the two treatments was not significant (p = 0.96).		⊕⊕○○ Low		CRITICAL	
Number of lesions, Any at 12 weeks (mean percent change from baseline)												
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	The mean percentage changes from baseline for 1450-nm diode laser + dermabrasion and 1450-nm diode laser sides were -54.4% and -61.1%, respectively. The difference between the two treatments was not significant (p = 0.28).		⊕⊕○○ Low		CRITICAL	
AE, Blister at 12 weeks												
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	0/19 (0.0%)	0/19 (0.0%)	not estimable		⊕⊕○○ Low	CRITICAL

AE, Edema at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1450 nm diode laser + dermabrasion	1450 nm diode laser	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^{c,d}	none	9/19 (47.4%)	8/19 (42.1%)	OR 1.24 (0.15 to 10.29)	53 more per 1,000 (from 323 fewer to 461 more)	⊕⊕○○ Low	IMPORTANT

AE, Edema, Mild at 12 weeks

1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^{c,d}	none	9/19 (47.4%)	8/19 (42.1%)	OR 1.24 (0.15 to 10.29)	53 more per 1,000 (from 323 fewer to 461 more)	⊕⊕○○ Low	IMPORTANT

AE, Erythema at 12 weeks

1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^c	none	19/19 (100.0%)	19/19 (100.0%)	not estimable		⊕⊕○○ Low	IMPORTANT

AE, Erythema, Mild at 12 weeks

1 ^{1,a}	randomised trials	serious ^b	not serious	not serious	serious ^{c,d}	none	15/19 (78.9%)	15/19 (78.9%)	OR 1.00 (0.10 to 9.95)	0 fewer per 1,000 (from 517 fewer to 184 more)	⊕⊕○○ Low	IMPORTANT

AE, Erythema, Moderate at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1450 nm diode laser + dermabrasion	1450 nm diode laser	Relative (95% CI)	Absolute (95% CI)		
11, ^a	randomised trials	serious ^b	not serious	not serious	serious ^{c,d}	none	3/19 (15.8%)	3/19 (15.8%)	OR 1.00 (0.09 to 11.32)	0 fewer per 1,000 (from 141 fewer to 522 more)	⊕⊕○○ Low	IMPORTANT

AE, Papules at 12 weeks

11, ^a	randomised trials	serious ^b	not serious	not serious	serious ^{c,d}	none	2/19 (10.5%)	2/19 (10.5%)	OR 1.00 (0.07 to 14.47)	0 fewer per 1,000 (from 97 fewer to 525 more)	⊕⊕○○ Low	IMPORTANT

AE, Papules, Mild at 12 weeks

11, ^a	randomised trials	serious ^b	not serious	not serious	serious ^{c,d}	none	2/19 (10.5%)	2/19 (10.5%)	OR 1.00 (0.07 to 14.47)	0 fewer per 1,000 (from 97 fewer to 525 more)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; OR: Odds ratio

Explanations

- a. RCT, Split face
- b. limited methods reporting and unblinded patients
- c. Small sample size
- d. CI includes appreciable benefits and harm

References

1. Wang, S.Q., et al., *Treatment of Inflammatory Facial Acne with the 1,450 nm Diode Laser Alone versus Microdermabrasion Plus the 1,450 nm Laser: A Randomized, Split-Face Trial*. Dermatologic Surgery, 2006. **32**(2): p. 249-255.

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78. Benzoyl peroxide 5% + Intense pulsed light vs. Adapalene 0.1% + Intense pulsed light

e-Table 158. GRADE Evidence Profile for benzoyl peroxide 5% + intense pulsed light vs. adapalene 0.1% + intense pulsed light

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzoyl peroxide 5% + Intense pulsed light	Adapalene 0.1% + Intense pulsed light	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Acne Global Severity Scale at 4 weeks (mean)												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	29	29	-	MD 0.17 lower (0.58 lower to 0.24 higher)	⊕⊕○○ Low	CRITICAL
Acne severity, Acne Global Severity Scale at 8 weeks (mean)												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	29	29	-	MD 0.56 lower (1.01 lower to 0.11 lower)	⊕⊕○○ Low	CRITICAL
Acne severity, Acne Severity Index at 4 weeks (mean)												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	29	29	-	MD 0.52 higher (7.23 lower to 8.27 higher)	⊕⊕○○ Low	CRITICAL
Acne severity, Acne Severity Index at 8 weeks (mean)												

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzoyl peroxide 5% + Intense pulsed light	Adapalene 0.1% + Intense pulsed light	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	29	29	-	MD 3.5 lower (9.73 lower to 2.73 higher)	⊕⊕○○ Low	CRITICAL

Number of lesions, Any at 4 weeks (mean)

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	29	29	-	MD 0.11 lesions lower (6.9 lower to 6.68 higher)	⊕⊕○○ Low	CRITICAL

Number of lesions, Any at 8 weeks (mean)

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	29	29	-	MD 3.59 lesions lower (9.16 lower to 1.98 higher)	⊕⊕○○ Low	CRITICAL

CI: Confidence interval; MD: Mean difference

Explanations

- a. Unclear allocation concealment and open label study
- b. Small sample size

c. CI includes appreciable benefits and harm

References

1. Mokhtari, F., et al., *Efficacy of Intense-pulsed Light Therapy with Topical Benzoyl Peroxide 5% versus Benzoyl Peroxide 5% Alone in Mild-to-moderate Acne Vulgaris: A Randomized Controlled Trial*. Journal of Research in Pharmacy Practice, 2017. 6(4): p. 199-205.

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e-Table 159. GRADE Evidence Profile for photodynamic therapy with ala 5% + isotretinoin vs. photodynamic therapy with ala 5%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 5% + Isotretinoin	Photodynamic therapy with ALA 5%	Relative (95% CI)	Absolute (95% CI)		
Number of lesions, Any, <30% reduction at 4 weeks												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	5/35 (14.3%)	10/35 (28.6%)	RR 0.50 (0.19 to 1.31)	143 fewer per 1,000 (from 231 fewer to 89 more)	⊕⊕○ ○ Low	CRITICAL
Number of lesions, Any, <30% reduction at 8 weeks												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	0/35 (0.0%)	0/35 (0.0%)	not estimable		⊕⊕○ ○ Low	CRITICAL
Number of lesions, Any, <30% reduction at 12 weeks												
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	0/34 (0.0%)	0/33 (0.0%)	not estimable		⊕⊕○ ○ Low	CRITICAL

Number of lesions, Any, 30-59% reduction at 4 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 5% + Isotretinoin	Photodynamic therapy with ALA 5%	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	serious _a	not serious	not serious	serious ^{b,c}	none	20/35 (57.1%)	17/35 (48.6%)	RR 1.18 (0.75 to 1.84)	87 more per 1,000 (from 121 fewer to 408 more)	⊕⊕○ ○ Low	CRITICAL

Number of lesions, Any, 30-59% reduction at 8 weeks

1 ¹	randomized trials	serious _a	not serious	not serious	serious ^{b,c}	none	4/35 (11.4%)	9/35 (25.7%)	RR 0.44 (0.15 to 1.31)	144 fewer per 1,000 (from 219 fewer to 80 more)	⊕⊕○ ○ Low	CRITICAL

Number of lesions, Any, 30-59% reduction at 12 weeks

1 ¹	randomized trials	serious _a	not serious	not serious	serious ^{b,c}	none	2/34 (5.9%)	7/33 (21.2%)	RR 0.28 (0.06 to 1.24)	153 fewer per 1,000 (from 199 fewer to 51 more)	⊕⊕○ ○ Low	CRITICAL

Number of lesions, Any, >=60% reduction at 4 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 5% + Isotretinoin	Photodynamic therapy with ALA 5%	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	10/35 (28.6%)	8/35 (22.9%)	RR 1.25 (0.56 to 2.79)	57 more per 1,000 (from 101 fewer to 409 more)	⊕⊕○ ○ Low	CRITICAL

Number of lesions, Any, ≥60% reduction at 8 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	31/35 (88.6%)	26/35 (74.3%)	RR 1.19 (0.95 to 1.50)	141 more per 1,000 (from 37 fewer to 371 more)	⊕⊕○ ○ Low	CRITICAL

Number of lesions, Any, ≥60% reduction at 12 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	31/34 (91.2%)	26/33 (78.8%)	RR 1.16 (0.94 to 1.42)	126 more per 1,000 (from 47 fewer to 331 more)	⊕⊕○ ○ Low	CRITICAL

Number of lesions, Any, 60-89% reduction at 4 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 5% + Isotretinoin	Photodynamic therapy with ALA 5%	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	10/35 (28.6%)	8/35 (22.9%)	RR 1.25 (0.56 to 2.79)	57 more per 1,000 (from 101 fewer to 409 more)	⊕⊕○ ○ Low	CRITICAL

Number of lesions, Any, 60-89% reduction at 8 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	13/35 (37.1%)	16/35 (45.7%)	RR 0.81 (0.46 to 1.43)	87 fewer per 1,000 (from 247 fewer to 197 more)	⊕⊕○ ○ Low	CRITICAL

Number of lesions, Any, 60-89% reduction at 12 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	4/34 (11.8%)	9/33 (27.3%)	RR 0.43 (0.15 to 1.27)	155 fewer per 1,000 (from 232 fewer to 74 more)	⊕⊕○ ○ Low	CRITICAL

Number of lesions, Any, >=90% reduction at 4 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 5% + Isotretinoin	Photodynamic therapy with ALA 5%	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	0/35 (0.0%)	0/35 (0.0%)	not estimable		⊕⊕○ ○ Low	CRITICAL

Number of lesions, Any, >=90% reduction at 8 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^b	none	19/35 (54.3%)	10/35 (28.6%)	RR 1.90 (1.04 to 3.48)	257 more per 1,000 (from 11 more to 709 more)	⊕⊕○ ○ Low	CRITICAL

Number of lesions, Any, >=90% reduction at 12 weeks

1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	28/34 (82.4%)	17/33 (51.5%)	RR 1.60 (1.11 to 2.30)	309 more per 1,000 (from 57 more to 670 more)	⊕⊕○ ○ Low	CRITICAL

Acne reoccurrence at 24 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Photodynamic therapy with ALA 5% + Isotretinoin	Photodynamic therapy with ALA 5%	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomized trials	serious ^a	not serious	not serious	serious ^{b,c}	none	2/28 (7.1%)	4/17 (23.5%)	RR 0.30 (0.06 to 1.48)	165 fewer per 1,000 (from 221 fewer to 113 more)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

- a. Limited methods reporting and open label study
- b. Small sample size
- c. CI includes appreciable benefits and harm

References

1. Liu, L., et al., *Combination of 5-Aminolevulinic acid photodynamic therapy and isotretinoin to treat moderate-to-severe acne*. Photodiagnosis and photodynamic therapy, 2021. 34: p. 102215.

80. Pneumatic broadband light + Adapalene 0.3% vs. Adapalene 0.3%

e-Table 160. GRADE Evidence Profile for pneumatic broadband light + adapalene 0.3% vs. adapalene 0.3%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pneumatic broadband light + Adapalene 0.3%	Adapalene 0.3%	Relative (95% CI)	Absolute (95% CI)		
Acne severity, Global Acne Grading Score, Modified at 4 weeks (median absolute change from baseline)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	11 patients were randomized to receive pneumatic broadband light + adapalene 0.3% on half of the face and adapalene 0.3% on the other half. The median absolute changes from baseline for pneumatic broadband light + adapalene 0.3% and adapalene 0.3% sides were 4 and 0, respectively. The difference between the two treatments was significant (p = 0.05).		⊕⊕○○ Low		CRITICAL	
Number of lesions, Any at 4 weeks (median absolute change from baseline)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The median absolute changes from baseline for pneumatic broadband light + adapalene 0.3% and adapalene 0.3% sides were -14 and -12, respectively. The difference between the two treatments was not significant (p = 0.24).		⊕⊕○○ Low		CRITICAL	
Number of lesions, Inflammatory at 4 weeks (median absolute change from baseline)												
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The median absolute changes from baseline for pneumatic broadband light + adapalene 0.3% and adapalene 0.3% sides were -6 and -6, respectively. The difference between the two treatments was not significant (p = 0.86).		⊕⊕○○ Low		CRITICAL	

Number of lesions, Non-inflammatory at 4 weeks (median absolute change from baseline)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pneumatic broadband light + Adapalene 0.3%	Adapalene 0.3%	Relative (95% CI)	Absolute (95% CI)		
1 ^{1,a}	randomized trials	serious ^b	not serious	not serious	serious ^c	none	The median absolute changes from baseline for pneumatic broadband light + adapalene 0.3% and adapalene 0.3% sides were -8 and -1% respectively. The difference between the two treatments was not significant (p = 0.34).				⊕⊕○○ Low	CRITICAL

CI: Confidence interval

Explanations

- a. RCT, Split face
- b. Limited methods reporting and unblinded patients
- c. Small sample size

References

1. Tangjaturonrusamee, C., P. Rattanaumpawan, and C.M. Ditre, *Comparison of pneumatic broadband light plus adapalene gel 0.3% versus adapalene gel 0.3% monotherapy in the treatment of mild to moderate acne*. *Cutis*, 2016. **98(1)**: p. 56-61.

Complementary / Alternative therapies

1. Tea tree oil vs. placebo

e-Table 161. GRADE Evidence Profile for tea tree oil vs. placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tea tree oil	placebo	Relative (95% CI)	Absolute (95% CI)		
Acne severity Index (ASI = Papules + [2×pustules] + [comedones/4]) at 6 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	very serious ^{a,b}	none	30	30	-	MD 5.75 lower (9.51 lower to 1.99 lower)	⊕⊕○○ Low	CRITICAL
Total lesion at 6 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	30	30	-	MD 7.53 lower (10.4 lower to 4.66 lower)	⊕⊕⊕○ Moderate	CRITICAL
Papule at 6 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	very serious ^{a,c}	none	30	30	-	MD 2.6 lower (4.1 lower to 1.1 lower)	⊕⊕○○ Low	CRITICAL

Pustule at 6 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tea tree oil	placebo	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	very serious ^{a,c}	none	30	30	-	MD 1.12 lower (1.77 lower to 0.47 lower)	⊕⊕○○ Low	CRITICAL

Comedone at 6 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	30	30	-	MD 3.74 lower (6.07 lower to 1.41 lower)	⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

a. Small sample size

b. Enshaieh 2007 reported acne severity index scores at baseline and at 6 weeks, percentage reduction from baseline at 6 weeks, 95% CI for the absolute change from baseline at 6 weeks. The reported 95% CI was used to estimate the standard deviations for the absolute change from baseline. However, the reported 95% for the control group seems inaccurately reported.

c. Enshaieh 2007 reported the lesion count at baseline and at 6 weeks, percentage reduction from baseline at 6 weeks, 95% CI for the absolute change from baseline at 6 weeks. The reported 95% CI was used to estimate the standard deviations for the absolute change from baseline. However, the reported 95% for the control group seems inaccurately reported.

References

1. Enshaieh, S., et al., *The efficacy of 5% topical tea tree oil gel in mild to moderate acne vulgaris: a randomized, double-blind placebo-controlled study*. Indian J Dermatol Venereol Leprol, 2007. **73**(1): p. 22-5.

2. Tea tree plus adapalene gel vs. adapalene gel

e-Table 162. GRADE Evidence Profile for tea tree plus adapalene gel vs. adapalene gel

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tea tree plus adapalene gel	adapalene gel	Relative (95% CI)	Absolute (95% CI)		
Treatment success, based on acne severity index (cutoff for success not reported), at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	38/53 (71.7%)	3/47 (6.4%)	RR 11.23 (3.71 to 34.01)	653 more per 1,000 (from 173 more to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL
Acne severity Index reduction at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	53	47	-	β ^b = -5.79 ± 1.020	⊕⊕⊕○ Moderate	CRITICAL
Total lesion reduction at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	53	47	-	β ^b = -8.832 ± 1.5189	⊕⊕⊕○ Moderate	CRITICAL
Inflammatory lesion reduction at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	53	47	-	β ^b = -3.282 ± 0.5989	⊕⊕⊕○ Moderate	CRITICAL
Noninflammatory lesion reduction at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	53	47	-	β ^b = -5.473 ± 1.1429	⊕⊕⊕○ Moderate	CRITICAL

Serious AE

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tea tree plus adapalene gel	adapalene gel	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	0/53 (0.0%)	0/47 (0.0%)	not estimable	-	⊕⊕⊕○ Moderate	CRITICAL

Skin irritation

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	Severity of adverse events was 'mild' in all patients treated with both formulations. Topical adverse events were observed in both groups, more increased in the TTO NE + ADA Gel group compared to the ADA Marketed Gel. Irritation at week 4 was significantly higher in TTO NE + ADA Gel compared to ADA Marketed Gel (43.4 vs 17%, p value = 0.005). However, in following visits, no statistically significant difference was observed between groups for irritation (22.6 vs 8.5% at week 8 and 7.5 vs 6.4% at week 12). Dryness occurred in 68.8% in the TTO NE + ADA Gel group and 53.2% in ADA Marketed Gel at week 4. Erythema occurred 32.1% in TTO NE + ADA Gel and 19.1% in ADA Marketed Gel at week 4, the incidence decreased in the following visits. Burning sensation was the adverse event barely reported by patients in both groups (11.3 vs 2.1%, 5. vs 2.1% and 3.8 vs 2.1% for TTO NE + ADA GEL compared to ADA Marketed Gel at week 4, 8 and 12 respectively; all between-group p-values >0.05).				⊕⊕⊕○ Moderate	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio; TTO NE: Tea tree oil nanoemulsion; ADA: Adapalene

Explanations

a. Small sample size

b. β is the estimated parameter from the tea tree oil plus adapalene gel vs. adapalene gel generalized estimating equation model adjusted for sex

References

1. Najafi-Taher, R., et al., *A topical gel of tea tree oil nanoemulsion containing adapalene versus adapalene marketed gel in patients with acne vulgaris: a randomized clinical trial*. Arch Dermatol Res, 2021.

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3. Tea tree oil vs. benzoyl peroxide 5%

e-Table 163. GRADE Evidence Profile for tea tree oil vs. benzoyl peroxide 5%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tea tree oil	BPO	Relative (95% CI)	Absolute (95% CI)		
Inflammatory lesion at 3 months												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^{b,c}	none	124 patients with mild to moderate acne were randomized to receive tea tree oil (n=61) or benzoyl peroxide (n=63) for 3 months. The mean inflammatory lesion counts at baseline were 23.07 and 23.26 for tea tree oil and benzoyl peroxide groups, respectively. At 3 months, the mean inflammatory lesion counts decreased to 16.35 and 15.27 for tea tree oil (n=61) and benzoyl peroxide (n=58) groups, respectively.			⊕⊕○○ Low	CRITICAL	
Noninflammatory lesion at 3 months												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^{b,c}	none	124 patients with mild to moderate acne were randomized to receive tea tree oil (n=61) or benzoyl peroxide (n=63) for 3 months. The mean inflammatory lesion counts at baseline were 34.58 and 38.04 for tea tree oil and benzoyl peroxide groups, respectively. At 3 months, the mean inflammatory lesion counts decreased to 18.1 and 11.17 for tea tree oil (n=61) and benzoyl peroxide (n=58) groups, respectively.			⊕⊕○○ Low	CRITICAL	

Skin irritation

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tea tree oil	BPO	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	124 patients with mild to moderate acne were randomized to receive tea tree oil (n=61) or benzoyl peroxide (n=63) for 3 months. There was no significant difference between the treatment groups for the assessment of skin erythema during treatment. Both skin scaling and pruritus were significantly greater at one month in the benzoyl peroxide group (p<0.02 and p<0.05 respectively), and dryness was significantly greater for benzoyl peroxide at one month (P<0.001) and two months (P<0.01).				⊕⊕○○ Low	IMPORTANT

Any AE^d

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	27/61 (44.3%)	50/63 (79.4%)	RR 0.56 (0.41 to 0.76)	349 fewer per 1,000 (from 468 fewer to 190 fewer)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

- Limited methods reporting and unblinded patients
- Small sample size.
- The data were from the figure using WebPlotDigitizer.
- Skin dryness, pruritus, stinging, burning, and redness were the main complaints, dryness being the most commonly reported problem in both groups.

References

- Bassett, I.B., D.L. Pannowitz, and R.S. Barnetson, *A comparative study of tea-tree oil versus benzoylperoxide in the treatment of acne*. Med J Aust, 1990. **153**(8): p. 455-8.

4. Green tea vs. placebo

e-Table 164. GRADE Evidence Profile for green tea vs. placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Green tea	Placebo	Relative (95% CI)	Absolute (95% CI)		
Revised Leeds score at 8 weeks (1% and 5% combined)												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	35	35	-	MD 2.64 lower (2.83 lower to 2.45 lower)	⊕⊕⊕○ Moderate	CRITICAL
Inflammatory lesion at 8 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	35	35	-	MD 6.99 lower (7.72 lower to 6.25 lower)	⊕⊕⊕○ Moderate	CRITICAL
>50 % reduction in papules and pustules, at 8 weeks												
1 ²	randomised trials	serious ^c	not serious	not serious	serious ^a	none	16/25 (64.0%)	5/24 (20.8%)	RR 3.07 (1.33 to 7.07)	431 more per 1,000 (from 69 more to 1,000 more)	⊕⊕○○ Low	CRITICAL

0-10% reduction in papules and pustules, at 8 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Green tea	Placebo	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	serious ^c	not serious	not serious	serious ^b	none	3/25 (12.0%)	8/24 (33.3%)	RR 0.36 (0.11 to 1.20)	213 fewer per 1,000 (from 297 fewer to 67 more)	⊕⊕○○ Low	CRITICAL

10-50 % reduction in papules and pustules, at 8 weeks

1 ²	randomised trials	serious ^c	not serious	not serious	serious ^b	none	6/25 (24.0%)	11/24 (45.8%)	RR 0.52 (0.23 to 1.19)	220 fewer per 1,000 (from 353 fewer to 87 more)	⊕⊕○○ Low	CRITICAL

Papule at 8 weeks

1 ²	randomised trials	serious ^c	not serious	not serious	serious ^a	none	25	24	-	MD 2.8 lower (4.02 lower to 1.58 lower)	⊕⊕○○ Low	CRITICAL

Pustule at 8 weeks

1 ²	randomised trials	serious ^c	not serious	not serious	serious ^a	none	25	24	-	MD 9.4 lower (11 lower to 7.8 lower)	⊕⊕○○ Low	CRITICAL

Non-inflammatory lesion at 8 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Green tea	Placebo	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	35	35	-	MD 32.57 lower (36.2 lower to 28.93 lower)	⊕⊕⊕○ Moderate	CRITICAL

Patient global assessment (VAS 0-10) at 8 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	35	35	-	MD 4.58 lower (5.23 lower to 3.93 lower)	⊕⊕⊕○ Moderate	IMPORTANT

Patients satisfaction, fully satisfied, at 8 weeks

1 ²	randomised trials	serious ^c	not serious	not serious	serious ^a	none	16/25 (64.0%)	1/24 (4.2%)	RR 15.36 (2.20 to 107.00)	598 more per 1,000 (from 50 more to 1,000 more)	⊕⊕○○ Low	IMPORTANT

Patients satisfaction, partially satisfied, at 8 weeks

1 ²	randomised trials	serious ^c	not serious	not serious	serious ^b	none	6/25 (24.0%)	3/24 (12.5%)	RR 1.92 (0.54 to 6.82)	115 more per 1,000 (from 57 fewer to 728 more)	⊕⊕○○ Low	IMPORTANT

Patients satisfaction, not satisfied, at 8 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Green tea	Placebo	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	serious ^c	not serious	not serious	serious ^a	none	3/25 (12.0%)	20/24 (83.3%)	RR 0.14 (0.05 to 0.42)	717 fewer per 1,000 (from 792 fewer to 483 fewer)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

- a. Small sample size
- b. Small sample size and a CI including appreciable benefits and harm
- c. Limited methods reporting and single-blind study (seemed unclear whether the patients or investigators were blinded)

References

1. Yoon, J.Y., et al., *Epigallocatechin-3-gallate improves acne in humans by modulating intracellular molecular targets and inhibiting P. acnes*. J Invest Dermatol, 2013. **133**(2): p. 429-40.
2. Sharquie, K.E., I.A. Al-Turfi, and W.M. Al-Shimary, *Treatment of acne vulgaris with 2% topical tea lotion*. Saudi Med J, 2006. **27**(1): p. 83-5.

5. Green tea vs. zinc 5%

e-Table 165. GRADE Evidence Profile for green tea vs. zinc 5%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Green tea	zinc 5%	Relative (95% CI)	Absolute (95% CI)		
Papules at 8 weeks												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	20	20	-	MD 2.4 lower (7.76 lower to 2.96 higher)	⊕⊕○○ Low	CRITICAL
Pustules at 8 weeks												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	20	20	-	MD 0.7 lower (6.97 lower to 5.57 higher)	⊕⊕○○ Low	CRITICAL

CI: Confidence interval; MD: mean difference

Explanations

- a. Limited methods reporting and single-blind study (unclear whether the patients or investigators were blinded)
- b. Small sample size and a wide CI including both appreciable benefit and harm

References

1. Sharquie, K.E., A.A. Noaimi, and M.M. Al-Salih, *Topical therapy of acne vulgaris using 2% tea lotion in comparison with 5% zinc sulphate solution*. Saudi Med J, 2008. **29**(12): p. 1757-61.

6. Green tea oral supplement vs. placebo

e-Table 166. GRADE Evidence Profile for green tea oral supplement vs. placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Green tea supplement PO	Placebo	Relative (95% CI)	Absolute (95% CI)		
Serious AE												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	0/40 (0.0%)	0/40 (0.0%)	not estimable		⊕⊕⊕○ Moderate	CRITICAL
Total lesion at 4 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	33	31	-	MD 1.1 higher (6.93 lower to 9.13 higher)	⊕⊕⊕○ Moderate	CRITICAL
Inflammatory lesion at 4 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	33	31	-	MD 1.9 lower (9.48 lower to 5.68 higher)	⊕⊕⊕○ Moderate	CRITICAL
Noninflammatory lesion at 4 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	33	31	-	MD 0.5 higher (0.7 lower to 1.7 higher)	⊕⊕⊕○ Moderate	CRITICAL

Withdrawal due to AE

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Green tea supplement PO	Placebo	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	0/40 (0.0%)	0/40 (0.0%)	not estimable		⊕⊕⊕○ Moderate	CRITICAL

Cardiff Acne Disability Index (CADI) at 4 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	33	31	-	MD 0.2 lower (1.65 lower to 1.25 higher)	⊕⊕⊕○ Moderate	IMPORTANT

CI: Confidence interval; MD: mean difference

Explanations

- a. Small sample size and zero events in both arms
- b. Small sample size and a CI including appreciable benefits and harm

References

1. Lu, P.H. and C.H. Hsu, *Does supplementation with green tea extract improve acne in post-adolescent women? A randomized, double-blind, and placebo-controlled clinical trial.* Complement Ther Med, 2016. **25**: p. 159-63.

7. Zinc 60mg vs. minocycline 100mg

e-Table 167. GRADE Evidence Profile for zinc 60mg vs. minocycline 100mg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral zinc 60mg	minocycline 100mg	Relative (95% CI)	Absolute (95% CI)		
Investigator's overall opinion on efficacy at 3 months												
1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	332 patients received either 30 mg elemental zinc or 100 mg minocycline over 3 months. The mean VAS score for the investigator's opinion was 0.5 mm in the zinc gluconate group and 0.64 mm in the minocycline hydrochloride group (p< 0.001; on a 100mm VAS scale with a ratio of 1 as normal value).				⊕⊕⊕⊕ High	CRITICAL
Inflammatory lesion at 3 months												
1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	143	145	-	MD 5.2 higher (2.62 higher to 7.78 higher)	⊕⊕⊕⊕ High	CRITICAL
Noninflammatory lesion at 3 months												
1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	143	145	-	MD 8.5 higher (1.86 higher to 15.14 higher)	⊕⊕⊕⊕ High	CRITICAL

Clinical success, more than 2/3 decrease in inflammatory lesions, at 3 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral zinc 60mg	minocycline 100mg	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	332 patients received either 30 mg elemental zinc or 100 mg minocycline over 3 months. The percentage of patients with a more than 2/3 decrease in superficial inflammatory lesions on the face was 31.2% in the zinc gluconate group and 63.4% in the minocycline hydrochloride group. The 90% confidence interval of the difference was -40.86 to -23.42, outside the predicted difference for equivalence.				⊕⊕⊕⊕ High	CRITICAL

Withdrawal due to AE

1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	5/163 (3.1%)	4/169 (2.4%)	RR 1.30 (0.35 to 4.74)	7 more per 1,000 (from 15 fewer to 89 more)	⊕⊕⊕○ Moderate	CRITICAL

Patient's overall opinion on clinical efficacy at 3 months

1 ¹	randomised trials	not serious	not serious	not serious	not serious	none	332 patients received either 30 mg elemental zinc or 100 mg minocycline over 3 months. The mean VAS score for the patient's opinion was 0.52 mm in the zinc gluconate group and 0.70 mm in the minocycline hydrochloride group (p< 0.001; on a 100mm VAS scale with a ratio of 1 as normal value)				⊕⊕⊕⊕ High	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

a. Small sample size and a wide CI including appreciable benefit and harm

References

1. Dreno, B., et al., *Multicenter randomized comparative double-blind controlled clinical trial of the safety and efficacy of zinc gluconate versus minocycline hydrochloride in the treatment of inflammatory acne vulgaris*. *Dermatology*, 2001. **203**(2): p. 135-40.

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8. Pantothenic acid vs. placebo

e-Table 168. GRADE Evidence Profile for pantothenic acid vs. placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pantothenic acid	placebo	Relative (95% CI)	Absolute (95% CI)		
Investigator global improvement, marked improvement or slight improvement, at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	17/20 (85.0%)	7/21 (33.3%)	RR 2.55 (1.36 to 4.80)	517 more per 1,000 (from 120 more to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL
Investigator global assessment, almost clear, few NIL and up to 1 IL, at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	9/20 (45.0%)	3/21 (14.3%)	RR 3.15 (0.99 to 9.99)	307 more per 1,000 (from 1 fewer to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL
Total lesion at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^{a,b}	none	20	21	-	MD 23.42 lower (33.04 lower to 13.8 lower)	⊕⊕⊕○ Moderate	CRITICAL

Inflammatory lesion at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pantothenic acid	placebo	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^{a,b}	none	20	21	-	MD 2.56 lower (2.85 lower to 2.27 lower)	⊕⊕⊕○ Moderate	CRITICAL

Noninflammatory lesion at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^{a,b}	none	20	21	-	MD 18.55 lower (19.3 lower to 17.8 lower)	⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. Small sample size

b. Data were captured from the figure using WebPlotDigitizer

References

1. Yang, M., et al., *A randomized, double-blind, placebo-controlled study of a novel pantothenic Acid-based dietary supplement in subjects with mild to moderate facial acne.* Dermatol Ther (Heidelb), 2014. 4(1): p. 93-101.

e-Table 169. GRADE Evidence Profile for minocycline vs. erythromycin/zinc lotion

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline 50 mg bd	zineryt bd (erythromycin 4%/zinc 1.2% lotion)	Relative (95% CI)	Absolute (95% CI)		
Physician's global assessment (follow up: 12 weeks; assessed with: change from baseline in Leeds grade)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	54	55	-	MD 0.01 higher (0.13 lower to 0.15 higher)	⊕⊕○○ LOW	CRITICAL
Inflammatory lesion (follow up: 12 weeks; assessed with: change from baseline)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	51	54	-	MD 9.4 lower (20.54 lower to 1.74 higher)	⊕⊕○○ LOW	CRITICAL
Total inflammatory lesion (follow up: 12 weeks; assessed with: percentage change from baseline)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	51	54	-	MD 17.9 higher (4.75 higher to 31.05 higher)	⊕⊕○○ LOW	CRITICAL
Superficial inflamed lesions (follow up: 12 weeks; assessed with: percentage change from baseline)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline 50 mg bd	zineryt bd (erythromycin 4%/zinc 1.2% lotion)	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	51	52	-	MD 29.1 higher (16.69 higher to 41.51 higher)	⊕⊕○○ LOW	CRITICAL

Inflammatory lesion (follow up: 12 weeks; assessed with: > 45% reduction from baseline)

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	22/51 (43.1%)	39/54 (72.2%)	RR 0.60 (0.42 to 0.85)	289 fewer per 1,000 (from 419 fewer to 108 fewer)	⊕⊕○○ LOW	CRITICAL

Noninflammatory lesion (follow up: 12 weeks; assessed with: change from baseline)

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	51	54	-	MD 26.2 lower (45 lower to 7.4 lower)	⊕⊕○○ LOW	CRITICAL

Noninflammatory lesion (follow up: 12 weeks; assessed with: percentage change from baseline)

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	51	51	-	MD 32.9 higher (16.2 higher to 49.6 higher)	⊕⊕○○ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline 50 mg bd	zineryt bd (erythromycin 4%/zinc 1.2% lotion)	Relative (95% CI)	Absolute (95% CI)		

Noninflammatory lesion (follow up: 12 weeks; assessed with: > 45% reduction from baseline)

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	15/51 (29.4%)	36/54 (66.7%)	RR 0.44 (0.28 to 0.70)	373 fewer per 1,000 (from 480 fewer to 200 fewer)	⊕⊕○○ LOW	CRITICAL

Any AE

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^c	none	6/51 (11.8%)	8/54 (14.8%)	RR 0.79 (0.30 to 2.13)	31 fewer per 1,000 (from 104 fewer to 167 more)	⊕⊕○○ LOW	IMPORTANT

Requiring therapy cessation

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^d	none	1/51 (2.0%)	0/54 (0.0%)	RR 3.17 (0.13 to 76.16)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	IMPORTANT

GI AE

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Minocycline 50 mg bd	zineryt bd (erythromycin 4%/zinc 1.2% lotion)	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^d	none	1/51 (2.0%)	0/54 (0.0%)	RR 3.17 (0.13 to 76.16)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

- This study had unclear random sequence generation, allocation concealment, and blinding of participants.
- Small sample size.
- Small sample size and wide CI including both appreciable benefits and harm.
- Small sample size, few events, and wide CI including both appreciable benefits and harm.

References

1. Stainforth, J., et al., *A single-blind comparison of topical erythromycin/zinc lotion and oral minocycline in the treatment of acne vulgaris*. Journal of dermatological treatment, 1993. 4(3): p. 119-122.

10. Element zinc 2% vs. placebo

e-Table 170. GRADE Evidence Profile for element zinc 2% vs. placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zinc	placebo	Relative (95% CI)	Absolute (95% CI)		
Michaëlsso score at 12 weeks												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	Thirty patients with mild to moderate acne were randomized to receive 2% elemental zinc or placebo (the number of patients in each group was not reported). The normalized means of Michaëlsso score at 12 weeks were 94.6 and 97.5 (data are from the figure using WebPlotDigitizer) in 2% elemental zinc and the placebo groups, respectively, and the difference between the two groups was not statistically significant.				⊕⊕○○ Low	CRITICAL

Explanations

a. Unclear methods reporting and risk of reporting bias

b. Small sample size and no CIs or p-values were provided. Data are from the figure using WebPlotDigitizer.

References

1. Cochran, R.J., S.B. Tucker, and S.A. Flannigan, *Topical zinc therapy for acne vulgaris*. Int J Dermatol, 1985. **24**(3): p. 188-90.

11. Topical antibiotics plus zinc vs. topical antibiotics

e-Table 171. GRADE Evidence Profile for topical antibiotics plus zinc vs. topical antibiotics

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotics plus zinc	topical antibiotics	Relative (95% CI)	Absolute (95% CI)		
Revised Leeds score, at 16 weeks												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^{b,c}	none	77	83	-	MD 0.2 lower (0.53 lower to 0.13 higher)	⊕⊕○○ Low	CRITICAL
Burke and Cunliffe Acne grade at 12 weeks												
1 ²	randomised trials	not serious	not serious	not serious	serious ^{b,c}	none	20	25	-	MD 0.11 higher (0.06 lower to 0.28 higher)	⊕⊕⊕○ Moderate	CRITICAL
Physican global assessment, VAS, at 16 weeks												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^{c,d}	none	77	83	-	MD 0.57 lower (5.93 lower to 4.79 higher)	⊕⊕○○ Low	CRITICAL

Total lesion at 16 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotics plus zinc	topical antibiotics	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^{c,d}	none	77	83	-	MD 0 (13.33 lower to 13.33 higher)	⊕⊕○○ Low	CRITICAL

Inflammatory lesion at the end of treatment

2 ^{1,2}	randomised trials	serious ^e	not serious	not serious	serious ^{c,d}	none	97	108	-	MD 0.72 higher (4.91 lower to 6.35 higher)	⊕⊕○○ Low	CRITICAL

Noninflammatory lesion at the end of treatment

2 ^{1,2}	randomised trials	serious ^e	not serious	not serious	serious ^{c,d}	none	97	108	-	MD 1.33 lower (7.64 lower to 4.99 higher)	⊕⊕○○ Low	CRITICAL

Withdrawal due to AE

1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^{c,d}	none	2/77 (2.6%)	2/83 (2.4%)	RR 1.08 (0.16 to 7.47)	2 more per 1,000 (from 20 fewer to 156 more)	⊕⊕○○ Low	CRITICAL

Patient global assessment, VAS, at 16 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topical antibiotics plus zinc	topical antibiotics	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^{c,d}	none	77	83	-	MD 0.74 lower (6.25 lower to 4.77 higher)	⊕⊕○○ Low	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

- Limited methods reporting, unblinded patients, and risk of attrition bias (last observation carried forward imputation method was used)
- Small sample size and a CI including small benefit and harm
- Data were captured from the figure using WebPlotDigitizer
- Small sample size and a CI including appreciable benefit and harm
- One study had limited methods reporting, unblinded patients, and risk of attrition bias (last observation carried forward imputation method was used)

References

- Cunliffe, W.J., et al., *An observer-blind parallel-group, randomized, multicentre clinical and microbiological study of a topical clindamycin/zinc gel and a topical clindamycin lotion in patients with mild/moderate acne*. J Dermatolog Treat, 2005. **16**(4): p. 213-8.
- Bojar, R., et al., *Inhibition of erythromycin-resistant propionibacteria on the skin of acne patients by topical erythromycin with and without zinc*. The British journal of dermatology, 1994. **130**(3): p. 329-336.

12. Erythromycin 4% plus zinc 1.2% solution vs. clindamycin 1% plus benzoyl peroxide 5% gel

e-Table 172. GRADE Evidence Profile for erythromycin 4% plus zinc 1.2% solution vs. clindamycin 1% plus benzoyl peroxide 5% gel

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Erythromycin/zinc	clindamycin/BPO	Relative (95% CI)	Absolute (95% CI)		
Revised Leeds Acne score at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	75	73	-	MD 0.08 higher (0.25 lower to 0.41 higher)	⊕⊕⊕ ○ Moderate	CRITICAL
Total lesion at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	75	73	-	MD 6.1 higher (4.65 lower to 16.85 higher)	⊕⊕⊕ ○ Moderate	CRITICAL
Total lesion, at least 30% reduction, at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	148 patients with mild to moderate acne were randomized to receive erythromycin 4% plus zinc acetate 1.2% solution twice daily or clindamycin phosphate 1% plus benzoyl peroxide 5% gel once daily for 12 weeks. At 12 week, 11% and 11% of the patients in erythromycin/zinc and clindamycin/BPO, respectively, achieved at least 30% reduction in total lesion count, and the difference between the two groups was not statistically significant (Data were captured from the figure using WebPlotDigitizer).			⊕⊕⊕ ○ Moderate	CRITICAL	

Inflammatory lesion at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Erythromycin/zinc	clindamycin/BPO	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	75	73	-	MD 0.1 higher (3.85 lower to 4.05 higher)	⊕⊕⊕ ○ Moderate	CRITICAL

Inflammatory lesion, at least 30% reduction, at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	148 patients with mild to moderate acne were randomized to receive erythromycin 4% plus zinc acetate 1.2% solution twice daily (n=95) or clindamycin phosphate 1% plus benzoyl peroxide 5% gel once daily (n=93) for 12 weeks. At 12 week, 83% and 87% of the patients in erythromycin/zinc and clindamycin/BPO, respectively, achieved at least 30% reduction in inflammatory lesion count, and the difference between the two groups was not statistically significant (Data are captured from the figure using WebPlotDigitizer).				⊕⊕⊕ ○ Moderate	CRITICAL

Inflammatory lesion at 12 weeks

1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	75	73	-	MD 6.4 higher (2.16 lower to 14.96 higher)	⊕⊕⊕ ○ Moderate	CRITICAL

Noninflammatory lesion, at least 30% reduction, at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Erythromycin/zinc	clindamycin/BPO	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^c	none	148 patients with mild to moderate acne were randomized to receive erythromycin 4% plus zinc acetate 1.2% solution twice daily (n=95) or clindamycin phosphate 1% plus benzoyl peroxide 5% gel once daily (n=93) for 12 weeks. At 12 week, 77% and 88% of the patients in erythromycin/zinc and clindamycin/BPO, respectively, achieved at least 30% reduction in non-inflammatory lesion count, and the difference between the two groups was not statistically significant (Data are captured from the figure using WebPlotDigitizer).				⊕⊕⊕ ○ Moderate	CRITICAL

Serious AE

1 ¹	randomised trials	not serious	not serious	not serious	serious ^d	none	1/75 (1.3%)	0/73 (0.0%)	RR 2.92 (0.12 to 70.56)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕⊕⊕ ○ Moderate	CRITICAL

Withdrawal due to AE

1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	1/75 (1.3%)	1/73 (1.4%)	RR 0.97 (0.06 to 15.27)	0 fewer per 1,000 (from 13 fewer to 195 more)	⊕⊕⊕ ○ Moderate	CRITICAL

Any AE

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Erythromycin/zinc	clindamycin/BPO	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious	not serious	not serious	serious ^b	none	23/75 (30.7%)	15/73 (20.5%)	RR 1.49 (0.85 to 2.63)	101 more per 1,000 (from 31 fewer to 335 more)	⊕⊕⊕ ○ Moderate	IMPORTANT

CI: Confidence interval; MD: Mean difference; RR: Risk ratio

Explanations

- Small sample size and a CI including small benefit and harm
- Small sample size and a CI including both appreciable benefit and harm
- Small sample size. Data are captured from the figure using WebPlotDigitizer
- Small sample size and zero event in the comparator arm

References

- Langner, A., R. Sheehan-Dare, and A. Layton, *A randomized, single-blind comparison of topical clindamycin + benzoyl peroxide (Duac) and erythromycin + zinc acetate (Zineryt) in the treatment of mild to moderate facial acne vulgaris*. J Eur Acad Dermatol Venereol, 2007. 21(3): p. 311-9.

13. Niacinamide 5% cream plus benzoyl peroxide 2.5% gel vs. benzoyl peroxide 2.5% gel

e-Table 173. GRADE Evidence Profile for niacinamide 5% cream plus benzoyl peroxide 2.5% gel vs. benzoyl peroxide 2.5% gel

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Niacinamide/ BPO	BPO	Relative (95% CI)	Absolute (95% CI)		
Physician global assessment, excellent improvement at 12 weeks												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	8/17 (47.1%)	3/17 (17.6%)	RR 2.67 (0.85 to 8.37)	295 more per 1,000 (from 26 fewer to 1,000 more)	⊕⊕⊕○ Moderate	CRITICAL
Physician global assessment, significant improvement at 12 weeks												
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	7/17 (41.2%)	11/17 (64.7%)	RR 0.64 (0.33 to 1.24)	233 fewer per 1,000 (from 434 fewer to 155 more)	⊕⊕⊕○ Moderate	CRITICAL
Physician global assessment, moderate improvement at 12 weeks												
1 ¹	randomised trials	not serious ¹	not serious	not serious	serious ^b	none	2/17 (11.8%)	3/17 (17.6%)	RR 0.67 (0.13 to 3.50)	58 fewer per 1,000 (from 154 fewer to 441 more)	⊕⊕⊕○ Moderate	CRITICAL

Inflammatory lesion at 12 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Niacinamide/BPO	BPO	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^c	none	A total of 21 patients (16 women, 5 men) with mild to moderate facial acne were enrolled, and after leaving 2.5% benzoyl peroxide water-based gel on the face, the patients applied 5% niacinamide cream on one half of the face and the placebo cream on the other half for 12 weeks. At baseline, the means of inflammatory lesion counts were 4.52 and 3.86 in the niacinamide and placebo groups, respectively. At the end of the treatment, inflammatory lesion counts decreased to 1.24 and 1.76 in the niacinamide and placebo groups, respectively. The percentage of inflammatory lesion change from baseline was not statistically significantly different between the two groups.				⊕⊕⊕○ Moderate	CRITICAL

Noninflammatory lesion at 12 weeks

1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^c	none	A total of 21 patients (16 women, 5 men) with mild to moderate facial acne were enrolled, and after leaving 2.5% benzoyl peroxide water-based gel on the face, the patients applied 5% niacinamide cream on one half of the face and the placebo cream on the other half for 12 weeks. At baseline, the means of noninflammatory lesion counts were 28.24 and 24.57 in the niacinamide and placebo groups, respectively. At the end of the treatment, noninflammatory lesion counts decreased to 13.59 and 15.53 in the niacinamide and placebo groups, respectively. And, percentage of noninflammatory lesion change from baseline was statistically different between the two groups (niacinamide group decreased 51% vs. cream base group decreased 34%; p=0.004) .				⊕⊕⊕○ Moderate	CRITICAL

Patient global assessment, excellent improvement at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Niacinamide/BPO	BPO	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	11/17 (64.7%)	9/17 (52.9%)	RR 1.22 (0.69 to 2.16)	116 more per 1,000 (from 164 fewer to 614 more)	⊕⊕⊕○ Moderate	IMPORTANT

Patient global assessment, significant improvement at 12 weeks

1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	3/17 (17.6%)	6/17 (35.3%)	RR 0.50 (0.15 to 1.68)	176 fewer per 1,000 (from 300 fewer to 240 more)	⊕⊕⊕○ Moderate	IMPORTANT

Patient global assessment, moderate improvement at 12 weeks

1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	1/17 (5.9%)	1/17 (5.9%)	RR 1.00 (0.07 to 14.72)	0 fewer per 1,000 (from 55 fewer to 807 more)	⊕⊕⊕○ Moderate	IMPORTANT

Patient global assessment, slight improvement at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Niacinamide/BPO	BPO	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	not serious ^a	not serious	not serious	serious ^b	none	2/17 (11.8%)	1/17 (5.9%)	RR 2.00 (0.20 to 20.04)	59 more per 1,000 (from 47 fewer to 1,000 more)	⊕⊕⊕○ Moderate	IMPORTANT

CI: Confidence interval; RR: Risk ratio

Explanations

- Split-face RCT
- Small sample size and a wide CI including both appreciable benefits and harm.
- Small sample size

References

- Kaewsanit, T., P. Chakkavittumrong, and N. Waranuch, *Clinical Comparison of Topical 2.5% Benzoyl Peroxide plus 5% Niacinamide to 2.5% Benzoyl Peroxide Alone in the Treatment of Mild to Moderate Facial Acne Vulgaris*. J Clin Aesthet Dermatol, 2021. 14(6): p. 35-41.

Diet

1. Low-glycemic-load diet vs. high-glycemic-load diet

e-Table 174. GRADE Evidence Profile for low-glycemic-load diet vs. high-glycemic-load diet

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low-glycaemic-load diet	high-glycaemic-load diet	Relative (95% CI)	Absolute (95% CI)		
Facial acne grade, change from baseline, at 8 weeks (0: no acne, 1: mild, 2: moderate, and 3: severe)												
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	23	20	-	MD 0.3 lower (0.39 lower to 0.21 lower)	⊕⊕○○ Low	CRITICAL
Revised Leeds acne score, at 10 weeks												
1 ²	randomised trials	not serious	not serious	not serious	serious ^b	none	A total of 32 patients with mild to moderate acne were randomly assigned to either a low glycaemic load diet (LGLD; n=17) or a control group diet (n=15), and completed a 10-week, parallel dietary intervention trial. The mean baseline acne scores for both LGLD and control groups were 2.18 and 2.08, respectively. After the 10-week dietary intervention, only the LGLD group demonstrated a significant decrease in acne grades, to 1.60 (p = 0.02).			⊕⊕⊕○ Moderate	CRITICAL	
Total lesion, change from baseline, at 12 weeks												
1 ^{3, 4, 5}	randomised trials	not serious ^c	not serious	not serious	serious ^b	none	23	20	-	MD 8.1 lower (14.89 lower to 1.31 lower)	⊕⊕⊕○ Moderate	CRITICAL

Inflammatory lesion, change from baseline, at 12 weeks

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low-glycaemic-load diet	high-glycaemic-load diet	Relative (95% CI)	Absolute (95% CI)		
1 ^{3, 4, 5}	randomised trials	not serious ^c	not serious	not serious	serious ^b	none	23	20	-	MD 7.6 lower (13.52 lower to 1.68 lower)	⊕⊕⊕○ Moderate	CRITICAL

Inflammatory lesion at 10 weeks

1 ²	randomised trials	not serious	not serious	not serious	serious ^b	none	A total of 32 patients with mild to moderate acne were randomly assigned to either a low glycaemic load diet (LGLD; n=17) or a control group diet (n=15), and completed a 10-week, parallel dietary intervention trial. The mean baseline inflammatory lesion counts for LGLD and control groups were 21.3+9.6 and 24.7+ 6.8, respectively. Inflammatory acne lesions were significantly decreased in the LGLD group at the earlier time-point of 5 weeks (p = 0.03). At the final visit, the mean number of lesions had decreased to 70.9% of baseline, while there was no significant reduction in the lesions in the control group.				⊕⊕⊕○ Moderate	CRITICAL

Non-inflammatory lesion count at 10 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low-glycaemic-load diet	high-glycaemic-load diet	Relative (95% CI)	Absolute (95% CI)		
1 ²	randomised trials	not serious	not serious	not serious	serious ^b	none	A total of 32 patients with mild to moderate acne were randomly assigned to either a low glycaemic load diet (LGLD; n=17) or a control group diet (n=15), and completed a 10-week, parallel dietary intervention trial. The mean baseline non-inflammatory lesion count for LGLD and control groups were 8.3+-7.1 and 8.1+-5.6, respectively. The mean non-inflammatory lesion counts for the LGLD group and the control group significantly decreased, by 27.6% and 14.2%, respectively (p = 0.02, p = 0.04), at the final visit compared with the baseline. The difference between the 2 groups was evident only after the full 10 weeks of dietary intervention (p = 0.02)				⊕⊕⊕○ Moderate	CRITICAL

CI: confidence interval; MD: mean difference

Explanations

- Risk of selection bias due to unclear random sequence generation and lack of allocation concealment, risk of performance bias due to the unblinded patients, and risk of attrition bias due to high dropout rate (26%)
- Small sample size
- 57.4% of the patients completed study

References

- Reynolds, R.C., et al., *Effect of the glycemic index of carbohydrates on Acne vulgaris*. *Nutrients*, 2010. **2**(10): p. 1060-72.
- Kwon, H.H., et al., *Clinical and histological effect of a low glycaemic load diet in treatment of acne vulgaris in Korean patients: a randomized, controlled trial*. *Acta Derm Venereol*, 2012. **92**(3): p. 241-6.
- Smith, R.N., et al., *The effect of a low glycemic load diet on acne vulgaris and the fatty acid composition of skin surface triglycerides*. *J Dermatol Sci*, 2008. **50**(1): p. 41-52.
- Smith, R.N., et al., *A low-glycemic-load diet improves symptoms in acne vulgaris patients: a randomized controlled trial*. *Am J Clin Nutr*, 2007. **86**(1): p. 107-15.
- Smith, R.N., et al., *The effect of a high-protein, low glycemic-load diet versus a conventional, high glycemic-load diet on biochemical parameters associated with acne vulgaris: a randomized, investigator-masked, controlled trial*. *J Am Acad Dermatol*, 2007. **57**(2): p. 247-56.

2. Low glycemic diet plus BPO 2.5% vs. BPO 2.5%

e-Table 175. GRADE Evidence Profile for low glycemic diet plus BPO 2.5% vs. BPO 2.5%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low glycemic diet plus BPO 2.5%	BPO 2.5%	Relative (95% CI)	Absolute (95% CI)		
Improvement in acne counts at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	42/42 (100.0%)	42/42 (100.0%)	RR 1.00 (0.96 to 1.05)	0 fewer per 1,000 (from 40 fewer to 50 more)	⊕⊕⊕○ Moderate	CRITICAL
Acne lesion count at 12 weeks												
1 ¹	randomised trials	not serious	not serious	not serious	serious ^a	none	42	42	-	MD 0.14 lower (3.36 lower to 3.07 higher)	⊕⊕⊕○ Moderate	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Small sample size.

References

1. Pavithra, G., G.M. Upadya, and M.S. Rukmini, *A randomized controlled trial of topical benzoyl peroxide 2.5% gel with a low glycemic load diet versus topical benzoyl peroxide 2.5% gel with a normal diet in acne (grades 1-3)*. Indian J Dermatol Venereol Leprol, 2019. **85**(5): p. 486-490.

3. Metformin and hypocaloric diet with PRN acne symptomatic treatment vs. PRN acne symptomatic treatment*

e-Table 176. GRADE Evidence Profile for metformin and hypocaloric diet with PRN acne symptomatic treatment vs. PRN acne symptomatic treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metformin and hypocaloric diet with PRN symptomatic treatment	PRN symptomatic treatment	Relative (95% CI)	Absolute (95% CI)		
1 ¹	randomised trials	serious ^a	not serious	not serious	serious ^b	none	20 young male patients (17-24) with acne resistant to common standard therapies were randomized to receive metformin 500 mg twice daily with a hypocaloric diet (1500-2000 kcal, rich in fruits, vegetables, and fish, low in carbohydrates) or no treatment. All patients continued the symptomatic anti-acne treatment (bland detergent and a sebostatic cream based on azelaic acid and nicotinamide) as needed. At baseline, global acne grading system (GAGS) scores were 25.1 ± 8.9 and 24.9 ± 7.6 in metformin and no treatment groups, respectively. At 6 months, GAGS scores decreased to 14.1 ± 10.4 and 19.4 ± 7.4 in metformin ($p < 0.03$ for within group difference) and no treatment (no p provided), respectively.				⊕⊕○ ○ Low	CRITICAL

CI: Confidence interval; RR: Risk ratio

* Metformin: 500 mg twice daily; Hypocaloric diet: 1,500-2,000 kcal, rich in fruits, vegetables, and fish, low in carbohydrates; PRN symptomatic treatment: bland detergent and a sebostatic cream based on azelaic acid and nicotinamide

Explanations

a. Minimal methods reporting.

b. Small sample size.

References

1. Fabbrocini, G., et al., *Low glycaemic diet and metformin therapy: a new approach in male subjects with acne resistant to common treatments*. Clin Exp Dermatol, 2016. 41(1): p. 38-42.

e-Table 177. Treatment comparisons that did not render recommendations due to insufficient evidence

Treatment class	Comparisons with insufficient evidence to support recommendation development
Topical treatments	• Topical antibiotic vs. BP • Topical antibiotic + BP vs. BP • Topical antibiotic + BP vs. topical antibiotic • Topical antibiotic + BP vs. vehicle • Topical antibiotic + BP vs. topical retinoid • Topical retinoid vs. BP • Topical retinoid vs. topical antibiotic • Topical retinoid + BP vs. BP • Topical retinoid + BP vs. topical retinoid • Topical retinoid + BP vs. vehicle • Topical retinoid + Topical antibiotic vs. topical antibiotic • Topical retinoid + Topical antibiotic vs. topical retinoid • Topical retinoid + Topical antibiotic + BP vs. vehicle • Topical retinoid + Topical antibiotic vs. vehicle • Clascoterone 1% daily vs. vehicle • Clascoterone 1% daily vs. clascoterone 1% twice daily • Tretinoin 0.05% vs. clascoterone 1% daily • Clindamycin 1% + Salicylic acid 2% vs. Clindamycin 1% • Clindamycin 1% + Tretinoin 0.025% vs. Clindamycin 1% + Salicylic acid 2% • Supramolecular salicylic acid 2% vs. adapalene 0.01% + BP 5% • Clindamycin 1% + salicylic acid 3% vs. clindamycin 1% + tretinoin • Tretinoin 0.02% + Clindamycin 0.8% + Glycolic acid 4% standard application vs. short contact therapy
Systemic antibiotics	• Doxycycline at different dosages • Doxycycline vs. erythromycin • Minocycline at different dosages • Minocycline vs. doxycycline • Minocycline vs. zinc gluconate • Minocycline vs. clindamycin lotion • Minocycline vs. erythromycin/zinc lotion • Minocycline vs. benzoyl peroxide

	• Minocycline vs. erythromycin/benzoyl peroxide • Minocycline/azelaic acid vs. isotretinoin • Minocycline vs. tazarotene gel • Minocycline vs. minocycline plus tazarotene gel • Azithromycin at different dosages • Azithromycin vs. Azithromycin plus NB-UVB • Trimethoprim/sulfamethoxazole vs. placebo • Doxycycline + tretinoin cream vs. azithromycin + tretinoin cream • Doxycycline + BP cleaner + clindamycin 1% vs. doxycycline + BP cleaner for truncal acne • Doxycycline + adapalene/BP gel vs. doxycycline • Doxycycline + adapalene gel vs. ALA-PDT* • Minocycline + tretinoin/erythromycin gel vs. tretinoin/erythromycin gel
Hormonal agents	• Drospirenone 3 mg/EE 30 µg vs. Levonorgestrel 150 µg/ EE 30 µg • Levonorgestrel 150 µg / EE 30 µg vs. Desogestrol 150 µg / EE 30 µg • Desogestrol 150 µg / EE 20 µg vs. Levonorgestrel 100 µg / EE 20 µg • Norgestimate/EE (triphasic) vs. Desogestrol/EE (biphasic) • Drospirenone 3 mg / EE 30 µg vs. Norgestimate 180-215-250 µg / EE 35 µg • Levonorgestrel 100 µg / EE 20 µg vs. Norethindrone acetate 1 mg / EE 20 µg • Drospirenone 3mg/EE 20 µg vs. topical azelaic acid twice daily • Metformin vs. placebo in PCOS • Metformin vs. COC in PCOS • Metformin plus COC vs. COC in PCOS • Metformin + tetracycline + BP vs. tetracycline + BP • Metformin and hypocaloric diet with PRN acne symptomatic treatment vs. PRN acne symptomatic treatment • Metformin plus lifestyle change vs. lifestyle change in PCOS • Metformin plus exercise vs. exercise in PCOS
Isotretinoin	• Traditional dosage (0.5-1.0mg/kg/day) isotretinoin vs. low dosage (<0.5mg/kg/day) isotretinoin • Isotretinoin 20mg daily vs. 20mg every other day • Isotretinoin 0.5-1.0mg/kg/day once daily vs. 0.5-1.0 mg/kg/day divided as twice daily • Isotretinoin vs. systemic antibiotics • Isotretinoin vs. systemic antibiotics + topical agent • Isotretinoin + topical agents vs. isotretinoin

Physical modalities	• Glycolic acid 40% vs. control • Combined 420 nm blue light and 660 nm red light vs. control • Pulse dye laser + isotretinoin vs. isotretinoin • Adding 585 nm pulsed dye laser to clindamycin 1% + BP 5% • Trichloroacetic acid 25% vs. Salicylic acid 30% • Mandelic acid 45% vs. salicylic acid 30% • Salicylic acid 30% vs. glycolic acid 30% • Jessner's solution vs. glycolic acid 70% • Nd:YAG laser vs. 595 nm pulsed dye laser • Pulsed dye laser vs. combined 585/1,064 nm laser • Acne lesion extraction vs. doxycycline • Salicylic acid 30% vs. Jessner's solution • Glycolic acid vs. amino fruit acid • Trichloroacetic acid 25% vs. topical tretinoin/BP • Trichloroacetic acid 25% vs. pulsed dye laser • Salicylic acid 30% vs. pneumatic broadband light • Salicylic acid 10% vs. combined blue and red light therapy • Microneedle radiofrequency vs. control • Infrared LED diode vs. control • IPL vs. control • 1450 nm diode laser vs. control • 595 nm PDL vs. control • 635-670 nm red light vs. control • Nd:YAG vs. control • KTP laser vs. control • Photodynamic therapy + ALA vs. control • 589/1319nm laser vs. control • Photodynamic therapy + ALA + minocycline vs. minocycline • 550 laser + isotretinoin vs. isotretinoin • 420 nanometer IPL + isotretinoin vs. isotretinoin • 1,450 nm diode laser + blue light vs. blue light • PDT ALA 5% vs. Combined blue and red LED • Pulsed dye laser vs. Combined 470 blue light + 623 red light

	• 407-420 nm blue light vs. BP 4% • IPL vs. BP 5% • Blue light vs. isotretinoin • Pulsed dye laser vs. topical tretinoin + BP
Complementary / Alternative Medicine	• Tea tree oil vs. placebo • Tea tree oil + adapalene vs. adapalene • Tea tree oil vs. BP • Green tea vs. placebo • Green tea vs. zinc 5% • Green tea oral supplement vs. placebo • Zinc 60mg vs. minocycline 100mg • Pantothenic acid vs. placebo • Minocycline vs. erythromycin/zinc lotion • Element zinc 2% vs. placebo • Topical antibiotics + zinc vs. topical antibiotics • Erythromycin 4% + zinc 1.2% vs. clindamycin 1% + BP 5% • Niacinamide 5% + BP 2.5% vs. BP 2.5%
Diet	• Low-glycemic-load diet vs. high-glycemic-load diet • Low glycemic diet + BP vs. BP • Metformin and hypocaloric diet with PRN acne symptomatic treatment vs. PRN acne symptomatic treatment