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Online Supplement

Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic agents

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e-Appendix 1. Detailed Methods

Expert Work Group Composition and Disclosures of Interest

The co-chairs of the Work Group (D.D. and R.S.) were reviewed for potential disclosures of interest (DOIs) and approved by the AAD's Clinical Guidelines Committee (CGC). Additional Work Group members were nominated by the co-chairs based on their expertise related to the clinical questions. All Work Group nominees were reviewed for potential DOIs by the CGC. The majority (at least 51%) of the Work Group was required to be free of financial DOIs relevant to the topic of the guideline. Nominees found to have no relevant financial DOIs were approved, whereas nominees found to have potentially relevant financial DOIs were approved with management. Work Group members approved with management were prohibited from discussions on and voting for recommendations in which they had relevant DOIs. Work Group members completed a DOI form that was periodically updated and reviewed for potential relevant DOIs throughout guideline development and used to ensure management terms were observed. The multidisciplinary Work Group consisted of the co-chairs, 10 members, an additional member serving as a methodologist, and a patient representative. The Work Group was supported by an AAD guidelines staff member (L.F.G) with health research methodology expertise.

Formulation of Questions and Rating the Importance of Outcomes

Based on the aim of the guideline to determine how effective and safe currently available and approved systemic agents and phototherapy are for the management of AD in adults, the expert Work Group identified four clinical questions, using the Population, Intervention, Comparator, Outcome (PICO) format (**Table I**). Next, the Work Group identified outcomes considered important for making clinical decisions regarding the systemic treatment of AD through discussion and review of the core outcome set for AD trials developed by the Harmonizing Outcome Measures for Eczema (HOME) initiative (**Table 1**).[1] The Work Group ranked the importance of each primary outcome for decision-making via anonymous online voting using a 9-point scale (a ranking of 7-9 was assigned to outcomes critical for decision-making, 4-6 for outcomes important for decision-making, and 1-3 for outcomes of limited importance for decision-making).[2] Results of voting were used to categorize outcomes as "critical", "important", or "not important".

Table 1. Primary Outcomes

Primary Outcome	**Importance Ranking**
Change in clinical signs/symptoms of disease as assessed by clinician	Critical
Prevention of flares	Critical
Serious adverse events	Critical
Withdrawal due to adverse events	Critical
Infection	Important
Change in patent-reported symptoms	Critical
Change in quality of life	Critical
Change in itch severity	Critical

Evidence Search and Review

A search of the literature for all PICO questions using MEDLINE (via PubMed), CENTRAL, and the Cochrane Database of Systematic Reviews was conducted in May 2021 and periodically updated through April 2022. Existing systematic reviews of randomized controlled trials published within the previous 3 years and meeting all eligibility criteria were identified (**Table 2**). If systematic reviews were not available or the identified systematic reviews did not include an intervention of interest a review was commissioned from an expert systematic review group or a de novo review was conducted by the Work Group with the assistance of AAD staff. The evidence review workflow is detailed in **Table 3**. All systematic reviews supporting this analysis met

or followed standard methodology including development of PICO questions, explicit inclusion criteria, systematic literature searches, and vetted risk of bias assessment procedures.

Table 2. Eligibility Criteria for Topical Management of Adults with AD

Category	Criteria
Population	Adults (≥ 18yo) with clinically diagnosed AD
Intervention	Phototherapy/photochemotherapy and systemic agents available and approved for use in the US. Including one of the following or a combination of: abrocitinib, apremilast, azathioprine, baricitinib, cyclosporine, dupilumab, omalizumab, tralokinumab, upadacitinib, ustekinumab, interferon-gamma, intravenous immunoglobins, leukotriene inhibitors, mepolizumab, methotrexate, mycophenolate mofetil, oral antibiotic or antihistamines, systemic calcineurin inhibitors or corticosteroids, tumor necrosis factor-alpha inhibitors.
Comparator	Placebo, no treatment, other systemic intervention
Outcomes	Change in clinical signs/symptoms of disease as assessed by clinician; Prevention of flares; Serious adverse events; Withdrawal due to adverse events Infection; Change in patent-reported symptoms; Change in quality of life; Change in itch severity
Study Design	Published RCTs, including parallel, cross-over, and cluster RCTs, randomizing different clusters, patients, or body sites for individual participants
Other	English language studies

For de novo reviews, studies retrieved by the literature searches were reviewed for relevance over two rounds of study selection. Two reviewers independently screened citations. All citations deemed relevant by one or both reviewers were obtained as full text. Two independent reviewers screened full text citations against the a priori established eligibility criteria (**Table 2**); discrepancies were resolved through discussion. Data extraction using structured data abstraction spreadsheets was initially performed by an independent reviewer with subsequent quality control performed by a second reviewer. Risk of bias was assessed in all included studies using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (ROB2).[3]

Table 3. Evidence Review Workflow

Intervention	Evidence Review Workflow
Abrocitinib Apremilast Azathioprine Baricitinib Cyclosporine Dupilumab Omalizumab Tralokinumab Upadacitinib Ustekinumab	Used existing high quality Bayesian network meta-analysis by Drucker, et al.[4,5] Relied on search and data updated from June 15, 2021 • De novo systematic review conducted in April 2022 for studies comparing JAK inhibitors to other systemic therapies. This review supported the JAKs vs dupilumab evidence profile.
Interferon-gamma	Updated an existing high quality systematic review & meta-analysis[6] Search for this specific intervention updated in March 2022 (no additional trials identified)
Intravenous immunoglobins	Updated an existing high quality systematic review & meta-analysis[6] Search for specific intervention updated in March 2022 (no additional trials identified)

Lebrikizumab	Updated the search from an existing high quality systematic review & meta-analysis[6] in August 2022. Two trial records were identified. Given the pending approval of the drug the trial data was used to supplement the published data from the existing review.
Leukotriene inhibitors	Used existing high quality Cochrane systematic review[7] Review search updated in April 2022 (no additional trials identified)
Mepolizumab	Used existing high quality systematic review & meta-analysis[6] Search for specific intervention updated in March 2022 (no additional trials identified)
Methotrexate	Used existing high quality systematic review & meta-analysis[6] Search for specific intervention updated in March 2022 (no additional trials identified)
Mycophenolate mofetil	Systematic review conducted April 2022 (no direct evidence identified)
Oral Antibiotics	Systematic review conducted April 2022 (no direct evidence identified)
Oral antihistamines	Existing high quality Cochrane review of oral H1 antihistamines as monotherapy[8] was updated in April 2022 (no direct evidence was identified); Systematic review of oral H4 antihistamines as monotherapy was conducted in April 2022 (no direct evidence identified)
Phototherapy	Cochrane systematic review contracted[9]; Review used
Systemic antivirals for eczema herpeticum	Systematic review conducted April 2022 (no direct evidence identified)
Systemic calcineurin inhibitors	Systematic review conducted April 2022 (no direct evidence identified)
Systemic corticosteroids	High quality existing systematic review & meta-analyses identified[6] Search specific to intervention updated in March 2022 (no additional trials identified) Existing review used
Tumor necrosis factor-alpha inhibitors	Systematic review for etanercept and infliximab conducted April 2022 (no direct evidence identified)

Assessing the Overall Certainty of the Body of Evidence

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach was used to assess the overall certainty of the evidence from systematic reviews for each critical or important outcome.[10] The GRADEPro Guideline Development Tool was used to create evidence profiles that categorized the overall certainty of the body of evidence for each outcome into one of four categories: high, moderate, low, or very low. Each category represents the confidence in the estimate of effect for an outcome (**Table 4**).

Table 4. Certainty of Evidence Ratings

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

Formulating and Grading Recommendations

The Work Group drafted recommendations using the evidence profiles and considering the following: the balance of desirable and undesirable consequences of an intervention, the overall certainty of the evidence, patient values and preferences, and feasibility.[11] GRADE evidence-to-decision (EtD) frameworks were compiled for each clinical question to facilitate recommendation drafting. Structured searches were conducted for evidence of patient values and preferences, resource use, and feasibility to inform the EtD process. The workgroup also included a patient representative to provide input on preferences and values.

In accordance with the GRADE approach, recommendations were either "strong" or "conditional".[12] The implications of each strength of recommendation are summarized in **Table 5**. Recommendations were also graded according to the GRADE approach.[12] In situations in which the supporting evidence for a recommendation was indirect only, but the certainty surrounding an intervention's impact was high and the benefits of the intervention clearly outweigh the harms (or vice versa), a Good Practice Statement was developed.[13] Good Practice Statements are strong recommendations as the certainty surrounding the impact of the recommended intervention is high.

Table 5. Strength of Recommendation Implications

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

Manuscript Review and Currency Statement

This guideline was developed in accordance with the AAD/AAD Association Administrative Regulations for Evidence-Based Clinical Practice Guidelines (March 2021), which includes the opportunity for review and comment by the entire AAD membership and final review and comment by the AAD Board of Directors.[14] This guideline will be considered current for a period of 5 years from the date of publication unless reaffirmed, updated, or retired before that time.

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e-Table 1. Insufficient Evidence

Intervention	Evidence Summary
Intravenous immune-globulins (IVIG)	No trials in adults compared IVIG to placebo or other systemic for AD. *Indirect adult data*: One trial in adults compared immediate treatment with IVIG 1k/kg as an 8-h infusion daily for 2 consecutive days (n=5) to no treatment for 30 days then IVIG 1k/kg/day (n=5) and reported reduction in SCORAD at 30 days of 15% (95%CI 6-24%) across all patients. Global evaluation of disease severity by patients did not show clinically significant change at 30 days.[1] *Pediatric data*: IVIG 2g/kg per month (n=30) was superior to placebo (n=10) for reduction in SCORAD at 12 weeks (mean change -24% vs -4%), but not at 36 weeks. Five children in the IVIG group discontinued therapy due to adverse effects (severe headache, nausea, fever).[2] A comparison of IVIG 2g/kg single dose (n=6) and cyclosporine 4mg/kg/day (n=8) reports at 12 weeks that IVIG was not associated with significant clinical improvement in SCORAD and cyclosporine was superior to IVIG: mean change in SCORAD at 12 weeks -70% vs -34%.[3]
Interferon-gamma (INF-γ)	No additional evidence identified since 2014 guideline, and no adult-specific evidence identified. *Mixed population data:* Two trials including 134 children and adults (2-65yo) compared INF-γ to placebo and reported non-validated outcome measures. One trial reported no significant difference in total clinical severity score (TCS) between rIFN-γ 50μg/m^2/day (n=40) and placebo (n=43) at 12 weeks.[4] The second trial reported significant reduction in TCS for both high dose (n=21) and low dose (n=20) rIFN-γ compared to placebo (n=10) at 12 weeks: -50%, -38, -8%, respectively.[5] Adverse events were significantly more common in the INF-γ arm of the first trial and were reported in 54% of those receiving INF-γ in the second trial (events included headache, fever, myalgia).
Omalizumab	No adult-specific evidence identified. *Pediatric & Mixed population Data:* A trial comparing omalizumab (n=31) to placebo (n=32) in a pediatric population (4-19) with severe AD found omalizumab to be superior to AD in mean change (%) in SCORAD, although reduction was not clinically significant, (-28% vs -12%), cDLQI/DLQI (-53% vs -31%) and POEM (-33% vs -27%) at 24 weeks. Serious AEs were reported in 19% of participants in each group with of the 3% of omalizumab discontinuing treatment due to AE compared to 0% of the placebo group.[6] Two trials comparing omalizumab to placebo in participants with severe or stable AD (aged 4-22 and 4-60) report omalizumab was not superior to placebo and reduction was not clinically significant for mean change in SCORAD (-25% vs -72%) and EASI (no data reported) at 24 weeks.[7,8] Both trials report no serious adverse events in any participants.
Tumor necrosis factor-alpha inhibitors	No evidence for etanercept or infliximab for atopic dermatitis identified.
Systemic Calcineurin Inhibitors (only systemic tacrolimus available in the US)	No direct evidence matching inclusion criteria was identified for systemic tacrolimus to manage AD. *Indirect evidence:* An open-label pilot study of sequential therapy with oral tacrolimus and topical tacrolimus for severe AD in adults (n=12) reported clinically meaningful improvement in EASI score at 14 weeks (mean change 17.93) and improvement in average pruritis score (mean change 4.37). 5/12 patients had nausea and/or vomiting with oral tacrolimus and 4/12 had diarrhea.[9] A trial of oral pimecrolimus at 10, 20 and 30 mg bid compared to placebo for moderate-to-severe AD in adults found significant superiority of pimecrolimus at both weeks 7 and 13 to reduce EASI and found a dose response gradient among the pimecrolimus arms: Week 7 mean change -5.8, -8.4, -13.5 vs -5.0; Week 13 mean change -5.3, -7.3, -11.1 vs -4.8. At both week 7 and week 13, all the pimecrolimus-treated groups had a greater percentage of patients with pruritus scores ≤ 1, compared with the placebo-treated group (the difference was only significant for 20mg of

	pimecrolimus vs placebo at week 13). There were no differences between groups in overall incidence of AEs: total % of patients with AE 77%, 83%, 85% vs 92%.[10]
Systemic Antibiotics	No direct evidence matching inclusion criteria was identified.
Noninfected AD	*Pediatric & mixed population data*: A crossover trial of cefuroxime axetil (dose not provided) and placebo bid for two weeks each with a one week washout in 20 patients (aged 6-58) with moderate-to-severe AD but no skin infection, reported "no difference were noted in the patients with respect to clinical severity" and no adverse events.[11] A trial of flucloxacillin 250 mg qid (n=25) for 4 weeks compared to placebo (n=25) in children with uninfected AD, reported a significantly lower rate of "good" or "excellent" global clinical outcomes in the flucloxacillin group (6/22 vs 17/24; RR 0.39, 95%CI 0.19, 0.8) and one withdrawal due to adverse event in each arm (RR 1 95%CI 0.07, 15.12).[12] The study also reported that the number of methicillin-resistant strains increased in the treatment group until 14 days after treatment. A trial of 74 AD patients (aged ≥12yo) with uninfected AD compared cefuroxime 500mg bid plus topical betamethasone dipropionate 0.05% bid for 2 weeks to betamethasone dipropionate alone.[13] Mean SCORAD reduction was clinically significant for both groups at weeks 1 and 2 and significantly greater in the oral antibiotic group: Week 1 -17.92 vs -10.05, p=0.003; Week 2 -28.0 vs -19.62, p<0.001. Adverse events were not discussed.
Infected AD	No direct evidence matching inclusion criteria was identified. *Pediatric & Mixed Population Data:* A trial of flucloxacillin 125mg-250mg qid for 7 days compared to placebo in 140 children with clinically infected AD reports no significant differences in mean change in EASI and POEM scores at two weeks: EASI MD 0.20 95%CI -0.12, 0.52; POEM MD 1.52 95%CI -1.35, 4.40.[14] No significant difference in change in POEM scores between groups was also reported at 3 months: MD -0.21 95%CI -3.12, 2.70. There were also no significant differences in change in QoL scores. There was one withdrawal due to worsening AD in each group and no difference in minor patient-reported adverse events between groups. A trial of cefadroxil 50mg/kg/day (n=16) for 2 weeks compared to placebo (n=17) in children with clinically infected AD (28/30 evaluable participants had infected AD) reports non-significant improvement in signs of AD in the antibiotic group compared to placebo: Global outcome of good or excellent 10/12 vs 9/17; RR 1.57 (95%CI 0.94, 2.63).[15] One withdrawal due to AE was reported in the antibiotic group. At 2 weeks, none of the participants in either the antibiotic or placebo group were found to have an antibiotic resistant organism. *Indirect Evidence:* A trial comparing two antibiotic agents (no control), mupirocin calcium cream tid (n=44) and cephalexin 250mg qid (n=38) for 10 days in patients (≥ 8yo) with secondarily infected AD found similar rates of clinical success (absence of exudate/pus, with or without complete resolution of other signs and symptoms of infection, a SIRS score of less than 8, and no use of additional antimicrobial): 89% vs 82%; p=0.29.[16] A non-significant difference in treatment-related adverse events was reported between the groups p=0.45. A trial comparing two antibiotic agents (no control), retapamulin ointment 1% bid (n=363) for 5 days and cephalexin 500mg (n=183) bid for 10 days in patients (≥ 9months) with secondarily infected dermatitis (including AD, psoriasis, and allergic contact dermatitis) found similar rates of clinical success 7-9 days post-therapy (total resolution of all signs and symptoms of infection such that no additional antibiotic therapy was required): 85.9% vs 89.7%; difference -3.8 95%CI -9.9, 2.3.[16] Adverse events were reported by 22% of patients receiving retapamulin and 22% of patients taking cephalexin.

TCS during oral antibiotic course in infected AD	No direct evidence matching inclusion criteria was identified. *Indirect evidence:* A trial comparing flucloxacillin and topical placebo (n=36), topical fusidic acid and oral placebo (n=37), and oral and topical placebos (control; n=40) for 1 week in children with non-severely infected AD reported at 2 weeks that neither oral or topical antibiotics produced a significant reduction in mean POEM scores compared to the placebo group : MD 1.5 (95%CI -1.4, 4.4) and 1.5 (95%CI -1.6, 4.5), respectively.[17] No serious adverse events were reported. A trial of 74 AD patients (aged ≥12yo) with uninfected AD compared cefuroxime 500mg bid plus topical betamethasone dipropionate 0.05% bid for 2 weeks to betamethasone dipropionate alone.[13] Mean SCORAD reduction was clinically significant for both groups at weeks 1 and 2 and significantly greater in the oral antibiotic group: Week 1 -17.92 vs -10.05, p=0.003; Week 2 -28.0 vs -19.62, p<0.001. Adverse events were not discussed.
Systemic antivirals for eczema herpeticum	No direct evidence matching inclusion criteria was identified. *Indirect evidence:* A systematic literature search identified one study that described participants as having "disseminated herpes simplex virus infections, such as eczema herpeticum"; 65% of the sample had AD.[18] For 32 patients randomized to 200mg acyclovir od for 5 days and 28 to placebo, treatment was "very effective" or "effective as assessed by investigators in 81.3% of the antiviral group compared to 42.9% if the placebo group (p<0.01). No adverse events were documented in the acyclovir group and 1 participant experienced an AE in the placebo group.
Oral antihistamines	No evidence for the use of oral H1 antihistamines as monotherapy for AD matching inclusion criteria was identified via updating the search conducted in support of a 2013 Cochrane review on the topic that also identified no trials (searches through 2012) that assessed the efficacy and safety of H1 antihistamines in adults or children with AD.[19] The majority of studies allow the use of concomitant therapies, so an assessment of the individual effects of oral H1 antihistamines on AD is not feasible.
Oral H1 antihistamines as monotherapy for AD	No evidence was identified for available FDA approved oral H4 antihistamines as monotherapy for AD in adults. *Investigational Data:* A trial compared an investigational oral H4 antihistamine 30mg qd (n=54 completed) for 8 weeks to placebo (n=24 completed) in adults with moderate-to-severe AD.[20] Concomitant therapy aside from emollients was not allowed but rescue therapy with topical steroids was permitted. Mean SCORAD scores were significantly reduced in the antihistamine group compared to placebo at weeks 4,6 and 8; MD at week 8 was 10.0 (p=0.004). Reduction in mean worst pruritus scores were not significantly different between the groups at week 8. The incidence of treatment-emergent adverse events was similar in both treatment groups: 66% in the antihistamine group and 64% in the placebo group.
Oral H4 antihistamines as monotherapy for AD	A trial compared two different doses of an investigational H4 antihistamine 100mg (n=27) or 300mg (n=27) to placebo (n=33) in adults with moderate AD.[21] No concomitant therapy was allowed but rescue therapy with topical steroid was permitted. The trial was stopped early by the sponsor, but 50 participants had evaluable 6-week data. Mean change in EASI score from baseline at 6 weeks was not significantly greater than placebo in either active arm (p=0.17 for 100 mg and 0.2 for 300 mg). Reduction in itch appeared to be dose-dependent with statistically significant reductions reported for the 300mg antihistamine group compared to placebo. Participants reporting adverse events were similar across the groups: 40.7%, 51.9%, and 54.5%, respectively. Two serious AEs were reported, both in the 300mg antihistamine group.

	A Cochrane systematic review of oral H1 antihistamines in combination with topical AD therapy concludes that based on low-to-moderate certainty evidence there is no consistent evidence that oral H1 antihistamine treatments are effective adjunctive therapy for AD when compared to placebo.[22] An update of the search identified no additional studies matching inclusion criteria. Key adult data from the review are presented below: One study assessed cetirizine 10 mg/d against placebo over four weeks in 84 adults. Results show no evidence of differences between groups in patient-assessed symptoms of eczema (pruritus measured as part of SCORAD; no numerical data given), numbers of adverse events (RR 1.11, 95% CI 0.50 to 2.45; mainly sedation, other skin-related problems, respiratory symptoms, or headache), or physician assessed changes in clinical signs, amount of local rescue therapy required, or number of applications as an indicator of eczema flares (nonnumerical data reported). Evidence for this comparison was of low quality. Compared with placebo, fexofenadine 120 mg/d taken in adults over one week (one study) probably leads to a small reduction in patient assessed symptoms of pruritus on a scale of 0 to 8 (mean difference (MD) -0.25, 95% CI -0.43 to -0.07; n = 400) and a greater reduction in the ratio of physician-assessed pruritus area to whole body surface area (P = 0.007; no further numerical data given); however, these reductions may not be clinically meaningful. Results suggest probably little or no difference in adverse events (mostly somnolence and headache) (RR 1.05, 95% CI 0.74 to 1.50; n = 411) nor in the amount of 0.1% hydrocortisone butyrate used (co-intervention in both groups) as an indicator of eczema flare, but no numerical data were given. Evidence for this comparison was of moderate quality.
Oral H1 antihistamines as add on therapy in AD	A study of 28 adults compared loratadine 10 mg/d taken over 4 weeks versus placebo. Researchers found no evidence of differences between groups in patient-assessed pruritus, measured by a 100-point visual analogue scale (MD -2.30, 95% CI -20.27 to 15.67); reduction in physician-assessed clinical signs (SCORAD) (MD -4.10, 95% CI -13.22 to 5.02); or adverse events. Study authors reported only one side effect (folliculitis with placebo) (RR 0.25, 95% CI 0.01 to 5.76). Evidence for this comparison was of low quality. Number of eczema flares was not measured for this comparison.

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e-Table 2. Monoclonal Antibodies

Adapted from: Drucker AM, Morra DE, Prieto-Merino D, Ellis AG, Yiu ZZN, Rochwerg B, Di Giorgio S, Arents BWM, Burton T, Spuls PI, Schmitt J, Flohr C. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Update of a Living Systematic Review and Network Meta-analysis. JAMA Dermatol. 2022 Mar 16:e220455. doi: 10.1001/jamadermatol.2022.0455. *Search Update June 15, 2021*

Estimates of effects, credible intervals, and certainty of the evidence for systemic monoclonal antibodies in adults with atopic dermatitis
Patients: Adults (≥ 18 yo) with moderate-to-severe AD

Interventions: dupilumab 600mg, the 300mg every 2 weeks; tralokinumab 600mg then 300mg every 2 weeks; mepolizumab 750mg for 2 doses (adjunctive topical anti-inflammatory therapy allowed)				
Comparison: Placebo (adjunctive topical anti-inflammatory therapy allowed)				
Settings: Outpatient, treated for ≥8 weeks and at least 2 doses of systemic immunomodulatory therapies				
Outcome	**Effects and confidence in the estimate of effects**			**Comments**
	On-Label		**Off -Label**	
	Dupilumab 600mg then 300mg every 2 weeks	**Tralokinumab 600mg then 300mg every 2 weeks**	**Mepolizumab 750 mg x 2**	
Change in EASI (Follow up: 16 weeks; assessed with mean change from baseline in EASI; presented as MD (95%CrI)); CRITICAL				
Placebo Comparator	MD -10.8 (-12.2, -9.5)	MD -7.3 (-9.1, -5.4)	No evidence	EASI MCID 6.6
Certainty of evidence	⨁⨁⨁⨁ High	⨁⨁⨁⨁ High		
	Direct evidence; 7 RCT[1-6]; n= 2,216	Direct evidence; 3 RCT[7,8]; n=1,927		
Change in SCORAD (Follow up: 2 weeks; assessed with: mean % change from baseline in SCORAD); CRITICAL				
Placebo Comparator	No evidence	No evidence	Mean change: -20% vs -6% (p=0.29)	SCORAD MCID -35%
Certainty of evidence			⨁⨁ Low [a]	
			Direct evidence; 1 RCT[9]; n=40	
Change in POEM (Follow up: 16 weeks; assessed with mean change from baseline in POEM; presented as MD (95%CrI); CRITICAL				
Placebo Comparator	MD -7.3 (-8, -6.6)	MD -4.6 (-5.6, -3.6)	No evidence	POEM MCID 3.4
Certainty of evidence	⨁⨁⨁⨁ High	⨁⨁⨁⨁ High		
	Direct evidence; 7 RCT[1-6]; n= 1,843	Direct evidence; 3 RCT[7,8]; n=1,919		
Change in itch (Follow up: 2 weeks (mepolizumab) and 16 weeks; assessed with change from baseline in SMD of itch; presented as SMD (95%CrI) and mean % change from basleine in VAS score); CRITICAL				
Placebo Comparator	SMD -0.8 (-0.9, -0.7)	SMD -0.4 (-0.6, -0.3)	Mean % change in VAS: -46% vs -24% (p>0.05)	
Certainty of evidence	⨁⨁⨁⨁ High	⨁⨁⨁⨁ High	⨁⨁ Low [a]	
	Direct evidence; 7 RCT[1-6]; n=2,213	Network estimate; 3 RCT[7,8]; n=1,911	Direct evidence; 1 RCT[9]; n=40	

Change in quality of life (Follow up: 16 weeks; assessed with mean change from baseline in DLQI; presented as change in DLQI (95%CrI); CRITICAL						
Placebo	MD -4.9 (-5.5, -4.3)		MD -3 (-3.9, -2)		No evidence	DLQI MCID 3.3
Certainty of evidence	⨁⨁⨁⨁ High		⨁⨁⨁⨁ High			
	Direct evidence; 7 RCT[1-6]; n=2,198		Direct evidence; 3 RCT[7,8]; n= 1,968			
Discontinuation due to adverse events (Follow up: up to 16 weeks; assessed with individuals discontinuing treatment due to AE; presented as ORs (95%CrI)); CRITICAL						
Placebo	OR 1 (0.5,1.8)	0 fewer per 1,000 (11 fewer to 17 more)	OR 0.9 (0.5, 1.8)	2 fewer per 1,000 (12 fewer to 18 more)	No evidence	
Event Rate	20/960 vs 18/839		37/1,553 vs 15/629			
Certainty of evidence	⨁⨁⨁ Moderate [b]		⨁⨁⨁ Moderate [b]			
	Direct evidence; 6 RCT[1,3-6]; n=1,799		Direct evidence; 4 RCT[7,8,10]; n=2,182			
Serious adverse events (Follow up: up to 16 weeks; assessed with individuals experiencing a serious AE; presented as ORs (95%CrI)); CRITICAL						
Placebo	OR 0.5 (0.3, 0.8)	23 fewer per 1,000 (32 fewer to 9 fewer)	OR 0.7 (0.4, 1.3)	8 fewer per 1,000 (20 fewer to 8 more)	Mepolizumab therapy caused some side effects of mild and temporary nature, showing no differences from side effects reported in the placebo group. (no further details provided).	
Event Rate	13/960 vs 39/839		37/1,553 vs 18/629			
Certainty of evidence	⨁⨁⨁ Moderate [c]		⨁⨁⨁ Moderate [b]		⨁ Very Low [d]	
	Direct evidence; 6 RCT[1,3-6]; n=1,799		Direct evidence; 4 RCT[7,8,10]; n=2,182		Direct evidence; 1 RCT[9]; n=40	

SoF table definitions & Interpretation

- A negative effect estimate favors the column-defining intervention
- SMD <0.2 small unimportant effect; SMD 0.2-0.8 small effect of unknown importance; SMD >0.8 moderate effect[11]

CrI: credible interval. Results are expressed in credible intervals as opposed to confidence intervals as a Bayesian analysis was conducted.
MD: Mean difference
MCID: Minimally clinically important difference
OR: Odds Ratio

GRADE Considerations & Explanations

a. Downgraded for high risk of bias (missing outcome data and concerns with randomization, outcome measurement and selective reporting); Downgraded for imprecision (small sample does not meet optimal information size criteria). b. Downgraded for inconsistency. Not downgraded for imprecision as reduction of or equitable risk with active treatment supports confidence in safety of the interventions and considering the context of recommendation development the end points of the CrI would lead to consistent clinical decisions. c. Downgraded for inconsistency. d. Downgraded two levels for high risk of bias and selective/missing outcome reporting specific to the safety data (missing outcome data and concerns with randomization, outcome measurement and selective reporting); Downgraded for imprecision (small sample does not meet optimal information size criteria).
Footnotes

e-Table 3. Long-Term Dupilumab

Estimates of effects, confidence intervals, and certainty of the evidence for long term use of systemic monoclonal antibodies in atopic dermatitis			
Patients: Adults with moderate-to-severe AD			
Interventions: Dupilumab 600mg then 300mg every 2 weeks (adjunctive topical anti-inflammatory therapy allowed)			
Comparison: Placebo (adjunctive topical anti-inflammatory therapy allowed)			
Settings: Outpatient			
Outcome	**Effects and confidence in the estimate of effects** **Dupilumab 600mg then 300mg every 2 weeks**		**Comments**
Change in EASI (follow up 52 weeks; assessed with LS % change from baseline in EASI score [SE])			
Placebo Comparator	-78.3% [SE 4.4] vs -45.8% [SE 2.7], p<0.0001		EASI MCID -50%
Certainty of evidence	⨁⨁⨁ Moderate [a]		
	Direct evidence; 1 RCT[2]; n=353		
Change in POEM (follow up 52 weeks; assessed with mean change from baseline in POEM, presented as MD (95%CI)); CRITICAL			
Placebo Comparator (Mean change -5.3 [SE 0.46])	Mean change: -13.7 [SE 0.75]	MD -8.4 (-10.12, -6.68)	POEM MCID 3.4
Certainty of evidence	⨁⨁⨁ Moderate [a]		
	Direct evidence; 1 RCT[2]; n=353		
Change in peak pruritus numeric rating scale (follow up 52 weeks; assessed with mean change from baseline in peak NRS score; presented as MD (95%CI)); CRITICAL			

Placebo Comparator (Mean change -2.1 [SE 0.16])	Mean change: -4.2 [SE 0.26]	MD -2.10 (-2.82, -1.38)	PP-NRS MCID 2.6
Certainty of evidence	⨁⨁⨁ Moderate [a]		
	Direct evidence; 1 RCT[2]; n=353		
Change in quality of life (follow up 52 weeks; assessed with mean change from baseline in DLQI score; presented as MD (95%CI))			
Placebo Comparator (Mean change -5.6 [SE 0.36])	Mean change: -10.9 [SE 0.59]	MD -5.3 (-6.94, -3.66)	DLQI MCID 3.3
Certainty of evidence	⨁⨁⨁ Moderate [a]		
	Direct evidence; 1 RCT[2]; n=353		
Discontinuation due to adverse event (Follow up: 52 weeks; assessed with individuals discontinuing treatment due to AE; presented as OR (95%CI)); CRITICAL			
Placebo Comparator (Event rate 24/315)	OR 0.22 (0.05, 0.97)	58 fewer per 1,000 (72 fewer to 2 fewer)	
Event Rate	2/110		
Certainty of evidence	⨁⨁⨁ Moderate [a]		
	Direct evidence; 1 RCT[2]; n= 425		
Serious adverse events (Follow up: 12 weeks; assessed with individuals experiencing a serious AE; presented as ORs (95%CI)); CRITICAL			
Placebo Comparator (Event rate 16/315)	OR 0.71 (0.23, 2.16)	14 fewer (39 fewer to 53 more)	
Event Rate	4/110		
Certainty of evidence	⨁⨁⨁ Moderate [a]		
	Direct evidence; 1 RCT[2]; n= 425		

SoF table definitions & Interpretation
LS: Least squares
SE: Standard error
CI: Confidence Interval
POEM:
MD: Mean difference
OR: Odds ratio

GRADE Considerations & Explanations
a. Study not adequately powered to detect long-term outcomes; downgraded for imprecision.
Footnotes

e-Table 4. Qualitative safety overview systemic monoclonal antibodies for AD

Treatment	Total n	Safety	RoB
Dupilumab	1799	**Cumulative incidence of AEs:** 50-78% for dupilumab and 53-81% with placebo.[1-6] **Most common AEs for dupilumab:** conjunctivitis, allergic conjunctivitis, exacerbation of AD, nasopharyngitis, headache, fatigue, allergic rhinitis, cough, diarrhea, vascular disorders, injection-site reactions, non-skin infections, herpes viral infections, upper respiratory tract infection. [1,3-6] **Most common SAEs for dupilumab:** meniscus injury, breast carcinoma [1], suicide[4], respiratory failure, syncope[5], lung adenocarcinoma[6].	Low
Tralokinumab	2182	**Cumulative incidence of AEs:** 46-76% for tralokinumab and 51-77% for placebo.[7,8,10] **Most common AEs for tralokinumab:** upper respiratory tract infection, conjunctivitis, headache, injection-site reaction, [7,8] **Most common SAEs for tralokinumab**: failure to thrive[10]	Low
Mepolizumab	43	**Most common AEs:** "mild side effects"[9] (see evidence profile)	High

RoB; Risk of bias; **AE:** Adverse event; **SAE:** Serious adverse event; "Most common" as defined by investigators for AEs and SAEs

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e-Table 5. JAK Inhibitors

Adapted from: Drucker AM, Morra DE, Prieto-Merino D, Ellis AG, Yiu ZZN, Rochwerg B, Di Giorgio S, Arents BWM, Burton T, Spuls PI, Schmitt J, Flohr C. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Update of a Living Systematic Review and Network Meta-analysis. JAMA Dermatol. 2022 Mar 16:e220455. doi: 10.1001/jamadermatol.2022.0455. *Search Update June 15, 2021*

Estimates of effects, credible intervals, and certainty of the evidence for systemic JAK inhibitors in adults with atopic dermatitis							
Patients: Adults (≥ 18 yo) with moderate-to-severe AD							
Interventions: Abrocitinib 100mg qd, Abrocitinib 200mg qd, Baricitinib 2mg qd, Baricitinib 4mg qd, Upadacitinib 15mg qd, Upadacitinib 30mg qd (adjunctive topical anti-inflammatory therapy allowed)							
Comparison: Placebo (adjunctive topical anti-inflammatory therapy allowed)							
Settings: Outpatient, treated for ≥8 weeks with at least 2 doses of systemic immunomodulatory therapies							
Outcome	**Effects and confidence in the estimate of effects**						**Comments**
			Off Label				
	Abrocitinib 100mg qd	**Abrocitinib 200mg qd**	**Baricitinib 2mg qd**	**Baricitinib 4mg qd**	**Upadacitinib 15mg qd**	**Upadacitinib 30mg qd**	
Change in EASI (Follow up: up to 16 weeks; assessed with mean change from baseline in EASI; presented as MD (95%CrI)); CRITICAL							
Placebo Comparator	MD -8.6 (-10.3, -6.9)	MD -13 (-14.7, -11.3)	MD -5.6 (-7.5, -3.7)	MD -7.6 (-9.6, -5.5)	MD -11 (-12.5, -9.5)	MD -13.5 (-15.1, -12)	EASI MCID 6.6
Certainty of evidence	⊕⊕⊕⊕ High	⊕⊕⊕⊕ High	⊕⊕⊕⊕ High	⊕⊕⊕⊕ High	⊕⊕⊕⊕ High	⊕⊕⊕⊕ High	
	Direct evidence; 3 RCT[1-3]; n= 575^	Direct evidence; 3 RCT[1-3]; n=564^	Direct evidence; 5 RCT[4-7]; n= 1,336	Direct evidence; 4 RCT[4-6]; n= 1,048	Direct evidence; 4 RCT[8-10]; n=1,323 *	Direct evidence; 4 RCT[8-10]; n=1,343 *	
Change in clinical signs (Follow up: up to 16 weeks; assessed with change from baseline in the SMD of clinical signs (95%CrI)); CRITICAL							
Placebo Comparator	SMD -0.8 (-0.9, -0.6)	SMD -1.2 (-1.3, -1)	SMD -0.4 (-0.5, -0.2)	SMD -0.5 (-0.7, -0.4)	SMD -1.1 (-1.3, -1)	SMD -1.4 (-1.5, -1.3)	
	⊕⊕⊕⊕ High	⊕⊕⊕⊕ High	⊕⊕⊕⊕ High	⊕⊕⊕⊕ High	⊕⊕⊕⊕ High	⊕⊕⊕⊕ High	

Certainty of evidence	Direct evidence; 4 RCT[1-3,11]; n= 910^		Direct evidence; 4 RCT[1-3,11]; n=900^		Direct evidence; 5 RCT[4-7]; n= 1,336		Direct evidence; 4 RCT[4-6]; n=1,048		Direct evidence; 4 RCT[8-10]; n= 1,323*		Direct evidence; 4 RCT[8-10]; n= 1,343*		
Change in POEM (Follow up: up to 16 weeks; assessed with mean change from baseline in POEM; presented as MD (95%CrI)); CRITICAL													
Placebo Comparator	MD -5 (-6, -3.9)		MD -8.2 (-9.2, -7.1)		MD -3.8 (-4.9, -2.6)		MD -5.4 (-6.6, -4.2)		MD -7 (-11.1, -2.9)		MD -10.6 (-14.8, -6.6)		POEM MCID 3.4
Certainty of evidence	⊕⊕⊕⊕ High		⊕⊕⊕⊕ High		⊕⊕⊕⊕ High		⊕⊕⊕⊕ High		⊕⊕⊕⊕ High		⊕⊕⊕⊕ High		
	Direct evidence; 4 RCT[1-3,11]; n= 910^		Direct evidence; 4 RCT[1-3,11]; n=900^		Direct evidence; 5 RCT[4,6,7,12]; n=927		Direct evidence; 4 RCT[4,6,12]; n=584		Direct evidence; 1 RCT[10]; n= 77		Direct evidence; 1 RCT[10]; n= 79		
Change in itch (Follow up: up to 16 weeks; assessed with SMD of itch scales (95% CrI)); CRITICAL													
Placebo Comparator	SMD -0.5 (-0.7, -0.4)		SMD -2.4 (-3, -1.9)		SMD -0.5 (-0.7, -0.3)		SMD -0.6 (-0.8, -0.4)		SMD 0.7 (0.6, 0.9)		SMD 1 (0.9, 1.2)		
Certainty of evidence	⊕⊕⊕⊕ High		⊕⊕⊕⊕ High		⊕⊕⊕⊕ High		⊕⊕⊕⊕ High		⊕⊕⊕⊕ High		⊕⊕⊕⊕ High		
	Direct evidence; 4 RCT[1-3]; n= 531		Direct evidence; 4 RCT[1-3]; n= 529		Direct evidence; RCT=4[4-7]; n=801		Direct evidence; RCT=4[4-6]; n= 538		Direct evidence; 4 RCT[8-10]; n=1,218*		Direct evidence; 4 RCT[8-10]; n=1,227*		
Change in quality of life (Follow up: up to 16 weeks; assessed with mean change from baseline in DLQI; presented as MD (95% CrI)); CRITICAL													
Placebo Comparator	MD -3.4 (-4.3, -2.5)		MD -5.5 (-6.4, -4.6)		MD -2.3 (-3.1, -1.4)		MD -3.5 (-4.4, -2.6)		No evidence		No evidence		DLQI MCID 3.3
Certainty of evidence	⊕⊕⊕⊕ High		⊕⊕⊕⊕ High		⊕⊕⊕⊕ High		⊕⊕⊕⊕ High						
	Direct evidence; 4 RCT[1-3,11]; n= 839		Direct evidence; 4 RCT[1-3,11]; n= 827		Direct evidence; 6 RCT[4-7,12]; n=1,012		Direct evidence; 5 RCT[4-6,12]; n= 670						
Discontinuation due to adverse events (Follow up: up to 16 weeks; assessed with individuals discontinuing treatment due to AE; presented as ORs (95%CrI)); CRITICAL													
Placebo Comparator	OR 0.7 (0.4, 1.3)	24 fewer per 1000 (49 fewer to 23 more)	OR 0.7 (0.4, 1.3)	24 fewer per 1000 (49 fewer to 23 more)	OR 0.8 (0.3,1.9)	4 fewer per 1,000 (14 fewer to 17 more)	OR 1.5 (0.7, 3.4)	9 more per 1,000 (5 fewer to 42 more)	OR 0.6 (0.3, 1)	15 fewer per 1,000 (26 fewer to 0 fewer)	OR 0.7 (0.4, 1.3)	11 fewer per 1,000 (22 fewer to 11 more)	
Event Rate	31/608 vs 29/342		30/590 vs 29/342		9/537 vs 16/796		13/397 vs 12/650		21/836 vs 34/902		26/906 vs 34/902		
Certainty of evidence	⊕⊕⊕ Moderate [a]		⊕⊕⊕ Moderate [a]		⊕⊕⊕ Moderate [a]		⊕⊕⊕ Moderate [b]		⊕⊕⊕ Moderate [c]		⊕⊕⊕ Moderate [a]		
	Direct evidence; 4 RCT[1-3,11]; n= 950		Direct evidence; 4 RCT[1-3,11]; n= 932		Direct evidence; 5 RCT[4-7]; n= 1,333		Direct evidence; 4 RCT[4-6]; n= 1,047		Direct evidence 4 RCT[8-10]; n= 1,738*		Direct evidence 4 RCT[8-10]; n= 1,808*		
Serious adverse events (Follow up: up to 16 weeks; assessed with individuals experiencing an event; presented as ORs (95%CrI)); CRITICAL													
Placebo Comparator	OR 1.2 (0.6, 2.6)	6 more per 1,000 (13	OR 0.6 (0.3, 1.5)	13 fewer per 1,000 (22	OR 0.5 (0.2, 1)	17 fewer per 1,000 (27	0.7 (0.3, 1.4)	11 fewer per 1,000	OR 0.7 (0.4, 1.3)	8 fewer per 1,000 (17 fewer to 8 more)	OR 0.7 (0.3, 1.2)	8 fewer (17 fewer to 6 more)	

Event Rate	19/608 vs 11/342	fewer to 47 more)	11/590 vs 11/342	fewer to 15 more)	8/537 vs 27/796	fewer to 0 fewer)	12/397 vs 24/650	(26 fewer to 14 more)	19/899 vs 26/902		19/906 vs 26/902	
Certainty of evidence	⊕⊕⊕ Moderate [b]		⊕⊕⊕ Moderate [b]		⊕⊕⊕ Moderate [a]		⊕⊕⊕ Moderate [a]		⊕⊕⊕⊕ High		⊕⊕⊕⊕ High	
	Direct evidence; 4 RCT[1-3,11]; n= 950		Direct evidence; 4 RCT[1-3,11]; n= 932		Direct evidence; 5 RCT[4-7]; n= 1,333		Direct evidence; 4 RCT[4-6]; n= 1,047		Direct evidence 4 RCT[8-10]; n= 1,801*		Direct evidence 4 RCT[8-10]; n= 1,808*	

Table definitions & interpretation

- A negative effect estimate favors the column-defining intervention
- SMD <0.2 small unimportant effect; SMD 0.2-0.8 small effect of unknown importance; SMD >0.8 moderate effect[13]

CrI: credible interval. Results are expressed in credible intervals as opposed to confidence intervals as a Bayesian analysis was conducted. Interpretation: there is a 95% probability that the true estimate lies within the interval, given the observed data.
MD: Mean difference
MCID: Minimally clinically important difference
SMD: Standardized mean difference
OR: Odds Ratio
AE: Adverse event

GRADE Considerations & Explanations

a. Downgraded for inconsistency. Not downgraded for imprecision as reduction of risk with active treatment supports confidence in safety of the interventions and considering the context of recommendation development the end points of the CrI would lead to consistent clinical decisions.
b. Downgraded for inconsistency. Not downgraded for imprecision as the low overall event rates suggest confidence in the safety of the intervention and considering the context of recommendation development the end points of the CrI would lead to consistent clinical decisions.

Footnotes

^ Includes two trials with adolescent and adult participants ≥ 12yo
* Includes three trials with adolescent and adult participants ≥ 12yo

e-Table 6. Qualitative Safety Overview of Systemic JAK Inhibitors for AD

Treatment	Total n	Safety	RoB
Abrocitinib	1059	**Cumulative incidence of AEs:** 51-69% for abrocitinib 100mg, 62-78% for abrocitinib 200mg, 53-57% for placebo.[2,3,11] **Most common AEs for abrocitinib**: nausea, nasopharyngitis, upper respiratory infection, headache, and acne[2,3,11] **Treatment-related SAEs for abrocitinib**: herpangina, pneumonia, chronic inflammatory bowel disease, acute pancreatitis[2,3,11]	Low
Baricitinib	1730	**Cumulative incidence of AEs:** 46-58% for baricitinib 2mg, 54-71% for baricitinib 4mg, and 38-56% for placebo.[4-7]	Low

		Most common AEs for baricitinib: headache, increased blood level of creatine phosphokinase, nasopharyngitis, upper respiratory tract infection, diarrhea, urinary tract infection, folliculitis, herpes simplex infection, vaginal infection.[4-7] **Treatment-emergent SAEs for baricitinib**: benign polyp of the large intestine[5] and pulmonary embolism[6]	
Upadacitinib	2702	**Cumulative incidence of AEs:** 60-76% for upadacitinib 15mg, 61-79% for upadacitinib 30mg, and 53-63 for placebo.[8-10] **Most common AEs for upadacitinib**: acne, upper respiratory tract infection, nasopharyngitis, headache, plasma creatine phosphokinase elevation, AD worsening, nausea, and oral herpes.[8-10] **Most common SAEs for upadacitinib**: appendicitis[10]	Low
JAK inhibitors	466993	A systematic review and meta-analysis including 2 cohort studies and 15 randomized clinical trials with 466,993 participants found no increased risk of incident VTE among patients with AD receiving JAK inhibitors.[14]	Low

RoB; Risk of bias; **AE:** Adverse event; **SAE:** Serious adverse event; "Most common" as defined by investigators for AEs and SAEs

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e-Table 7. Immunosuppressants

Adapted from: Drucker AM, Morra DE, Prieto-Merino D, Ellis AG, Yiu ZZN, Rochwerg B, Di Giorgio S, Arents BWM, Burton T, Spuls PI, Schmitt J, Flohr C. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Update of a Living Systematic Review and Network Meta-analysis. JAMA Dermatol. 2022 Mar 16:e220455. doi: 10.1001/jamadermatol.2022.0455. *Search Update June 15, 2021*

Estimates of effects, credible intervals, and certainty of the evidence for systemic immunosuppressants in adults with atopic dermatitis								
Patients: Adults (≥ 18 yo) with moderate-to-severe AD								
Interventions: Azathioprine 2.5mg qd, Azathioprine TPMT^, Cyclosporine, Ustekinumab 45mg or 90mg bid, Ustekinumab 45 or 90mg 3 times (adjunctive topical anti-inflammatory therapy allowed)								
Comparison: Placebo (adjunctive topical anti-inflammatory therapy allowed)								
Settings: Outpatient, treated for ≥8 weeks and at least 2 doses of systemic immunomodulatory therapies								
Outcome	**Effects and confidence in the estimate of effects**							**Comments**
	Azathioprine 2.5mg qd	**Azathioprine TPMT^**	**Cyclosporine Low Dose (≤3mg/kg/d and 150mg/d)**	**Cyclosporine High Dose (>3mg/kg/d and ≤5 mg/kg/d)**	**Ustekinumab 45 mg bid**	**Ustekinumab 90mg bid**	**Ustekinumab 45/90 x3***	
Change in clinical signs (Follow up: 4 to 12 weeks; assessed with mean change from baseline in SASSAD score; mean change from baseline in EASI score; presented as MD (95%CrI); change from baseline in the SMD of clinical signs (95% CrI), and patients attaining a SCORAD50 response); CRITICAL								
Placebo Comparator	Mean improvement in SASSAD 10.2 points vs 1.0 point (p<0.01)	Mean improvement in SASSAD 12.0 points vs 6.6 points (MD 17% 95%CI 4.3-29%)	Change in clinical signs SMD -0.7 (-1.3, -0.1)	Change in clinical signs SMD -2.01 (-2.66, -1.36)	Change in EASI MD -0.5 (-7.1, 6.4)	Change in EASI MD -0.5 (-7.4, 6.6)	Odds of attaining SCORAD50: 1.93 (95%CI 0.30, 15.33) Event rate: 5/16 vs 3/16	EASI MCID 6.6

Certainty of evidence	⊕⊕ Low [a]	⊕⊕ Low [b]	⊕ Very Low [c]	⊕⊕ Low [d]	⊕⊕⊕ Moderate [e]	⊕⊕⊕ Moderate [e]	⊕⊕⊕ Moderate [e]	
	Direct evidence; 1 RCT[1]; n=35~	Direct evidence; 1 RCT[2]; n= 61^^	Network estimate; 2 RCT[3,4]; n= 87	Direct evidence: 3 RCT[5-7]; n= 86~	Direct evidence; 1 RCT[8]; n= 51	Direct evidence; 1 RCT[8]; n= 55	Direct evidence; 1 RCT[9]; n= 32	
Change in itch (Follow up: 8 to 12 weeks; assessed with change from baseline in the SMD of itch scales (95%CrI); and reduction in VAS itch score from baseline); CRITICAL								
Placebo Comparator	Reduction in VAS itch score= -33% (vs -13%)	SMD -0.6 (-1.2, 0)	SMD -0.7 (-1.6, 0.3)	SMD -0.7 (-1.5, 0.2)	SMD 0.1 (-0.5, 0.7)	SMD -0.1 (-0.7, 0.5)	No evidence	
Certainty of evidence	⊕⊕ Low [a]	⊕⊕ Low [d]	⊕ Very Low [c]	⊕⊕ Low [d]	⊕⊕⊕ Moderate [f]	⊕⊕⊕ Moderate [e]		
	Direct evidence; 1 RCT[1]; n=37~	Direct evidence; 1 RCT[2]; n= 61^^	Network estimate; 2 RCT[3,4]; n= 87	Direct evidence; 2 RCT[3,5]; n= 77	Direct evidence; 1 RCT[8]; n= 51	Direct evidence; 1 RCT[8]; n= 55		
Change in quality of life (Follow up: up to 16 weeks; assessed with SMD change from baseline in QoL on QoL scales (95%CrI)); CRITICAL								
Placebo Comparator	No evidence	SMD -0.6 (-1.2, 0)	SMD -0.5 (-1.1, 0.2)	SMD -0.4 (-1.1, 0.3)	SMD -1 (-3.3, 1.3)	SMD -0.9 (-3.2, 1.3)	SMD 0.7 (-5.6, 7)	
Certainty of evidence		⊕⊕ Low [d]	⊕ Very Low [c]	⊕⊕ Low [d]	⊕⊕⊕ Moderate [e]	⊕⊕⊕ Moderate [e]	⊕⊕⊕ Moderate [e]	
		1 RCT[2]; n= 61^^	Network estimate; 2 RCT[3,4]; n= 87	Direct evidence; 1 RCT[6]; n=33~	Direct evidence; 1 RCT[8]; n= 51	Direct evidence; 1 RCT[8]; n= 55	Direct evidence; 1 RCT[9]; n=32	
Discontinuation due to adverse events (Follow up: up to 16 weeks; assessed with individuals discontinuing treatment due to AE; presented as ORs (95%CrI)); CRITICAL								
Placebo Comparator	-	-	OR 3.3 (0.3, 29.1)	98 more per 1,000 (34 fewer to 555 more)	No evidence	-	-	-	OR 3.5 (0.1, 90.3)	-	-	-	-	-
Event Rate	3/19 vs 0/18		6/41 vs 1/20			0/36 vs 0/36		1/24 vs 0/27		0/28 vs 0/27		0/16 vs 0/16	
Certainty of evidence	⊕⊕ Low [a]		⊕⊕ Low [b]			⊕⊕ Low [d]		⊕⊕⊕ Moderate [f]		⊕⊕⊕ Moderate [f]		⊕⊕⊕ Moderate [f]		
	Direct evidence; 1 RCT[1]; n= 37~		Direct evidence; 1 RCT[2]; n=61			Direct evidence; 3 RCT[5,6,10]; n=72~		Direct evidence; 1 RCT[8]; n= 51		Direct evidence; 1 RCT[8]; n= 55		Direct evidence; 1 RCT[9]; n= 32		
Serious adverse events (Follow up: up to 16 weeks; assessed with individuals experiencing a serious AE; presented as ORs (95%CrI)); CRITICAL														

Placebo Comparator	No evidence	-	-	No evidence	OR 1.00 (0.26, 3.83)	0 fewer per 1,000 (45 fewer to 172 more)	-	-	-	-	-	-
Event Rate		4/41 vs 0/20			4/66 vs 4/66		0/24 vs 0/27		0/28 vs 0/27		0/16 vs 0/16	
Certainty of evidence		⊕⊕ Low [b]			⊕⊕ Low [d]		⊕⊕⊕ Moderate [f]		⊕⊕⊕ Moderate [f]		⊕⊕⊕ Moderate [f]	
		Direct evidence; 1 RCT[2]; n=61			Direct evidence; 3 RCT[6,7,10]; n= 132~		Direct evidence; 1 RCT[8]; n= 51		Direct evidence; 1 RCT[8]; n= 55		Direct evidence; 1 RCT[9]; n= 32	

Table definitions & Interpretation

- A negative effect estimate favors the column-defining intervention
- SMD <0.2 small unimportant effect; SMD 0.2-0.8 small effect of unknown importance; SMD >0.8 moderate effect[11]

CrI: credible interval. Results are expressed in credible intervals as opposed to confidence intervals as a Bayesian analysis was conducted. Interpretation: there is a 95% probability that the true estimate lies within the interval, given the observed data.
SASSAD: Six Area, Six Sign, AD score; assessment of six signs (erythema, exudation, excoriation, dryness, cracking and lichenification) at six sites (hands, feet, arms, legs, head and neck, trunk). Each sign is graded at each site using a four-point scale of 0–3, representing grades of none, mild, moderate and severe; Maximum score 108.
MD: Mean difference
MCID: Minimally clinically important difference
SMD: Standardized mean difference
OR: Odds Ratio
AE: Adverse event

GRADE Considerations & Explanations

a. High risk of bias due to incomplete outcome data reporting (ITT analysis but 44% drop out rate with no information on how missing data was managed) and baseline imbalances in SASSAD scores; downgraded for imprecision as small sample does not meet optimal information size.
b. Study is of a high risk of bias due to insufficient information available to assess blinding of outcome assessment and complete data reporting and selective outcome reporting; downgraded for imprecision as small sample does not optimal information size.
c. No direct estimate; first-order indirect loop includes low certainty evidence; downgraded for imprecision (estimate imprecise and would suggest different conclusions at either end of the 95% CrI).
d. Study is of a high risk of bias due to insufficient information available to assess blinding of outcome assessment and complete data reporting and selective outcome reporting; downgraded for imprecision as small sample does not meet optimal information size criteria.
e. Downgraded for imprecision (estimate suggests different conclusions at either end of the 95%CrI).
f. Downgraded for imprecision as small sample does not meet optimal information size criteria.

Footnotes

^ Dosed by thiopurine methyltransferase activity; Patients with heterozygous range TPMT activity received azathioprine 1.0 mg/kg qd; patients with normal TPMT activity received azathioprine 2.5mg/kg qd. Patients received a lower dose of azathioprine, 0.5 and 1.0 mg/kg/qd, respectively for the initial 4 weeks of treatment to reduce gastrointestinal side-effects.
*Dosing by weight with patients ≤100kg receiving 45mg and patients>100kg receiving 90mg per injection; All patients received 3 injections.

~ Includes adolescents aged ≥ 17yo
^^ Includes adolescents aged ≥16yo

Table 8. Qualitative overview of systemic cyclosporine compared to other active treatments for AD in adults

Adapted from: Siegels D, Heratizadeh A, Abraham S, Binnmyr J, Brockow K, Irvine AD, Halken S, Mortz CG, Flohr C, Schmid-Grendelmeier P, Van der Poel LA, Muraro A, Weidinger S, Werfel T, Schmitt J; European Academy of Allergy, Clinical Immunology Atopic Dermatitis Guideline group. Systemic treatments in the management of atopic dermatitis: A systematic review and meta-analysis. Allergy. 2021 Apr;76(4):1053-1076. doi: 10.1111/all.14631. Epub 2020 Nov 4. PMID: 33074565. *Search updated March 2022*

Comparison	Total n	Efficacy	Certainty
CSA vs UVAB phototherapy[12]	72	*CSA superior to phototherapy*: Mean change in SCORAD at 8 weeks -54% vs -34%	Low
CSA vs Oral prednisolone[13]	38	CSA superior to oral prednisolone: Mean change in SCORAD at 6 weeks -55% vs -43%	Low
CSA vs Methotrexate[4]	97	CSA and methotrexate similarly effective: Mean change in SCORAD at 12 weeks -49% vs -28%; at 24 weeks -56% vs -48%	Low
CSA vs Extracorporeal photopheresis[14]	20	CSA and ECP were similarly effective: Mean change in SCORAD at 16 weeks -34% vs -46%	Low
CSA vs Tacrolimus ointment 0.1%[15]	30	CSA and topical tacrolimus were similarly effective^; Mean change in SCORAD at 6 weeks -88% vs -89%	Low

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e-Table 9. Antimetabolites (Indirect Estimates)

Adapted from: Drucker AM, Morra DE, Prieto-Merino D, Ellis AG, Yiu ZZN, Rochwerg B, Di Giorgio S, Arents BWM, Burton T, Spuls PI, Schmitt J, Flohr C. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Update of a Living Systematic Review and Network Meta-analysis. JAMA Dermatol. 2022 Mar 16:e220455. doi: 10.1001/jamadermatol.2022.0455. *Search Update June 15, 2021*

Estimates of effects, confidence intervals, and certainty of the evidence for systemic methotrexate compared to placebo in atopic dermatitis		
Patients: Adults AD		
Interventions: Methotrexate		
Comparison: Placebo		
Settings: Outpatient		
Outcome	**Effects and confidence in the estimate of effects** **Methotrexate**	**Comments**
Change in clinical signs (Follow up: up to 16 weeks; assessed with change in standardized mean difference of clinical signs; presented as SMD (95%CrI)); CRITICAL		
Placebo Comparator	SMD -0.6 (-1.3, 0)	Negative effect estimates favor methotrexate.
Certainty of evidence	⨁⨁ Low [a] Indirect estimate[1]	
Change in itch (Follow up: up to 16 weeks; assessed with change in itch; presented as SMD (95% CrI)); CRITICAL		
Placebo Comparator	SMD -0.5 (-1.4, 0.3)	Negative effect estimates favor methotrexate.
Certainty of evidence	⨁⨁ Low [b]	

	Indirect estimate[1]	
Change in quality of life (Follow up: up to 16 weeks; assessed with change in QoL on the standardized mean scale; presented as SMD (95%CrI)); CRITICAL		
Placebo Comparator	SMD -0.4 (-1.1, 0.3)	Negative effect estimates favor methotrexate.
Certainty of evidence	⨁⨁ Low [b]	
	Indirect estimate[1]	
SoF table definitions & Interpretation **CrI:** Credible interval **SMD**: Standardized mean difference		
GRADE Considerations & Explanations a. Downgraded for high risk of bias; Downgrade for imprecision as CrI consistent with moderate and trivial effect. b. Downgraded for high risk of bias; Downgrade for imprecision as CrI consistent with moderate and small effect.		

e-Table 10. Methotrexate vs Cyclosporine

Estimates of effects, confidence intervals, and certainty of the evidence for systemic methotrexate compared to cyclosporine in atopic dermatitis			
Patients: Adults with moderate-to-severe AD			
Interventions: Methotrexate 15mg per week for 8 weeks increased to 25mg/week for 16 weeks in patients not achieving 50% reduction in SCORAD (adjunctive TCS, tacrolimus and antihistamines, and oral antibiotics allowed)			
Comparison: Cyclosporine 2.5mg/kg of body weight qd for 8 weeks increased to 5mg/kg for 16 weeks in patients not achieving 50% reduction in SCORAD(adjunctive TCS, tacrolimus and antihistamines, and oral antibiotics allowed)			
Settings: Outpatient			
Outcome	**Effects and confidence in the estimate of effects** **Methotrexate 15mg q1w (increased to 25mg)**		**Comments**
Change in EASI (Follow up: 16 weeks; assessed with mean % change in EASI; presented as MD [95%CI]); CRITICAL			
Cyclosporine Comparator (Mean Change -68.2 [SD 23.9])	Mean Change -57.0% [SD 27.6]	MD -11.2% [-24.3, 1.9], p=0.10	EASI MCID -50%; Noninferiority of MXT not achieved per study.
Certainty of evidence	⨁⨁ Low [a]		
	Direct evidence; 1 RCT[2]; n=61		
Change in EASI (follow up: 24 weeks; assessed with mean % change in EASI; presented as MD [95%CI]); CRITICAL			
Cyclosporine Comparator (Mean change -67.4% [SD 30.0])	Mean change -67.7% [24.4]	MD -0.30 [-14.22, 14.82], p=0.97	EASI MCID -50%; Noninferiority of MXT achieved per study.

Certainty of evidence	⨁⨁ Low [b]		
	Direct evidence; 1 RCT[2]; n=54		
Change in DLQI (Follow up: 16 weeks; assessed with mean change in DLQI; presented as MD); CRITICAL			
Cyclosporine Comparator (Mean reduction 8.9 points)	Mean reduction: 7.2 points	MD +1.7	DLQI MCID 3.3
Certainty of evidence	⨁⨁ Low [c]		
	Direct evidence; 1 RCT[2]; n=62		
Change in DLQI (Follow up: 24 weeks; assessed with mean change in DLQI; presented as MD); CRITICAL			
Cyclosporine Comparator (Mean reduction 9.9 points)	Mean reduction: 7.3 points	MD: + 2.6	DLQI MCID 3.3
Certainty of evidence	⨁⨁ Low [c]		
	Direct evidence; 1 RCT[2]; n=54		
Discontinuation due to adverse event (Follow up: 24 weeks; assessed with individuals discontinuing treatment due to AE; presented as OR (95%CI)); CRITICAL			
Cyclosporine Comparator (Event rate 1/47**)**	OR 6.27 (0.73, 54.23)	99 more per 1,000 (6 fewer to 520 more)	
Event Rate	6/50		
Certainty of evidence	⨁⨁ Low [c]		
	Direct evidence; 1 RCT[2]; n=97		
Serious adverse events (Follow up: 16 weeks; assessed with individuals experiencing an AE; presented as ORs (95%CI)); CRITICAL			
Cyclosporine Comparator (Event rate 1/47**)**	OR 0.31 (0.01, 7.72)	-	
Event Rate	0/50		
Certainty of evidence	⨁⨁ Low [c]		
	Direct evidence; 1 RCT[2]; n=97		

SoF table definitions & Interpretation **CI:** Confidence Interval **SD:** Standard deviation **MD**: Mean difference **OR:** Odds ratio
GRADE Considerations & Explanations a. Downgraded for high risk of bias due to concerns about deviations from intended intervention, missing outcome data, and selective outcome reporting; Downgraded for imprecision as a small sample and the CI compatible with minimal and important difference. b. Downgraded for high risk of bias due to concerns about deviations from intended intervention, missing outcome data, and selective outcome reporting; Downgraded for imprecision as a small sample and CI consistent with no difference and important difference. c. Downgraded for high risk of bias due to concerns about deviations from intended intervention, missing outcome data, and selective outcome reporting; Downgraded for imprecision as a small sample.

e-Table 11. Methotrexate vs Azathioprine

Estimates of effects, confidence intervals, and certainty of the evidence for systemic methotrexate compared to azathioprine in atopic dermatitis			
Patients: Adults severe AD			
Interventions: Methotrexate 10mg to 22.5mg weekly (adjunctive TCS and oral antihistamines allowed)			
Comparison: Azathioprine 1.5 to 2.5mg/kg/ qd (adjunctive TCS and oral antihistamines allowed)			
Settings: Outpatient			
Outcome	**Effects and confidence in the estimate of effects** **Methotrexate 10mg to 22.5mg weekly**		**Comments**
Change in EASI (Follow up: 12 weeks; assessed with mean change from baseline in EASI score; presented as MD (95%CI)); CRITICAL			
Azathioprine Comparator (Mean Change -17.2 [SD 14.1])	Mean Change -17.4 [SD 6.6]	MD -0.20 (-6.8, 6.4), p=0.95	EASI MCID 6.6
Certainty of evidence	⨁⨁ Low [a]		
	Direct evidence; 1 RCT[3]; n=42		
Change in POEM (Follow up: 12 weeks; assessed with mean change from baseline in POEM score; presented as MD (95%CI)); CRITICAL			
Azathioprine Comparator (Mean Change -7.9 [SD7.7])	Mean Change -6.9 [SD 5.7]	MD 1.0 (-3.1, 5.1), p=0.64	POEM MCID 3.4
Certainty of evidence	⨁⨁ Low [a]		
	Direct evidence; 1 RCT[3]; n=42		

Change in VAS itch (Follow up: 12 weeks; assessed with mean change from baseline in VAS itch score; presented as MD (95%CI)); CRITICAL			
Azathioprine Comparator (Mean Change -2.6 [SD 2.2])	Mean Change -2.5 [SD 2.2]	MD 0.1 (-1.2, 1.4), p= 0.88	VAS for itch MCID 2-3 (for chronic itch)
Certainty of evidence	⨁⨁ Low [a]		
	Direct evidence; 1 RCT[3]; n=42		
Change in quality of life (Follow up: 12 weeks; assessed with mean change from baseline in Skindex-17); CRITICAL			
Azathioprine Comparator (Mean change -10.3 [SD 12.9])	Mean change -12.9 [SD 8.8]	MD -2.6 (-9.2, 4.0), p=0.45	Reduction in score indicates improvement in QoL; score range 0-85).
	⨁⨁ Low [a]		
	Direct evidence; 1 RCT[3]; n=42		
Discontinuation due to adverse event (Follow up: 12 weeks; assessed with individuals discontinuing treatment due to AE; presented as OR (95%CI)); CRITICAL			
Azathioprine Comparator (Event rate 2/22**)**	OR 0.53 (0.04, 6.29)	41 fewer peer 1,000 (87 fewer to 295 more)	
Event Rate	1/20		
Certainty of evidence	⨁⨁ Low [b]		
	Direct evidence; 1 RCT[3]; n=42		
Serious adverse events (Follow up: 12 weeks; assessed with individuals experiencing the event; presented as OR (95%CI)); CRITICAL			
Azathioprine Comparator (Event rate 0/22**)**	-	-	
Event Rate	0/20		
Certainty of evidence	⨁⨁ Low [b]		
	Direct evidence; 1 RCT[3]; n=42		
SoF table definitions & Interpretation **CI:** Confidence Interval **MD**: Mean difference **RR:** Risk ratio **OR:** Odds ratio			
GRADE Considerations & Explanations			

a. Downgraded for High risk of bias due to concerns about blinding and deviations from intended intervention; Downgraded for imprecision as CI consistent with important benefit and harm.
b. Downgraded for High risk of bias due to concerns about blinding and deviations from intended interventions; Downgraded for imprecision for insufficient sample.

1. Drucker AM, Morra DE, Prieto-Merino D, et al. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Update of a Living Systematic Review and Network Meta-analysis. *JAMA Dermatol.* 2022.
2. Goujon C, Viguier M, Staumont-Salle D, et al. Methotrexate Versus Cyclosporine in Adults with Moderate-to-Severe Atopic Dermatitis: A Phase III Randomized Noninferiority Trial. *J Allergy Clin Immunol Pract.* 2018;6(2):562-569 e563.
3. Schram ME, Roekevisch E, Leeflang MM, Bos JD, Schmitt J, Spuls PI. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. *J Allergy Clin Immunol.* 2011;128(2):353-359.

e-Table 12. Mycophenolate

Intervention	Evidence Summary	2014 Guideline Recommendations
Mycophenolate mofetil	No direct evidence matching inclusion criteria identified. *Limited clinical trial data:* A noninferiority trial compared enteric-coated mycophenolate sodium (EC-MPS) 1440mg/day (n=24) to cyclosporine A 3mg/kg/day (n=26) as maintenance therapy *after a 6-week run-in phase of CsA 5mg/kg/day* in adults with AD.[1] At 3 weeks after randomization to study treatments, increase in SCORAD was larger in the EC-MPS group with the mean difference between arms of 6.6 points (95%CI 1.5, 11.7). At 10 weeks, average SCORAD scores between the study arms were comparable: MD 0.8 (95%CI -4.4, 6.0) and SCORAD scores remained comparable at 33 weeks. No serious adverse events (requiring additional medication or discontinuation of study medication) were reported in either arm. The authors conclude EC-MPS is as effective as CsA for maintenance therapy. *Pooled individual patient data*: A systematic review and meta-analysis of individual patient data (primarily from low certainty case studies, and low certainty case series, cohort studies, and trials) reports that for patients with refractory AD (mean age 38.21±22.8) there was a clinical and statistically significant reduction in SCORAD scores following mycophenolate mofetil treatment: MD 18.01 (95%CI 8.54, 27.48, p=0.0002; n=37).[2] Across the 140 patients included in the review MMF was effective (complete or partial remission) in 77% with relapses occurring in 8.2%. The most common adverse effects reported across cases were headaches (10.7%), gastric discomfort (10.7%), herpes infection (9.3%), deranged liver function tests (7.9%), and other infections (6.4%).	Mycophenolate mofetil may be considered as an alternative, variably effective therapy for refractory AD. C III (Recommendation based on consensus, opinion, case studies, or disease-oriented evidence).

1. Haeck IM, Knol MJ, Ten Berge O, van Velsen SG, de Bruin-Weller MS, Bruijnzeel-Koomen CA. Enteric-coated mycophenolate sodium versus cyclosporin A as long-term treatment in adult patients with severe atopic dermatitis: a randomized controlled trial. *J Am Acad Dermatol.* 2011;64(6):1074-1084.
2. Phan K, Smith SD. Mycophenolate mofetil and atopic dermatitis: systematic review and meta-analysis. *J Dermatolog Treat.* 2020;31(8):810-814.

e-Table 13. Corticosteroids

Adapted from: Siegels D, Heratizadeh A, Abraham S, Binnmyr J, Brockow K, Irvine AD, Halken S, Mortz CG, Flohr C, Schmid-Grendelmeier P, Van der Poel LA, Muraro A, Weidinger S, Werfel T, Schmitt J; European Academy of Allergy, Clinical Immunology Atopic Dermatitis Guideline group. Systemic treatments in the management of atopic dermatitis: A systematic review and meta-analysis. Allergy. 2021 Apr;76(4):1053-1076. doi: 10.1111/all.14631. Epub 2020 Nov 4. PMID: 33074565. *Search updated March 2022*

Estimates of effects, confidence intervals, and certainty of the evidence for systemic corticosteroids compared to cyclosporine in atopic dermatitis			
Patients: Adults (18-55yo) with severe AD			
Interventions: Prednisolone initial dosage 0.5-0.8 mg/kg tapered to 0 over 2 weeks (adjunctive TCS and antihistamines allowed)			
Comparison: Cyclosporine 2.7-4.0 mg/kg daily for 6 weeks (adjunctive TCS and antihistamines allowed)			
Settings: Outpatient			
Outcome	**Effects and confidence in the estimate of effects** **Prednisolone initial dosage 0.5-0.8 mg/kg tapered to 0 over 2 weeks**		**Comments**
Change in clinical signs (Follow up: 6 weeks; assessed with mean change from baseline in SCORAD; MD (95%CI)); CRITICAL			
Cyclosporine Comparator (Mean Change - 42.7%± 24.8)	Mean Change -54.5% ± 24.0	MD -11.8 (-27.98, 4.38)	
Certainty of evidence	⨁⨁ Low [a]		
	Direct evidence; 1 RCT[1]; n= 38		
Prevention of flares-relapse rate (follow up: 12 weeks; assessed with participants experiencing relapse after initial response; RR (95%CI)); CRITICAL			
Cyclosporine Comparator (Event rate 5/11)	RR 1.96 (0.98, 3.89)	436 more per 1,000 (9 fewer to 1,000 more)	Trial stopped early due to safety issues based on the high rate of relapse in the prednisolone group.
Event Rate	8/9		
Certainty of evidence	⨁ Very Low [b]		
	Direct evidence; 1 RCT[1]; n= 20		
Discontinuation due to adverse event (Follow up: 6 weeks; assessed with individuals discontinuing treatment due to AE; presented as OR (95%CI)); CRITICAL			

Cyclosporine Comparator (Event rate 5/17**)**	OR 2.9 (0.7, 10.9)	253 more per 1,000 (68 fewer to 525 more)	
Event Rate	11/21		
Certainty of evidence	⨁⨁ Low [a]		
	Direct evidence; 1 RCT[1]; n= 38		
Serious adverse events (Follow up: 12 weeks; assessed with individuals experiencing a serious AE; presented as OR (95%CI)); CRITICAL			
Cyclosporine Comparator (Event rate 0/17 **)**	OR 4.5 (0.2, 100.0)	-	
Event Rate	2/21		
Certainty of evidence	⨁⨁ Low [a]		
	Direct evidence; 1 RCT[1]; n= 38		

SoF table definitions & Interpretation
CI: Confidence Interval
MD: Mean difference
RR: Risk ratio
OR: Odds ratio
AE: Adverse event

GRADE Considerations & Explanations
a. High risk of bias due to deviations from intended interventions (although ITT analysis was employed) and incomplete outcome reporting due to selection of reported outcomes; downgraded for imprecision due to small sample not meeting optimal information size criteria.
b. High risk of bias due to deviations from intended interventions (although ITT analysis was employed), incomplete outcome reporting due to selection of reported outcomes, and trial stopping early; downgraded for imprecision as CI consistent with no difference and important harm.

References

1. Schmitt J, Schäkel K, Fölster-Holst R, et al. Prednisolone vs. ciclosporin for severe adult eczema. An investigator-initiated double-blind placebo-controlled multicentre trial. *Br J Dermatol.* 2010;162(3):661-668.

e-Table 14. Leukotriene Inhibitors

Adapted from: Ferguson L, Futamura M, Vakirlis E, Kojima R, Sasaki H, Roberts A, Mori R. Leukotriene receptor antagonists for eczema. Cochrane Database of Systematic Reviews 2018, Issue 10. Art. No.: CD011224. DOI: 10.1002/14651858.CD011224.pub2. *Search updated 14 April 2022. No new evidence published since the 2014 AD guidelines*

Estimates of effects, confidence intervals, and certainty of the evidence for systemic montelukast compared to placebo in atopic dermatitis			
Patients: Adults (aged ≥16) with moderate-to-severe AD			
Interventions: Montelukast 10 mg qd (adjunctive TCS and antihistamines allowed in one trial)			
Comparison: Placebo			
Settings: Outpatient			
Outcome	**Effects and confidence in the estimate of effects**		**Comments**
	Montelukast 10mg qd		
Change in clinical signs (Follow up: 4 to 8 weeks; assessed with modified EASI score and SASSAD; presented as SMD (95%CI)); CRITICAL			
Placebo Comparator	SMD 0.29 higher (-0.23, 0.81)		
Certainty of evidence	⨁⨁ Low [a]		
	Direct evidence; 3 RCT[1-3]; n= 131^		
Change in itch (follow up: 8 weeks; assessed with mean change in VAS itch score; presented as MD); CRITICAL			
Placebo Comparator (Mean improvement 0.8)	MD -0.7		Authors state the difference is non-significant but do not provide a p-value or SDs.
Certainty of evidence	⨁⨁ Low [a]		
	Direct evidence; 1 RCT[1]; n=58		
Discontinuation due to adverse event (Follow up: 6 weeks; assessed with individuals discontinuing treatment due to AE; presented as OR (95%CI)); CRITICAL			
Placebo Comparator (Event rate 3/67**)**	OR 2.21 (0.53, 9.23)	49 more per 1,000 (21 fewer to 257 more)	
Event Rate	6/64		
Certainty of evidence	⨁⨁ Low [a]		
	Direct evidence; 3 RCT[1-3]; n= 131^		
Serious adverse events (Follow up: 12 weeks; assessed with individuals experiencing the event; presented as Odds Ratios (95%CI)); CRITICAL			

Placebo Comparator (Event rate 0/67 **)**	-	-	
Event Rate	1/64		
Certainty of evidence	⨁⨁ Low [a]		
	Direct evidence; 3 RCT[1-3]; n= 131^		

SoF table definitions & Interpretation

- A negative effect estimate favors the column-defining intervention
- SMD <0.2 small unimportant effect; SMD 0.2-0.8 small effect of unknown importance; SMD >0.8 moderate effect[4]

CI: Confidence Interval
SMD: Standardized mean difference
MD: Mean difference
OR: Odds ratio

GRADE Considerations & Explanations

a. Downgraded for risk of bias (minimal outcome reporting) and for imprecision as the total sample is insufficient.

Footnotes

^ Two trials included individuals aged ≥ 16 yo and considered them adult participants.

References

1. Friedmann PS, Palmer R, Tan E, et al. A double-blind, placebo-controlled trial of montelukast in adult atopic eczema. *Clin Exp Allergy.* 2007;37(10):1536-1540.
2. Nettis E, Pannofino A, Fanelli M, Ferrannini A, Tursi A. Efficacy and tolerability of montelukast as a therapeutic agent for severe atopic dermatitis in adults. *Acta Derm Venereol.* 2002;82(4):297-298.
3. Veien NK, Busch-Sørensen M, Stausbøl-Grøn B. Montelukast treatment of moderate to severe atopic dermatitis in adults: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol.* 2005;53(1):147-149.
4. Drucker AM, Morra DE, Prieto-Merino D, et al. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Update of a Living Systematic Review and Network Meta-analysis. *JAMA Dermatol.* 2022.