American Academy of Dermatology Association

Online Supplement

Guidelines of care for the management and treatment of atopic dermatitis in adults with topical therapies

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e-Table 1. All non-prescription moisturizers versus vehicle, placebo, or no treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	moisturizers	control	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in disease severity as assessed by investigators (follow up: range 28 days to 41 days; assessed with: SCORAD and EASI)												
5 [1-5]	randomized trials	not serious	not serious	not serious	serious [a]	none	279	207	SMD **0.51 SD lower** (0.85 lower to 0.17 lower)		⊕⊕⊕◯ MODERATE	CRITICAL
Change in disease severity as assessed by investigators (follow up: 4 weeks; assessed with: EASI)												
1 [6]	randomized trial	not serious	not serious	not serious	serious [b]	none	For 12 AD patients randomized to Lipopolysaccharide-containing moisturizing cream, bid and 13 AD patients randomized to vehicle cream only, at 4 weeks EASI scores of both groups improved significantly.				⊕⊕⊕◯ MODERATE	CRITICAL
Change from baseline in disease severity as assessed by participants (follow up: range 21 days to 56 days; assessed with: number of participants who considered their skin to have improved)												
3 [1,2,7]	randomized trials	not serious	not serious	not serious	serious [c]	none	230/291 (79.0%)	66/154 (42.9%)	**RR 2.24** (0.89 to 5.64)	**53 more per 100** (from 5 fewer to 100 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Change from baseline in itch (follow up: range 22 days to 56 days; assessed with: Visual Analog Scale)												
3 [1,2,4]	randomized trials	not serious [d]	not serious	not serious	serious [e]	none	209	137	SMD 0.90 SD **lower** (1.89 lower to 0.10 higher)		⊕⊕⊕◯ MODERATE	CRITICAL
Change from baseline in itch (follow up: 4 weeks; assessed with: VAS from 0 (no itching) to 10 (severe itching))												
1 [6]	randomized trial	not serious	not serious	not serious	serious [b]	none	For 12 AD patients randomized to Lipopolysaccharide-containing moisturizing cream, bid and 13 AD patients randomized to vehicle cream only, at 4 weeks in the treatment group, improvements were observed with significant differences between baseline and VAS scores at both 2 and 4 weeks. In the placebo group, there was a significant improvement at 2 weeks, but no significant difference was observed between scores at baseline and at 4 weeks.				⊕⊕⊕◯ MODERATE	CRITICAL
Flare prevention (follow up: range 50 days to 6 months; assessed with: Number of participants who experienced a flare)												
3 [1,8,9]	randomized trials	serious [f]	not serious	not serious	not serious	none	23/192 (12.0%)	64/118 (54.2%)	**RR 0.30** (0.14 to 0.63)	**38 fewer per 100** (from 47 fewer to 20 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Withdrawal due to adverse event (follow up: range 22 days to 50 days; assessed with: participants discontinuing treatment due to AE)												
2 [1,2]	randomized trials	serious [g]	not serious	not serious	not serious [h]	none	2/160 (1.3%)	0/86 (0.0%)	**RR 2.67** (0.13 to 54.97)	**0 fewer per 100** (from 0 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse events (follow up: range 22 days to 50 days; assessed with: number of participants experiencing an adverse event)												
5 [1,2,5,7,10]	randomized trials	serious [i]	not serious	not serious	serious [j]	none	117/341 (34.3%)	45/204 (22.1%)	**RR 1.32** (1.01 to 1.74)	**7 more per 100** (from 0 fewer to 16 more)	⊕⊕◯◯ LOW	IMPORTANT
Change from baseline in quality of life (follow up: range 28 days; assessed with: Skindex-16)												

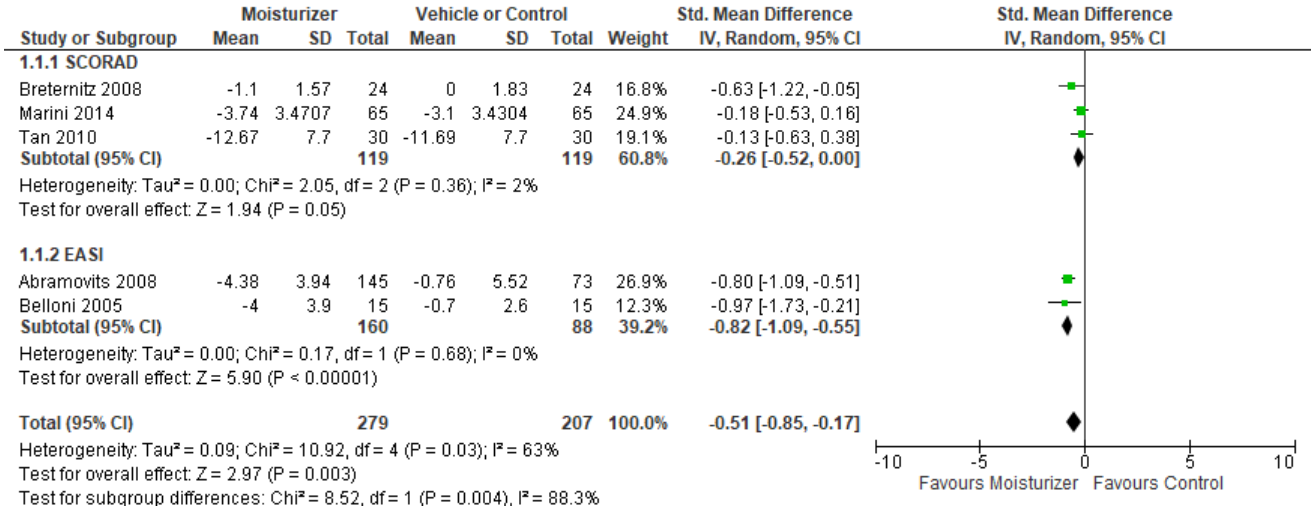
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	moisturizers	control	Relative (95% CI)	Absolute (95% CI)		
1 [11]	randomized trials	not serious	serious [k]	not serious	serious [l]	none	For 27 AD patients randomized to a pseudo-ceramide and eucalyptus moisturizing gel b.i.d and 17 AD patients not using any moisturizer, at 4 weeks analysis by Skindex-16 revealed significant improvements in emotions (p<0.05), functioning (p<0.001), and global (p<0.05) but not symptom. The non-treated group did not have significant improvement in any domain.[11]				⊕⊕◯◯ LOW	IMPORTANT

AD: Atopic dermatitis**; CI:** Confidence interval; **SMD:** Standardized mean difference; **RR:** Risk ratio; **MD:** Mean difference; **SCORAD**: SCORing Atopic Dermatitis; **EASI:** Eczema Area and Severity Index; **VAS:** Visual analog scale

Explanations

a. CI consistent with very small (0.17) and large (0.75) benefit.
b. Study relied on a small sample, concerning for precision.
c. CI consistent with the possibility of no risk difference and important benefit.
d. Not downgraded for borderline risk of bias as two studies are of a low risk of bias and one study (contributing less weight to the effect estimate) is of a high risk of bias, due to attrition, an unbalanced number of drop-outs (11% vs 21%) and per-protocol analysis.
e. CI consistent with the possibility of no difference.
f. Two studies are of a moderate risk of bias, due to lack of or unclear masking; one study is of a high risk of bias, due to attrition, an unbalanced number of drop-outs (11% vs 21%), and per-protocol analysis.
g. The largest study is of a high risk of bias, due to attrition, unbalanced number of drop-outs (11% vs 21%) and per-protocol analysis.
h. CI consistent with both no effect and appreciable benefit and harm but low event rate indicative of intervention safety despite imprecision related to relative safety.
i. One study is of a high risk of bias, due to attrition, an unbalanced number of drop-outs (11% vs 21%), and per-protocol analysis; One study is of unclear risk of bias due to minimal investigator masking methods reporting and unmasked participants.
j. CI consistent with little to no harm and appreciable harm.
k. One study suggests significant improvement via Skindex-16 assessment and one study reports a non-significant difference in QoL as assessed via DQLI.
l. Both studies relied on small samples: CI for MD consistent with no risk difference and appreciable benefit and harm.

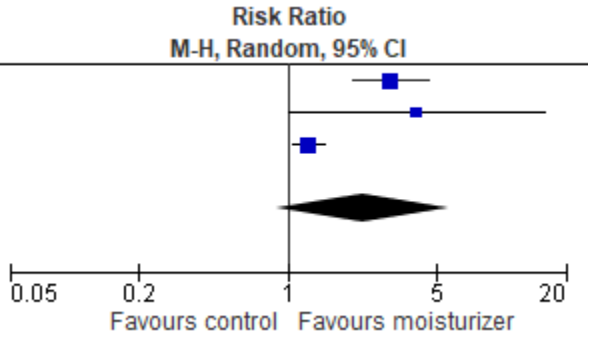
Analysis 1a. Change in disease severity as assessed by investigators (SCORAD & EASI)



Analysis 1b. Number of participants who experienced improvement (self-assessed)

Study or Subgroup	Moisturizer Events	Moisturizer Total	Vehicle or Control Events	Vehicle or Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Abramovits 2008	108	145	18	73	38.0%	3.02 [2.00, 4.56]
Belloni 2005	8	15	2	15	21.5%	4.00 [1.01, 15.81]
Loden 2002	114	131	46	66	40.5%	1.25 [1.05, 1.48]
Total (95% CI)		**291**		**154**	**100.0%**	**2.24 [0.89, 5.64]**
Total events	230		66			

Heterogeneity: Tau² = 0.54; Chi² = 24.63, df = 2 (P < 0.00001); I² = 92%
Test for overall effect: Z = 1.72 (P = 0.09)



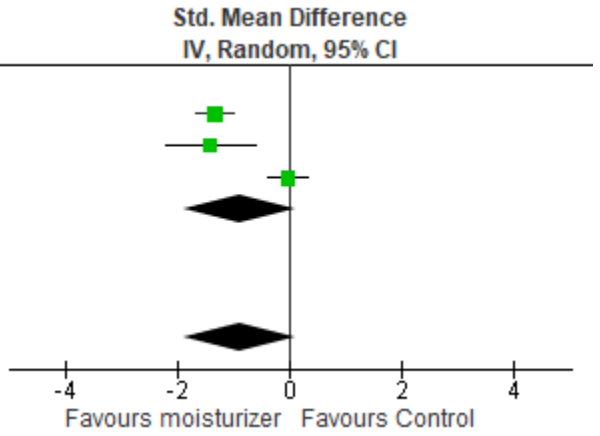
Analysis 1c. Change from baseline in itch.

Study or Subgroup	Moisturizer Mean	Moisturizer SD	Moisturizer Total	Vehicle or Control Mean	Vehicle or Control SD	Vehicle or Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.3.1 VAS								
Abramovits 2008	-5.8	2.5	129	-2.1	3.3	57	35.3%	-1.33 [-1.67, -0.99]
Belloni 2005	-1.3	0.5	15	-0.5	0.6	15	29.5%	-1.41 [-2.22, -0.60]
Marini 2014	-23.98	32.4935	65	-22.92	34.8653	65	35.2%	-0.03 [-0.38, 0.31]
Subtotal (95% CI)			**209**			**137**	**100.0%**	**-0.90 [-1.89, 0.10]**

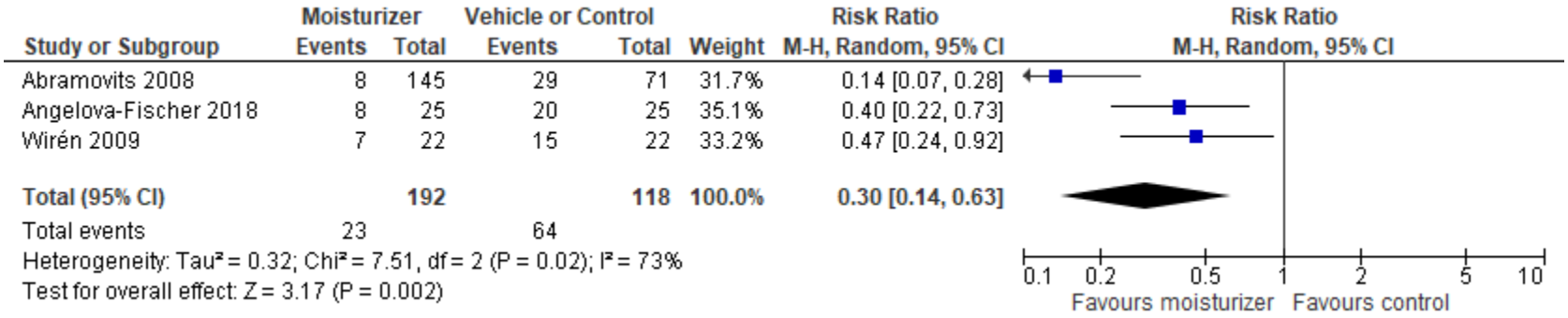
Heterogeneity: Tau² = 0.70; Chi² = 30.52, df = 2 (P < 0.00001); I² = 93%
Test for overall effect: Z = 1.77 (P = 0.08)

Total (95% CI)			**209**			**137**	**100.0%**	**-0.90 [-1.89, 0.10]**

Heterogeneity: Tau² = 0.70; Chi² = 30.52, df = 2 (P < 0.00001); I² = 93%
Test for overall effect: Z = 1.77 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 1d. Number of participants who experienced a flare.



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e-Table 2. Bathing & bathing practices

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Skin Roughness (follow up: 6 weeks; assessed with: Microtopography of the skin using PRIMOS optical 3D device)									
1 [1]	randomized trials	not serious	not serious	not serious	serious [a]	none	For 30 adults with AD randomized to bathing a forearm in tap water and the contralateral forearm in a bath solution of 5% Dead Sea salt, a significant decrease in skin roughness occurred at 3 weeks and after 6 weeks was reduced by 40% ($p<0.05$) for the treated arm and a non-significant decrease in skin roughness was noted for the control arm over the 6 weeks.	⨁⨁⨁◯ MODERATE	IMPORTANT
Skin Redness/Inflammation (follow up: 6 weeks; assessed with: Chromameter CR 300 measurement)									
1 [1]	randomized trials	not serious	not serious	not serious	serious [a]	none	For 30 adults with AD randomized to bathing a forearm in tap water and the contralateral forearm in a bath solution of 5% Dead Sea salt, a significant decrease in skin redness was found at 6 weeks of treatment with salt bath but skin redness was unchanged after tap water bath.	⨁⨁⨁◯ MODERATE	IMPORTANT

AD: Atopic dermatitis

Explanations

a. Small sample is concerning for precision.

Bibliography

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e-Table 3. Bleach Bath vs placebo or bath emollient

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bleach Baths	Water Baths	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in clinical severity as assessed by investigators (follow-up: 1 months; assessed with: mean change from baseline in EASI or SCORAD scores)												
4[1-4]	randomized trials	serious[a]	not serious	not serious[b]	very serious[c]	none	For 18 patients (aged 2-30yo) with moderate to severe uninfected AD randomized to bleach baths and 18 randomized to placebo twice weekly for 2, there was a significant within-group reduction from baseline in mean EASI score at one month in the bleach bath group (MD -9.30, p=0.017) but no significant within-group reduction for placebo (MD -8.90, p=0.06) or between the groups: MD -5.2 (95%CI -13.34, 2.94). A significant, but not clinically meaningful^, between-group difference was reported at 2 months: MD -12.70 95%CI -20.06, -5.34.[1] For 9 children with moderate to severe uninfected AD randomized to bleach baths plus corticosteroids and 9 to placebo bath plus corticosteroids, at one month mean EASI score improved significantly in both groups but there was no difference between the groups: MD -0.96 (95%CI -7.05, 5.13).[2] For 40 children with moderate to severe AD randomized to either beach bath or placebo bath 2 to 3 times/week for 4 weeks, then crossed over after a 4 week washout period, there was a mean change from baseline in objective SCORAD of -0.50 (SD 10.63) during the bleach bath period compared with -3.95 (SD 10.54) during the placebo period; the difference between the groups was not statistically significant: MD 3.45; 95% CI -1.66 to 8.56.[3] For 8 children with moderate to severe AD randomized to bleach bath 3 times/week and 11 randomized to bath emollient, at 12 weeks after adjusting for baseline imbalances there was a significant, but not clinically meaningful^^ between-group differences in reduction in mean SCORAD from baseline: MD -17.0 95%CI -31.31, -2.69.[4]			⊕◯◯◯ Very low	CRITICAL
Quality of Life (follow-up: 28 days; assessed with: Change from baseline in CDLQI; range 0-30; higher values indicate reduced QoL)												
1[3]	randomized trials	not serious	not serious	not serious[d]	serious[e]	none	For 40 children with moderate to severe AD randomized to either beach bath or placebo bath 2 to 3 times/week for 4 weeks, then crossed over after a 4 week washout period, after bleach bath treatment there was a 0.53 point reduction in CDLQI compared to a 1.43 point reduction following placebo: MD 0.90 95%CI -1.32, 3.12.[3]			⊕⊕⊕◯ Moderate	CRITICAL
Withdrawals due to adverse events (follow-up: 2 months; assessed with: participants discontinuing treatment due to AE)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bleach Baths	Water Baths	Relative (95% CI)	Absolute (95% CI)		
4[1,3-5]	randomized trials	serious[f]	not serious	not serious[b]	serious[g]	none	Across bleach bath studies withdrawal due to AE rates were low, one parallel-group study[4] reported no AEs across treatment arms(n=19) and an interindividual study[5] (n=10) also reported no withdrawals due to AE. For 18 patients (aged2-30yo) with moderate to severe uninfected AD randomized to bleach baths and 18 randomized to placebo twice weekly for 2, one participant withdrew from the placebo group due to worsening itch; there were no withdrawals due to adverse events in the bleach bath group: RR 0.33; 95% CI 0.01 to 7.74.[1] For 40 children with moderate to severe AD randomized to either beach bath or placebo bath 2 to 3 times/week for 4 weeks, then crossed over after a 4 week washout period, during the crossover period one participant withdrew from treatment during the bleach bath period due to itch and one participant withdrew from treatment during the placebo period due to dryness.[3]				⨁⨁◯◯ Low	CRITICAL

AD: Atopic Dermatitis; **CI:** confidence interval; **MD:** mean difference; **CDLQI;** Children's Dermatology Life Quality Index; **AE:** Adverse event

Explanations

a.Three studies were of a high risk of bias for possible performance bias and baseline imbalances in study populations.
b.Studies include adults and children but the inclusion of children was not considered important indirectness.
c.All included studies relied on small samples (total n=113); Two CIs for between-group differences consistent with important reduction, no reduction, and minimal increase; heterogeneity in control group means.
d.Study includes only children, age of the population was not considered important indirectness.
e.Small sample; CI is imprecise consistent with both important increase in risk, no difference and some decrease in risk.
f.Two studies were of a high risk of bias for possible performance bias and baseline imbalances in study populations.
g.All included studies relied on very small samples and the rates of events were too low to produce meaningful estimates.

Study Characteristics

Study	Study Population	Intervention	Comparator
Gonzalez 2016	21 (18 evaluable) children with moderate to severe uninfected AD	bleach baths (bottle of bleach diluted with bath water two times per week to achieve a 0.005% sodium hypochlorite concentration) + topical corticosteroid for 4 weeks.	placebo bath (bottle of water) + topical corticosteroid 2x weekly for 4 weeks
Hon 2016	40 children with moderate to severe AD with previous *S. aureus* colonization.	bleach bath (0.005% sodium hypochlorite) for 10 minutes two to three times per week for 4 weeks	placebo bath (water) for 10 minutes two to three times per week for 4 weeks
Leins 2013	19 children with moderate to severe eczema (infective status not specified) for 12 weeks	bleach bath (sodium hypochlorite 0.005%) three times per week + oral antibiotics.	bath emollient (bath oil containing liquid paraffin 95% volume per volume) three times per week for 12 weeks + oral antibiotics.
Shi 2016	10 patients (children and adults) with AD (severity and infective status not specified)	bleach bath (sodium hypochlorite 0.005%) 10-minute immersion	Placebo (water) bath 10-minute immersion
Wong 2013	42 children and adults (36 evaluable) with moderate to severe uninfected eczema	bleach baths (100 mL of sodium hypochlorite (bleach) in 100 L (or roughly half a tub) of water, sodium hypochlorite 0.005%; for children under twelve years old, 50 mL bleach was added to a quarter tub of water) 10-minute immersion twice weekly for 8 weeks.	placebo baths (100 mL of distilled water in 100 L of water) 10-minute immersion twice weekly for 8 weeks.

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e-Table 4. Medium potnecy topical corticosteroid (prednicarbate) + Wet wrap therapy vs Medium potency topical corticosteroid (prednicarbate) alone

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Wet-wrap + TCS	TCS alone	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in severity as assessed by investigators (follow up: range 48 hrs to 72 hrs; assessed with: Mean change in local SCORAD (six parameters erythema, papulation, lichenification, exudation, excoriation and dryness judged by the physician (on a scale of 0–3; 0 = absent, 1 = mild, 2 = moderate, 3 = severe)))												
1 [1]	randomized trials	not serious	not serious	not serious	serious [a]	none	24 -4.4 (95%CI -5.34, -3.46)	24 -3.0 (95%CI -4.07, -1.93)	MD **1.4 lower** (2.75 lower to 0.05 lower)		⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse events (follow up: 14 days; assessed with: Participants experiencing adverse events)												
1 [1]	randomized trials	not serious	not serious	not serious	serious [a]	none	In 24 AD patients (mean age 30.5yo), contralateral limbs were randomized to prednicarbate and wet wrap dressing or prednicarbate alone for 48 to 72 hours. No side effects and no withdrawal effects were observed in both treatment sides during the study and a follow-up period of 14 days.				⊕⊕⊕◯ MODERATE	CRITICAL

AD: Atopic dermatitis**; TCS:** Topical corticosteroid; **CI:** Confidence interval; **MD:** Mean difference; **SCORAD:** SCORing Atopic Dermatitis

Study Intervention Characteristics

Study	Intervention	Comparator
Foelster-Holst 2006	0.1% prednicarbate + wet wrap dressing (Coverflex), 48-72 hours	0.1% prednicarbate, 48-72 hours

Explanations

a. Small, intraindividual sample suggests imprecision.

Bibliography

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e-Table 5. Medium potency topical corticosteroid (mometasone furoate) + Wet wrap therapy vs Vehicle + Wet wrap therapy

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WWT+ TCS	Vehicle + TCS	Relative (95% CI)	Absolute (95% CI)		
Change in severity from baseline as assessed by investigators (follow up: range 5 days to 28 days; assessed with: local SCORAD-assesses the clinical symptoms erythema, edema/papulation, oozing/crusts, excoriations, lichenification and the subjective parameter local pruritus. Each item was graded on a 4-point scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe) resulting in a maximum count of 18 points- or objective SCORAD maximum score 83; Lower score indicates lesser severity.)												
2 [1,2]	randomized trials	not serious	not serious	serious [a]	serious [b]	none	For 20 AD patients (aged 2-17yo) randomized to 0.1% mometasone furoate bid + WWT bid, 5 days on one arm and vehicle emollient cream bid + WWT bid, 5 days on the contralateral arm, initially, the severity of the lesions was almost identical on both arms, SCORAD values at day 3 and 5 continuously improved in both groups. However, in comparison to the emollient-only group, the improvement in the mometasone furoate group was significantly better (p<0.01). [1] For 19 AD patients (aged 6 months-10yo) randomized to diluted corticosteroids (1:3 mometasone furoate 0.1% ointment and for the face 1:19 mometasone furoate 0.1% ointment) under wet wrap bodysuit and face mask and 20 patients randomized to placebo emollient under wet wraps applied qd on the whole-body during week 1 and applied qd to lesions for 4 consecutive days during weeks 2-4. Emollients used in both groups on the other 3 days of weeks 2-4, mean objective SCORAD scores declined in both groups with the decline more pronounced in the TCS group: MD in objective SCORAD at day 28 -9.927 (SE 3.268, p=0.0028).[2]				⊕⊕◯◯ LOW	CRITICAL
Infection (follow up: 28 days; assessed with: Participants developing secondary infected AD during treatment)												
1 [2]	randomized trials	not serious	not serious	serious [c]	serious [d]	none	0/20 (0.0%)	2/19 (10.5%)	**RR 0.20** (0.01 to 3.92)	**84 fewer per 1,000** (from 104 fewer to 307 more)	⊕⊕◯◯ LOW	IMPORTANT

AD: Atopic dermatitis**; TCS:** Topical corticosteroid; **WWT:** Wet wrap therapy; **SCORAD:** SCORing Atopic Dermatitis; **MD**: Mean difference

Explanations

a. One study included a sample aged 2-7yo and the other study included a sample age 6 months to 10 years old differing importantly from the clinical question focused on the management of AD in adults.
b. One study relied on a small, intraindividual sample and the other study relied on a small parallel group sample.
c. Study included a sample aged 6 months to 10 years old differing importantly from the clinical question focused on the management of AD in adults.
d. Study relied on a small sample.

Study Intervention Characteristics

Study	Intervention	Comparator
Janmohamed 2014	diluted corticosteroids (1:3 mometasone furoate 0.1% ointment and for the face 1:19 mometasone furoate 0.1% ointment) applied qd to the whole body +WWT therapy (Tubifast garments and face mask), 1 week, then diluted corticosteroids applied qd to lesions only + WWT for 4 consecutive days, 3 weeks. Emollients used on the other 3 days of the 3 week per lesion treatment.	emollient (petrolatum 20% in cetomacrogol cream) applied qd on the whole-body + WWT therapy (Tubifast garments and face mask, 1 week, then emollient applied qd to lesions for 4 consecutive days + WWT for 4 consecutive days, 3 weeks. Emollients on the other 3 days of weeks 2-4.
Schnopp 2002	0.1% mometasone furoate bid + WWT (Tubifast bandages) bid, 5 days	Vehicle cream bid + WWT (Tubifast bandages) bid, 5 days

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e-Table 6. Lowest potency topical corticosteroid (hydrocortisone) + Wet wrap therapy vs Lowest potency topical corticosteroid (hydrocortisone)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WWT+TCS	TCS alone	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in severity as assessed by investigators (follow up: 4 weeks; assessed with: mean change in SCORAD from baseline)												
1 [1]	randomized trials	not serious	not serious	serious [a]	serious [b]	none	23 MD-29.0 (-38.0, -20.0)	22 MD -24.0 (-32.5, -15,5)	MD **5 lower** (16.68 lower to 6.68 higher)		⊕⊕◯◯ LOW	CRITICAL
Change from baseline in severity as assessed by investigators (follow up: 2 weeks; assessed with: mean change from baseline in SASSAD; Maximum score 108; lower score indicates lesser severity)												
1 [2]	randomized trials	not serious	not serious	serious [c]	serious [d]	none	For 10 children with AD randomized to qd application of 1% hydrocortisone with wet wraps daily for 1 week, then only at night for the following week and 9 children with AD randomized to 1% HC bid daily for two weeks, the mean SASSAD score in the WWT group improved from 28 at baseline to 16.6 at the end of week 2, in the HC alone group mean SASSAD score improved from 29.9 at baseline to 13.2 at the end of week 2. The mean improvement in SASSAD score was 8 (95%CI -18, 2) more in the HC alone group compared to the WWT group.				⊕⊕◯◯ LOW	CRITICAL
Withdrawal due to AE (follow up: 2 weeks; assessed with: Participants discontinuing treatment due to AE)												
1 [2]	randomized trials	not serious	not serious	serious [c]	serious [d]	none	2/10 (20.0%)	0/9 (0.0%)	**RR 4.55** (0.25 to 83.70)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ LOW	CRITICAL
Change from baseline in quality of life												
1 [2]	randomized trials	not serious	not serious	serious [c]	serious [e]	none	10 MD 4.5 (-0.01, 9.0)	9 MD 8.10 (3.5, 12.7)	MD **3.6 lower** (9.14 lower to 1.94 higher)		⊕⊕◯◯ LOW	CRITICAL

AD: Atopic dermatitis**; TCS:** Topical corticosteroid; **WWT:** Wet wrap therapy; **SCORAD:** SCORing Atopic Dermatitis; **SASSAD**: Six Area, Six Sign Atopic Dermatitis Severity Score; **MD**: Mean difference; **RR**: risk ratio; **AE:** Adverse event

Explanations

a. Study sample aged 4-27 months, differs importantly form the clinical question focused on the management of AD in adults.
b. CI consistent with the possibility of no difference and important benefit.
c. Study sample aged 4 months to 3 years differs importantly from the clinical question focused on the management of AD in adults.
d. Small study samples leading to CI consistent with the possibility of no difference in risk and important harm and benefit.
e. CI consistent with the possibility of no difference and important harm

Study Intervention Characteristics

Study	Intervention	Comparator
Beattie 2004	1% hydrocortisone qd + WWT bid for 1 week, then 1% hydrocortisone qd + WWT qd for 1 week	1% hydrocortisone bid, 2 weeks

Hindley 2006	1% hydrocortisone (or if necessary more potent steroid) qd + WWT for 24 hours for 1 week, then 1% hydrocortisone (or if necessary more potent steroid) qd + WWT for 12 or 24 hours depending on progress as assessed by investigator, 3 weeks	Emollients ≥ 3 times daily + 1% hydrocortisone (or if necessary more potent steroid) bid, 4weeks

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e-Table 7. Pimecrolimus 1% vs vehicle

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pimecrolimus	vehicle	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in disease severity as assessed by investigators (follow up: range 1 weeks to 6 weeks; assessed with: ADSI, EASI, IGA and TSS; for all scales lower score indicates lesser severity)												
6 [1-6]	randomized trials	not serious	not serious	not serious	not serious	none	For 20 adult AD patients randomized to bid application of 1% pimecrolimus to one arm and vehicle on the contralateral arm, after 3 weeks of treatment with pimecrolimus there was a mean reduction of -5.05 (SD 2.50) in ADSI scores vs a mean reduction of -2.35 (SD 2.50) at the vehicle-treated sites (MD -2.70 (5%CI -4.25, -1.15).[5] For 30 adult AD patients randomized to qd application of 1% pimecrolimus to a target lesion and vehicle to another target lesion, after 2 weeks of treatment with 1% pimecrolimus there was a mean reduction of -2.93 in TSS vs a mean reduction of -2.21 at the vehicle-treated sites (MD -0.72 95%cl -1.92, 0.48).[6] For 34 adult AD patients randomized to qd or bid application of 1% pimecrolimus to one arm and vehicle on the contralateral arm, within 3 weeks of treatment with 1% pimecrolimus, there was a mean reduction of 71.9% in ADSI score vs a mean reduction of 10.3% at the placebo-treated sites.[4] For 101 AD patients (≥ 12 yo; median age 28 yo) randomized to 1% pimecrolimus bid and 99 randomized to vehicle, a reduction in head and neck EASI score of at least 60% at 6 weeks was achieved by 50.5% of the pimecrolimus-treated patients vs. 18.2% treated with vehicle ($p < 0.001$). [3] For 100 adult AD patients randomized to 1% pimecrolimus bid and 98 to vehicle, at day 7, 53% of pimecrolimus-treated patients vs 20% of vehicle-treated patients ($p < 0.001$) experienced a ≥1-point reduction in their IGA scores. [1] For 45 adult AD patients randomized to 1% pimecrolimus bid and 43 to vehicle, at 3 weeks 5/45 (11.1%) pimecrolimus-treated patients vs 0/43 vehicle-treated patients were clear or almost clear per IGA assessment.[2]				⊕⊕⊕⊕ HIGH	CRITICAL
Change from baseline in itch (follow up: range 1 weeks to 6 weeks; assessed with: VAS 10-cm and NRS 0=no itch; 3=severe itch)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pimecrolimus	vehicle	Relative (95% CI)	Absolute (95% CI)		
4 [1-3,5]	randomized trials	not serious	not serious	not serious	not serious	none	For 146 adult AD patients randomized to pimecrolimus 1% bid and 142 to vehicle reported in two studies, pimecrolimus treatment was associated with mild to no itch (NRS scores of 0 or 1): RR 2.09 (95%CI 1.58-2.75). [2,3] For 98 adult AD patients randomized to 1% pimecrolimus bid and 91 to vehicle, at day 7, 81% of pimecrolimus-treated patients vs 63% of vehicle-treated patients showed improvement in NRS itch score (≥1 point compared with baseline), p < 0.001.[1] For 20 adult AD patients randomized to application of 1% pimecrolimus bid on one arm and vehicle on the contralateral arm, mean reduction in VAS 10cm itch scores at 3 weeks were -3.5±1.8 vs -2.1±2.7 (MD 1.4 95%CI -0.07, 2.87), respectively.[5]				⊕⊕⊕⊕ HIGH	
Flare prevention (follow up: range 24 weeks to 26 weeks; assessed with: mean number of days without TCS use for flare or number of participants experiencing a flare)												
2 [7,8]	randomized trials	not serious	not serious	not serious	not serious	none	For 265 AD patients randomized to 1% pimecrolimus bid and 257 to vehicle, at 26 weeks, treatment with pimecrolimus significantly increased the mean number of days without TCS use for a flare from 138.7±53.2 to 152.0±44.0 days (p < 0.001), in comparison with vehicle application.[7] For 96 AD patients randomized to 1% pimecrolimus bid and 96 to vehicle, at 24 weeks, 43/96 pimecrolimus vs 18/96 vehicle-treated patients had not experienced a flare: RR 1.95, 95%CI 1.20, 3.20.[8]				⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse events (follow up: 3 weeks; assessed with: number of participants experiencing at least one serious AE))												
1 [5]	randomized trials	not serious	not serious	not serious	not serious [b]	none	0/20 (0.0%)	0/20 (0.0%)	**RR 1.00** (0.02 to 48.09)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse events (follow up: 26 weeks; assessed with: number of participants experiencing at least one serious AE))												
1 [7]	randomized trials	not serious	not serious	not serious	not serious [c]	none	5/264 (1.9%)	7/254 (2.8%)	**RR 0.69** (0.22 to 2.16)	**9 fewer per 1,000** (from 21 fewer to 32 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Withdrawal due to adverse event (follow up: range 1 weeks to 6 weeks; assessed with: participants discontinuing treatment due to AE)												
3 [1-3]	randomized trials	not serious	not serious	not serious	not serious [d]	none	8/245 (3.3%)	15/240 (6.3%)	**RR 0.56** (0.24 to 1.27)	**27 fewer per 1,000** (from 48 fewer to 17 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Withdrawal due to adverse event (follow up: range 24 weeks to 26 weeks)												
2 [7,8]	randomized trials	not serious	not serious	not serious	not serious [d]	none	2/360 (0.6%)	10/350 (2.9%)	**RR 0.20** (0.04 to 0.90)	**23 fewer per 1,000** (from 27 fewer to 3 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

AD: Atopic dermatitis; **ADSI:** Atopic Dermatitis Severity Index; **TSS:** Total Sign Score; **EASI:** Eczema Area and Severity Index; **IGA:** Investigator Global Assessment; **CI:** Confidence interval; **SMD:** Standardized mean difference; **MD:** Mean difference; **RR:** Risk ratio; **NRS:** Numeric rating scale; **VAS:** Visual analog scale; **TCS:** Topical corticosteroids; **AE**: Adverse event

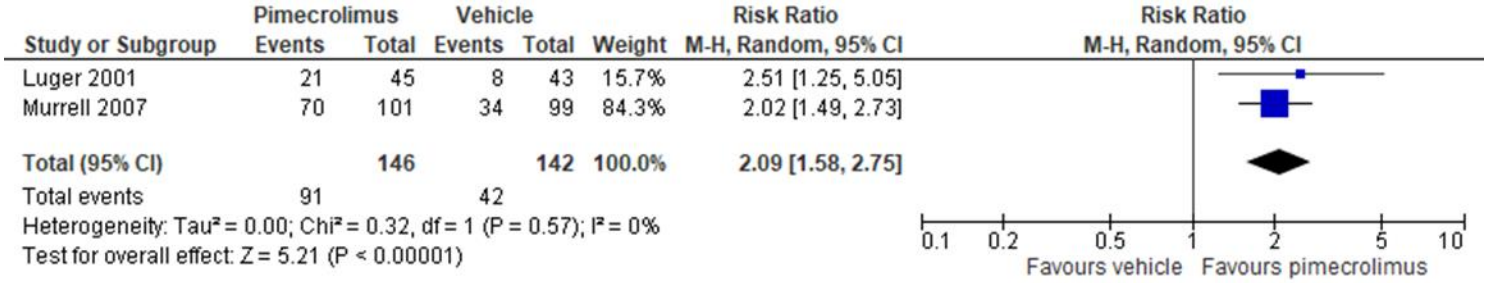
Explanations

a. CI consistent with very small and large difference.

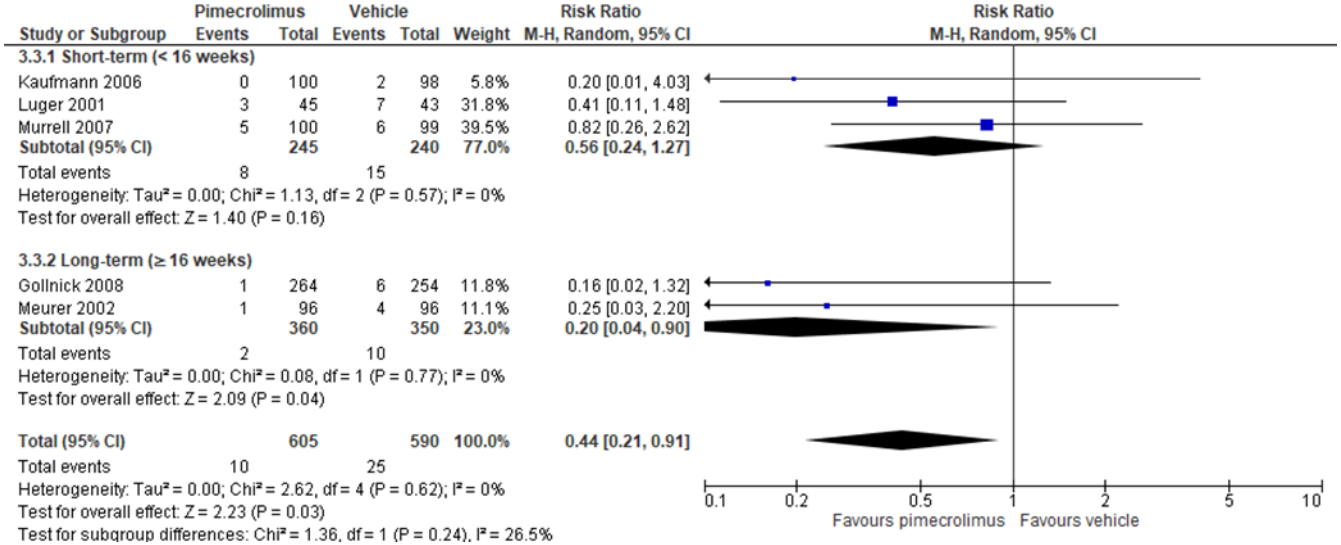
b. Small sample suggests imprecision, however across the evidence base serious adverse events are rare and indicative of a non-important increase in risk with the intervention so the evidence was not downgraded.

c. Due to low event rate across treatment groups the CI is consistent with the possibility of no risk difference and benefit or harm; however, across the evidence base serious adverse events are rare and indicative of a non-important increase in risk with the intervention leading to no important concerns about safety, so the evidence was not downgraded.
d. Due to low event rates the CI is consistent with clinically meaningful difference and unimportant difference; however, the evidence of low discontinuation rates is indicative of a non-important increase in risk with the intervention leading to no important concerns about safety, so the evidence was not downgraded.

Analysis 7a. Mild or no itch (itch score 0 or 1)



Analysis 7b. Withdrawal due to adverse event



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e-Table 8. Tacrolimus 0.03%, 0.1%, or 0.3% vs vehicle

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tacrolimus	vehicle	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in disease severity as assessed by investigators (follow up: range 3 weeks to 12 weeks; assessed with: Participants scored "cleared" or "excellent improvement" via physician global evaluation; Participants scored "clear" or "almost clear" via the IGA; Percent reduction in investigator assessed severity scores)												
3 [1-3]	randomized trials	not serious [a]	not serious	not serious	not serious	none	For 211 adult AD patients randomized to 0.03% tacrolimus, 209 AD patients randomized to 0.1% tacrolimus, and 212 AD patients randomized to vehicle bid for 12 weeks, 58/211 (27.5%), 77/209 (36.8%), and 14/212 (6.6%), respectively achieved improvement in disease severity as assessed by physician global evaluation (p<0.001 for both treatment groups compared to vehicle).[2] For 152 adult AD patients randomized to 0.03% tacrolimus and 148 AD patients to vehicle bid for 6 weeks, 74/152 (48.7%) and 48/148 (32.4%), respectively were clear or almost clear as assessed by IGA.[1] For 54 AD patients (mean age 30±12) randomized to 0.03% tacrolimus, 54 patients (mean age 28 ±9) randomized to 0.1% tacrolimus, 51 patients (mean age 27±10) randomized to 0.3% tacrolimus, and 54 patients (mean age 29±11) randomized to vehicle bid for 3 weeks, median percentage decreases in the investigator assessed severity scores (0 to 3)^ for the trunk and extremities were 66.7, 83.3, 75.0, 22.5%, respectively.[3]				⊕⊕⊕⊕ HIGH	CRITICAL
Change from baseline in disease severity as assessed by investigators (follow up: 12 months; assessed with: change in median EASI scores)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tacrolimus	vehicle	Relative (95% CI)	Absolute (95% CI)		
1 [4]	randomized trials	not serious	not serious	not serious	not serious	none	For 116 AD patients (mean age 31±12) randomized to 0.1% tacrolimus and 108 to vehicle b.i.d when IGA was ≤2 (following up to 6 weeks of 0.1% tacrolimus induction treatment), the median EASI score for the treatment group at 12mos compared with the score on day 1 of randomization indicates that disease was stable: 1.6 (range 0.0–33.7) and 1.8 (range 0.0–22.2), respectively. In contrast, the median EASI score for the vehicle group at 12mos compared with day 1 indicates a slight worsening of AD: 3.2 (range: 0.0–53.7) and 2.0 (range: 0.0–12.8), respectively.				⊕⊕⊕⊕ HIGH	CRITICAL
Change from baseline in itch (follow up: >4 weeks; assessed with: VAS itch VAS itch max=100)												
3 [1,2,5]	randomized trials	not serious	not serious	not serious	not serious	none	For 310 AD patients (aged 2-79) randomized to 0.03% tacrolimus bid and 307 randomized to vehicle, as early as day 4 of treatment and continuing throughout 6 weeks, mean VAS itch score was significantly lower in the tacrolimus treatment group than in the vehicle treatment group.[1] For 211 adults with AD randomized to 0.03% tacrolimus bid, 209 randomized to 0.1% tacrolimus and 212 to vehicle, with up to 12 weeks of treatment significantly greater improvement ($p<0.001$) was observed for tacrolimus-treated patients (0.03% or 0.1%) compared with vehicle-treated.[2] For 21 AD patients (aged >10yo; mean age 30.5yo) randomized to tacrolimus bid (0.03% for children, 0.1% for adults) and 21 to vehicle after achieving itch reduction (>20 VAS points) during induction therapy with tacrolimus, mean VAS-itch score in the tacrolimus group was well controlled as shown by values of 28.1±15.4 at the start and 29.6±20.9 at the end of maintenance treatment (>4 weeks), while that in the vehicle group significantly increased from 19.3±16.7 to 50.7±17.0. The mean change in VAS-itch scores was 1.50±3.30 in the tacrolimus monotherapy and 31.4±2.59 in the emollient group, respectively, in maintenance treatment (MD 28.6 (95% CI, 19.8, 37.5, $p<0.0001$).				⊕⊕⊕⊕ HIGH	CRITICAL
Flare prevention (follow up: range 40 weeks to 56 weeks; assessed with: Number of participants experiencing a flare)												
2 [4,6]	randomized trials	not serious	not serious	not serious	serious [b]	none	133/240 (55.4%)	123/179 (68.7%)	**RR 0.80** (0.59 to 1.09)	**137 fewer per 1,000** (from 282 fewer to 62 more)	⊕⊕⊕◯ MODERATE	CRITICAL ^^
Serious adverse events (follow up: 6 weeks; assessed with: participants experiencing a serious AE)												
1 [1]	randomized trial	not serious	not serious	not serious	not serious [c]	none	0/152 (0.0%)	0/148 (0.0%)	**RR 0.97** (0.02 to 48.76)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse events (follow up: 12 months; assessed with: participants experiencing a serious AE)												
1 [4]	randomized trial	not serious	not serious	not serious	not serious [c]	none	5/116 (4.3%)	3/108 (2.8%)	**RR 1.53** (0.37 to 6.25)	**15 more per 1,000** (from 17 fewer to 146 more)	⊕⊕⊕⊕ HIGH	CRITICAL

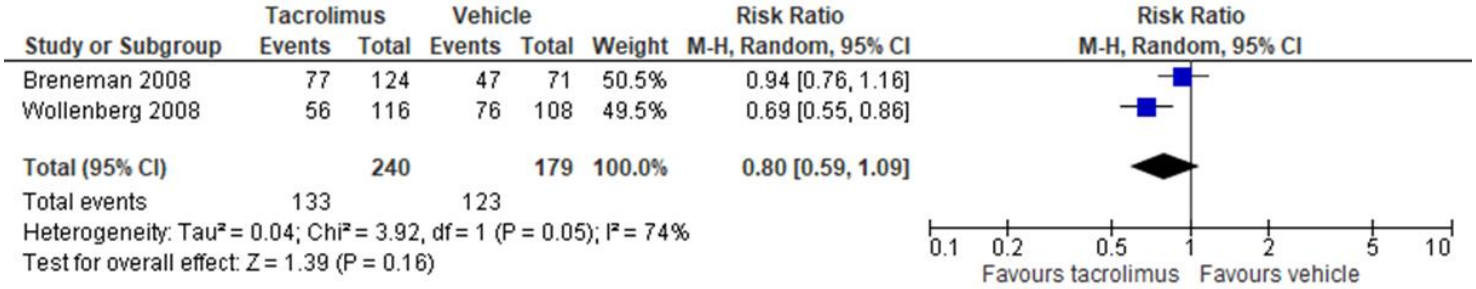
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tacrolimus	vehicle	Relative (95% CI)	Absolute (95% CI)		
Withdrawal due to adverse event (follow up: range 3 weeks to 12 weeks; assessed with: participants discontinuing treatment due to AE)												
2 [3,7]	randomized trials	not serious	not serious	not serious	not serious	none	29/528 (5.5%)	31/266 (11.7%)	**RR 0.47** (0.29 to 0.77)	**62 fewer per 1,000** (from 83 fewer to 27 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Infection (follow up: 12 weeks; assessed with: Incidence rate of skin infections)												
1 [8]	randomized trial	serious [d]	not serious	not serious	not serious	none	For 210 adult AD patients randomized to 0.03% tacrolimus, 209 patients randomized to 0.1% tacrolimus, and 212 randomized to vehicle bid for 12 weeks, adjusted incidence rates of cutaneous infections were 24.8, 17.7, and 18.0, respectively (p=0.15 for 0.03% vs vehicle, p=0.96 for 0.1% vs vehicle).				⊕⊕⊕◯ MODERATE	IMPORTANT
Quality of life (follow up: 12 weeks; assessed with: change in total DLQI score from baseline)												
1 [9]	randomized trial	not serious	not serious	not serious	not serious	none	For 176 adult AD patients (>16yo) randomized to 0.03% tacrolimus, 177 patients randomized to 0.1% tacrolimus, and 160 patients randomized to vehicle for 12 weeks, the mean change in DLQI scores from baseline were -21.1 (SE 1.4), -27.1 (SE 1.4), and -5.6 (SE 1.4), respectively (p=0.000 for both vehicle vs 0.03% and 0.1%).				⊕⊕⊕⊕ HIGH	CRITICAL

AD: Atopic dermatitis; **CI:** Confidence interval; **RR:** Risk ratio; **IGA:** Investigator Global Assessment; **VAS:** Visual analog scale; **AE**: Adverse event; **SE:** Standard error; **MD**: Mean difference

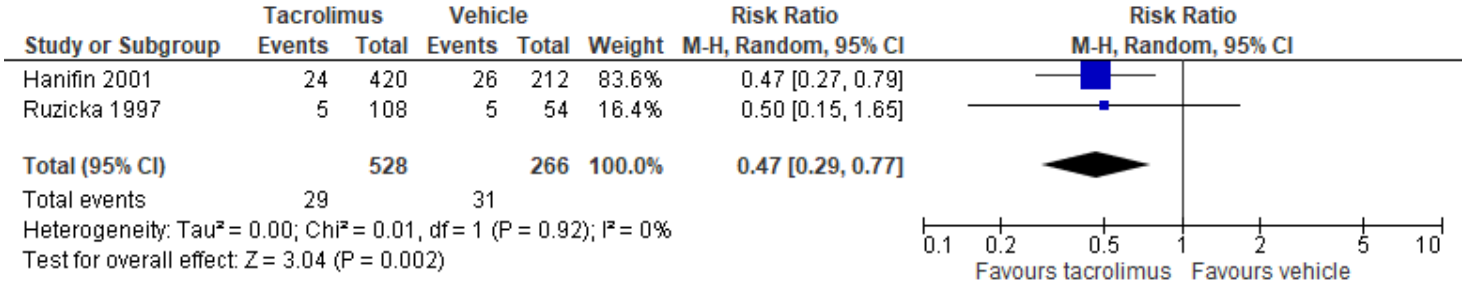
^ Scale of 0-3 for severity of erythema, edema, oozing, crusting, excoriation, and lichenification.
^^ In general for AD management, flare prevention is a critical outcome but this specific outcome data on long-term flare prevention was not a primary consideration for development of the recommendation related to short-term tacrolimus use to manage AD. Outcome data on change in clinical signs, itch, and safety informed recommendation development.

Explanations
a. Two studies are of low risk of bias and one study is of a moderate risk of bias for unclear selection methods and a high risk of attrition bias. Not downgraded for borderline risk of bias as downgraded for imprecision.
b. CI compatible with no risk difference, benefit, and small risk of harm.
c. Due to low event rate across treatment groups the CI is consistent with the possibility of no risk difference and benefit or harm; however, across the evidence base serious adverse events are rare and indicative of a non-important increase in risk with the intervention leading to no important concerns about safety, so the evidence was not downgraded.
d. Study is of a moderate risk of bias for unclear randomization and a high risk of attrition bias.

Analysis 8a. Number of participants who experienced a flare.



Analysis 8b. Withdrawal due to adverse event.



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e-Table 9. Tacrolimus 0.1% vs Pimecrolimus 1% (bid)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tacrolimus	pimecrolimus	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in severity as assessed by investigators (follow up: range 13 days to 6 weeks; assessed with: Investigator assessment of "clear" or "almost clear" via IGA or IGADA)												
3 [1-3]	randomized trials	not serious	not serious	not serious	not serious	none	153/351 (43.6%)	86/343 (25.1%)	**RR 1.74** (1.40 to 2.16)	**186 more per 1,000** (from 100 more to 291 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Change in baseline in severity as assessed by investigators (follow up: 6 weeks; assessed with: percent reduction in mean EASI scores from baseline)												
2 [2,3]	randomized trials	not serious	not serious	not serious	not serious	none	For 210 AD patients (≥16yo) randomized to 0.1% tacrolimus and 203 patients randomized to 1% pimecrolimus bid for 6 weeks, mean EASI scores were reduced by 54.1% and 34.9%, respectively (p<0.001). [3] For 141 AD patients (≥16yo) randomized to 0.1% tacrolimus and 140 to 1% pimecrolimus for 6 weeks, mean EASI scores were reduced by 57% and 39%, respectively (p=0.0002). [2]				⊕⊕⊕⊕ HIGH	CRITICAL
Reduction in itch (follow up: 6 weeks; assessed with: VAS itch 10cm)												
1 [3]	randomized trial	serious [a]	not serious	not serious	not serious	none	For 210 AD patients (≥16yo) randomized to 0.1% tacrolimus and 203 patients randomized to 1% pimecrolimus bid for 6 weeks, mean VAS itch scores decreased from 6.0 to 3.1 (no SD provided, p<0.01) in tacrolimus-treated patients and from 6.2 to 3.8 (noted as non-significant) in pimecrolimus-treated patients.				⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse events (follow up: 13 days; assessed with: participants experiencing a serious AE)												
1 [1]	randomized trial	not serious	not serious	not serious	serious [b]	none	2/19 (10.5%)	0/18 (0.0%)	**RR 4.32** (0.22 to 84.48)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Withdrawal due to adverse event (follow up: 6 weeks; assessed with: participants discontinuing treatment due to adverse event)												
2 [2,3]	randomized trials	not serious	not serious [c]	not serious	not serious [d]	none	9/351 (2.6%)	10/343 (2.9%)	**RR 0.88** (0.36 to 2.18)	**3 fewer per 1,000** (from 19 fewer to 34 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Skin infection (follow up: 6 weeks; assessed with: participants experiencing skin infection)												
1 [3]	randomized trials	not serious	not serious	not serious	serious [b]	none	0/210 (0.0%)	2/203 (1.0%)	**RR 0.20** (0.01 to 4.04)	**8 fewer per 1,000** (from 10 fewer to 30 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

AD: Atopic dermatitis; **CI:** Confidence interval; **RR:** Risk ratio; **IGA:** Investigator Global Assessment; **IGADA:** Investigators' Global Atopic Dermatitis Assessment; **VAS:** Visual analog scale; **AE**: Adverse event

Explanations

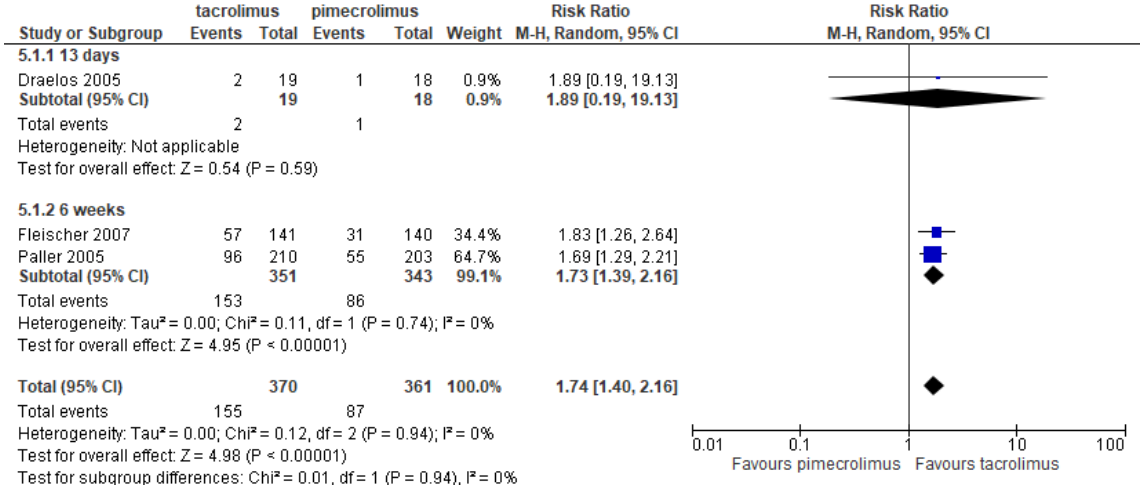
a. Outcome data is minimally reported for itch reduction.

b. Very wide CI consistent with no risk difference and substantial benefit and harm.

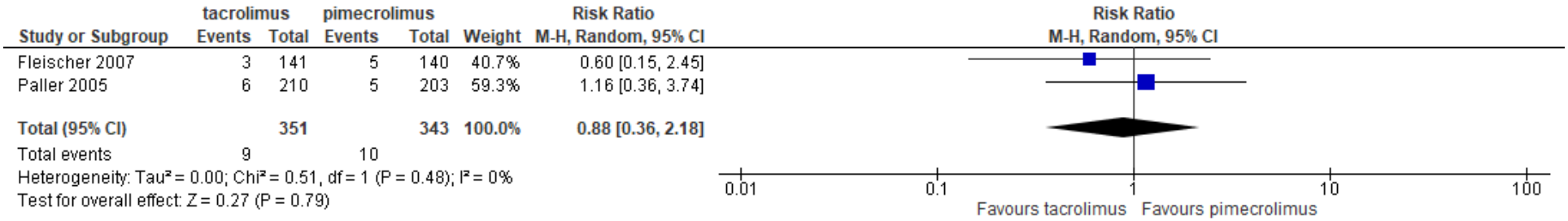
c. One study suggests increased risk with tacrolimus and one study suggests reduced risk with tacrolimus. However, the effect estimates largely overlap suggesting borderline inconsistency.

d. CI consistent with the possibility of no risk difference and important benefit and harm; however, the evidence of low discontinuation rates is indicative of a non-important increase in risk with the intervention leading to no important concerns about safety, so the evidence was not downgraded.

Analysis 9a. Investigator assessment of "clear" or "almost clear" (IGA/IGADA)



Analysis 9b. Withdrawal due to adverse event.



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e-Table 10. Very High Potency TCS vs Vehicle

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	very high potency TCS	vehicle	Relative (95% CI)	Absolute (95% CI)		
Change in severity as assessed by investigators (follow up: 2 weeks; assessed with: participants consider by investigators to be clear or almost clear/mild severity)												
3 [1-3]	randomized trials	not serious	not serious	not serious	not serious	none	305/454 (67.2%)	37/166 (22.3%)	**RR 2.76** (1.91 to 3.99)	**392 more per 1,000** (from 203 more to 666 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Withdrawal due to adverse events (follow up: 2 weeks; assessed with: participants discontinuing treatment due to AE)												
2 [2,3]	randomized trials	not serious	not serious	not serious	not serious [a]	none	2/262 (0.8%)	17/151 (11.3%)	**RR 0.13** (0.01 to 1.55)	**98 fewer per 1,000** (from 111 fewer to 62 more)	⊕⊕⊕⊕ HIGH	CRITICAL

AD: Atopic dermatitis; **TCS:** Topical corticosteroid; **RR:** Risk ratio; **AE**: Adverse event

Explanations

a. CI consistent with no risk difference, and important benefit and harm; however the low discontinuation rate in the intervention group suggests no concerns about the safety of the intervention, so the evidence was not downgraded.

Table. Study Treatment Characteristics

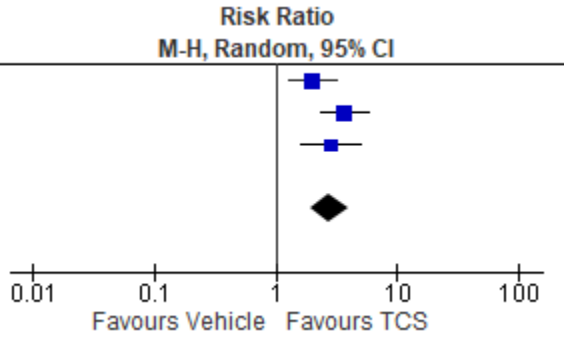
Study	Intervention	Comparator
Breneman 2005	Clobetasol propionate lotion or Clobetasol propionate cream b.i.d, 2 weeks	Vehicle lotion b.i.d, 2 weeks
Del Ross 2009	Fluocinonide 0.1% cream q.d or b.i.d, 2 weeks	Vehicle cream q.d or b.i.d, 2 weeks
Guzzo 1991	Halobetasol propionate 0.05% ointment, b.i.d, 2 weeks	Vehicle ointment b.i.d, 2 weeks

Analysis 10a. Investigator assessment of global response of “clear” or “almost clear/mild” (Global Severity Score/Physician Global Assessment)

Study or Subgroup	TCS Events	TCS Total	Vehicle Events	Vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
Breneman 2005	144	196	12	33	36.2%	2.02 [1.28, 3.20]
Del Ross 2009	122	211	16	102	35.7%	3.69 [2.32, 5.86]
Guzzo 1991	39	47	9	31	28.1%	2.86 [1.62, 5.03]
Total (95% CI)		**454**		**166**	**100.0%**	**2.76 [1.91, 3.99]**
Total events	305		37			

Heterogeneity: Tau² = 0.04; Chi² = 3.36, df = 2 (P = 0.19); I² = 40%

Test for overall effect: Z = 5.39 (P < 0.00001)

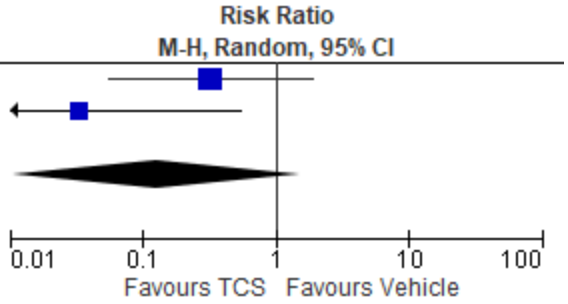


Analysis 10b. Withdrawal due to adverse events

Study or Subgroup	TCS Events	TCS Total	Vehicle Events	Vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
Del Ross 2009	2	211	3	102	59.0%	0.32 [0.05, 1.90]
Guzzo 1991	0	51	14	49	41.0%	0.03 [0.00, 0.54]
Total (95% CI)		**262**		**151**	**100.0%**	**0.13 [0.01, 1.55]**
Total events	2		17			

Heterogeneity: Tau² = 1.94; Chi² = 2.36, df = 1 (P = 0.12); I² = 58%

Test for overall effect: Z = 1.62 (P = 0.11)



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e-Table 11. High Potency TCS: Betamethasone dipropionate vs Vehicle (bid)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	high potency TCS	vehicle	Relative (95% CI)	Absolute (95% CI)		
Change in severity from baseline as assessed by investigators (follow up: 3 weeks; assessed with: Participants with excellent or good clinical response (50-100% improvement) based on PGA severity scale of 0=none to 4=very severe)												
1 [1]	randomized trial	not serious	not serious	not serious	serious [a]	none	16/17 (94.1%)	2/16 (12.5%)	**RR 4.36** (1.13 to 16.89)	**420 more per 1,000** (from 16 more to 1,000 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Reduction in itch (follow up: 4 days; assessed with: Change in VAS itch score)												
1 [2]	randomized trial	serious [b]	not serious	not serious	serious [c]	none	For 26 adult AD patients treated according to a crossover protocol with placebo cream for 4 days then betamethasone dipropionate (concentration not provided) for 4 days bid following a 9–10-day washout period, during treatment with TCS itch intensity as determined via VAS was significantly lower than with placebo (days 3-4 p<0.0001; nights 3-4 p<0.005).				⊕⊕◯◯ LOW	CRITICAL

AD: Atopic dermatitis; **TCS:** Topical corticosteroid; **CI:** Confidence interval; **RR:** Risk ratio

Explanations

a. CI consistent with a clinically unimportant and clinically important benefit.
b. Study is of a moderate risk of bias due to loss to follow-up, reporting bias, and other sources of bias.
c. Small, intra-individual sample suggests imprecision.

Study Treatment Characteristics

Study	Intervention	Comparator
Vanderploeg 1976	Betamethasone dipropionate 0.05% ointment bid, 3 weeks	Vehicle ointment bid, 3 weeks
Wahlgren 1988	Betamethasone dipropionate bid, 4 days	Vehicle cream bid, 4 days

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e-Table 12. Medium Potency TCS vs vehicle

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	medium potency TCS	vehicle	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in severity as assessed by investigators (follow up: 4 weeks; assessed with: Participants experiencing "Treatment success" defined as ≥50% lesional clearance plus stable/improved scores from baseline in ≥75% of 20 sign/symptom assessments)												
1 [1]	randomized trial	not serious	not serious	not serious	not serious	none	156/221 (70.6%)	62/217 (28.6%)	**RR 1.86** (1.45 to 2.39)	**246 more per 1,000** (from 129 more to 397 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Change in severity as assessed by investigators (follow up: 22 days; assessed with: Difference in TIS scores: TIS score is the sum of 3 intensity items (erythema, oedema/papulation, excoriation) scored on a 4-point scale from 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe) with a maximum of 9 points.)												
1 [2]	randomized trial	not serious	not serious	not serious	serious [a]	none	For 15 adult AD patients randomized to the treatment of a lesion with FP 0.05% and 25 patients randomized to the treatment of a lesion with vehicle cream, FP vs vehicle displayed a significant reduction of the TIS score: -1.51 (95%CI -2.65, -0.36).				⊕⊕⊕◯ MODERATE	CRITICAL
Flare prevention (follow up: 16 weeks; assessed with: Risk of flare following disease stabilization)												
3 [3-5]	randomized trials	not serious	not serious	not serious	not serious	none	For 117 adult AD patients randomized to maintenance therapy with daily emollients and either intermittent FP 0.05% or vehicle, once daily 4 days per week for 4 weeks followed by once daily 2 days per week for 16 weeks following achievement of treatment success with up to 4 weeks of FP 0.05% 2x daily, those treated with FP were 7.0 times less likely to have an AD relapse (95%CI 3.0, 16.7, p<0.001). For 23 adult AD patients randomized to maintenance therapy with FP 0.005%, qd 2 times a week for 16 weeks and 31 patients randomized to vehicle for the same regimen following an initial 4-week FP treatment period that resulted in "complete healing" of AD, patients receiving FP maintained their improvement, whereas the vehicle group deteriorated. The difference between treatments in the change in SCORAD values was statistically significant (difference= 13.4;95% CI: 2.66, 24.3; p=0·017). Overall, 21 of 31 patients (68%) in the placebo group and nine of 23 (39%) in the FP group withdrew because of recurrence and relapse of their AD. For 138 AD patients (mean age 28.1yo) randomized to maintenance therapy with daily emollient plus twice-weekly FP cream or ointment and 157 patients randomized to daily emollient plus twice-weekly base cream or ointment for 16 weeks following stabilization of AD after initial treatment with FP 0.05% cream or FP 0.005% ointment qd or bid for 4 weeks, 40/138 FP-treated patients experienced a flare compared to 95/157 vehicle-treated patients. The HR for FP cream compared to vehicle cream was 5.8 (95%CI 3.1, 10.8, p<0.001). The HR for FP ointment compared to vehicle ointment was 1.9 (95%CI 1.2, 3.2, p=0.010).				⊕⊕⊕⊕ HIGH	CRITICAL

AD: Atopic dermatitis; **TCS:** Topical corticosteroid; **CI:** Confidence interval; **RR:** Risk ratio; **FP**: Fluticasone propionate

Explanations

a. Study relied on small, intraindividual lesion-focused samples.

Study Treatment Characteristics

Study	Intervention	Comparator
Berth-Jones 2003	Fluticasone propionate cream or ointment twice weekly + emollient qd, 16 weeks	Base cream twice weekly + emollient qd, 16 weeks
Dolle 2015	Fluticasone propionate 0.05%, qd, 21+/- 2 days	Placebo cream, qd, 21+/- 2 days
Eichenfield 2006	Fluticasone propionate, 0.05%, qd, 4 weeks	Placebo cream, qd, 4 weeks
Hanifin 2002	Fluticasone propionate (FP) cream 0.05%, qd, intermittent 4 days per week for 4 weeks, followed by once daily 2 days per week for 16 weeks; emollient cream, qd, 20 weeks	Vehicle, qd, intermittent 4 days per week for 4 weeks, followed by once daily 2 days per week for 16 weeks; emollient cream, qd, 20 weeks
Van Der Meer 1999	Fluticasone propionate 0.005%, qd, 2 times a week, for 16 weeks	Placebo, qd, 2 times a week, for 16 weeks

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e-Table 13. Lower Medium Potency TCS: Hydrocortisone buteprate 0.1% vs Vehicle (qd)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	lower medium potency TCS	vehicle	Relative (95% CI)	Absolute (95% CI)		
Change in severity from baseline as assessed by investigators (follow up: 2 weeks; assessed with: Mean difference in change in total lesion scores from baseline: Total lesion score calculated as 7 disease signs (infiltration, scaling, erythema, lichenification, vesicles, papules, and excoriation) evaluated on a 4 point scale: absent (0), mild (1), moderate (2), and severe (3). Disease severity was determined by the total score for the seven signs.)												
1 [1]	randomized trials	serious [a]	not serious	not serious	serious [b]	none	121 MD -6.38 ± 3.90	73 MD -3.39 ± 3.46	MD **2.99 lower** (4.26 lower to 1.72 lower)		⨁⨁◯◯ LOW	CRITICAL
Serious adverse events (follow up: 2 weeks; assessed with: participants experiencing a serious adverse event)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	lower medium potency TCS	vehicle	Relative (95% CI)	Absolute (95% CI)		
1 [1]	randomized trials	serious [a]	not serious	not serious	serious [b]	none	0/121 (0.0%)	0/73 (0.0%)	**RR 0.660** (0.012 to 30.250)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL

AD: Atopic dermatitis; **TCS:** Topical corticosteroid; **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Study is of a moderate risk of bias due to potential selection, attrition, and reporting bias.

b. Study relied on a small sample.

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e-Table 14. Studies Comparing TCSs

KQ2 Topical corticosteroids Duke, 1983[1] NR Article Parallel trial Age group: Adults and children	AD N: 68 NR% female Inclusion criteria: Patients over 15 years old with atopic dermatitis	**Alclometase depropionate 0.05**% ointment, bid, for 3 weeks Control: Comparator: Other topical **Clobetasone butyrate 0.05%** ointment, bid, for 3 weeks **Low vs Moderate potency steriods**	Erythema, induration and pruritus Clinical sign scores improved continuously during the study period and at the end of therapy, favored alclometasone conclusively over clobetasone 2 transient adverse events to alclometasone and 3 to clobetasone
KQ2 Topical corticosteroids Bagatell, 1983[2] NR Article Parallel trial Age group: Adults and children	Moderate-severe AD N: 249 64% female Inclusion criteria: 12 years or older; AD pre-established for at least one year and diagnosed as stable or as worsening for more than one week	Alclometasone dipropionate cream 0.05%, tid, for 3 weeks Control: Comparator: Other topical Hydrocortisone cream 1.0%, tid, for 3 weeks **Low vs Very Low Potency**	Physician's global evaluation Intervention patients showed a significantly better therapeutic effect for all measures of efficacy, except erythema, compared to comparator group Pruritus Intervention was more effective than comparator in producing rapid improvement as evidenced by significantly better results for pruritus Dropout due to AE 3 w I: 3/127, Comp: 0/122
KQ2 Topical corticosteroids Bicker, 1984[3]	acute or subacute eczema N: 33	Amcinonide 0.1%, bid, 2 weeks Control:	Investigator's Evaluation of Overall Improvement (1-5); 1= Cleared, 5= Poor 2w I: 2.0 (0.18)

NR Article Parallel trial Age group: Adults and children	24% female Inclusion criteria: 17-84 years old; acute or subacute eczematous dermatitis; minimum baseline score of 6 based on sign and symptom rating scale	Comparator: Other topical Halcinonide 0.1%, bid, two weeks **High vs High potency**	Comp: 1.77 (0.28) Amcinonide treatment group had significantly better improvement of edema at week 2 than halcinonide group; no differences in any other signs or symptoms
KQ2 Topical corticosteroids Savin, 1976[4] NR Article Parallel trial Age group: Adults	AD N: 27 NR% female Inclusion criteria: Patients with atopic dermatitis	Betamethasone dipropionate ointment 0.05%, bid, for 3 weeks Control: Comparator: Other topical Hydrocortisone ointment 1%, bid, for 3 weeks **High vs Low potency steroids**	Total symptom score Betamethasone dipropionate 0.05% ointment was found to be significantly than 1% hydrocortisone in the treatment of atopic dermatitis
KQ2 Topical corticosteroids Reidhav, 1996[5] NR Article Parallel trial Age group: Adults and children	Symmetrical AD N: 30 NR% female Inclusion criteria: Consecutive patients between 15 and 66 years with atopic dermatitis	Betamethasone valerate, qd, for 4 weeks Control: mometasone furoate Cream, qd, for 4 weeks Comparator: **Medium potency vs medium potency**	Clinical effectiveness No significant difference in clinical effectiveness between 2 treatment groups Betamethasone was significantly superior with respect to several cosmetic properties and was greatly preferred for its overall cosmetic quality
KQ2 Topical corticosteroids Nilsson, 1992a[6] Nilsson, 1992b[7] Study 1 Article Parallel trial Age group: NR	Mild to moderate AD N: 70 NR% female Inclusion criteria: Patients with mild to moderate atopic dermatitis	Clobetasol propionate 0.05% cream, bid, for 2 weeks (**high potency**) Control: Comparator: Other topical Alclometasone, bid, for 2 weeks **(low potency**) Other topical Clobetasone, bid, for 2 weeks Other topical Betamethasone with neomycin, bid, for 2 weeks	Severity score Both corticosteroids reduced the severity score significantly after week 1 but there was no significant difference between 2 groups Effects of treatment on self-assessment evaluation 2 w I: 0.5 (0.9) Comp: 1.9 (1.4), Comp 2: 2.2 (2.0), Comp 3: 1.7 (1.6)
KQ2 Topical corticosteroids Nilsson, 1992b[7] Nilsson, 1992a[6] Study 2 Article Parallel trial Age group: Adults and children	Moderate to severe atopic eczema N: 30 NR% female Inclusion criteria: Patients with moderate to severe atopic eczema	Corticosteroid Clobetasol propionate 0.05% cream, bid, for the first week and qd for the second week Control: Comparator: Betamethasone valerate 0.1% cream + neomycin, bid, for the first week and qd for the second week **Very High vs Medium Potency**	Severity score Both groups showed significantly reduce in severity score but no significant difference between 2 groups
KQ2 Topical corticosteroids Trookman, 2011[8] NR Article	Mild to moderate AD N: 46 NR% female	Desonide hydrogel 0.05%, gel, bid, for 4 weeks Control: Comparator: Other topical	EASI, BSA, ADSI, Target lesion assessment, TWEL Whole body EASI decreased significantly from baseline at weeks 2 and 4 for desonide hydrogel and desonide ointment; overall BSA declined in the treatment groups (significant for desonide ointment at week 4); no significant difference in BSA between desonide hydrogel and ointment groups; overall ADSI decreased significantly from baseline at weeks 2 and 4 for

Parallel trial Age group: Adults and children	Inclusion criteria: Patients older than 12 with mild to moderate atopic dermatitis	Desonide ointment, bid, for 4 weeks **Low potency gel vs ointment**	desonide hydrogel and ointment. Overall target lesion assessment of severity decreased significantly from Baseline at Weeks 2 and 4 for desonide hydrogel and ointment Patient preference Significantly more patients were generally pleased with the attributes and efficacy of desonide hydrogel than ointment SAEs 4 w I: 0/22, Comp: 0/22
KQ2 Topical corticosteroids Fisher, 1979[9] NR Article Parallel trial Age group: Adults and children	AD N: 107 63% female Inclusion criteria: NR	Fluocinonide 0.05% cream, tid, 3 weeks Control: Comparator: Other topical Betamethasone valerate 0.1% cream, tid, 3 weeks **High vs Medium Potency**	Clinical response (1-5 scale) Clinical response favored intervention significantly over comparator at 3 weeks. Dropout due to AE 3w I: 0/53, Comp: 0/54
KQ2 Topical corticosteroids Bleehen, 1995[10] NR Article Parallel trial Age group: Adults and children	Moderate-severe AD N: 270 NR% female Inclusion criteria: Between 1 and 65 yeas old; diagnosis of AD confirmed by dermatologist; eczema score of at least moderate severity (not less than 6)	Fluticasone propionate 0.05%, qd, 4 weeks Control: Comparator: Other topical Fluticasone propionate 0.05%, bid, 4 weeks **Medium Potency qd vs bid**	Investigators' overall assessment of the target area The majority of the intent-to-treat population was classified a treatment success according to investigators' overall assessment of the target area, however there was no significant difference between groups Hospitalization 4w I: 1/137, Comp: 1/133 Dropout due to AE 4w I: 3/137, Comp: 3/133
KQ2 Topical corticosteroids El-Hefnawi, 1978[11] NR Article Same person trial Age group: Adults and children	AD N: 5 NR% female Inclusion criteria: Aged 5 months to 65 years; patients with inflammatory dermatoses; rated moderately severe to severe	Halcinonide 0.1% + neomycin sulfate 0.25% + amphotericin 1%, tid, up to 3 weeks Control: Comparator: Other topical Hydrocortisone 1%, tid, up to 3 weeks **High potency vs Lowest potency**	Overall Comparative Clinical Response No statistically significant difference between the two drugs was found for AD patients
KQ2 Topical corticosteroids Fattah, 1976[12] NR Article Same person trial Age group: Adults and children	AD N: 4 NR% female Inclusion criteria: Presence of bilateral, symmetrical lesions of similar etiology and severity	Halcinonide 0.1% cream, tid, 2-3 weeks Control: Comparator: Other topical Hydrocortisone 1% cream, tid, 2-3 weeks **High potency vs Lowest potency**	SAE 3w I: 0/4, Comp: 0/4 Withdrawal from treatment due to AE 3w I: 0/4, Comp: 0/4 Intervention was markedly superior in two patients and slightly superior in one patient, with comparator slightly superior in one patient
KQ2 Topical corticosteroids	AD	Halcinonide 0.1%, bid, 2 weeks	Efficacy

Bleeker, 1975[13] NR Article Same person trial Age group: Adults	N: 27 NR% female Inclusion criteria: NR	Control: Comparator: Other topical Clobestasol propionate 0.05%, bid, 2 weeks **Very High vs High potency**	Both treatments were similar in their efficacy and rapid onset of action, the clinical response was a very high order
KQ2 Topical corticosteroids Leibsohn, 1974[14] NR Article Same person trial Age group: Adults and children	AD N: 9 51% female Inclusion criteria: NR	Halcinonide cream, tid, for 3 weeks Control: Comparator: Other topical Betamethasone 17-valerate cream, tid, for 3 weeks **High vs Medium potency**	Clinical responses Mixed results across patients Adverse events (including SAE) 3w I: 0/8, Comp: 0/8
KQ2 Topical corticosteroids Almeyda, 1974[15] NR Article Same person trial Age group: Adults and children	Atopic eczema N: 36 50% female Inclusion criteria: NR	Hydrocortisone (1% UHc powder cream), tid, 2 weeks (in a few instances 4 weeks) Control: Comparator: Other topical 0.1% betamethasone 17-valerate, tid, 2 weeks (in a few instances 4 weeks) **Medium vs Lowest Potency**	State of lesions State of lesions after 4 weeks- Intervention- Excellent: 25, Good: 10, No Improvement: 1, Deterioration: 0; Comparator- Excellent: 18, Good:16, No Improvement: 2, Deterioration: 0 Patient comment 14 patients preferred the UHc powder-cream
KQ2 Topical corticosteroids Yasuda, 1976[16] NR Article Parallel trial Age group: NR	AD N: 144 NR% female Inclusion criteria: Patients with atopic dermatitis	Hydrocortisone 17-butyrate (HC) , bid, for 1 week **(lower-medium potency)** Control: Comparator: Other topical Triamcinolone acetonide (TA), bid, for 1 week **(Medium potency)** Other topical Hydrocortisone 21-acetate (HA) 1%, bid, for 1 week **(lowest potency)**	Clinical efficacy The overall effectiveness at days 3 and 7 showed HC to be superior to HA and TA
KQ2 Topical corticosteroids Rajka, 1986[17] NR Article Same person trial Age group: Adults and children	Moderate to severe AD N: 30 NR% female Inclusion criteria: Patients over 16 years of age with moderate to severe dermatitis	Hydrocortisone 17-butyrate (Locoid) 0.1% fatty cream application cream, bid, until the clearance less than 4 weeks Control: Comparator: Other topical Desonide (Apolar) 0.1% ointment, bid, until the clearance less than 4 weeks **Lower medium vs Low potency**	Global severity, Erythema Global severity was significantly reduced on both treated sides; score reductions on sides treated with Locoid were found to be more marked than Apolar One patient experienced slight itching, mainly on the side treated with Apolar ointment and another patient found Apolar ointment some- what sticky in comparison with Locoid fatty cream
KQ2 Topical corticosteroids Wake Forest University, 2006[18] NCT00693693 Trial record	Mild to moderate AD N: 26 56% female	Hydrocortisone 17-butyrate 0.1% cream , bid, for 2 weeks Control: Comparator: Other topical	SAEs 2 w I: 0/6, Comp: 0/7, Comp 2: 0/8

Parallel trial Age group: Adults	Inclusion criteria: Adult patients with mild to moderate atopic dermatitis	Hydrocortisone 17-butyrate 0.1% ointment, bid, for 2 weeks Other topical Hydrocortisone 17-butyrate 0.1% Lipocream, bid, for 2 weeks **Lower-medium potency creams vs ointments**	
KQ2 Topical corticosteroids Roth, 1978a[19] Study 1 Article Same person trial Age group: Adults and children	AD N: 29 NR% female Inclusion criteria: Aged 2-75 years; bilateral lesions typical of chronic AD, involving primarily the limbs	Hydrocortisone valerate cream 0.2%, tid, until clearing or up to 4 weeks Control: Comparator: Other topical Hydrocortisone 1.0% cream, tid, until clearing or up to 4 weeks **Lower-medium vs Lowest potency**	Overall judgement Overall judgement showed HCV)to be statistically superior to HC Significant side effects 4 w I: 0/29, Comp: 0/29
KQ2 Topical corticosteroids Roth, 1978b[20] HCV vs BMV Study 2 Article Same person trial Age group: Adults and children	AD N: 19 NR% female Inclusion criteria: Aged 2-75 years; bilateral lesions typical of chronic AD, involving primarily the limbs	Hydrocortisone valerate cream 0.2%, tid, until clearing or up to 4 weeks Control: Comparator: Other topical Betamethasone valerate cream 0.1%, tid, until clearing or up to 4 weeks **Medium vs Lower-medium potency**	Overall therapeutic response With the exception of a slightly more rapid response to HCV (intervention) in some patients, the effect of the two medications appeared to be essentially the same Significant side effects 4 w I: 0/19, Ctrl: 0/19
KQ2 Topical corticosteroids Haneke, 1992[21] NR Article Same person trial Age group: NR	AD N: 276 NR% female Inclusion criteria: Patients with atopic dermatitis	Methylprednisolone aceponate 0.1% cream, bid, for 4 weeks MPA, qd, for 4 weeks Control: Other topical alone 0.1 % BMV, bid, for 4 weeks Comparator: Other topical 0.1% MPA, qd, for 4 weeks 0.1% BMV, bid, for 4 weeks **High vs Medium potency**	Healing, marked improvement There were no differences between MPA used once and twice daily, respectively, with 66% complete healing and 27% marked improvement as compared with BMV twice daily with 68% complete healing and 30% marked improvement The local and systemic tolerance was excellent
KQ2 Topical corticosteroids Rajka, 1993[22] NR Article Parallel trial Age group: Adults and children	Mild to moderate AD N: 153 59% female Inclusion criteria: Patients with atopic dermatitis	Mometasone furoate fatty cream 0.1%, qd, for 3 weeks Control: Comparator: Other topical Betamethasone valerate cream 0.1%, bid, for 3 weeks **Medium vs Medium potency**	Clinical efficacy Difference regarding clinical efficacy was statistically significantly in favor of mometasone 3 adverse events in mometasone furoate and 1 in betamethasone
KQ2 Topical corticosteroids Ruzicka, 2012[23] Almirall, 2010[24] EudraCT-No. 2009-017407-28; NCT 01119313	Mild to moderate AD N: 20 NR% female Inclusion criteria: Patients were older than 18 years	Mometasone furoates 0.1% with a water content of 33%, once daily, for 2 weeks Control: Other topical alone	TSS 2 w I: 2.6 (1.76), Ctrl: 2.5 (1.76) The statistical comparison of the intraindividual outcomes did not show significant differences between the treatments comparing mean corneometric values at baseline with day 8 and 15 DLQI

Article Parallel trial Age group: Adults	with mild to moderate atopic dermatitis	0.1% mometasone furoate with a marginal water content below 5%, once daily, for 2 weeks Comparator: **Medium potency TCS w/ high water content vs low water content**	Quality of life could be improved by treating with both preparations SAEs 2 w I: 0/20, Ctrl: 0/20 The corneometry results (arbitrary units) showed considerable increase in skin moisturization with both preparations. No significant differences between the treatments comparing mean corneometric values at baseline with day 8 and 15
KQ2 Topical corticosteroids Hoybye, 1991[25] NR Article Parallel trial Age group: Adults	AD N: 96 NR% female Inclusion criteria: Between 18-70 years old; clinical diagnosis of AD	Mornetasone furoate, qd, for 3 weeks, followed by qd, three consecutive days/week, an additional 3 weeks Control: Comparator: Other topical Hydrocortisone, bid, for 3 weeks, followed by bid, three consecutive days/week, an additional 3 weeks **Medium potency vs Lowest potency**	Physicians's Global Evaluation The results of the global evaluation carried out after a total treatment period of six weeks showed significantly greater improvement in the patients using intervention treatment Patient visual analogue scale (VAS) A comparison of the evaluations made by the patients on a visual analog scale after three and six weeks of treatment showed no difference in efficacy between the two groups Pruritus severity Both groups experienced statistically significant improvement during the initial three weeks of treatment; intervention improved pruritus significantly better than comparator
KQ2 Topical corticosteroids Aliaga, 1996[26] NR Article Parallel trial Age group: Adults	AD N: 67 64% female Inclusion criteria: Adult patients with atopic dermatitis	Prednicarbate 0.25%, bid for 3 weeks Control: Other topical alone Fluocortin butyl ester 0.75%, bid, for 3 weeks Comparator: **Medium vs Medium potency**	Overall efficacy Evaluations by investigators and patients of the overall efficacy of treatment were significantly higher for prednicarbate than for fluocortin butyl ester Two patients treated with fluocortin butyl ester manifested possible adverse reactions to the medication: probable irritant contact dermatitis in one case and pigmentation in the other; No adverse reactions were observed in the patients treated with prednicarbate
KQ2 Topical corticosteroids Draelos, 2015[27] NR Article Same person trial Age group: Adults	Mild AD or eczema N: 50 76% female Inclusion criteria: 18 or older; symmetrical mild eczema or AD on the arms or legs	Triamcinolone acetonide 0.2% spray (2 second spray) +rubbing in, tid, 2 weeks Control: Comparator: Other topical Triamcinolone acetonide 0.2% spray (2 second spray) + no rubbing in, tid, 2 weeks **Medium potency TCS rubbed in vs not rubbed in**	Investigator assessment 5-point scale for irritation, erythema, desquamation, roughness, dryness, and overall skin appearance Highly clinical and statistical improvement in all investigator parameters with no difference between groups Patient 5-point scale to evaluate irritation, redness, itching, discomfort, and overall skin appearance Highly clinical and statistical improvement in all patient parameters with no difference between groups SAE 2w I: 0/50, Comp: 0/50 Dropout due to AE 2w I: 0/50, Comp: 0/50
KQ2 Topical corticosteroids Koopmans, 1995[28] NR Article	Atopic eczema N: 150 63% female	Locoid lipocream fatty cream, bid, for 4 weeks (Hydrocortisone butyrate 0.1%) Control: Other topical alone	Clearance rate Both treatments significantly reduced all clinical features equally, but the clearance rate was significantly higher with the twice daily regimen Adverse events occurred in eight patients, 4 in each group

Parallel trial Age group: Adults and children	Inclusion criteria: Patients over 12 years old with atopic eczema	Locoid lipocream, qd, for 4 weeks Comparator: Other topical Locobase (**OTC moisturizer**), qd, for 4 weeks **Lower-medium potency**	**Data provided for active treatment arms but not control (Locobase) arm**

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e-Table 15. Mupirocin + Topical corticosteroid vs Topical corticosteroid + Vehicle

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mupirocin + TCS	TCS + Vehicle	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in severity as assessed by investigators (follow up: 4 weeks; assessed with: Change in mean EASI score)												
1 [1]	randomized trials	not serious	not serious	not serious	serious [a]	none	58 MD 12.50 (10.24, 14.77)	61 MD 11.11 (8.62, 13.61)	MD **1.39 higher** (1.9 lower to 4.68 higher)		⊕⊕⊕◯ MODERATE	CRITICAL
Change from baseline in clinical severity as assessed by investigator (follow up: 8 weeks; assessed with: Patients were assessed clinically on a 0-3 scale for six features (extent, erythema, pustulation, excoriations, dryness and cracking) at 16 body sites.)												
1 [2]	randomized trials	not serious	not serious	not serious	serious [a]	none	Forty-five AD patients (mean age 20.4 yo) started 0.5% clobetasol butyrate ointment b.i.d for 2 weeks pre-trial then q.d during the trial, then were randomly allocated to receive placebo or mupirocin ointment q.d in addition to the TCS for 2 weeks, crossing over to the alternative treatment (placebo or mupirocin) for weeks 2-4. After the first trial period, clinical severity was virtually unchanged in the P/M group (using placebo) mean score 68.0 (baseline mean score±SEM 69.9±6.9) but fell significantly in the M/P group (using mupirocin) to a mean of 37.6 (baseline score 59.5±6.4). This was significantly different both from the M/P group pretreatment baseline (P < 0. 001) and from the P/M group (p<0.002). After the cross-over period at 4 weeks, the P/M group improved significantly (p < 0.05) whereas the M/P group, (now on placebo) showed a slight, but not statistically significant deterioration. Clinical activity then remained stable in both groups for the remainder of the trial (through week 8). Calculation of the change in clinical severity scores over the whole trial period taking visit o as the baseline value showed that the change in clinical severity was virtually identical for the two groups.			⊕⊕⊕◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mupirocin + TCS	TCS + Vehicle	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: 8 weeks; assessed with: Participants experiencing a serious AE)												
1 [2]	randomized trials	not serious	not serious	not serious	serious [a]	none	For 45 AD patients (mean age 20.4 yo) started on 0.5% clobetasol butyrate ointment b.i.d for 2 weeks pre-trial then q.d during the trial, then were randomly allocated to receive placebo or mupirocin ointment q.d in addition to the TCS for 2 weeks, crossing over to the alternative treatment (placebo or mupirocin) for weeks 2-4., over the 8-week study period no serious adverse events were reported.				⨁⨁⨁◯ MODERATE	CRITICAL

AD: Atopic dermatitis; **CI:** Confidence interval; **MD:** Mean difference; **TCS:** Topical corticosteroid; **AE:** Adverse event; **EASI:** Eczema Area and Severity Index

Explanations
a. Study relied on a small sample.

Study Treatment Characteristics

Study	Intervention	Comparator
Lever 1988	Mupirocin bid in polyethylene glycol ointment base + 0.5% clobetasol butyrate ointment, each qd, for 2 weeks	Polyethylene glycol ointment base cream base + 0.5% clobetasol butyrate ointment, qd, for 2 weeks
Gong 2006	Mupirocin + hydrocortisone butyrate ointment, each qd, 4 weeks	Vehicle ointment + hydrocortisone butyrate ointment, each qd, 4 weeks

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e-Table 16. Gentamicin + Topical corticosteroid (betamethasone valerate) vs Topical corticosteroid (betamethasone valerate) alone vs Gentamicin alone

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Change from baseline in severity as assessed by investigators (follow up: 22 days; assessed with: Change in mean overall severity scores (0=complete absence to 10=very severe-worst case ever seen))									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
1 [1]	randomized trials	serious [a]	not serious	not serious	serious [b]	none	For 25 AD patients (age NR) treated with gentamicin + betamethasone valerate cream, 27 treated with betamethasone valerate alone, and 27 treated with gentamicin alone t.i.d for 3 weeks, mean overall severity scores decreased from 6.1 to 1.0, 6.1 to 1.8, and 6.6 to 4.2, respectively.	⊕⊕⊕◯ MODERATE	CRITICAL

AD: Atopic dermatitis; **NR**: Not reported

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e-Table 17. Tacrolimus 0.1% + Clocortolone pivalate 0.1% vs Clocortolone pivalate 0.1% alone vs Tacrolimus 0.1% alone

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Change from baseline in severity as assessed by investigators (follow up: 21 days; assessed with: Change in mean DSS -the sum of scores for excoriation, induration, and erythema)									
1[1]	randomized trial	not serious	not serious	not serious	serious [a]	none	For 19 AD patients (aged 16-65 yo; primarily >18yo) randomized to treatment with clocortolone pivalate cream 0.1% and tacrolimus ointment 0.1%, 19 patients randomized to TCS alone, and 19 patients randomized to tacrolimus alone bid for 21 days, reduction in the mean DSS from baseline (computed as actual change from day 21) was statistically significant (<0.001) for each treatment group (TCS+TCI, -1.53; TCS alone, -0.76; and TCI alone, -1.42).	⊕⊕⊕◯ MODERATE	CRITICAL

AD: Atopic dermatitis; **DSS:** Dermatologic Sum Score; **TCS:** Topical corticosteroid; **TCI:** Topical calcineurin inhibitors

Explanations

a. Study relied on a small sample.

Bibliography

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e-Table 18. Very High Potency: Pimecrolimus 1% vs Clobetasol propionate 0.05% (qd)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pimecrolimus 1%	clobetasol 0.05%	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in severity as assessed by investigators (follow up: 15 days; assessed with: Change from baseline in Total Sign Score (0= absent; 18= severe))												
1 [1]	randomized trial	not serious	not serious	not serious	serious [a]	none	30 MD -2.93±2.37	30 MD -5.59±2.37	MD **2.66 higher** (1.46 higher to 3.85 higher)		⊕⊕⊕◯ MODERATE	CRITICAL

AD: Atopic dermatitis; **CI:** Confidence interval; **MD:** Mean difference

Explanations
a. Study relied on a small, intraindividual sample.

Bibliography

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e-Table 19. Pimecrolimus 1% vs Betamethasone dipropionate 0.05% (qd)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pimecrolimus 1%	betamethasone dipropionate 0.05%,	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in severity as assessed by investigators (follow up: 15 days; assessed with: Change from baseline in Total Sign Score (0=absent;18=severe))												
1 [1]	randomized trials	not serious	not serious	not serious	serious [a]	none	30	30	MD **2 higher** (0.8 higher to 3.2 higher)		⊕⊕⊕◯ MODERATE	CRITICAL

AD: Atopic dermatitis; **CI:** Confidence interval; **MD:** Mean difference

Explanations
a. Study relied on a small, intraindividual sample.

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1. Guttman-Yassky E, Ungar B, Malik K, et al. Molecular signatures order the potency of topically applied anti-inflammatory drugs in patients with atopic dermatitis. *J Allergy Clin Immunol.* 2017;140(4):1032-1042.e1013.

e-Table 20. Pimecrolimus 1% vs Medium Potency Steroids (bid)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pimecrolimus 1%	medium potency TCS	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in severity as assessed by investigators (follow up: range 3 weeks to 4 weeks; assessed with: participants moderately clear or better determined by IA score of 0 to 3 or PGA score indicating >50% improvement)												
2 [1,2]	randomized trials	serious [a]	not serious	not serious	not serious	none	For 328 adult AD patients randomized to pimecrolimus 1% and 330 patients randomized to 0.1% triamcinolone acetonide cream (on trunk & limbs) plus 1% hydrocortisone acetate cream (on face, neck and intertriginous areas) bid until complete clearance, at 4 weeks, 186/328 (56.7%) and 251/330 (76.1%), respectively were assessed as moderately clear or better according to IA scores: RR 0.84 95%CI 0.72, 0.97.[2] For 45 adult AD patients randomized to pimecrolimus 1% and 42 patients randomized to 0.1% betamethasone valerate cream bid for 3 weeks, 24/45 (53.3%) and 37/42 (88.1%), respectively were assessed as moderately clear or better according to PGA scores: RR 0.74 95%CI 0.50, 1.11.[1]				⊕⊕⊕◯ MODERATE	CRITICAL
Change from baseline in severity as assessed by investigators (follow up: range 22 days to 29 days; assessed with: change in pEASI scores)												
2 [3,4]	randomized trials	serious [b]	not serious	not serious	serious [c]	none	For 15 adult AD patients randomized to pimecrolimus 1% on one arm and 0.1% betamethasone valerate cream on the contralateral arm bid for 29 days, as assessed via the pEASI, considerable improvement with seen in both groups after 8 days; symptoms of those on betamethasone continued to improve (no quantitative data provided).[3] For 15 adult AD patients randomized to pimecrolimus 1% on one arm and 0.1% triamcinolone acetonide cream on the contralateral arm bid for 22 days, scoring via pEASI revealed a faster improvement in the TA-treated group compared with the pimecrolimus-treated group: at day 8 there was a significant difference between the treatment groups (p = 0.022). The difference was even more pronounced at day 22 (p = 0.0008) (no quantitative data provided).[4]				⊕⊕◯◯ LOW	CRITICAL
Change from baseline in severity as assessed by investigators (follow up: 13 months; assessed with: participants moderately clear or better determined by IA score of 0 to 3)												
1 [2]	randomized trial	serious [d]	not serious	not serious	serious [e]	none	267/328 (81.4%)	293/330 (88.8%)	**RR 0.95** (0.84 to 1.08)	**44 fewer per 1,000** (from 142 fewer to 71 more)	⊕⊕◯◯ LOW	CRITICAL
Itch reduction (follow up: range 7 days to 22 days; assessed with: VAS 10cm or NRS 0= no itch; 3= severe itch)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pimecrolimus 1%	medium potency TCS	Relative (95% CI)	Absolute (95% CI)		
3 [1,3,4]	randomized trials	serious [f]	not serious	not serious	serious [g]	none	For 15 adult AD patients randomized to pimecrolimus 1% on one arm and 0.1% betamethasone valerate cream on the contralateral arm bid at 1 week, the pimecrolimus group experienced a mean reduction from baseline in VAS scores of -2.6 (p=0.0003) and the TCS group experienced a mean reduction from baseline of -2.4 (p=0.0015). [3] For 15 adult AD patients randomized to pimecrolimus 1% on one arm and 0.1% triamcinolone acetonide cream on the contralateral arm bid for 22 days, using the VAS, patients in both groups reported a reduction in itch. For the pimecrolimus-treated side, there was a transitory increase in pruritus followed by a significant decrease in pruritus (p = 0.0010). The TA-treated arm improved continuously (p < 0.0001). The difference between the treatment groups was statistically significant at most of the time-points (p < 0.05).[4] For 45 adult AD patients randomized to pimecrolimus 1% and 41 patients randomized to 0.1% betamethasone valerate cream bid for 3 weeks, 21/45 (46.7%) and 34/41 (82.9%), respectively reported no or mild itch according to NRS scoring (0=no itch, 3=severe itch).[1]				⊕⊕◯◯ LOW	CRITICAL
Serious adverse events (follow up: 13 months; assessed with: participants experiencing a serious AE)												
1 [2]	randomized trial	serious [d]	not serious	not serious	serious [h]	none	16/328 (4.9%)	21/330 (6.4%)	**RR 0.78** (0.41 to 1.46)	**14 fewer per 1,000** (from 38 fewer to 29 more)	⊕⊕◯◯ LOW	CRITICAL
Withdrawal due to adverse events (follow up: 22 days; assessed with: participants discontinuing treatment due to AE)												
1 [1]	randomized trial	serious [d]	not serious	not serious	serious [e]	none	3/45 (6.7%)	1/42 (2.4%)	**RR 2.69** (0.29 to 24.88)	**40 more per 1,000** (from 17 fewer to 569 more)	⊕⊕◯◯ LOW	CRITICAL
Withdrawal due to adverse events (follow up: 13 months; assessed with: participants discontinuing treatment due to AE)												
1 [2]	randomized trial	serious [d]	not serious	not serious	not serious	none	28/328 (8.5%)	5/330 (1.5%)	**RR 5.27** (2.06 to 13.49)	**65 more per 1,000** (from 16 more to 189 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Infection (follow up: 13 months; assessed with: participants experiencing at least 1 skin infection)												
1 [2]	randomized trial	serious [d]	not serious	not serious	serious [h]	none	69/328 (21.0%)	80/330 (24.2%)	**RR 0.89** (0.67 to 1.19)	**27 fewer per 1,000** (from 80 fewer to 46 more)	⊕⊕◯◯ LOW	CRITICAL

AD: Atopic dermatitis; **TCS:** Topical corticosteroid; **IA**: Investigator assessment (7-point scale 0=clear; 6=very severe disease); **PGA:** Physician's Global Assessment; **pEASI**: partial Eczema Area and Severity Index; **CI:** Confidence interval; **RR:** Risk ratio; **VAS:** Visual analog scale; **AE**: Adverse event

Explanations

a. Both studies are of a moderate risk of bias due to unclear allocation methods and high attrition.

b. Minimal reporting of severity outcome data across the studies.
c. Studies rely on small, intraindividual samples.
d. Study is of a moderate risk of bias due to unclear allocation methods and high attrition.
e. CI consistent with the possibility of no difference and important harm and moderate benefit.
f. One study is of a moderate risk of bias due to unclear allocation methods reporting and high attrition and two studies minimally reported outcome data.
g. All studies rely on small samples.
h. CI consistent with the possibility of no difference and equitable harm and benefit.

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e-Table 21. Tacrolimus 0.1% vs fluticasone 0.005%

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tacrolimus 0.1%	fluticasone 0.005%	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in disease severity as assessed by investigators (follow up: 21 days; assessed with: percentage of participants with ≥60% reduction in modified local eczema and severity Index score; lower score indicates decreased severity)												
1 [1]	randomized trial	not serious	not serious	not serious	serious [a]	none	264/283 (93.3%)	245/279 (87.8%)	**RR 1.03** (0.91 to 1.17)	**26 more per 1,000** (from 79 fewer to 149 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Withdrawal due to adverse event (follow up: 21 days; assessed with: participants discontinuing treatment due to AE)												
1	randomized trial	not serious	not serious	not serious	serious [b]	none	7/288 (2.4%)	8/280 (2.9%)	**RR 0.85** (0.31 to 2.33)	**4 fewer per 1,000** (from 20 fewer to 38 more)	⊕⊕⊕◯ MODERATE	CRITICAL

AD: Atopic dermatitis; **CI:** Confidence interval; **RR:** Risk ratio; **AE**: Adverse event

Explanations
a. CI consistent with the possibility of no difference and both small benefit and harm.

b. CI consistent with the possibility of no difference and both benefit and harm.

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e-Table 22. Tacrolimus 0.1% vs Class I-III Steroids

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tacrolimus	class I-III TCS	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in severity as assessed by investigators (follow up: mean 335 days; assessed with: Change in EASI score)												
1 [1]	randomized trials	not serious	not serious	not serious	serious [a]	none	For 20 adults with AD randomized to 0.1% tacrolimus and 20 randomized to topical treatment with a class I to class III steroid* applied per "usual treatment habits" and followed for a mean of 335 days, mean improvement in EASI score from 14.35 to 6.4 (p=0.0057) was reported in the tacrolimus group and from 17.4 to 9.8 in the TCS group (p=0.0137). No significant difference in improvement between treatment groups was noted (p=0.2816).				⊕⊕⊕◯ MODERATE	CRITICAL

AD: Atopic dermatitis; **TCS:** Topical corticosteroid; **EASI**: Eczema Area and Severity Index

*Class I-III topical steroids in the German classification according to Niedner (no citation provided).

Explanation
a. Study relied on a small sample.

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e-Table 23. Tacrolimus 0.1% vs Lower medium potency steroids (bid)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tacrolimus 0.1%	lower-medium potency TCS	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in severity as assessed by investigators (follow up: 3 weeks; assessed with: SCORAD and mEASI)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	tacrolimus 0.1%	lower-medium potency TCS	Relative (95% CI)	Absolute (95% CI)		
2 [1,2]	randomized trials	not serious	not serious	not serious	serious [a]	none	For 11 adults with AD randomized to tacrolimus 0.1% and 10 to 0.1% hydrocortisone butyrate bid for 3 weeks, for tacrolimus treated patients median SCORAD scores were reduced from 44.3 (range 27.4-57.2) at baseline to 3.8 (range 0-21.9). For TCS treated patients median SCORAD scores were reduced from 40.1 (range 25.4-58.3) at baseline to 10.2 (range 2.3-23.9).[1] For 191 adults (aged 16-70) with AD randomized to tacrolimus 0.1% and 186 randomized to 0.1% hydrocortisone butyrate bid for 3 weeks, tacrolimus treated patients experienced a median improvement in mEASI scores from baseline of 63.5% and the TCS group experienced a median improvement from baseline of 63.9% (no significant difference is reported; p-value not provided).[2]				⨁⨁⨁◯ MODERATE	CRITICAL
Change from baseline in severity as assessed by investigators (follow up: 6 months; assessed with: mEASI)												
1 [3]	randomized trials	not serious	not serious	not serious	not serious	none	For 487 adults with AD randomized to 0.1% tacrolimus and 485 randomized to 1% hydrocortisone acetate (head and neck) and 0.1% hydrocortisone butyrate (trunk and extremities) bid, at 6 months, the median percentage change in mEASI from baseline was -87.7% in the tacrolimus group and -82.5% in the TCS group (p<0.008).				⨁⨁⨁⨁ HIGH	CRITICAL
Serious adverse events (follow up: 6 months; assessed with: participants experiencing a serious AE related to treatment)												
1 [3]	randomized trials	not serious	not serious	not serious	serious [b]	none	5/487 (1.0%)	9/485 (1.9%)	**RR 0.56** (0.19 to 1.65)	**8 fewer per 1,000** (from 15 fewer to 12 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Withdrawal due to adverse event (follow up: 3 weeks; assessed with: participants discontinuing treatment due to AE)												
1 [2]	randomized trials	not serious	not serious	not serious	serious [c]	none	8/191 (4.2%)	3/186 (1.6%)	**RR 2.53** (0.68 to 9.40)	**25 more per 1,000** (from 5 fewer to 135 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Withdrawal due to adverse events (follow up: 6 months; assessed with: participants discontinuing treatment due to AE)												
1 [3]	randomized trials	not serious	not serious	not serious	serious [d]	none	10/487 (2.1%)	16/485 (3.3%)	**RR 0.63** (0.29 to 1.37)	**12 fewer per 1,000** (from 23 fewer to 12 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Skin infections (follow up: 3 weeks; assessed with: participants experiencing a skin infection)												
1 [2]	randomized trials	not serious	not serious	not serious	serious [c]	none	15/191 (7.9%)	13/186 (7.0%)	**RR 1.11** (0.54 to 2.28)	**8 more per 1,000** (from 32 fewer to 89 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Skin infections (follow up: 6 months; assessed with: participants experiencing a skin infection)												
1 [3]	randomized trials	not serious	not serious	not serious	serious [e]	none	60/487 (12.3%)	58/485 (12.0%)	**RR 1.03** (0.73 to 1.44)	**4 more per 1,000** (from 32 fewer to 53 more)	⨁⨁⨁◯ MODERATE	CRITICAL

AD: Atopic dermatitis; **TCS:** Topical corticosteroid; **RR:** Risk ratio; **AE**: Adverse event; **mEASI**: Modified Eczema Area and Severity Index; **SCORAD:** SCORing Atopic Dermatitis

Explanations

a. One study relies on a very small sample and one study relies on a moderate sample.
b. CI consistent with no difference and both moderate increase and a small decrease in risk.
c. CI consistent with no difference and a large increase in risk.
d. CI consistent with no difference and both a moderate decrease and small increase in risk.
e. CI consistent with no difference and both a moderate increase and decrease in risk.

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e-Table 24. All topical antimicrobial agents versus vehicle

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	antimicrobials/antiseptics	vehicle	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in disease severity as assessed by investigators (follow up: range 28 days to 42 days; assessed with: SCORAD and EASI)												
4 [1-4]	randomized trials	serious [a]	not serious	not serious	serious [b]	none	113	117	SMD **0.05 SD lower** (0.52 lower to 0.41 higher)		⨁⨁◯◯ LOW	CRITICAL
Change from baseline disease severity as assessed by participants (follow up: 42 days; assessed with: POEM)												
1 [1]	randomized trial	serious [c]	not serious	not serious	serious [d]	none	32 MD -1.79±6.32	34 MD -1.09±6.68	MD **0.7 lower** (3.84 lower to 2.44 higher)		⨁⨁◯◯ LOW	CRITICAL
Change from baseline in itch (follow up: range 28 days to 42 days; assessed with: Numeric Rating Scales (lower score indicates less itch) & VAS 10cm (0=no itch; 10=most severe itch))												
3 [1,2,4]	randomized trials	not serious	not serious	not serious	serious [e]	none	91	95	SMD **0.18 SD lower** (0.47 lower to 0.11 higher)		⨁⨁⨁◯ MODERATE	CRITICAL
Flare prevention (follow up: 84 days; assessed with: Number of doctor-reported flares)												
1 [1]	randomized trial	serious [c]	not serious	not serious	serious [f]	none	For 43 adult AD patients randomized to topical endolysin treatment against S. aureus and 44 patients randomized to placebo bid, there was no significant difference in the number of doctor-reported flares: 14 vs 17, respectively, p=0.55.				⨁⨁◯◯ LOW	CRITICAL
Serious adverse events (follow up: range 28 days to 42 days; assessed with: number of participants experiencing at least one serious AE)												

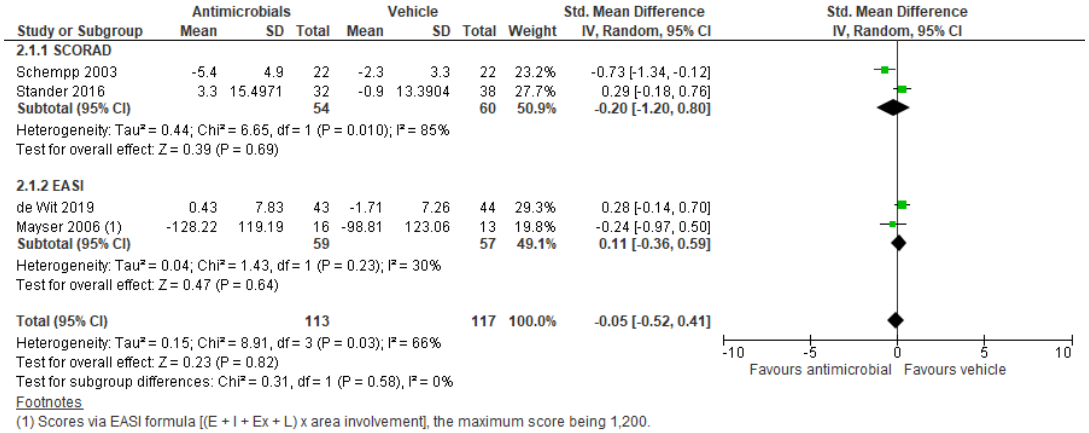
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	antimicrobials/antiseptics	vehicle	Relative (95% CI)	Absolute (95% CI)		
2 [1,3]	randomized trials	not serious	serious [g]	not serious	serious [h]	none	40/64 (62.5%)	40/65 (61.5%)	**RR 1.01** (0.72 to 1.42)	**6 more per 1,000** (from 172 fewer to 258 more)	⨁⨁◯◯ LOW	CRITICAL
Change from baseline in quality of life (follow up: 42 days; assessed with: Skindex-29- higher scores indicate lower levels of health-related quality of life)												
1 [1]	randomized trial	serious [c]	not serious	not serious	serious [i]	none	43 MD -8.38±12.98	44 MD -4.66±13.87	MD **3.72 lower** (9.36 lower to 1.92 higher)		⨁⨁◯◯ LOW	CRITICAL

SCORAD: SCORing Atopic Dermatitis; **EASI:** Eczema Area and Severity Index; **POEM:** Patient Oriented Eczema Measure; **CI:** Confidence interval; **SMD:** Standardized mean difference; **MD:** Mean difference; **RR:** Risk ratio; **VAS:** Visual analog scale

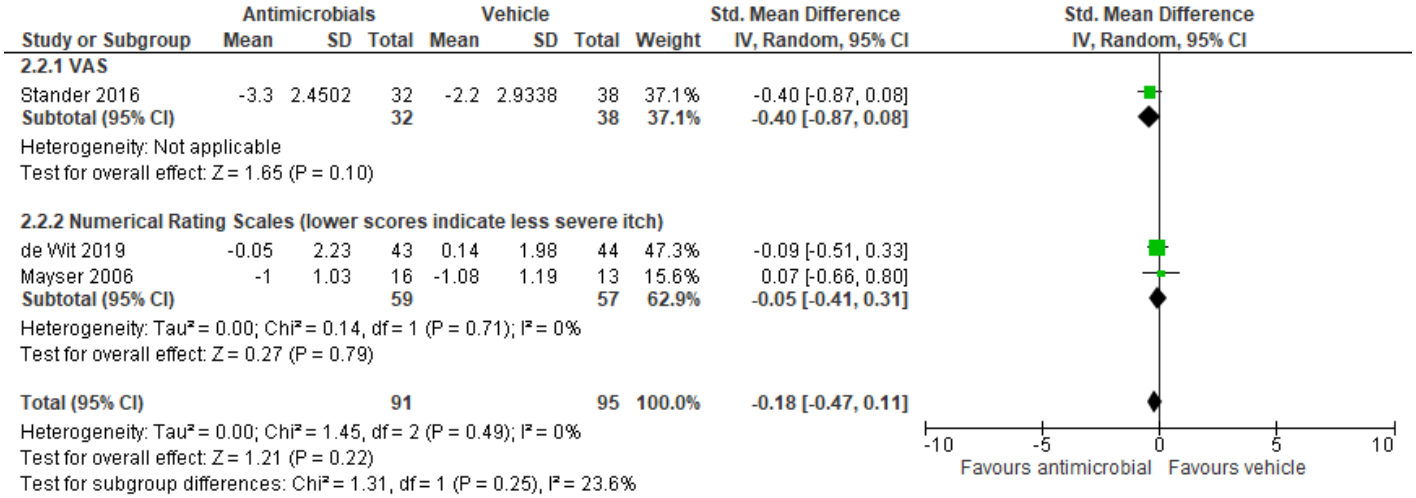
Explanations

a. Two studies are of a low risk of bias; two studies are of moderate risk of bias due to unclear randomization and masking methods and unclear loss to follow-up and missing outcome data.
b. CI compatible with no difference and both appreciable benefit and harm.
c. This study is of a moderate risk of bias due to unclear randomization and masking methods.
d. CI compatible with no difference, important benefit and moderate harm.
e. CI consistent with moderate effect to small harmful effect.
f. A small sample of 87 is concerning for precision.
g. One study suggests the majority of participants experienced serious AEs and one study suggests no participants experienced serious AEs.
h. CI consistent with no risk difference and appreciable benefit and harm.
i. CI consistent with no difference and clinically meaningful benefit and small harmful effect.

Analysis 24a. Change in disease severity as assessed by investigators (SCORAD & EASI)



Analysis 24b. Change from baseline in itch.



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e-Table 25. Triclosan vs vehicle or placebo

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Change from baseline in clinical severity as assessed by investigator (follow-up: range 27 days to 42 days; assessed with: Change in mean SCORAD from baseline; Change from baseline in Investigator global evaluation (-5 severe worsening to 5 total clearing)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
2[1,2]	randomized trials	serious[a]	not serious	not serious	serious[b]	none	For 30 patients (aged 12-40yo) with mild to moderate uninfected AD randomized to 1% triclosan emollient and 30 to vehicle emollient bid for 27 days (0.025% betamethasone valerate cream also provide for both groups), mean change in SCORAD from baseline was significantly reduced in the triclosan arm compared to the vehicle on day 14 (-8.86 vs -4.74, p<0.05) but not on day 27 (-11.46 vs -9.71, p>0.05).[1] For 50 patients (aged 12-74yo) with moderate to severe AD randomized to either daily bathing with 1.5% triclocarban soap or placebo soap (0.025% triamcinolone acetonide cream allowed) for 6 weeks, global improvement in AD was significantly greater in the triclosan soap group (no data provided).[2]	⨁⨁◯◯ Low	CRITICAL
Withdrawal due to adverse events (follow-up: 27 days; assessed with: participants discontinuing treatment due to AE)									
1[1]	randomized trials	not serious	not serious	not serious	serious[b]	none	For 30 patients (aged 12-40yo) with mild to moderate uninfected AD randomized to 1% triclosan emollient and 30 to vehicle emollient bid for 27 days (0.025% betamethasone valerate cream also provide for both groups), no participants withdrew from either group due to AE.	⨁⨁⨁◯ MODERATE	CRITICAL
Topical corticosteroid use (assessed with: amount of topical corticosteroids used)									
2[1,2]	randomized trials	serious[a]	serious[c]	not serious	serious[b]	none	For 30 patients (aged 12-40yo) with mild to moderate uninfected AD randomized to 1% triclosan emollient and 30 to vehicle emollient bid for 27 days (0.025% betamethasone valerate cream also provide for both groups), there was a significantly lower amount of topical steroid application by patients in the treatment group compared to the control: 22 g and 44.2 g, respectively; p < 0.05).[1] For 50 patients (aged 12-74yo) with moderate to severe AD randomized to either daily bathing with 1.5% triclocarban soap or placebo soap (0.025% triamcinolone acetonide cream allowed) for 6 weeks, there was no significant difference in the amount of topical corticosteroid used by either treatment group (P=.86).[2]	⨁◯◯◯ Very low	IMPORTANT

AD: Atopic dermatitis; **SCORAD:** SCORing Atopic Dermatitis

Explanations

a.One study is of a high risk of bias due to minimal methods reporting, minimal reporting of essential study information, and minimal reporting of outcome data.

b.Studies relied on very small samples suggesting imprecision.
c.One study suggests steroid sparring effects, while the other study does not.

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e-Table 26. Topical doxepin 5% compared to vehicle cream

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	antihistamines	control	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in itch (follow up: 7 days; assessed with: VAS 100-mm)												
1 [1]	randomized trials	serious [a]	not serious	not serious	serious [b]	none	For 132 AD patients randomized to Doxepin 5%, bid baseline visit and qd remainder of days doxepin 5%, bid baseline visit and qd remainder of days and 138 randomized to vehicle cream for 7 days, VAS itch scores were reduced by a mean of 68.6 and 54.6, respectively (SD not reported; p<0.01)				⊕⊕◯◯ LOW	CRITICAL
Withdrawal due to adverse events (follow up: 7 days; assessed with: participants discontinuing treatment due to AEs)												
1 [1]	randomized trials	serious [a]	not serious	not serious	serious [b]	none	16/132 (12.1%)	3/138 (2.2%)	**RR 5.08** (1.51 to 17.06)	**89 more per 1,000** (from 11 more to 349 more)	⊕⊕◯◯ LOW	CRITICAL

AD: Atopic dermatitis**; CI:** Confidence interval; **SMD:** Standardized mean difference; **RR:** Risk ratio; **VAS:** Visual analog scale

Explanations

a. Study is of a moderate risk of bias due to minimal methods reporting and missing outcome data.
b. Study relies on a small sample not meeting optimal information size (>400).

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e-Table 27. Crisaborole 2% bid vs vehicle

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	crisaborole	vehicle	Relative (95% CI)	Absolute (95% CI)		
Change from baseline in disease severity as assessed by investigator (follow-up: range 15 days to 29 days; assessed with: Change from baseline in TSS or ADSI; ISGA success [participants assessed as clear (0) or almost clear (1) with ≥ 2-grade improvement from baseline])												
4 [1-4]	randomized trials	not serious	not serious	not serious [a]	not serious	none	Across two identical trials, 1,016 AD patients (aged 2-79) were randomized to crisaborole ointment 2% b.i.d and 506 randomized to vehicle for 28 days. On day 29, significantly more crisaborole-treated patients achieved ISGA success (clear or almost clear with 2-grade or greater improvement from baseline): 326 (32.1%) vs 110 (21.7%); RR 1.80 95%CI 1.48, 2.18, p<0.0001.[4] In 21 AD patients (mean age 33.9 SD 11.0), two AD lesions of comparable severity were randomized to crisaborole ointment 2% or vehicle b.i.d for 15 days: mean reduction from baseline in lesional TSS was significantly greater with crisaborole: -4.8 (SE 0.53) vs -2.7 (SE 0.47), p<0.01.[2] In 40 adults with AD, two AD lesions of identical severity were randomized to crisaborole ointment 2% or vehicle b.i.d for 14 days. Mean reduction from baseline in lesional TSS at day 15 was greater for crisaborole-treated than vehicle-treated lesions: -4.5 vs -2.1, p < .0001.[1] In 25 adults with AD, AD lesions of similar severity were randomized to crisaborole ointment 2% or vehicle b.i.d for 6 weeks. The mean difference in change from baseline in ADSI score at day 28 favored crisaborole: MD 2.2±2.99, p=0.001).[3]			⊕⊕⊕⊕ High	CRITICAL
Change from baseline in itch (follow-up: 15 days; assessed with: Mean change in lesion pruritus numerical rating scale NRS (0=non itch; 10 worst itch))												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	crisaborole	vehicle	Relative (95% CI)	Absolute (95% CI)		
3 [1,2,4]	randomized trials	not serious	not serious	not serious [b]	not serious	none	Across two identical trials, 1,016 AD patients (aged 2-79) were randomized to crisaborole ointment 2% b.i.d and 506 randomized to vehicle for 28 days. On day 29, significantly more crisaborole-treated patients achieved improvement in pruritus as assessed by an NRS itch score of 0 or 1 with at least a 1-grade reduction from baseline: 640 (63%) vs 268 (53%), p=0.002.[4] In 21 AD patients (mean age 33.9 SD 11.0), two AD lesions of comparable severity were randomized to crisaborole ointment 2% or vehicle b.i.d for 15 days: mean reduction from baseline in mean(SE) NRS itch scores were greater with crisaborole treatment: -3.7(0.47) vs -2.9 (0.46); MD -0.80 95%CI -2.09, 0.49.[2] In 40 adults with AD, 2 AD lesions of identical severity were randomized to crisaborole ointment 2% or vehicle for b.i.d for 14 days. Mean change from baseline in lesional itch NRS at day 15 was greater for crisaborole-treated than vehicle-treated lesions: -3.9 vs -2.0, p < 0.0001.[1]				⊕⊕⊕⊕ High	CRITICAL
Serious adverse events (follow-up: range 15 days to 48 weeks; assessed with: Participants experiencing serious adverse events [as defined by investigators])												
5 [1-5]	randomized trials	not serious	not serious	not serious [a]	not serious [c]	none	Across two identical trials, 1,016 AD patients (aged 2-79) were randomized to crisaborole ointment 2% b.i.d and 506 randomized to vehicle for 28 days. During treatment, 65% of patients reported at least 1 treatment-emergent AE of which 51.2% were mild and 44.6% were moderate and most were considered unrelated to treatment (93.1%).[4] A long term safety assessment of 517 participants of the trials who continued crisaborole treatment for 48 weeks found 7 patients experienced at least one serious AE as assessed by 12 week treatment period from 1 to 48 weeks.[5] Across three intraindividual trials, including 86 participants, that randomized individual AD lesions to crisaborole ointment 2% or vehicle b.i.d for up to 6 weeks, no serious adverse events were reported for lesions treated with either crisaborole or vehicle.[1-3]				⊕⊕⊕⊕ High	CRITICAL
Withdrawal due to adverse event (follow-up: 48 weeks; assessed with: Participants discontinuing treatment due to AE)												
2 [4,5]	randomized trials	not serious	not serious	not serious [b]	not serious [d]	none	Across two identical trials, 1,016 AD patients (aged 2-79) were randomized to crisaborole ointment 2% b.i.d and 506 randomized to vehicle for 28 days. The rates of study discontinuation because of AEs were the same in the crisaborole (1.2%) and vehicle (1.2%) treatment groups.[4] A long-term safety assessment of 517 participants of the trials who continued crisaborole treatment for 48 weeks found 9 (1.7%) patients discontinued long-term crisaborole treatment due to AEs.[5]				⊕⊕⊕⊕ High	CRITICAL

AD: Atopic dermatitis; **TSS**: Total Sign Score; **ADSI**: Atopic Dermatitis Severity Index; **ISGA:** Investigator's Static Global Assessment; **MD:** Mean difference

Explanations

a. Three trials included adults and children; In one trial the mean age of participants was 33.9 suggesting alignment with the research question focused on adults and in 2 trials the response of adult and pediatric participants was considered similar, so the evidence was not downgraded for indirectness.
b. Two trials included adults and children; in these trials the response of adult and pediatric participants was considered similar, so the evidence was not downgraded for indirectness.
c. Across the evidence base serious adverse events are rare and indicative of a non-important increase in risk with the intervention so the evidence was not downgraded.
d. Across the evidence base, discontinuation of treatment is rare and indicative of a non-important increase in risk with the intervention, so the evidence was not downgraded.

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e-Table 28. Ruxolitinib Cream 1.5% bid vs vehicle

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ruxolitinib	vehicle	Relative (95% CI)	Absolute (95% CI)		
Change in clinical severity as assessed by investigator (follow-up: 8 weeks; assessed with: patients achieving an IGA score of 0 to 1 who have an improvement of 2 or more points from baseline)												
3[1,2A]	randomized trials	not serious	not serious	not serious [a]	not serious	none	277/531 (52.2%)	33/296 (11.1%)	**RR 4.60** (3.05 to 6.95)	**401 more per 1,000** (from 229 more to 663 more)	⊕⊕⊕⊕ High	CRITICAL
Change in itch severity (follow-up: 8 weeks; assessed with: patients with ≥ 4-point reduction in itch NRS score from baseline)												
3 [2,3]	randomized trials	not serious	not serious	not serious [a]	not serious	none	270/519 (52.0%)	43/279 (15.4%)	**RR 3.38** (2.54 to 4.51)	**367 more per 1,000** (from 237 more to 541 more)	⊕⊕⊕⊕ High	CRITICAL
Change in Health-Related Quality of Life (follow-up: 8 weeks; assessed with: mean percent improvement from baseline in Skindex-16 overall scores)												
1 [3]	randomized trials	not serious	not serious	not serious	serious [b]	none	The mean percent improvement from baseline in Skindex-16 overall scores in patients treated with 1.5% RUX cream twice daily (n=50) was 63.5% at week 2 (vehicle n=52, 10.5%; p= 0.001) and 73.2% at week 8 (vehicle, 19.7%; p<0.001).				⊕⊕⊕◯ Moderate	CRITICAL
Withdrawal from treatment due to treatment emergent adverse events (follow-up: 8 weeks; assessed with: Participants discontinuing treatment due to emergent adverse events)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ruxolitinib	vehicle	Relative (95% CI)	Absolute (95% CI)		
3[1,2]	randomized trials	not serious	not serious	not serious [a]	not serious [c]	none	In a phase II trial comparing 1.5% RUX BID (n=50) to a vehicle (n=52) for 8 weeks, no participants receiving RUX discontinued treatment, and 1 participant in the vehicle arm discontinued due to an AE. In pooled results from two phase III trials, 4/499 participants receiving 1.5% RUX BID for 8 weeks and 8/250 participants in the vehicle arm discontinued treatment due to AE (RR 0.25 95%CI 0.08, 0.82).				⊕⊕⊕⊕ High	CRITICAL
Serious treatment emergent adverse events (follow-up: 8 weeks; assessed with: participants experiencing an AE considered serious by investigators)												
3[1,2]	randomized trials	not serious	not serious	not serious [a]	not serious [d]	none	In a phase II trial comparing 1.5% RUX BID (n=50) to a vehicle (n=52) for 8 weeks, no participants in either arm experienced a serious AE. In pooled results from two phase III trials, 3/499 participants receiving 1.5% RUX BID for 8 weeks and 2/250 participants in the vehicle arm experienced a serious AE (RR 0.75 95%CI 0.13, 4.47).				⊕⊕⊕⊕ High	CRITICAL
Most common treatment-related adverse events (follow-up: 8 weeks; assessed with: adverse events occurring in >0.5% or >1% of the total patient population)												
3[1,2]	randomized trials	not serious	not serious	not serious [a]	not serious	none	In a phase II trial comparing 1.5% RUX BID (n=50) to a vehicle (n=52) for 8 weeks, application site pain occurred in >1% of the total study population and in 1/50 participants randomized to RUX and 2/52 participants randomized to vehicle. In pooled results from two phase III trials, application site burning and application site pruritus occurred in >0.5% of the pooled study population occurring in 0.8% and 0% of the RUX arm, respectively compared to 4.4% and 2.5% of the vehicle arm, respectively.				⊕⊕⊕⊕ High	IMPORTANT

AD: Atopic dermatitis; **CI:** confidence interval; **RUX**: ruxolitinib; **RR:** risk ratio**; AE:** Adverse event

^ Three trials reported in two publications

Explanations

a. Two trials included participants aged 12 years and older but this was not considered important variation from the research question focused on adults.
b. Small study sample does not meet optimal information size.
c. Discontinuation was a rare event across studies and study populations indicating short-term safety was not a concern for the intervention so the evidence was not downgraded due to the low event rates.
d. Serious adverse events were rare and considered by investigators to be unrelated to treatment; the evidence was not downgraded for imprecision as the low rates across the studies suggest short-term safety is not a concern.

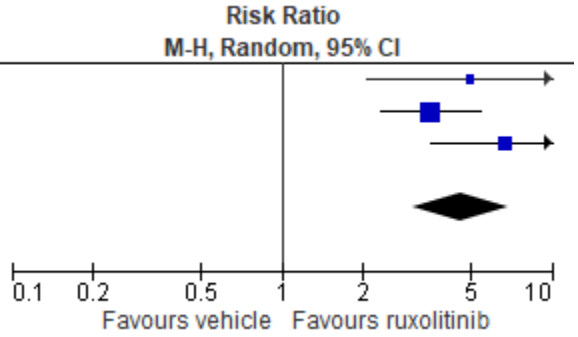
Intervention Notes:

a. As with some other drugs in the class, ruxolitinib cream carries boxed warnings for serious infections, mortality, cancer, major adverse cardiovascular events, and thrombosis.
b. Long term safety data is currently unavailable, so ruxolitinib cream was approved for the short-term and noncontinuous treatment of mild to moderate AD individuals 12 years of age or older whose disease is not controlled with topical prescription therapies, or when those therapies are not advisable (per FDA).

Analysis 28a. Investigator Global Assessment Response

Study or Subgroup	ruxolitinib Events	Total	vehicle Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kim 2020 J Allergy Clin Immunol	24	50	5	52	18.4%	4.99 [2.07, 12.06]
Papp 2021 TRuE-AD1	136	253	19	126	51.2%	3.56 [2.32, 5.48]
Papp 2021 TRuE-AD2	117	228	9	118	30.5%	6.73 [3.55, 12.77]
Total (95% CI)		**531**		**296**	**100.0%**	**4.60 [3.05, 6.95]**
Total events	277		33			

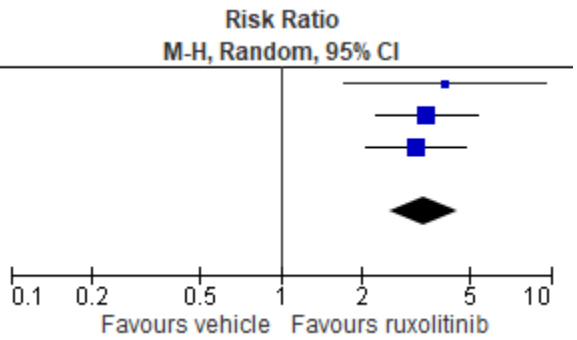
Heterogeneity: Tau² = 0.04; Chi² = 2.75, df = 2 (P = 0.25); I² = 27%
Test for overall effect: Z = 7.26 (P < 0.00001)



Analysis 28b. Clinically Relevant Itch Response

Study or Subgroup	ruxolitinib Events	Total	vehicle Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kim 2020 JAAD	22	38	5	35	11.3%	4.05 [1.72, 9.54]
Papp 2021 TRuE-AD1	132	253	19	126	44.4%	3.46 [2.25, 5.32]
Papp 2021 TRuE-AD2	116	228	19	118	44.3%	3.16 [2.05, 4.86]
Total (95% CI)		**519**		**279**	**100.0%**	**3.38 [2.54, 4.51]**
Total events	270		43			

Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 2 (P = 0.87); I² = 0%
Test for overall effect: Z = 8.32 (P < 0.00001)



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