Topical treatments for atopic dermatitis (eczema): Systematic review and network meta-analysis of randomized trials

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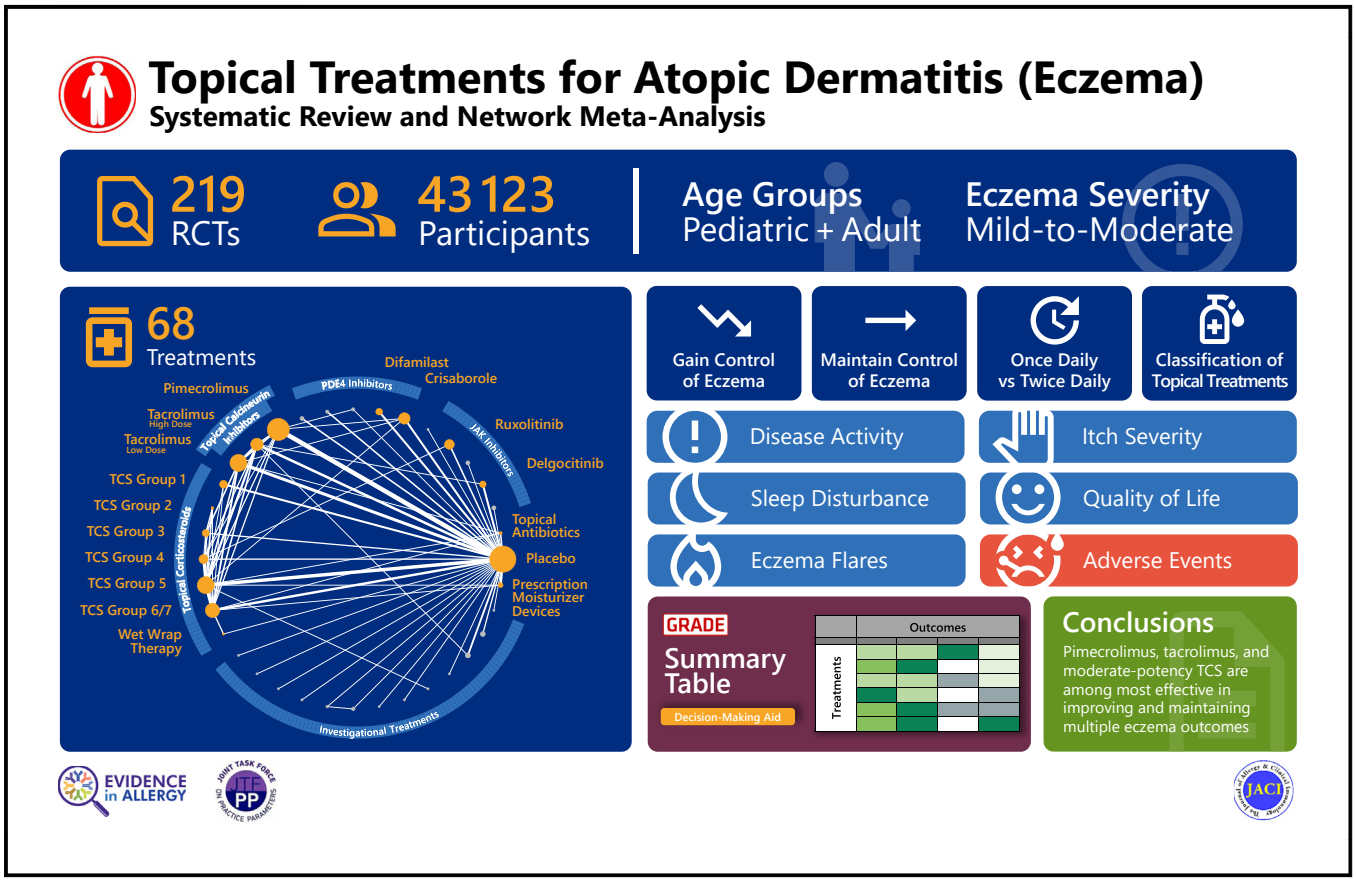
GRAPHICAL ABSTRACT



Capsule summary: This systematic review and NMA compares patient-important outcomes and assesses certainty of evidence among 68 topical treatments evaluating 43,123 participants across 219 RCTs. These findings inform optimal AD management among patients, caregivers, and clinicians.

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Topical treatments for atopic dermatitis (eczema): Systematic review and network meta-analysis of randomized trials

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Background: Atopic dermatitis (AD) is a common skin condition with multiple topical treatment options, but uncertain comparative effects.

Objective: We sought to systematically synthesize the benefits and harms of AD prescription topical treatments.

Methods: For the 2023 American Academy of Allergy, Asthma & Immunology and American College of Allergy, Asthma, and Immunology Joint Task Force on Practice Parameters AD guidelines, we searched MEDLINE, EMBASE, CENTRAL, CINAHL, LILACS, ICTRP, and GREAT databases to September 5, 2022, for randomized trials addressing AD topical treatments. Paired reviewers independently screened records, extracted data, and assessed risk of bias. Random-effects network meta-analyses addressed AD severity, itch, sleep, AD-related quality of life, flares, and harms. The Grading of Recommendations Assessment, Development and Evaluation approach informed certainty of evidence ratings. We classified topical corticosteroids (TCS) using 7 groups—group 1 being most potent. This review is registered in the Open Science Framework (https://osf.io/q5m6s).

Results: The 219 included trials (43,123 patients) evaluated 68 interventions. With high-certainty evidence, pimecrolimus improved 6 of 7 outcomes—among the best for 2; high-dose tacrolimus (0.1%) improved 5—among the best for 2; low-dose tacrolimus (0.03%) improved 5—among the best for 1. With moderate- to high-certainty evidence, group 5 TCS improved 6—among the best for 3; group 4 TCS and delgocitinib improved 4—among the best for 2; ruxolitinib improved 4—among the best for 1; group 1 TCS improved 3—among the best for 2. These interventions did not increase harm.

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Crisaborole and difamilast were intermediately effective, but with uncertain harm. Topical antibiotics alone or in combination may be among the least effective. To maintain AD control, group 5 TCS were among the most effective, followed by tacrolimus and pimecrolimus.
Conclusions: For individuals with AD, pimecrolimus, tacrolimus, and moderate-potency TCS are among the most effective in improving and maintaining multiple AD outcomes. Topical antibiotics may be among the least effective. (J Allergy Clin Immunol 2023;152:1493-519.)

Key words: *Atopic dermatitis (eczema), topical treatments (therapy), topical corticosteroids (steroids), topical calcineurin inhibitors (pimecrolimus, tacrolimus), topical phosphodiesterase-4 (PDE-4) inhibitors (crisaborole, difamilast, lotamilast, roflumilast), topical Janus kinase (JAK) inhibitors (ruxolitinib, delgocitinib), patient-important outcomes (eczema severity, intensity, itch, sleep, quality of life, flares or flare-ups or exacerbations), disease severity, network meta-analysis (comparative effects), induction of remission and maintenance of remission (reactive or proactive therapy)*

Abbreviations used

AAAAI:	American Academy of Allergy, Asthma & Immunology
ACAAI:	American College of Allergy, Asthma, and Immunology
AD:	Atopic dermatitis
CrI:	Credible interval
EASI:	Eczema Area and Severity Index
GRADE:	Grading of Recommendations Assessment, Development and Evaluation
IQR:	Interquartile range
JAK:	Janus kinase
MD:	Mean difference
MID:	Minimally important difference
NMA:	Network meta-analysis
OR:	Odds ratio
QoL:	Quality of life
RCT:	Randomized controlled trial
RR:	Relative risk
SCORAD:	SCORing Atopic Dermatitis
TCS:	Topical corticosteroid

Atopic dermatitis (AD), often referred to as eczema, represents the most common chronic inflammatory skin disease, affecting 15% to 20% of children and 3% to 10% of adults around the world, and manifests as inflamed skin, itch (pruritus), and impaired patient and caregiver sleep and quality of life (QoL).[1,2] A combination of skin barrier defects, microbial interactions, irritants, allergens, and abnormal immune responses drive skin inflammation in AD.[3] Optimally managing the often relapsing and potentially lifelong nature of AD requires effective and safe treatments.[3]

Prescription topical agents represent a core component of managing AD.[1,2,4] These agents include topical corticosteroids (TCS), topical calcineurin inhibitors, phosphodiesterase 4 inhibitors, Janus kinase (JAK) inhibitors, prescription moisturizers, and emerging investigational medicines.[1] Treatment goals include induction of remission (controlling active disease) and maintenance of remission (maintaining clear subclinical disease after initial induction of remission and preventing subsequent exacerbations [referred to as flares]).[5] With increasing numbers of topical therapy options for patients with AD, achieving optimal AD outcomes requires clarity in the relative merits and potential harms of each treatment approach.

Previous systematic reviews of topical treatments for AD explored specific subclasses of therapies in isolation,[6-8] but none have addressed the comparative efficacy and safety among all competing topical treatments. The abundance of randomized trials but lack of structured and systematically appraised comparative evidence hinders evidence-based decision making by patients and caregivers, clinicians, and policymakers.[9,10] Network meta-analyses (NMAs) provide comparative evidence by accounting for both direct and indirect evidence and allowing for the classification of multiple treatments. As part of the 2023 American Academy of Allergy, Asthma & Immunology (AAAAI) and American College of Allergy, Asthma, and Immunology (ACAAI) guideline addressing AD,[1,4] we systematically reviewed all randomized trials of topical treatments for AD and conducted NMAs.

METHODS

Search strategy and inclusion criteria

We performed this systematic review and NMA considering Cochrane Collaboration[11] and Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidance.[12-14] Our report adheres to Preferred Reporting Items for Systematic Reviews and Meta-Analyses NMA extension guidance[15,16] (see this article's Online Repository at www.jacionline.org). We registered the review, which is linked to the updated AAAAI/ACAAI Joint Task Force on Practice Parameters for Atopic Dermatitis Guidelines,[4,17-22] in the Open Science Framework (https://osf.io/q5m6s).

We searched MEDLINE, EMBASE, CENTRAL, CINAHL, LILACS, World Health Institution International Clinical Trials Registry Platform, and GREAT (Global Resource of EczemA Trials) databases from inception to September 5, 2022, without language restrictions, for published and unpublished randomized controlled trials (RCTs) comparing prescription topical treatments at any dose or frequency for AD against another prescription topical treatment or a control (ie, placebo or standard of care alone such as a nonprescription moisturizer) with outcomes of interest (for search terms used, see the Online Repository). The linked guideline panel defined the most relevant alternative interventions, including prescription moisturizer devices, which are defined as those marketed as a medical device under Food and Drug Administration 510(k) regulatory authorization, such as Atopiclair (K024367), Dexeryl (K113807), Eletone (K092297), EpiCeram (K052643), MimyX (K041342), Neosalus (K070309), PruMyx (K082089), and Zenieva (K073246), and excluding nonprescription (ie, over the counter) moisturizers.[23,24] To identify additional potentially relevant studies, we cross-referenced other systematic reviews, conducted forward and backward citation analyses of all included studies using Web of Science (all databases), and conferred with clinical experts from the linked guideline panel. This approach is consistent with principles of systematic reviews in addressing the totality of the evidence and with Cochrane[11] and GRADE[25] guidance to mitigate the risk of publication bias. We excluded trials using split-body

designs (ie, individual patients received different treatments simultaneously on nonoverlapping sites of the body).

Data collection

Paired and calibrated reviewers (A.W.L.C., D.G.R., M.M.W., R.C., I.X.Z., M.M., J.B.) independently screened titles and abstracts and reviewed full texts using Covidence (Veritas Health Innovation, Melbourne, Victoria, Australia). Following Cochrane guidance, we piloted and calibrated reviewers iteratively before data extraction independently and in duplicate and resolved disagreements by consensus and, if necessary, through discussion with a third reviewer (D.K.C.). Authors with potential conflicts of interest did not participate in data collection or formal analysis. We collected study bibliographic information, design, setting, patient characteristics, intervention and comparator characteristics, outcomes according to the intention-to-treat principle, and sources of funding. We classified the design of the studies as either inducing remission (ie, the use of interventions to control active AD at randomization) or maintaining remission (ie, the use of interventions to prevent an AD flare, randomized after initial control and meeting a certain clinical threshold)—both of which are highly valued by patients in managing AD.[22]

For multiple records pertaining to the same trial, after collecting all relevant data, we conducted analysis as a single study. In the case of discrepancies, we used the more complete data set. If a single record reported on more than 1 study, we treated each as a separate study. If a trial investigated multiple conditions, we analyzed only the patients with AD and excluded trials that did not report data specific to patients with AD. We also accounted for within study–level subgroup analyses (eg, separate reporting of data by age groups). When studies did not report the data in corresponding tabular or narrative formats, we used WebPlotDigitizer 4.6 (https://automeris.io/WebPlotDigitizer) to extract values from figures. We contacted authors for clarification in case of missing, unpublished, or unclear data.

For trials that did not report means or SDs, we imputed data according to Furukawa et al,[26] Weir et al,[27] and Cochrane guidance.[11] If a trial reported data as median and interquartile range (IQR) or range, we assessed skewness, and if not present, we converted values to means and SDs according to Shi et al[28] and Cochrane guidance.[11] If present, we estimated mean and SD values using quantile estimation, Box-Cox transformation, or approximate Bayesian computation—preferring the estimate that was the most consistent with other values within and between trials.[29] If trials varied in the instruments used to measure an outcome, we followed GRADE guidance and used linear transformation to convert each measure to the one most familiar to clinicians, unless otherwise specified.[30,31]

Outcomes

Following Cochrane[11] and GRADE guidance,[30] through discussion among our multistakeholder guideline development group, including frontline clinicians, AD experts, and patient and caregiver partners,[17] and through consideration of the Harmonising Outcome Measures for Eczema initiative[32-34] that also interviewed patients about the outcomes they value, we selected the following patient-important outcome data addressing similar outcome constructs: clinician-reported and patient-reported (including proxy-reported for children) AD severity, itch severity, sleep disturbance, eczema-related QoL, long-term control, number of patients experiencing AD flares, adverse events including those leading to discontinuation, and skin infections at the longest available time point. As most studies reported results using SCORing Atopic Dermatitis (SCORAD), it was initially preferred over Eczema Area and Severity Index (EASI) to limit the number of transformations to a common scale. We did sensitivity analyses using EASI instead. Flares constitute exacerbations that represent periods of worsened disease often requiring escalation of treatment.[35-37] This approach to outcome priority setting with patient partners is consistent with patient values and preferences for the treatment of AD.[22] The use of the longest available time point in meta-analyses is consistent with meta-analyses across multiple fields of medicine to draw meaningful influences, and the GRADE approach explicitly examines differences between studies that would reduce confidence in the results.[12]

Risk of bias assessment

Similar to the data extraction process, paired and calibrated reviewers assessed risk of bias independently for each study outcome using the modified Cochrane Risk of Bias tool version 2 (RoB 2) for randomized trials.[38] We subclassified "some concerns" judgments as "some concerns, probably high" and "some concerns, probably low." If at least one domain was high or probably high risk of bias, we considered the outcome at high risk of bias for that trial.

Data analysis

With the exception of TCS, network nodes represented unique topical interventions. In cases where a unique drug was investigated in different concentrations or formulations, we assessed for differences in treatment effects using pairwise comparisons and, if there was no credible effect modification, merged the interventions into a single node (see the Online Repository). For TCS groups, we used the US system (see the Online Repository), which classifies TCS group 1 as the most potent and TCS group 7 as the least potent.[39,40] Due to similarity in clinical use, we considered TCS groups 6 and 7 together as a single node in the main analyses. All TCS in the trials were classified. To facilitate readability, we present the estimates in relation to controls throughout the main text. Controls include placebo or standard care alone, such as no-medicated moisturizers.

We summarized dichotomous outcomes using odds ratios (ORs) based on the 2×2 tables from each study and continuous outcomes as mean differences (MDs) with 95% credible intervals (CrIs) or, as indicated, CIs. Following GRADE guidance,[41] we calculated risk differences by multiplying the baseline risk by the meta-analyzed OR. If mean differences produced counterintuitive or extremely heterogeneous results, we evaluated alternative summary measures (eg, standardized MDs).

We calculated effect estimates in conventional pairwise meta-analyses using DerSimonian-Laird random-effects models. For the NMA, we performed Bayesian random effects NMA using Markov chain Monte Carlo approaches with minimally informative mean effect priors.[20,21,29,42] To mitigate potential limitations

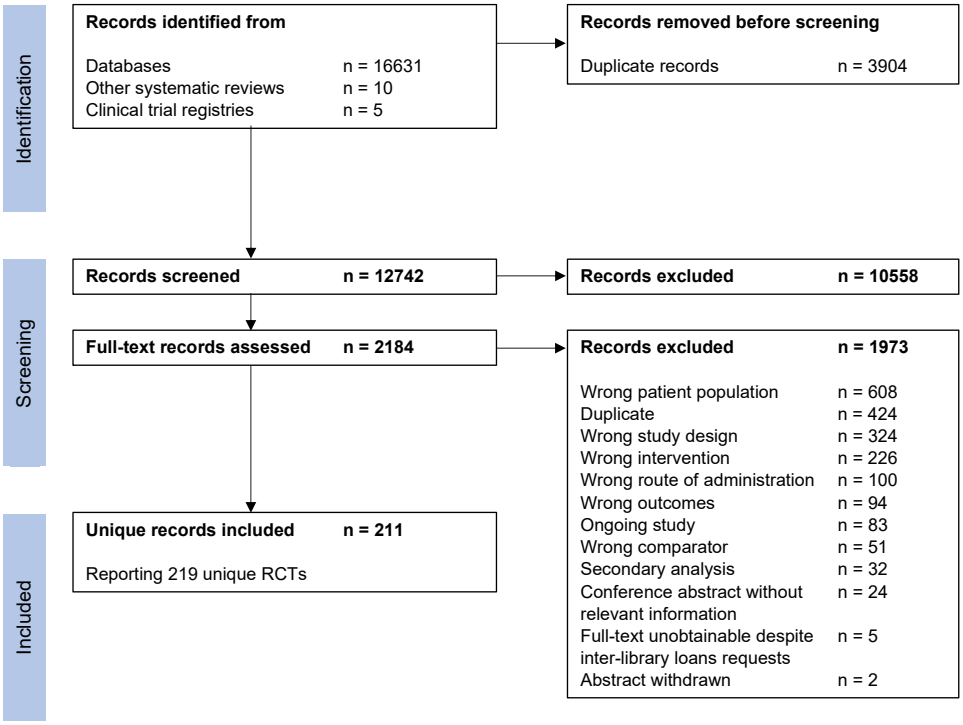

FIG 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection.

of network sparsity, we used between-study priors informed by established predictive distributions of between-study heterogeneity from 14,886 Cochrane meta-analyses.[43] Trace and density plots and Gelman-Rubin statistics of less than 1.01 after at least a burn-in of 10,000, sampling of 100,000, and thinning of 10 confirmed, in all cases, convergences of 4 chains. We initially specified using frequentist approaches in the main analyses, but in the course of the review, we changed statisticians to leverage our Bayesian NMA workflows developed for our COVID-19 NMAs[42,44] supporting the World Health Organization and therefore present the Bayesian analyses as the main analyses. The corresponding frequentist sensitivity analyses yield similar inferences (see the Online Repository). There were otherwise no notable changes to the protocol.

We evaluated the certainty (quality) of the evidence using the GRADE approach,[12,13] including the domains of risk of bias, imprecision, inconsistency, indirectness, publication bias, intransitivity, and incoherence, and report our findings using standardized terminology.[45] GRADE guidance on incoherence includes assessing the uncertainty, direction, magnitude, and importance of inconsistency of direct and indirect estimates and each of their contributions to the network estimate.[46] We provide a case example in the Online Repository. We interpreted and present NMA findings according to GRADE guidance using a minimally contextualized framework[46-51] with a target of certainty rating of a nonzero effect (ie, any benefit relative to control and interventions relative to one another).[52] We categorized the interventions as among the most effective, of intermediate superior effectiveness, intermediate inferior effectiveness, and among the least effective, differentiating between treatments with high- or moderate-certainty evidence versus control and treatments with low- or very low–certainty evidence. The minimally contextualized framework primarily uses CrIs to categorize interventions, placing high value on the precision of the estimate when compared with both the control and other interventions. This approach provides advantages over the narrow focus on traditional, but potentially misleading, ranking metrics such as surface under the cumulative ranking curve or comparison of point estimates alone.[47,53] We assessed publication bias using the GRADE approach, which included inspecting funnel plots and reviewing trial registries for completed trials without a corresponding publication or report.[25] As NMA uses common heterogeneity models and represents a combination of direct and indirect evidence, the number of trials and metrics such as I^2 are irrelevant to the network estimates, and instead appraisals of these factors are done using the GRADE domains of imprecision and inconsistency. We present such appraisals in the summary tables via color coding and incorporate each domain's assessment into the evidence profiles.

We analyzed prespecified subgroups—baseline AD severity (eg, mild to moderate vs severe), age group (pediatric vs adult), risk of bias (low vs high), and study duration (≤4 weeks vs >4 weeks)—using pairwise comparisons or random-effects (network) meta-regression, and we appraised the credibility of the subgroup effects using the Instrument for assessing the Credibility of Effect Modification Analyses.[54] We hypothesized that treatment effects would be greater in patients with more severe disease, in pediatric patients, and in studies at high risk of bias and longer duration. We further analyzed subgroups by publications status (published vs unpublished), by reported data (mean/SD vs median/IQR), and conducted sensitivity analyses using alternative topical corticosteroid classification systems (eg, three- or four-category systems). We used node-splitting models to assess for local incoherence, using the GRADE guidance described above, and followed GRADE guidance to assess

TABLE I. Characteristics of included studies

Study	Country	Age Group	No. Randomized	Age (y), mean (SD)	No. of Females (%)	Duration (wk)	Intervention
Abbasi et al, 2017[55]	Iran	Pediatric	59	31.33 (3.04)	23/45 (51%)	2	TCS group 6/7 Standard care
Abramovits and Oquendo, 2010[56]	USA	Pediatric	264	7.08 (NR)	114 (43%)	4	TCS group 5 Standard care
Amerio et al, 1998[57]	Italy	Adult and pediatric	97	19.50 (12.39)	54 (56%)	4	TCS group 4 TCS group 5
Antiga et al, 2011[58]	Italy	Adult	24	40.90 (NR)	13 (54%)	3	Tacrolimus (high dose) TCS group 5
Archer and MacDonald, 1987[59]	UK	Adult and pediatric	20	24.00 (NR)	10 (50%)	2	β-Agonist Standard care
Arenberger et al, 2011[60]	Czech Republic	Adult and pediatric	280	30.06 (16.30)	177/278 (64%)	8	Heparin Levomenol Levomenol + heparin Standard care
Arnold and Van Der Meer, 2005[61]	The Netherlands	Adult and pediatric	20	19.70 (NR)	NR	2	TCS group 5 TCS group 5 + antibiotic
Bangert et al, 2011[62]	USA	Adult	67	32.70 (NR)	0 (0%)	3	Pimecrolimus Standard care
Beattie and Lewis-Jones, 2004[63]	UK	Pediatric	19	1.61 (2.18)	9 (47%)	2	TCS group 6/7 TCS group 6/7 (wet wrap therapy)
Belloni et al, 2005[64]	Italy	Adult	30	22.50 (7.35)	16 (53%)	3	Prescription moisturizer Standard care
Berardesca et al, 2001[65]	Italy	Adult	91	28.41 (11.34)	44 (48%)	8	TCS group 5 Standard care
Berberian et al, 1999[66]	Multiple	Adult	349	33.74 (12.30)	229 (66%)	1	TCS group 4 TCS group 4 + doxepin TCS group 6/7 TCS group 6/7 + doxepin
Berth-Jones et al, 2003[67]	Multiple	Adult and pediatric	295	28.80 (12.40)	162 (55%)	16	TCS group 3 TCS group 5 Standard care
Beutner et al, 2007[68]	USA	Adult	103	NR	NR	4	Pimecrolimus Standard care
Bieber et al, 2007[69]	Multiple	Pediatric	265	7.65 (4.18)	NR	3	Tacrolimus (low dose) TCS group 5
Bissonnette et al, 2010[70]	Canada	Adult	37	NR	NR	4	Tapinarof Standard care
Bissonnette et al, 2012[72]	Canada	Adult	148	32.89 (12.28)	88 (59%)	6	Tapinarof Standard care
Bissonnette et al, 2016[71]	Canada	Adult	69	31.40 (9.95)	37 (54%)	4	Tofacitinib Standard care
Boguniewicz et al, 1998[73]	USA	Pediatric	180	10.46 (2.64)	100 (56%)	3	Tacrolimus (high dose) Tacrolimus (low dose) Standard care
Boguniewicz et al, 2008[74]	USA	Pediatric	142	4.99 (3.30)	74 (52%)	3	Prescription moisturizer Standard care

(Continued)

TABLE I. *(Continued)*

Study	Country	Age Group	No. Randomized	Age (y), mean (SD)	No. of Females (%)	Duration (wk)	Intervention
Breneman et al, 2005[76]	USA	Adult and pediatric	229	40.86 (18.42)	130 (57%)	2	TCS group 1 Standard care
Breneman et al, 2008[75]	USA	Adult and pediatric	197	22.92 (20.32)	116 (59%)	40	Tacrolimus Standard care
Buhles, 1992[77]	Germany	Adult	80	35.50 (NR)	54 (68%)	4	COX inhibitor Standard care
Canpolat et al, 2012[78]	Turkey	Pediatric	83	1.17 (0.31)	NR	1	TCS group 6/7 TCS group 6/7 + antibiotic Standard care
Caproni et al, 2007[79]	Italy	Adult	20	38.01 (NR)	9/16 (56%)	3	Tacrolimus (high dose) TCS group 5
Cato et al, 2001[80]	USA	Adult	150	NR	94 (63%)	2	TCS group 4 TCS group 4 + laurocapram Standard care
Chapman et al, 2005[81]	USA	Adult and pediatric	618	27.75 (13.37)	363 (59%)	6	Tacrolimus (low dose) Standard care
Charney and Leibsohn, 1975[82]	USA	NR	30	NR	NR	3	TCS group 5 Standard care
Clement and Lucas, 1967[83]	USA	NR	33	NR	NR	4	TCS group 6/7 + liquor carbonis detergens TCS group 6/7
Czarnowicki et al, 2018[84]	Multiple	Adult	103	34.10 (12.67)	55 (53%)	4	LXR agonist Standard care
Dahnhardt et al, 2021[85]	Germany	Adult	20	NR	8 (40%)	1	Tacrolimus (high dose) TCS group 4
Das et al, 2020[86]	Bangladesh	Pediatric	200	3.54 (2.73)	94 (47%)	12	Tacrolimus (high dose) TCS group 5
De Belilovsky et al, 2011[87]	Spain	Pediatric	80	2.35 (NR)	44 (55%)	3	TCS group 5 Oleodistillate
Del Rosso and Bhambri, 2009[88]	USA	Adult	313	42.46 (14.42)	173 (55%)	2	TCS group 1 Standard care
Doss et al, 2009[90]	Multiple	Adult and pediatric	568	35.05 (14.68)	302/562 (54%)	3	Tacrolimus (high dose) TCS group 3
Doss et al, 2010[89]	Multiple	Pediatric	479	6.75 (3.99)	247/473 (52%)	3	Tacrolimus (low dose) TCS group 3
Dou et al, 2006[91]	China	Adult and pediatric	327	NR	NR	3	Tacrolimus (high dose) Tacrolimus (low dose) Standard care
Draelos et al, 2005[92]	USA	Adult	37	41.72 (14.31)	29 (78%)	2	Pimecrolimus Tacrolimus (high dose)
Drake et al, 1994[93]	USA	Adult	270	33.00 (NR)	195 (72%)	1	Doxepin Standard care
Eichenfield et al, 2002[94]	Multiple	Pediatric	403	6.73 (2.90)	201 (50%)	6	Pimecrolimus Standard care

(Continued)

TABLE I. *(Continued)*

Study	Country	Age Group	No. Randomized	Age (y), mean (SD)	No. of Females (%)	Duration (wk)	Intervention
Eichenfield et al, 2006[95] (1)	USA	Adult and pediatric	220	NR	NR	4	TCS group 5 Standard care
Eichenfield et al, 2006[95] (2)	USA	Adult and pediatric	218	NR	NR	4	TCS group 5 Standard care
EUCTR2021-006538-38	Multiple	Adult and pediatric	391	18.26 (15.06)	186 (48%)	4	Crisaborole Standard care
Foelster Holst et al, 2010[96]	Multiple	Adult	93	32.87 (12.10)	56 (60%)	4	Protease inhibitor Standard care
Fowler et al, 2007[97]	USA	Pediatric	174	6.96 (4.13)	NR	1	Pimecrolimus Standard care
Francis et al, 2016[98]	UK	Pediatric	77	3.10 (2.10)	43 (56%)	2	Antibiotic Standard care
Fukuie et al, 2016[99]	Japan	Pediatric	30	1.96 (1.75)	10 (33%)	52	TCS group 3 (proactive) TCS group 3 (reactive)
Furue et al, 2014[100]	Japan	Adult	78	31.20 (NR)	34 (44%)	4	Lotamilast Standard care
Gao et al, 2021[101]	China	Adult	66	NR	NR	2	Cannabidiol Cannabidiol + aspartame Standard care
Gehring and Gloor, 1996[102]	Germany	Adult and pediatric	63	28.48 (12.17)	39 (62%)	1	TCS group 6/7 Standard care
Gelmetti et al, 1994[103]	Italy	Pediatric	40	3.02 (3.10)	19 (48%)	2	TCS group 5 TCS group 6/7
GlaxoSmithKline, 2007[104]	Multiple	Adult	143	33.30 (NR)	69 (48%)	3	GW842470X Standard care
Glazenburg et al, 2009[105]	Multiple	Pediatric	75	5.85 (NR)	46 (61%)	16	TCS group 3 Standard care
Gollnick et al, 2008[106]	Multiple	Adult	543	35.11 (13.61)	189 (35%)	26	Pimecrolimus Standard care
Gooderham et al, 2021[107]	Multiple	Adult and pediatric	136	41.59 (16.85)	93 (68%)	4	Roflumilast Standard care
Granlund et al, 2001[108]	Finland	Adult	14	NR	NR	2	Tacrolimus (high dose) Standard care
Handa et al, 2022[109]	India	Pediatric	50	5.09 (3.56)	25 (50%)	6	Tacrolimus (high dose) TCS group 5
Hanifin et al, 2001[112]	USA	Adult	633	38.56 (14.07)	357/632 (56%)	12	Tacrolimus (high dose) Tacrolimus (low dose) Standard care
Hanifin et al, 2002[110]	Multiple	Adult and pediatric	348	16.80 (15.60)	202 (58%)	20	TCS group 5 Standard care
Hanifin et al, 2016[111]	Multiple	Adult and pediatric	121	34.30 (15.60)	72 (60%)	4	Difamilast Standard care
Hebert et al, 2007[113]	USA	Pediatric	582	6.70 (NR)	320 (55%)	4	TCS group 5 Standard care
Hindley et al, 2006[114]	UK	Pediatric	50	NR	NR	4	TCS group 6/7 TCS group 6/7 (wet wrap therapy)
Ho et al, 2003[115]	Multiple	Pediatric	186	1.06 (0.52)	84 (45%)	6	Pimecrolimus Standard care

(Continued)

TABLE I. *(Continued)*

Study	Country	Age Group	No. Randomized	Age (y), mean (SD)	No. of Females (%)	Duration (wk)	Intervention
Hoeger et al, 2009[116]	Multiple	Pediatric	200	5.30 (1.65)	99 (50%)	6	Pimecrolimus Standard care
Hofman et al, 2006[117]	Multiple	Pediatric	257	6.10 (2.97)	127/232 (55%)	5	Tacrolimus (low dose) TCS group 6/7
Niemeyer-van der Kolk et al, 2020[170]	The Netherlands	Adult	36	24.90 (7.80)	27 (75%)	4	Antibiotic Standard care
Hoybye et al, 1991[118]	Denmark	Adult	94	26.00 (10.47)	NR	3	TCS group 4 TCS group 5
Hung et al, 2007[119]	Taiwan	Adult and pediatric	60	15.60 (9.18)	34 (57%)	8	Tacrolimus (low dose) Tacrolimus (low dose) + fusidic acid TCS group 5 TCS group 5 + antibiotic
Iraji et al, 2015[120]	Iran	Pediatric	70	8.87 (4.75)	35 (50%)	8	TCS group 5 TCS group 5 + azathioprine cream
Janmohamed et al, 2014[121]	The Netherlands	Pediatric	39	3.37 (4.64)	14 (36%)	4	TCS group 3 (wet wrap therapy) Standard care
Jorizzo et al, 1995[122]	USA	Pediatric	113	4.80 (NR)	62 (55%)	5	TCS group 5 TCS group 6/7
Kaplan et al, 1978[123]	USA	Adult and pediatric	90	18.50 (NR)	58 (64%)	3	TCS group 5 TCS group 6/7
Kapp et al, 2002[124]*	Multiple	Pediatric	251	1.01 (NR)	86/250 (34%)	52	Pimecrolimus Standard care
Katas et al, 2021[125]	Malaysia	Adult	9	NR	NR	4	TCS group 6/7 Standard care
Kaufmann et al, 2004[127]	Germany	Pediatric	196	1.00 (0.50)	67/195 (34%)	4	Pimecrolimus Standard care
Kaufmann et al, 2006[126]	Multiple	Adult	198	33.45 (12.33)	117 (59%)	1	Pimecrolimus Standard care
Kempers et al, 2004[128]	USA	Pediatric	141	7.95 (4.21)	79 (56%)	6	Pimecrolimus Tacrolimus (low dose)
Kim et al, 2020[129]	Multiple	Adult	307	38.10 (14.82)	168 (55%)	4	Ruxolitinib TCS group 4 Standard care
Kimball et al, 2008[130]	USA	Adult and pediatric	377	NR	NR	2	TCS group 1 Standard care
Kirkup et al, 2003[131]	Multiple	Pediatric	137	8.00 (2.98)	73 (54%)	12	TCS group 5 TCS group 6/7
Korting et al, 1994[132]	Germany	Adult and pediatric	143	NR	89 (62%)	1	TCS group 5 TCS group 5 + antibiotic
Lassus, 1983[133]	Finland	Pediatric	40	7.95 (NR)	23 (58%)	2	TCS group 5 TCS group 6/7
Lassus, 1984[134]	Finland	Pediatric	43	NR	27 (59%)	2	TCS group 5 TCS group 6/7
Lawlor et al, 1995[135]	UK	Adult and pediatric	51	30.74 (11.33)	34 (67%)	4	TCS group 5 Standard care
Lebrun-Vignes et al, 2000[136]	France	Pediatric	29	1.17 (0.95)	14 (48%)	3	TCS group 5 TCS group 6/7

(Continued)

TABLE I. *(Continued)*

Study	Country	Age Group	No. Randomized	Age (y), mean (SD)	No. of Females (%)	Duration (wk)	Intervention
Lebwohl, 1996[137] (1)	USA	Adult and pediatric	203	NR	114/195 (58%)	4	TCS group 3 Standard care
Lebwohl, 1996[137] (2)	USA	Adult and pediatric	169	NR	101/158 (64%)	4	TCS group 3 Standard care
Lebwohl, 1999[138]	USA	Pediatric	219	NR	NR	3	TCS group 4 TCS group 5
Lee et al, 2006[139]	South Korea	Adult	44	25.78 (NR)	12/40 (30%)	1	Doxepin Standard care
Lee et al, 2014[140]	South Korea	Pediatric	55	0.70 (0.40)	18 (33%)	4	Pimecrolimus TCS group 6/7
Lee et al, 2019[141]	South Korea	Adult	194	27.49 (NR)	100/189 (53%)	8	TRPV1 antagonist Standard care
Lembo et al, 2011[142]	Italy	Pediatric	38	4.20 (NR)	14 (37%)	2	Antibiotic Standard care
Leo et al, 2004[143]	USA	Pediatric	19	10.27 (3.02)	9 (47%)	2	Pimecrolimus Standard care
Lessard and Labelle, 1980[144]	Canada	Adult	29	26.19 (NR)	18 (62%)	2	TCS group 2 TCS group 5
Leung et al, 2009[145]	Multiple	Adult and pediatric	73	18.50 (13.70)	41 (56%)	6	Pimecrolimus Standard care
Levy et al, 2005[146]	USA	Adult	135	NR	NR	4	Tacrolimus (low dose) Standard care
Liang et al, 2019[147]	China	Pediatric	125	6.50 (2.78)	55/121 (45%)	6	Tacrolimus (low dose) Standard care
Lisante et al, 2017[148]	USA	Pediatric	90	8.10 (3.96)	49 (54%)	3	Prescription moisturizer Standard care
Liu et al, 2007[151]	China	Adult and pediatric	336	20.04 (13.66)	127 (38%)	4	Pimecrolimus Standard care
Liu et al, 2014[150]	China	Adult and pediatric	120	NR	70 (58%)	2	TCS group 5 Standard care
Liu and Ong, 2018[149]	China	Pediatric	107	5.00 (2.60)	53 (50%)	20	TCS group 5 Standard care
Liu et al, 2020[152]	China	Pediatric	59	0.42 (0.22)	19 (32%)	2	TCS group 4 TCS group 4 + antibiotic
Luger et al, 2001[153]	Multiple	Adult	260	28.42 (NR)	133 (51%)	3	Pimecrolimus TCS group 5 Standard care
Luger et al, 2004[154]*	Multiple	Adult	658	33.45 (NR)	359 (55%)	56	Pimecrolimus TCS group 4
Maloney et al, 1998[155]	USA	Adult and pediatric	81	NR	NR	4	TCS group 1 Standard care
Marchesi et al, 1994[156]	Italy	Adult	60	39.80 (16.81)	22 (37%)	3	TCS group 1 TCS group 3
Matheson et al, 2008[157]	USA	Pediatric	284	7.14 (5.19)	141 (50%)	4	TCS group 5 Standard care
Meurer et al, 2002[159]*	Germany	Adult	192	32.15 (10.84)	115 (60%)	24	Pimecrolimus Standard care
Meurer et al, 2010[158]	Multiple	Pediatric	376	8.30 (4.61)	184/373 (49%)	4	TCS group 5 TCS group 5 + pimecrolimus
Miller et al, 2011[160]	USA	Pediatric	39	7.00 (4.59)	22 (56%)	3	Prescription moisturizer Standard care

(Continued)

TABLE I. *(Continued)*

Study	Country	Age Group	No. Randomized	Age (y), mean (SD)	No. of Females (%)	Duration (wk)	Intervention
Mudaliyar et al, 2020[161]	India	Pediatric	37	10.13 (3.55)	16 (43%)	4	Tacrolimus (low dose) TCS group 3
Murrell et al, 2007[162]	Multiple	Adult and pediatric	200	30.00 (NR)	123 (62%)	6	Pimecrolimus Standard care
Nakagawa et al, 2018[163]	Japan	Adult and pediatric	327	30.80 (10.00)	116/326 (36%)	4	Delgocitinib Tacrolimus (high dose) Standard care
Nakagawa et al, 2018[167]	Japan	Adult	20	27.56 (6.20)	2 (10%)	1	Delgocitinib Standard care
Nakagawa et al, 2019[166]	Japan	Pediatric	103	8.50 (4.00)	45 (44%)	4	Delgocitinib Standard care
Nakagawa et al, 2020[165]	Japan	Adult and pediatric	158	31.70 (10.10)	60 (38%)	4	Delgocitinib Standard care
Nakagawa et al, 2021[164]	Japan	Pediatric	137	8.30 (3.80)	67 (49%)	4	Delgocitinib Standard care
NCT00120302	UK	Adult	90	48.49 (19.08)	47/82 (57%)	4	Pimecrolimus Standard care
NCT00510003	Spain	Pediatric	109	4.74 (2.70)	55/106 (52%)	3	Pimecrolimus Standard care
NCT00828412	USA	Pediatric	100	5.20 (3.40)	55 (55%)	6	Prescription moisturizer TCS group 6/7
NCT00946478	USA	Adult	40	27.40 (9.00)	NR	3	Pimecrolimus Standard care
NCT01037881	Multiple	Adult	183	35.10 (12.50)	70 (38%)	4	LEO29102 Pimecrolimus Standard care
NCT01053247	Multiple	Adult	793	43.30 (16.70)	467 (59%)	2	Tacrolimus (low dose) Standard care
NCT01139450	Multiple	Adult	899	28.00 (18.14)	566 (63%)	4	Tacrolimus (low dose) Standard care
NCT01428297	Multiple	Adult	49	35.00 (NR)	25 (51%)	4	BPR277 Standard care
NCT01856764	Germany	Adult	40	34.60 (10.66)	20 (50%)	2	Roflumilast Standard care
NCT02120833	USA	Pediatric	51	1.68 (0.82)	25 (49%)	2	Prescription moisturizer Standard care
NCT02404493	USA	Pediatric	23	1.83 (0.81)	7 (30%)	2	Prescription moisturizer Standard care
NCT02791308	USA	Adult and pediatric	587	36.80 (18.69)	338/577 (59%)	2	Pimecrolimus Standard care
NCT03107611	Multiple	Adult and pediatric	654	35.40 (20.30)	404/649 (62%)	2	Pimecrolimus Standard care
NCT03386032	USA	Adult and pediatric	65	37.30 (14.40)	47 (72%)	8	TCS group 6/7 Standard care
NCT03539601	Multiple	Adult and pediatric	235	20.40 (17.79)	139 (59%)	4	Crisaborole Pimecrolimus TCS group 5 Standard care
NCT03725722	Multiple	Adult	251	40.50 (17.00)	172 (69%)	8	Delgocitinib cream Standard care

(Continued)

TABLE I. *(Continued)*

Study	Country	Age Group	No. Randomized	Age (y), mean (SD)	No. of Females (%)	Duration (wk)	Intervention
Nemoto et al, 2016[168]	Japan	Pediatric	62	9.93 (2.80)	33 (53%)	2	Lotamilast Standard care
Neumann, et al 2008[169]	Germany	Adult and pediatric	50	36.95 (13.55)	23/40 (58%)	89	Tacrolimus (high dose) TCS group 6/7
Nilsson, et al 1992[171] (1)	Sweden	Adult and pediatric	38	13.00 (13.11)	NR	2	TCS group 5 TCS group 6/7
Nilsson, et al 1992[171] (2)	Sweden	Adult and pediatric	28	13.00 (13.92)	NR	2	TCS group 1 TCS group 5 + antibiotic
Nolting, 1985[172]	Germany	Adult	34	NR	17 (51%)	2	TCS group 2 TCS group 5
Nolting et al, 1991[173]	Germany	Adult and pediatric	67	5.51 (3.31)	34 (51%)	3	TCS group 4 TCS group 5
Novartis, 2005[174]	Japan	Adult and pediatric	173	27.26 (7.80)	65/172 (38%)	26	Pimecrolimus Standard care
Novartis, 2005[175]	Japan	Pediatric	240	8.16 (3.39)	120 (50%)	26	Pimecrolimus Standard care
Novartis, 2005[176]	USA	Adult	264	38.10 (12.04)	172 (65%)	24	Pimecrolimus Standard care
Novartis, 2005[177]	Multiple	Adult	543	35.11 (13.63)	169 (31%)	26	Pimecrolimus Standard care
Ohba et al, 2016[178]	Japan	Adult	40	27.20 (7.30)	0 (0%)	1	Lotamilast Standard care
Prado de Oliveira et al, 2002[195]	Brazil	Pediatric	25	6.05 (2.78)	NR	6	TCS group 4 TCS group 6/7
Ono et al, 2020[179]	Japan	Adult	12	33.10 (11.24)	0 (0%)	1	Crisaborole Standard care
Onumah and Kircik, 2013[180]	USA	Adult and pediatric	20	25.00 (NR)	11 (55%)	4	Pimecrolimus Tacrolimus (low dose)
Otsuki et al, 2003[181]	Japan	Pediatric	221	8.40 (4.10)	92 (42%)	3	Tacrolimus (high dose) Tacrolimus (low dose) Standard care
Paller et al, 2001[182]	USA	Pediatric	351	6.10 (NR)	186 (53%)	12	Tacrolimus (high dose) Tacrolimus (low dose) Standard care
Paller et al, 2003[184]	USA	Pediatric	94	NR	49 (52%)	2	TCS group 6/7 Standard care
Paller et al, 2005[183] (1)	Multiple	Adult	413	39.06 (14.75)	249 (60%)	6	Pimecrolimus Tacrolimus (high dose)
Paller et al, 2005[183] (2)	Multiple	Pediatric	226	6.40 (3.88)	105/225 (47%)	6	Pimecrolimus Tacrolimus (high dose)
Paller et al, 2005[183] (3)	Multiple	Pediatric	426	6.40 (3.74)	234/425 (55%)	6	Pimecrolimus Tacrolimus (low dose)
Paller et al, 2016[185] (1)	USA	Adult and pediatric	763	12.13 (NR)	427/759 (56%)	4	Crisaborole Standard care
Paller et al, 2016[185] (2)	USA	Adult and pediatric	764	12.34 (NR)	420/763 (55%)	4	Crisaborole Standard care
Papp et al, 2021[186] (1)	Multiple	Adult and pediatric	631	35.20 (18.15)	391 (62%)	8	Ruxolitinib Standard care

(Continued)

TABLE I. *(Continued)*

Study	Country	Age Group	No. Randomized	Age (y), mean (SD)	No. of Females (%)	Duration (wk)	Intervention
Papp et al, 2021[186] (2)	Multiple	Adult and pediatric	618	36.40 (18.38)	380 (61%)	8	Ruxolitinib Standard care
Parikh-Das and Moreira, 2017[187]	USA	Adult and pediatric	53	43.60 (17.55)	34 (64%)	1	Prescription moisturizer Standard care
Park et al, 2021[188]	South Korea	Adult and pediatric	240	25.76 (8.17)	104/237 (44%)	8	TRPV1 antagonist Standard care
Patrizi et al, 2008[189]	Italy	Pediatric	60	5.52 (3.49)	30 (50%)	6	Prescription moisturizer Standard care
Patrizi et al, 2016[190]	Italy	Adult and pediatric	44	22.60 (NR)	29 (66%)	4	Vitamin E Standard care
Peppers et al, 2019[192]	Multiple	Adult	247	29.30 (14.83)	121 (49%)	12	Tapinarof Standard care
Perala et al, 2020[193]*	Finland	Pediatric	152	1.43 (0.22)	73 (48%)	156	Tacrolimus (low dose) TCS group 6/7
Peserico et al, 2008[194]	Multiple	Adult and pediatric	221	30.85 (14.63)	142 (64%)	16	TCS group 5 Standard care
Queille et al, 1984[196]	Multiple	Pediatric	26	3.42 (3.91)	8 (31%)	1	TCS group 2 TCS group 3 TCS group 4 TCS group 5 TCS group 6/7
Rafanelli et al, 1993[244]	Italy	Pediatric	60	7.25 (3.10)	36 (60%)	3	TCS group 4 TCS group 5
Rahman et al, 2008[198]	Bangladesh	Adult and pediatric	60	7.75 (8.87)	33 (55%)	3	Tacrolimus (low dose) Standard care
Rahman et al, 2015[197]	Bangladesh	Pediatric	60	5.97 (2.42)	28 (47%)	3	Tacrolimus (high dose) TCS group 6/7
Rajka et al, 1993[199]	Multiple	Adult and pediatric	117	NR	NR	3	TCS group 4 TCS group 5
Ramsay et al, 1996[200] (1)	Canada	Adult and pediatric	174	NR	NR	2	TCS group 6/7 TCS group 6/7 + antibiotic
Ramsay et al, 1996[200] (2)	Canada	Adult and pediatric	65	NR	NR	2	Antibiotic TCS group 6/7 + antibiotic
Reitamo et al, 2002[203]	Multiple	Pediatric	560	7.34 (4.10)	293 (52%)	3	Tacrolimus (high dose) Tacrolimus (low dose) TCS group 6/7
Reitamo et al, 2004[201]	Multiple	Pediatric	624	6.93 (4.06)	322 (52%)	3	Tacrolimus (low dose) TCS group 6/7
Reitamo et al, 2005[202]*	Multiple	Adult	972	32.50 (11.79)	523 (54%)	24	Tacrolimus (high dose) TCS group 5
Rubio-Gomis et al, 2018[204]	Spain	Pediatric	49	5.31 (2.52)	26 (53%)	16	TCS group 5 Standard care
Ruzicka et al, 1997[205]	Multiple	Adult and pediatric	215	28.52 (10.47)	120/213 (56%)	3	Tacrolimus (high dose) Tacrolimus (low dose)

(Continued)

TABLE I. *(Continued)*

Study	Country	Age Group	No. Randomized	Age (y), mean (SD)	No. of Females (%)	Duration (wk)	Intervention
Ryu et al, 1997[206]	South Korea	Pediatric	24	NR	NR	2	TCS group 4 TCS group 6/7
Saeki et al, 2019[210]	Japan	Adult and pediatric	200	30.90 (9.89)	70 (35%)	8	Difamilast Standard care
Saeki et al, 2020[208]	Japan	Pediatric	73	8.30 (3.41)	21 (29%)	4	Difamilast Standard care
Saeki et al, 2022[207]	Japan	Pediatric	251	7.10 (3.09)	116 (46%)	4	Difamilast Standard care
Saeki et al, 2022[209]	Japan	Adult and pediatric	364	31.90 (10.72)	167 (46%)	4	Difamilast Standard care
Salavec and Bučková, 2004[211]*	Czech Republic	Pediatric	40	8.67 (NR)	NR	52	Pimecrolimus Standard care
Sanabria-Silva et al, 1991[212]	Mexico	Pediatric	45	NR	14 (31%)	4	TCS group 5 TCS group 6/7 Standard care
Savin, 1976[213]	USA	NR	27	NR	NR	3	TCS group 1 TCS group 6/7
Schachner et al, 2005[214]	USA	Pediatric	317	6.85 (4.04)	168 (53%)	6	Tacrolimus (low dose) Standard care
Schneider et al, 2016[215]	USA	Pediatric	1091	0.61 (0.33)	412/1087 (38%)	156	Pimecrolimus Standard care
Sears et al, 1997[216]	USA	Adult	194	37.70 (NR)	107 (55%)	2	TCS group 5 Standard care
Siegfried et al, 2006[217]	USA	Pediatric	275	4.99 (3.25)	NR	1	Pimecrolimus Standard care
Sigurgeirsson et al, 2008[219]	Multiple	Pediatric	521	6.70 (3.74)	308 (59%)	26	Pimecrolimus Standard care
Sigurgeirsson et al, 2015[218]	Multiple	Pediatric	2439	0.59 (0.23)	940 (39%)	6	Pimecrolimus TCS group 6/7
Sikder et al, 2005[220]	Bangladesh	Pediatric	45	10.50 (2.30)	20 (44%)	4	Tacrolimus (low dose) TCS group 5 TCS group 5 + tacrolimus (low dose)
Smitt et al, 1993[221]	The Netherlands	Adult and pediatric	41	4.05 (NR)	NR	2	TCS group 4 TCS group 6/7
Stander et al, 2016[222]	Germany	Adult	70	34.10 (14.29)	40 (57%)	4	Sertaconazole Standard care
Sugarman and Parish, 2009[223]	USA	Pediatric	121	7.59 (NR)	73 (60%)	4	Prescription moisturizer TCS group 5
Takeuchi et al, 2012[224]	Japan	Adult and pediatric	43	31.30 (13.30)	21/42 (50%)	8	Tacrolimus Standard care
Tan et al, 2010[225]	Singapore	Adult and pediatric	60	17.95 (NR)	21 (35%)	6	Antibiotic Standard care
Thaci et al, 2008[226]	Multiple	Pediatric	250	6.95 (3.99)	131 (52%)	52	Tacrolimus Standard care
Tharp, 1996[227]	USA	Adult and pediatric	238	37.00 (16.97)	78 (33%)	4	TCS group 5 Standard care
Thomas et al, 2002[228]	UK	Pediatric	207	5.50 (3.75)	104 (50%)	18	TCS group 3 TCS group 6/7
Tiplica et al, 2018[229]	Multiple	Pediatric	335	4.08 (1.36)	174 (52%)	12	Prescription moisturizer Standard care

(Continued)

TABLE I. *(Continued)*

Study	Country	Age Group	No. Randomized	Age (y), mean (SD)	No. of Females (%)	Duration (wk)	Intervention
Torok et al, 2003[230]	USA	Adult and pediatric	57	NR	35 (61%)	3	Tacrolimus (high dose) TCS group 4 TCS group 4 + tacrolimus (high dose)
Ulrich and Andresen, 1991[231]	Germany	Adult and pediatric	165	26.00 (NR)	77 (47%)	2	TCS group 3 TCS group 5
Van Delrey et al, 1983[232]	Brazil	Adult and pediatric	29	NR	NR	3	TCS group 5 TCS group 6/7
Van Der Meer et al, 1999[232]	The Netherlands	Adult and pediatric	54	25.00 (NR)	32 (59%)	16	TCS group 3 Standard care
Vanderploeg, 1976[234]	USA	Adult and pediatric	36	24.77 (14.83)	23/33 (70%)	3	TCS group 1 Standard care
Vernon et al, 1991[235]	USA	Pediatric	48	NR	NR	6	TCS group 4 TCS group 6/7
Wahn et al, 2002[236]*	Multiple	Pediatric	713	7.97 (NR)	375/711 (53%)	52	Pimecrolimus Standard care
Wang et al, 1995[238]	China	Adult	65	NR	35 (54%)	3	TCS group 5 Standard care
Wang et al, 2014[237]	China	Adult	100	38.14 (NR)	53 (53%)	4	TCS group 2 TCS group 3
Wollenberg et al, 2008[239]	Multiple	Adult and pediatric	224	30.04 (11.80)	136 (61%)	52	Tacrolimus (high dose) Standard care
Wu et al, 2013[240]	China	Pediatric	60	0.35 (0.34)	21/55 (38%)	2	Lipoxin A4 TCS group 4 Standard care
Yawalkar and Schwerzmann, 1991[241]	Germany	Adult and pediatric	117	NR	NR	2	TCS group 1 TCS group 5
Zhang et al, 2014[242]	China	Adult	67	49.00 (NR)	26 (39%)	4	TCS group 4 TCS group 4 + heparin
Zuberbier et al, 2007[243]	Germany	Pediatric	184	7.60 (4.90)	95 (52%)	24	Pimecrolimus Standard care

NR, Not reported.
*Denotes studies that induced remission of AD including application of the intervention at least once daily, followed by variable treatment periods that maintained remission with reduction of application frequency.

intransitivity. If network sparsity produced implausibly wide CrIs, we conducted the analysis using a fixed-effect model.[49]

We conducted the meta-analyses, subgroup, and sensitivity analyses using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria), Stata 17.0 (StataCorp LLC, College Station, Texas), and DataParty (DataParty Inc, Hamilton, Canada).

Role of the funding source

The AAAAI and ACAAI Joint Task Force on Practice Parameters contributed to defining the scope of the review, but otherwise had no role in study design, data collection, data analysis, or data interpretation. The funder received a copy of the report before submission for publication. The review team had the ability, but not the obligation, to consider the funders' feedback.

Data sharing

Data can be requested from the corresponding author.

RESULTS

Our systematic search yielded 12,742 unique records, 2,184 potentially relevant full texts, and 211 eligible records including 219 unique RCTs[55-244] (EUCTR2011-000917-38, EUCTR2021-006538-38, NCT00120302, NCT00510003, NCT00828412, NCT00946478, NCT01037881, NCT01053247, NCT01139450, NCT01856764, NCT02120833, NCT02404493, NCT02791308, NCT03107611, NCT03386032, NCT03539601, NCT03725722) (Fig 1; Table I; Online Repository). We cross-referenced author correspondence from other systematic reviews,[8] and it proved necessary to contact authors for only 1 record regarding missing data, and this trial ultimately proved ineligible.

The studies included a total of 43,123 patients, of whom 11,143 were randomly assigned to control and 31,980 were randomly assigned to 1 of 68 interventions. Table I summarizes characteristics of each included trial. Of the 219 RCTs, 156 included children, 59 included only adults, 67 included both children and adults, and 4 did not report age data. The studies included participants with median of mean ages of 18.5 years (range of means

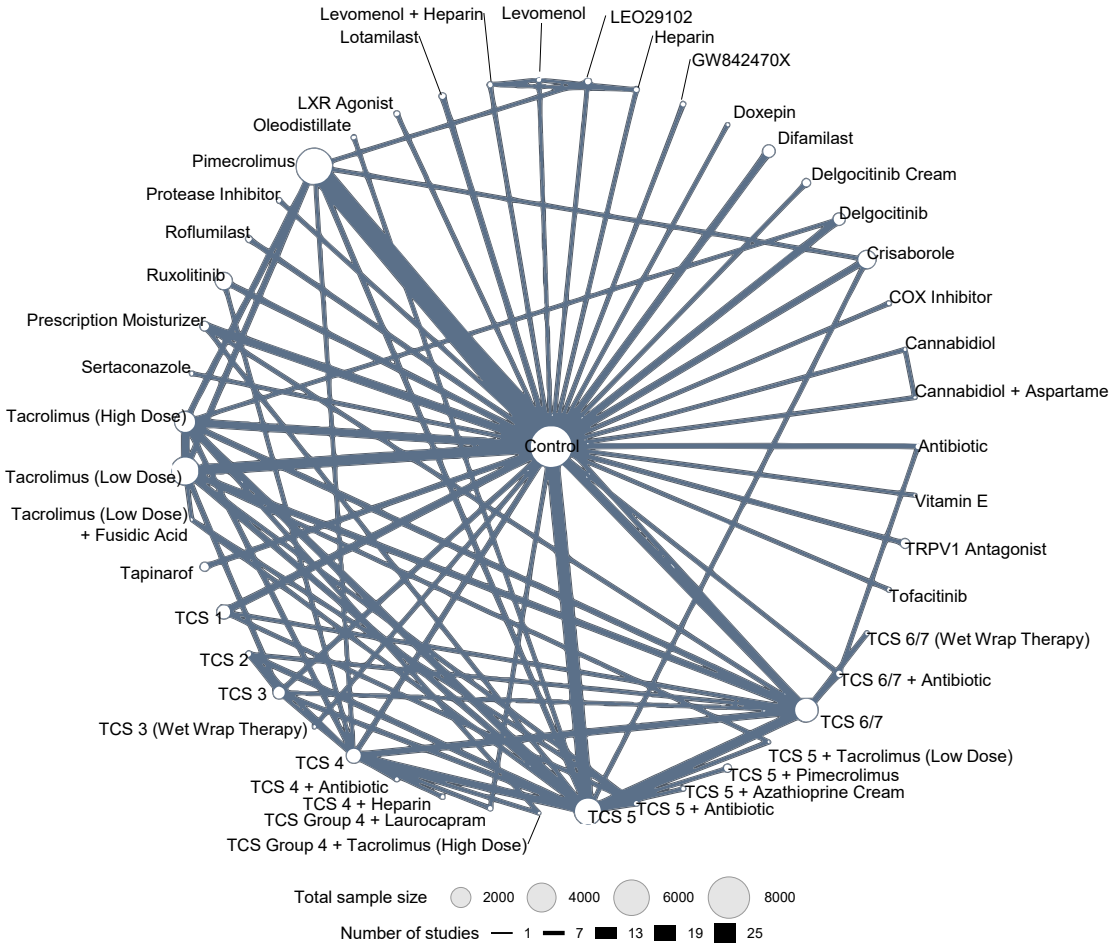

FIG 2. Network plot of topical treatments for AD (eczema). Clinician-reported severity for induction of remission.

0.35-49 years), and a median 53% were female (range of proportions 0-78%); most studies addressed patients with mild to moderate AD. Median study duration among studies investigating induction of remission was 4 weeks (range 1-156 weeks), and median study duration among studies investigating maintenance of remission was 16 weeks (range 2-52 weeks).

Individual outcomes of most studies were at overall low risk of bias. The Online Repository presents risk of bias assessments at the outcome level, grouped by outcomes with similar ratings (ie, efficacy outcomes and, separately, safety outcomes). Limitations from missing outcome data provided the most frequent risk of bias issue. We did not, however, find any credible evidence of different treatment effect estimates from studies at high versus low risk of bias or detect clear evidence of publication bias, network intransitivity, or incoherence (see the Online Repository).

Effects of interventions for inducing remission of AD

Fig 2 presents the network plot for the outcome AD severity, measured using SCORAD (0-103, higher scores indicate greater severity). The Online Repository presents all other network plots.

Fig 3 presents the GRADE summary of comparative effects for the most clinically relevant interventions, as defined by the linked guideline panel. The Online Repository presents the forest plots, NMA evidence profiles, and categorization of the remaining interventions. With high-certainty evidence, pimecrolimus improved 6 of 7 patient-important outcomes and was among the most effective for 2 outcomes; high-dose tacrolimus (0.1%) improved 5 outcomes and was among the most effective for 2 outcomes; and low-dose tacrolimus (0.03%) improved 5 outcomes and was among the most effective for 1 outcome. With moderate- or high-certainty evidence, TCS group 5 improved 6 patient-important outcomes and was among the best for 3 outcomes; TCS group 4 and delgocitinib improved 4 outcomes and was among the best for 2 outcomes; and ruxolitinib improved 4 outcomes and was among the best for 1 outcome. Crisaborole and difamilast were of intermediate effectiveness, but their effects on adverse events were less certain.

AD severity

A total of 187 RCTs[55-58,62-65,68-74,76-82,84-89,92,94-102,104,105,107-109,111-134,136-155,157-173,178,180-186,188-190,192-218,220-223,225,227,229-239,242] (EUCTR2021-006538-38, NCT00120302, NCT00510003, NCT00828412, NCT01037881, NCT01053247, NC

		Atopic Dermatitis Severity SCORAD (0–103)	Itch NRS (0–10)	Sleep Disturbance NRS (0–10)	Eczema-Related Quality of Life DLQI (0–30)	Atopic Dermatitis Flare	Any Adverse Event	Discontinuation due to Adverse Event
		MD (95%CrI)	MD (95%CrI)	MD (95%CrI)	MD (95%CrI)	RD (95%CrI)	RD (95%CrI)	RD (95%CrI)
Baseline		25.96	5.40	4.89	9.43	95 per 1000	305 per 1000	28 per 1000
JAK Inhibitors								
Delgocitinib Cream		-5.64 (-8.36 to -2.91)						
Delgocitinib Ointment		-9.98 (-13.81 to -6.15)	-1.47 (-2.17 to -0.77)		-7.41 (-10.16 to -4.66)	-74 (-84 to -51)	-37 (-93 to 25)	-21 (-25 to -15)
Ruxolitinib		-4.82 (-5.65 to -4.00)	-2.11 (-2.96 to -1.26)	-0.57 (-1.15 to 0.02)	-4.82 (-6.35 to -3.44)	-74 (-84 to -51)	-37 (-93 to 25)	-21 (-25 to -15)
PDE4 Inhibitors								
Crisaborole		-4.89 (-8.69 to -1.08)	-0.64 (-1.11 to -0.15)		-1.23 (-2.34 to -0.09)	-59 (-81 to -12)	43 (-32 to 124)	9 (-15 to 58)
Difamilast		-5.41 (-9.12 to -1.68)	-1.26 (-2.09 to -0.42)		-1.55 (-3.00 to -0.03)	-45 (-71 to 2)	-41 (-110 to 39)	-17 (-22 to -9)
Lotamilast		-2.89 (-8.84 to 3.06)	0.04 (-1.53 to 1.62)			-23 (-80 to 196)	6 (-153 to 211)	-10 (-25 to 28)
Roflumilast		-2.15 (-4.20 to -0.12)	-1.55 (-3.39 to 0.29)				177 (-38 to 408)	23 (-27 to 367)
Topical Calcineurin Inhibitors								
Pimecrolimus		-7.23 (-8.76 to -5.72)	-1.61 (-2.00 to -1.21)	-2.13 (-3.15 to -1.01)	-1.44 (-2.38 to -0.62)	-53 (-66 to -39)	21 (-15 to 59)	-11 (-16 to -3)
Tacrolimus 0.1% (High Dose)		-13.05 (-15.15 to -10.95)	-2.27 (-2.84 to -1.70)		-3.65 (-5.59 to -1.83)	-70 (-85 to -41)	29 (-18 to 79)	-15 (-19 to -10)
Tacrolimus 0.03% (Low Dose)		-9.38 (-11.22 to -7.55)	-1.97 (-2.44 to -1.50)	-0.17 (-1.97 to 1.60)	-1.72 (-3.47 to -0.02)	-70 (-85 to -41)	29 (-18 to 79)	-15 (-19 to -10)
Topical Corticosteroids								
Conventional TCS Potency Classification ▲ High	**TCS Group 1**	-17.81 (-21.32 to -14.30)	-2.34 (-4.37 to -0.32)				-96 (-179 to 11)	-25 (-27 to -18)
High	**TCS Group 2**	-13.82 (-18.74 to -8.89)	-3.39 (-5.02 to -1.76)				-16 (-278 to 479)	
Medium (Moderate or Mid)	**TCS Group 3**	-11.57 (-14.80 to -8.37)	-2.37 (-3.18 to -1.57)	-0.22 (-2.23 to 1.72)	-1.23 (-3.71 to 1.17)	-11 (-83 to 312)	-62 (-138 to 24)	-12 (-23 to 9)
Medium (Moderate or Mid)	**TCS Group 4**	-12.26 (-15.02 to -9.50)	-2.62 (-3.26 to -1.98)		-5.96 (-8.53 to -3.56)	-66 (-92 to 49)	-76 (-142 to -1)	85 (-15 to 381)
Medium (Moderate or Mid)	**TCS Group 5**	-8.46 (-10.90 to -6.03)	-2.09 (-2.54 to -1.64)	-0.92 (-2.57 to 0.71)	-3.82 (-6.21 to -1.44)	-83 (-92 to -57)	-102 (-138 to -63)	-18 (-23 to -12)
Low ▼	**TCS Group 6/7**	-4.68 (-7.10 to -2.29)	-1.33 (-1.89 to -0.76)	0.32 (-1.51 to 2.10)	-1.48 (-3.38 to 0.34)	-13 (-78 to 234)	-33 (-105 to 47)	-6 (-18 to 13)
Other								
Antibiotic		-1.48 (-6.77 to 3.81)	-0.32 (-2.15 to 1.51)		-1.33 (-3.35 to 0.69)	-56 (-94 to 499)	50 (-153 to 306)	229 (-5 to 834)
Prescription Moisturizers		-1.94 (-4.83 to 0.95)	-1.63 (-2.28 to -0.97)			-60 (-82 to -5)	-8 (-111 to 111)	-10 (-23 to 17)
Tapinarof		-11.26 (-16.55 to -6.03)	-1.93 (-2.99 to -0.89)			-64 (-88 to 20)	155 (19 to 299)	-14 (-23 to 9)

High to moderate certainty evidence	Low to very low certainty evidence
Among the most effective	Possibly among the most effective
Among the intermediate (superior) effective	Possibly among the intermediate (superior) effective
Among the intermediate (inferior) effective	Possibly among the intermediate (inferior) effective
Not clearly different from control	Possibly not clearly different from control

FIG 3. Summary table of comparative effects of topical treatments on patient-important outcomes for controlling AD (eczema). The certainty of the evidence was rated by the GRADE criteria. We categorized the interventions according to a minimally contextualized framework with a target of certainty of a nonzero effect. The effectiveness categories depict the magnitude of effect, whereas the certainty of the evidence shows whether the estimated effect is trustworthy or not. Detailed individual categorizations of all 68 analyzed interventions are presented in the Online Repository at www.jacionline.org. *DLQI,* Dermatology Life Quality Index *RD,* risk difference.

T01139450, NCT01856764, NCT02120833, NCT02404493, NCT02791308, NCT03107611, NCT03386032, NCT03539601, NCT03725722) (n = 34,926) informed effects of topical interventions on AD severity. Throughout the article, the results are presented as measured using SCORAD (0-103, higher score indicates greater severity). TCS group 1 (MD −17.81 [95% CrI −21.32 to −14.30]; high certainty) was the most effective intervention. High-dose tacrolimus (MD −13.05 [95% CrI −15.15 to −10.95]; high-certainty evidence), TCS group 2 (MD −13.82 [95% CrI −18.74 to −8.89]; high-certainty evidence), TCS group 3 (MD −11.57 [95% CrI −14.80 to −8.37]; high-certainty evidence), and TCS group 4 (MD −12.26 [95% CrI −15.02 to −9.50]; high-certainty evidence) were among those with intermediate superior effectiveness. Pimecrolimus (MD −7.23 [95% CrI −8.76 to −5.72]; high-certainty evidence), low-dose tacrolimus (MD −9.38 [95% CrI −11.22 to −7.55]; moderate-certainty evidence), TCS group 5 (MD −8.46 [95% CrI −10.90 to −6.03]; high-certainty evidence), TCS group 6/7 (MD −4.68 [95% CrI −7.10 to −2.29]; moderate-certainty evidence), combination TCS group 5 and pimecrolimus (MD −10.45 [95% CrI −18.64 to −2.20]; moderate-certainty evidence), combination TCS group 5 and tacrolimus (MD −10.22 [95% CrI −19.01 to −1.33]; low-certainty evidence), delgocitinib (MD −9.98 [95% CrI −13.81 to −6.15]; high-certainty evidence), ruxolitinib (MD −4.82 [95% CrI −5.65 to −4.00]; high-certainty evidence), crisaborole (MD −4.89 [95% CrI −8.69 to −1.08]; high-certainty evidence), and difamilast (MD −5.41 [95% CrI −9.12 to −1.68]; high-certainty evidence) were among those with intermediate inferior effectiveness. There was moderate-certainty evidence that topical antibiotics (MD −1.48 [95% CrI −6.77 to 3.81]) were not different from control and low-certainty evidence that prescription moisturizers (MD −1.94 [95% CrI −4.83 to 0.95]) may not be different from control. The Online Repository presents similar findings when using EASI as the outcome measure.

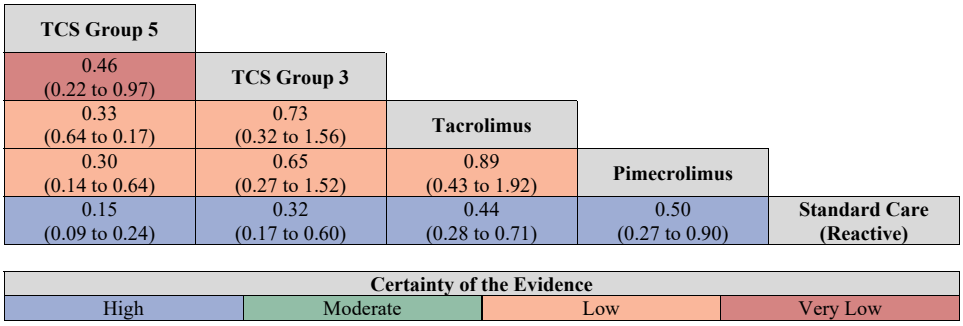

FIG 4. League table for maintenance of remission on AD (eczema) flares. The league table shows the comparative effects of each intervention in the column compared with the intervention of the row, presented as OR and 95% CrI. The color of each cell indicates the certainty of evidence according to the GRADE criteria.

Itch severity

A total of 100 RCTs[55-57,59,60,63-66,69,70,72-74,77,80-82,84,89,90,92-94,97,100,102-104,108,111-113,116,123,124,126-129,131,133,134,137,139,141,143-145,148,150,156-160,162-167,170,173,182-189,192,193,195,198,201,207,209,210,214,217,221-223,227,232,240,242,244] (EUCTR2021-006538-38, NCT00510003, NCT01856764, NCT02404493, NCT03107611, NCT03539601) (n = 19,685) informed effects of topical interventions on itch severity. The results are presented as measured using a numeric rating scale (0-10, higher score indicates greater severity). High-certainty evidence showed that high-dose tacrolimus (MD −2.27 [95% CrI −2.84 to −1.70]), TCS group 2 (MD −3.39 [95% CrI −5.02 to −1.76]), TCS group 3 (MD −2.37 [95% CrI −3.18 to −1.57]), TCS group 4 (MD −2.62 [95% CrI −3.26 to −1.98]), and TCS group 5 (MD −2.09 [95% CrI −2.54 to −1.64]) were among the most effective interventions. Other interventions were of lower effectiveness or certainty.

Sleep disturbance

A total of 15 RCTs[69,84,89,104,127,131,141,148,186,188,201,222,223] (NCT00510003) (n = 3801) informed effects of topical interventions on sleep disturbance. The results are presented as measured using a numeric rating scale (0-10, higher score indicates greater sleep disturbance). High-certainty evidence showed that pimecrolimus (MD −2.13 [95% CrI −3.15 to −1.01]) was the most effective intervention. No trials investigating tacrolimus, crisaborole, delgocitinib, or prescription moisturizers reported on sleep disturbance. Other interventions were of lower effectiveness.

Eczema-related QoL

A total of 33 RCTs[63,87,91,94,96,98,111,121,124,129,143,158,159,161,165,180,185,186,193,209,210,215,218,222,228,236,240,243] (EUCTR2021-006538-38, NCT00120302, NCT03539601) (n = 8170) informed effects of topical interventions on eczema QoL. The results are presented as measured using the Dermatology Life Quality Index (0-30, higher score indicates greater impairment to eczema QoL). High-certainty evidence showed that delgocitinib (MD −7.41 [95% CrI −10.16 to −4.66]) was the most effective intervention. High-dose tacrolimus (MD −3.65 [95% CrI −5.59 to −1.83]; high-certainty evidence), TCS group 4 (MD −5.96 [95% CrI −8.53 to −3.56]; moderate-certainty evidence), and ruxolitinib (MD −4.82 [95% CrI −6.35 to −3.44]; high-certainty evidence) were among those with intermediate superior effectiveness. Other interventions were of lower effectiveness.

AD flares

A total of 44 RCTs[74,84,95,96,100,111,117,124,126,128,129,158,159,163,167,174-179,185,186,189,190,192,200,202,207-209,211,217,228,236,243] (NCT01037881, NCT01053247, NCT01139450, NCT02791308, NCT03539601, NCT03725722) (n = 13,557) informed effects of topical interventions on reducing the number of patients experiencing flares. Moderate- or high-certainty evidence showed that tacrolimus (OR 0.25 [95% CrI 0.10 to 0.54]; risk difference: 70 fewer per 1000 patients [95% CrI 85 to 41 fewer]), pimecrolimus (OR 0.42 [95% CrI 0.29 to 0.57]; risk difference: 53 fewer per 1000 [95% CrI 66 to 39 fewer]), TCS group 5 (OR 0.12 [95% CrI 0.03 to 0.38]; risk difference: 83 fewer per 1000 [95% CrI 92 to 57 fewer]), and prescription moisturizers (OR 0.35 [95% CrI 0.13 to 0.94]; risk difference: 60 fewer per 1000 [95% CrI 82 to 5 fewer]) were among the most effective in decreasing the number of patients experiencing flares. Other interventions were of lower effectiveness or lower certainty.

Adverse events

A total of 130 RCTs[56,62,64,69,71,72,74,75,80,81,84,87-90,92,94-96,98,100,101,105,107,109-111,113,115-117,126-131,133-138,141,142,145-151,153-160,162-168,174,175,177-179,183,185-190,192,194,200,202,204-210,214-216,218,219,222,226-228,234,235,237-239,241-243] (n = 32,200) (EUCTR2021-006538-38, NCT00120302, NCT00510003, NCT00828412, NCT00946478, NCT01037881, NCT01053247, NCT01139450, NCT01428297, NCT01856764, NCT02120833, NCT02404493, NCT02791308, NCT03107611, NCT03386032, NCT03539601, NCT03725722) informed effects of topical interventions on the number of patients experiencing any adverse events, which included any untoward medical occurrence that may or may not be caused by the intervention. High-certainty evidence demonstrated that TCS group 4 (OR 0.67 [95% CrI 0.44 to 0.99]; risk difference: 76 fewer per 1000 [95% CrI 142 to 1 fewer]) and TCS group 5 (OR 0.58 [95% CrI 0.46 to 0.73]; risk difference: 102 fewer per 1000 [95% CrI 138 to 63 fewer]) were among the best in reducing the number of patients experiencing any adverse events. Moderate-certainty evidence demonstrated that the JAK inhibitors (OR 0.83 [95% CrI 0.62 to 1.12]; risk difference: 37 fewer per 1000 [95% CrI 93 fewer to 25 more]), pimecrolimus (OR 1.10 [95%

CrI 0.93 to 1.31]; risk difference: 21 more per 1000 [95% CrI 15 fewer to 59 more]), and tacrolimus (OR 1.14 [95% CrI 0.92 to 1.42]; risk difference: 29 more per 1000 [95% CrI 18 fewer to 79 more]) were not different from control. All other interventions were of lower-certainty evidence.

Adverse event leading to discontinuation

A total of 115 RCTs (n = 30,483)[59,62-64,66,69-76,80,81,83,84,87-90,92-98,100,106,107,111-113,116,119,120,123,127-129,131,137,139,141,145,148,150,153,155,158,160,162-166,168,170,174-179,182,183,185-188,190,192,194,200-203,205,207-210,214-216,218,219,222,226,227,233,235,239,241,243] (EUCTR2021-006538-38, NCT00120302, NCT00510003, NCT00946478, NCT01037881, NCT01053247, NCT01139450, NCT01428297, NCT01856764, NCT02120833, NCT02404493, NCT03539601, NCT03725722) informed effects of topical interventions on the number of patients experiencing adverse events leading to discontinuation. Moderate-certainty evidence demonstrated that TCS group 1 (OR 0.09 [95% CrI 0.02 to 0.33]; risk difference: 25 fewer per 1000 [95% CrI 27 to 18 fewer]) and the JAK inhibitors (OR 0.22 [95% CrI 0.10 to 0.47]; risk difference: 21 fewer per 1000 [95% CrI 25 to 15 fewer]) were among the best in reducing the number of patients experiencing adverse events leading to discontinuation. Moderate- or high-certainty evidence demonstrated that pimecrolimus (OR 0.61 [95% CrI 0.41 to 0.91]; risk difference: 11 fewer per 1000 patients [95% CrI 16 to 3 fewer]), tacrolimus (OR 0.43 [95% CrI 0.30 to 0.62]; risk difference: 15 fewer per 1000 [95% CrI 19 to 10 fewer]), and TCS group 5 (OR 0.32 [95% CrI 0.16 to 0.57]; risk difference: 18 fewer per 1000 [95% CrI 23 to 12 fewer]) were among those with intermediate effect in reducing the number of patients experiencing adverse events leading to discontinuation. Other interventions were of lesser effect or lower-certainty evidence.

Effects of interventions for maintaining remission of AD (long-term control)

In maintaining AD remission (long-term control), 15 RCTs (n = 3029)[67,75,105,106,109,110,147,149,194,204,219,226,233,239] (NCT01428297) informed effects of topical interventions on reducing the number of AD flares by evaluating proactive versus reactive topical therapy (Fig 4). Moderate-certainty evidence that tacrolimus (OR 0.44 [95% CrI 0.28 to 0.71]; risk difference: 202 fewer per 1000 patients [95% CrI 305 to 84 fewer]), pimecrolimus (OR 0.50 [95% CrI 0.27 to 0.90]; risk difference: 171 fewer per 1000 [95% CrI 312 to 25 fewer]), TCS group 3 (OR 0.32 [95% CrI 0.17 to 0.60]; risk difference: 276 fewer per 1000 [95% CrI 398 to 126 fewer]), and TCS group 5 (OR 0.15 [95% CrI 0.09 to 0.24]; risk difference: 418 fewer per 1000 [95% CrI 484 to 336 fewer]) decreased the number of flares. No other interventions investigated maintenance of AD remission. The Online Repository presents the associated forest plots.

Other analyses

Other outcomes. Skin infections (bacterial, viral, or overall) as an adverse event were seldom reported and were low- to very low–certainty evidence (see the Online Repository). Similarly, patient-reported measures of AD severity were seldom reported (see the Online Repository). No trials addressed patient anxiety and depression.

Once-daily versus twice-daily application. A total of 9 RCTs[88,156,201,227,245-249] (n = 1257) compared effects of once-daily versus twice-daily application of topical treatments (see the Online Repository). Four studies investigated TCS group 5[227,247-249]; 2 studies investigated TCS groups 2 and 3[156,246]; and 1 study each investigated low-dose tacrolimus,[201] TCS group 1,[88] and TCS group 4.[245] Comparisons of twice-daily application with once-daily application consistently found little to no difference in outcomes among the included interventions, and thus the results are presented across all interventions. There was high-certainty evidence that twice-daily treatment slightly improves AD severity (relative risk [RR] to improve baseline AD severity by 50% 1.06 [95% CI 1.01 to 1.11]; risk difference: 46 more per 1000 patients [95% CI 7 to 85 more]) and has little or no difference on the risk of adverse events (RR 0.95 [95% CI 0.77 to 1.18]; risk difference: 10 fewer per 1000 patients [95% CI 45 fewer to 35 more]). There was moderate-certainty evidence that twice-daily treatment probably slightly improves itch severity (MD −0.45 [95% CI −0.79 to −0.11]) and sleep disturbance (MD −0.90 [95% CI −1.35 to −0.45]). There was low-certainty evidence that twice-daily treatment may have little or no difference on AD flares (RR 0.41 [95% CI 0.18 to 0.92]; risk difference: 46 fewer per 1000 patients [95% CI 64 to 6 fewer]) or adverse events leading to discontinuation (RR 1.60 [95% CI 0.65 to 3.91]; risk difference: 8 more per 1000 patients [95% CI 5 fewer to 40 more]). These differences may be too small to be important to patients.

Subgroup and sensitivity analyses

Overall, subgroup analyses and (network) meta-regression showed no differential treatment effects according to age, risk of bias, study duration, or baseline severity (see the Online Repository). The findings were robust to sensitivity analyses regardless of whether Bayesian or frequentist analytic approaches were used, whether RCTs were published or unpublished/from conference abstracts, whether mean and SD were estimated using median and IQR, considering the harms of JAK inhibitors as a class, considering topical antibiotics as a class, using either a 3- or 4-level classification for TCS, or no grouping whatsoever when defining nodes (see the Online Repository). The use of simplified classifications for TCS, however, led to the loss of multiple nodes, studies, number of patients, and connections in the network, and these classifications were therefore less informative compared to the main analysis.

DISCUSSION

This systematic review and NMA including 43,123 participants with primarily mild-to-moderate AD in 219 RCTs evaluating 68 interventions provides comprehensive comparative evidence addressing topical treatments for AD. We found that TCS group 1 was among the best in improving AD severity; tacrolimus (high dose) and TCS groups 2 to 5 were among the best in improving itch severity; pimecrolimus was among the best in improving sleep disturbance; and delgocitinib was among the best in improving eczema-related QoL. Topical antibiotics alone or in combination with topical treatments were among the least effective and lowest in certainty across all outcomes. There was

little to no difference in the effectiveness of once-daily versus twice-daily topical treatments. Patients may prefer once-daily treatment over twice-daily treatment as it is a simpler regimen,[22] and it may be safer. To achieve AD control, pimecrolimus improved the greatest number of patient-important outcomes. To maintain long-term AD control, TCS group 5 ranked among the best, followed by topical tacrolimus and pimecrolimus.

In terms of implications for clinical practice, our findings of increasing efficacy in improving eczema severity from the lowest-potency (TCS group 6/7) to the highest-potency (TCS Group 1) TCS, while broadly consistent with their classified potency in vasoconstrictor assays, differ by providing a framework for clinical practice of 4 main classes of topical treatment effectiveness (Fig 3), based on the clinical evidence rather than solely *in vitro* assays, and applicable to interventions beyond TCS. The optimal way of classifying TCS, which likely represents a continuum of potency (see the Online Repository), has been debated, and it has often been thought that clinicians should use one or more systems in a mutually exclusive manner. A potentially important message of our findings is that the 7-class system (see the Online Repository) is likely optimal to statistically combine and fully synthesize the totality of the evidence, but that in clinical practice, 4 comparative effectiveness categories (Fig 3) can be employed instead. Hence, both systems are necessary to use the best evidence to improve patient AD outcomes. These findings may help reconcile historically opposing views on TCS classification.

Our findings also demonstrate variability in impact of intervention potency across outcomes. For example, pimecrolimus proved intermediate inferior for eczema severity, similar in rank to low-dose (0.03%) tacrolimus or delgocitinib and in between TCS group 5 and TCS group 6/7, but just above the least effective in rank for eczema QoL.[250] Conversely, delgocitinib is intermediate in rank for improving eczema severity, but among the most effective for improving eczema QoL. These findings suggest that treatment potency can vary by outcome. The best topical treatments for AD, consistent with findings from NMAs of treatments for other diseases,[42,251] will importantly improve multiple patient-important outcomes and align with patient values and preferences.[22]

While, at face value, some between-group differences may appear small in relation to established minimally important differences (MIDs),[252,253] we have previously shown that misinterpreting between-group changes in this way will misleadingly lead one to infer that effects smaller than MIDs result in no patients benefiting, when, in fact, even if the MD between a treatment and a comparator (or control) is appreciably less than the MID, the treatment may have an important impact for many patients.[253]

More broadly, our findings that different classes of interventions improve different AD outcomes illustrate that AD is driven by multiple different inflammatory pathways. This is also true of other allergic diseases.[254] The small effects and low-certainty evidence for antibiotics suggest the strategy's limitations to achieve optimal AD outcomes. Nevertheless, the findings must be contextualized among patient values and preferences[22] and health care implementation considerations, such as health inequalities that may be linked to sociodemographic factors, including ethnicity.[255-261] Overall, our findings provide patients, clinicians, and policymakers with evidence-based comparative estimates to inform optimal decision making.

Our findings' implications for future research include providing systematic comparative effectiveness data to plan future studies and new treatment approaches. We identified limitations of the available topical treatment evidence that could have important implications for clinicians, researchers, policymakers, and other stakeholders. First, by addressing the historical lack of comparative effects data,[9,10] our findings could inform regulatory/licensing bodies and researchers regarding target treatment effects and optimal comparators (eg, TCS groups 4 or 5, pimecrolimus, or tacrolimus) to use when developing new treatments for AD. The question to address, including for emerging interventions, is not whether the drug works in principle compared to suboptimal care (ie, placebo alone), but rather whether the interventions provide any added benefits over existing standard care. Given that the comparative effectiveness among TCS groups 2, 3, and 4, with or without combination with topical calcineurin inhibitors (or other agents), is least certain and addresses the fewest patient-important outcomes, future research should address these important gaps. Second, some study durations were too short to adequately address patient-important long-term outcomes, such as those associated with the uncertain risk of malignancy, major cardiovascular events, serious infections, and death associated with JAK inhibitors. We and others have shown no increase in patient-important risks for topical steroids and topical calcineurin inhibitors in associated systematic reviews.[6,8,21] Future studies should address interventions as long-term treatment strategies. Third, studies frequently described and reported flares of AD as an adverse safety event, rather than as an outcome of efficacy (long-term disease control). It may be helpful for researchers and decision makers to separately evaluate flares and other expected AD complications from the harms of interventions. Fourth, despite their critical importance to patients, few studies addressed patient-reported outcomes (eg, patient-reported AD severity, sleep disturbance, eczema QoL). Many regulatory bodies still focus on clinician assessments of AD severity—not the patient perspective—for drug approval. Given the critical importance of the patient perspective to clinical decision making,[17,262,263] regulators, study trialists, and clinicians should focus on patient-important effects for patient-important outcomes and eschew historical overemphasis on a clinician's snapshot and superficial determination (eg, investigator's global assessment) of a patient's multifaceted experience with AD (eg, Patient-Oriented Eczema Measure, itch, sleep, QoL),[264,265] especially among "old" drug molecules. Fifth, studies investigating the long-term usage of high-potency TCS are lacking. Although this reflects current clinical practice, further investigation of higher-potency TCS may improve the evidence pertaining to the maintenance of AD remission. Sixth, in addressing health inequities that may be linked to socioeconomic factors, including ethnicity and skin color, future research must remain vigilant that it is serving the whole population of individuals with AD, not just segments thereof.

Strengths of this review include its comprehensive search encompassing all eligible published and unpublished studies. To the best of our knowledge, this review, along with our associated NMA investigating all systemic interventions for AD, is the first comprehensive synthesis comparing all the available interventions for AD. Our review also involved a multidisciplinary guideline panel including content experts, frontline clinicians, and patients with AD or their caregivers.[17] The panel defined the

clinical questions, selected patient-important outcomes, and selected the subgroups for analysis, ensuring the applicability to this review clinical practice. Furthermore, we interpreted the results using standardized approaches (GRADE and Instrument for assessing the Credibility of Effect Modification Analyses) and fully met requirements for using GRADE.[266]

Potential limitations of this review include the large nature of this review, incorporating more than 55 years of trials, meaning that it is possible that some trials, primarily very early and small studies of TCS, may have been missed. We are confident, however, that the included evidence (43,123 patients in 219 RCTs) represents the large majority of the available evidence, which we ensured by seeking unpublished data from pharmaceutical registries and company websites and cross-referencing previous systematic reviews of individual (sub)classes of the medications addressed here.[6-8,267] Second, we excluded studies with split-body designs, which could contain relevant information. As AD is recognized as a systemic, rather than purely cutaneous, disease, we believe that split-body designs have significant limitations in sample size, in maintaining blinding, and in adequately assessing efficacy and adverse events (eg, it may be difficult to attribute a systemic adverse event to a single intervention when a patient is using multiple agents). Similarly, for crossover trials, we mitigated risks for carryover and period biases per Cochrane guidance[11] by including data from the first period at the potential cost of some information loss from subsequent periods. This potential limitation is likely mitigated by the large number of included patients and RCTs.

This systematic review and NMA, representing a rigorous synthesis of the cumulative knowledge addressing topical AD treatments to date, assesses efficacy and safety data of treatments and categorizes them according to certainty (quality) of evidence to inform optimal selection of topical treatments for managing AD. Considering that AD is the most common chronic inflammatory skin disorder globally, our findings have important and immediate implications for achieving optimal AD outcomes.

DISCLOSURE STATEMENT

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Clinical implications: In managing AD, moderate-potency TCS, tacrolimus, and pimecrolimus are among most effective in improving and maintaining multiple patient-important outcomes. Other agents improve fewer outcomes, with less effect or lower certainty.

REFERENCES

1. Schneider L, Tilles S, Lio P, Boguniewicz M, Beck L, LeBovidge J, et al. Atopic dermatitis: a practice parameter update 2012. J Allergy Clin Immunol 2013;131:295-9.e1-27.
2. Boguniewicz M, Fonacier L, Guttman-Yassky E, Ong PY, Silverberg J, Farrar JR. Atopic dermatitis yardstick: practical recommendations for an evolving therapeutic landscape. Ann Allergy Asthma Immunol 2018;120:10-22.e2.
3. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. Lancet 2020;396:345-60.
4. Wheeler KE, Chu DK, Schneider L. What parents should know about atopic dermatitis. JAMA Pediatr 2022;176:1156.
5. Tang TS, Bieber T, Williams HC. Are the concepts of induction of remission and treatment of subclinical inflammation in atopic dermatitis clinically useful? J Allergy Clin Immunol 2014;133:1615-25.e1.
6. Axon E, Chalmers JR, Santer M, Ridd MJ, Lawton S, Langan SM, et al. Safety of topical corticosteroids in atopic eczema: an umbrella review. BMJ Open 2021;11:e046476.
7. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. Health Technol Assess 2000;4:1-191.
8. Lax SJ, Harvey J, Axon E, Howells L, Santer M, Ridd MJ, et al. Strategies for using topical corticosteroids in children and adults with eczema. Cochrane Database Syst Rev 2022;3:CD013356.
9. Wilkes SR, Nankervis H, Tavernier E, Maruani A, Williams HC. How clinically relevant are treatment comparisons of topical calcineurin inhibitor trials for atopic eczema? J Invest Dermatol 2016;136:1944-9.
10. Williams HC. New topical treatments for atopic dermatitis: active comparators are needed. J Am Acad Dermatol 2021;85:1065-6.
11. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane handbook for systematic reviews of interventions version 6.2 (updated February 2021). Cochrane; 2021. Available at: www.training.cochrane.org/handbook. Accessed March 23, 2023.
12. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
13. Chu DK, Golden DBK, Guyatt GH. Translating evidence to optimize patient care using GRADE. J Allergy Clin Immunol Pract 2021;9:4221-30.

14. Izcovich A, Chu DK, Mustafa RA, Guyatt G, Brignardello-Petersen R. A guide and pragmatic considerations for applying GRADE to network meta-analysis. BMJ 2023;381:e074495.
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. J Clin Epidemiol 2021;134:178-89.
16. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777-84.
17. Agarwal A, Chen L, Capozza K, Roberts A, Golden DBK, Shaker MS, et al. Trustworthy patient-centered guidelines: insights from atopic dermatitis and a proposal for the future. J Allergy Clin Immunol Pract 2022;10:2875-7.
18. Bakaa L, Pernica JM, Couban RJ, Tackett KJ, Burkhart CN, Leins L, et al. Bleach baths for atopic dermatitis: a systematic review and meta-analysis including unpublished data, Bayesian interpretation, and GRADE. Ann Allergy Asthma Immunol 2022;128:660-8.e9.
19. Oykhman P, Dookie J, Al-Rammahy H, de Benedetto A, Asiniwasis RN, LeBovidge J, et al. Dietary elimination for the treatment of atopic dermatitis: a systematic review and meta-analysis. J Allergy Clin Immunol Pract 2022;10:2657-66.e8.
20. Yepes-Nunez JJ, Guyatt GH, Gomez-Escobar LG, Perez-Herrera LC, Chu AWL, Ceccaci R, et al. Allergen immunotherapy for atopic dermatitis: systematic review and meta-analysis of benefits and harms. J Allergy Clin Immunol 2023;151:147-58.
21. Devasenapathy N, Chu A, Wong M, Srivastava A, Ceccacci R, Lin C, et al. Cancer risk with topical calcineurin inhibitors, pimecrolimus and tacrolimus, for atopic dermatitis: a systematic review and meta-analysis. Lancet Child Adolesc Health 2023;7:13-25.
22. Maleki-Yazdi KA, Heen AF, Zhao IX, Guyatt GH, Suzumura EA, Makhdami N, et al. Values and preferences of patients and caregivers regarding treatment of atopic dermatitis (eczema): a systematic review. JAMA Dermatol 2023;159:320-30.
23. Draelos ZD. An evaluation of prescription device moisturizers. J Cosmet Dermatol 2009;8:40-3.
24. Hebert AA, Rippke F, Weber TM, Nicol NH. Efficacy of nonprescription moisturizers for atopic dermatitis: an updated review of clinical evidence. Am J Clin Dermatol 2020;21:641-55.
25. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. J Clin Epidemiol 2011;64:1277-82.
26. Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. J Clin Epidemiol 2006;59:7-10.
27. Weir CJ, Butcher I, Assi V, Lewis SC, Murray GD, Langhorne P, et al. Dealing with missing standard deviation and mean values in meta-analysis of continuous outcomes: a systematic review. BMC Med Res Methodol 2018;18:25.
28. Shi J, Luo D, Weng H, Zeng XT, Lin L, Chu H, et al. Optimally estimating the sample standard deviation from the five-number summary. Res Synth Methods 2020;11:641-54.
29. Oykhman P, Paramo FA, Bousquet J, Kennedy DW, Brignardello-Petersen R, Chu DK. Comparative efficacy and safety of monoclonal antibodies and aspirin desensitization for chronic rhinosinusitis with nasal polyposis: a systematic review and network meta-analysis. J Allergy Clin Immunol 2022;149:1286-95.
30. Guyatt GH, Thorlund K, Oxman AD, Walter SD, Patrick D, Furukawa TA, et al. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles—continuous outcomes. J Clin Epidemiol 2013;66:173-83.
31. Thorlund K, Walter SD, Johnston BC, Furukawa TA, Guyatt GH. Pooling health-related quality of life outcomes in meta-analysis—a tutorial and review of methods for enhancing interpretability. Res Synth Methods 2011;2:188-203.
32. Schmitt J, Langan S, Deckert S, Svensson A, von Kobyletzki L, Thomas K, et al. Assessment of clinical signs of atopic dermatitis: a systematic review and recommendation. J Allergy Clin Immunol 2013;132:1337-47.
33. Schmitt J, Spuls PI, Thomas KS, Simpson E, Furue M, Deckert S, et al. The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. J Allergy Clin Immunol 2014;134:800-7.
34. Williams HC, Schmitt J, Thomas KS, Spuls PI, Simpson EL, Apfelbacher CJ, et al. The HOME Core outcome set for clinical trials of atopic dermatitis. J Allergy Clin Immunol 2022;149:1899-911.
35. Barbarot S, Rogers NK, Abuabara K, Aubert H, Chalmers J, Flohr C, et al. Strategies used for measuring long-term control in atopic dermatitis trials: a systematic review. J Am Acad Dermatol 2016;75:1038-44.
36. Langan SM, Thomas KS, Williams HC. What is meant by a "flare" in atopic dermatitis? A systematic review and proposal. Arch Dermatol 2006;142:1190-6.
37. Thomas KS, Stuart B, O'Leary CJ, Schmitt J, Paul C, Williams HC, et al. Validation of treatment escalation as a definition of atopic eczema flares. PLoS One 2015;10:e0124770.
38. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
39. Goldstein BG, Goldstein AO. Comparison of representative topical corticosteroid preparations (classified according to the United States system). Waltham, MA: UpToDate. Available at: https://www.uptodate.com/contents/topical-corticosteroids-use-and-adverse-effects. Accessed January 9, 2023.
40. US Food & Drug Administration. Guidance for industry: topical dermatological corticosteroids: in vivo bioequivalence. 1995. Available at: https://www.fda.gov/media/70931/download. Accessed January 9, 2023.
41. Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol 2013;66:158-72.
42. Siemieniuk RA, Bartoszko JJ, Zeraatkar D, Kum E, Qasim A, Martinez JPD, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ 2020;370:m2980.
43. Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JP. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Stat Med 2015;34:984-98.
44. Bartoszko JJ, Siemieniuk RAC, Kum E, Qasim A, Zeraatkar D, Martinez JPD, et al. Prophylaxis against covid-19: living systematic review and network meta-analysis. BMJ 2021;373:n949.
45. Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. J Clin Epidemiol 2020;119:126-35.
46. Brignardello-Petersen R, Mustafa RA, Siemieniuk RAC, Murad MH, Agoritsas T, Izcovich A, et al. GRADE approach to rate the certainty from a network meta-analysis: addressing incoherence. J Clin Epidemiol 2019;108:77-85.
47. Brignardello-Petersen R, Florez ID, Izcovich A, Santesso N, Hazlewood G, Alhazanni W, et al. GRADE approach to drawing conclusions from a network meta-analysis using a minimally contextualised framework. BMJ 2020;371:m3900.
48. Brignardello-Petersen R, Guyatt GH, Mustafa RA, Chu DK, Hultcrantz M, Schunemann HJ, et al. GRADE guidelines 33: addressing imprecision in a network meta-analysis. J Clin Epidemiol 2021;139:49-56.
49. Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerg B, et al. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. J Clin Epidemiol 2018;93:36-44.
50. Brignardello-Petersen R, Murad MH, Walter SD, McLeod S, Carrasco-Labra A, Rochwerg B, et al. GRADE approach to rate the certainty from a network meta-analysis: avoiding spurious judgments of imprecision in sparse networks. J Clin Epidemiol 2019;105:60-7.
51. Chu DK, Brignardello-Petersen R, Guyatt GH, Ricci C, Genuneit J. Method's corner: allergist's guide to network meta-analysis. Pediatr Allergy Immunol 2022;33:e13609.
52. Zeng L, Brignardello-Petersen R, Hultcrantz M, Siemieniuk RAC, Santesso N, Traversy G, et al. GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings. J Clin Epidemiol 2021;137:163-75.
53. Trinquart L, Attiche N, Bafeta A, Porcher R, Ravaud P. Uncertainty in treatment rankings: reanalysis of network meta-analyses of randomized trials. Ann Intern Med 2016;164:666-73.
54. Schandelmaier S, Briel M, Varadhan R, Schmid CH, Devasenapathy N, Hayward RA, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. CMAJ 2020;192:E901-6.
55. Abbasi S, Kamalinejad M, Babaie D, Shams S, Sadr Z, Gheysari M, et al. A new topical treatment of atopic dermatitis in pediatric patients based on Ficus carica L. (Fig): A randomized, placebo-controlled clinical trial. Complement Ther Med 2017;35:85-91.
56. Abramovits W, Oquendo M. Hydrocortisone butyrate 0.1% lipocream in pediatric patients with atopic dermatitis. Skinmed 2010;8:72-9.
57. Amerio PL, Biggio P, Bossi G, Cainelli T, Cappugi P, Cerimele D, et al. Mometasone furoato 0.1% in monoapplicazione giornaliera nella dermatite allergica da contatto e nella dermatite atopica: Studio controlato verso betametasone valerato. Dermatol Clin 1998;18:255-60.
58. Antiga E, Volpi W, Torchia D, Fabbri P, Caproni M. Effects of tacrolimus ointment on Toll-like receptors in atopic dermatitis. Clin Exp Dermatol 2011;36:235-41.
59. Archer CB, MacDonald DM. Treatment of atopic dermatitis with salbutamol. Clin Exp Dermatol 1987;12:323-5.
60. Arenberger P, Arenbergerova M, Drozenova H, Hladikova M, Holcova S. Effect of topical heparin and levomenol on atopic dermatitis: a randomized four-arm,

placebo-controlled, double-blind clinical study. J Eur Acad Dermatol Venereol 2011;25:688-94.
61. Arnold W, Van Der Meer Y. Does adding of chlorhexidine 0.5% to topical corticosteroids enhance efficacy in the treatment of atopic dermatitis and inverse psoriasis? Results of a double-blind study. Nederlands Tijdschrift voor Dermatologie en Venereologie 2005;15:340-2.
62. Bangert C, Strober BE, Cork M, Ortonne JP, Luger T, Bieber T, et al. Clinical and cytological effects of pimecrolimus cream 1% after resolution of active atopic dermatitis lesions by topical corticosteroids: a randomized controlled trial. Dermatology 2011;222:36-48.
63. Beattie PE, Lewis-Jones MS. A pilot study on the use of wet wraps in infants with moderate atopic eczema. Clin Exp Dermatol 2004;29:348-53.
64. Belloni G, Pinelli S, Veraldi S. A randomised, double-blind, vehicle-controlled study to evaluate the efficacy and safety of MAS063D (Atopiclair) in the treatment of mild to moderate atopic dermatitis. Eur J Dermatol 2005;15:31-6.
65. Berardesca E, Barbareschi M, Veraldi S, Pimpinelli N. Evaluation of efficacy of a skin lipid mixture in patients with irritant contact dermatitis, allergic contact dermatitis or atopic dermatitis: a multicenter study. Contact Dermatitis 2001; 45:280-5.
66. Berberian BJ, Breneman DL, Drake LA, Gratton D, Raimir SS, Phillips S, et al. The addition of topical doxepin to corticosteroid therapy: an improved treatment regimen for atopic dermatitis. Int J Dermatol 1999;38:145-8.
67. Berth-Jones J, Damstra RJ, Golsch S, Livden JK, Van Hooteghem O, Allegra F, et al. Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. BMJ 2003;326:1367.
68. Beutner K, Jones T, Bucko A, Loss R. A randomized, double-blind, vehicle-controlled, multi-center study to evaluate the safety and efficacy of topically applied AN0128 cream, 1% for the treatment of mild to moderate atopic dermatitis. Abstract P717. American Academy of Dermatology 65th Annual Meeting February 2-6, 2007. J Am Acad Dermatol 2007;56:AB72.
69. Bieber T, Vick K, Folster-Holst R, Belloni-Fortina A, Stadtler G, Worm M, et al. Efficacy and safety of methylprednisolone aceponate ointment 0.1% compared to tacrolimus 0.03% in children and adolescents with an acute flare of severe atopic dermatitis. Allergy 2007;62:184-9.
70. Bissonnette R, Chen G, Bolduc C, Maari C, Lyle M, Tang L, et al. Efficacy and safety of topical WBI-1001 in the treatment of atopic dermatitis: results from a phase 2A, randomized, placebo-controlled clinical trial. Arch Dermatol 2010; 146:446-9.
71. Bissonnette R, Papp KA, Poulin Y, Gooderham M, Raman M, Mallbris L, et al. Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. Br J Dermatol 2016;175:902-11.
72. Bissonnette R, Poulin Y, Zhou Y, Tan J, Hong HC, Webster J, et al. Efficacy and safety of topical WBI-1001 in patients with mild to severe atopic dermatitis: results from a 12-week, multicentre, randomized, placebo-controlled double-blind trial. Br J Dermatol 2012;166:853-60.
73. Boguniewicz M, Fiedler VC, Raimer S, Lawrence ID, Leung DY, Hanifin JM. A randomized, vehicle-controlled trial of tacrolimus ointment for treatment of atopic dermatitis in children. Pediatric Tacrolimus Study Group. J Allergy Clin Immunol 1998;102:637-44.
74. Boguniewicz M, Zeichner JA, Eichenfield LF, Hebert AA, Jarratt M, Lucky AW, et al. MAS063DP is effective monotherapy for mild to moderate atopic dermatitis in infants and children: a multicenter, randomized, vehicle-controlled study. J Pediatr 2008;152:854-9.
75. Breneman D, Fleischer AB Jr, Abramovits W, Zeichner J, Gold MH, Kirsner RS, et al. Intermittent therapy for flare prevention and long-term disease control in stabilized atopic dermatitis: a randomized comparison of 3-times-weekly applications of tacrolimus ointment versus vehicle. J Am Acad Dermatol 2008;58:990-9.
76. Breneman D, Fleischer AB Jr, Kaplan D, Lebwohl M, Miller B, Pariser D, et al. Clobetasol propionate 0.05% lotion in the treatment of moderate to severe atopic dermatitis: a randomized evaluation versus clobetasol propionate emollient cream. J Drugs Dermatol 2005;4:330-6.
77. Buhles N. Non-steroidal topical therapy of atopic dermatitis. Nichtsteroidale Lokaltherapie des endogenen Ekzems 1992;18:112.
78. Canpolat F, Erkocoglu M, Tezer H, Kocabas CN, Kandi B. Hydrocortisone acetate alone or combined with mupirocin for atopic dermatitis in infants under two years of age—a randomized double blind pilot trial. Eur Rev Med Pharmacol Sci 2012;16:1989-93.
79. Caproni M, Torchia D, Antiga E, Terranova M, Volpi W, del Bianco E, et al. The comparative effects of tacrolimus and hydrocortisone in adult atopic dermatitis: an immunohistochemical study. Br J Dermatol 2007;156:312-9.
80. Cato A, Swinehart JM, Griffin EI, Sutton L, Kaplan AS. Azone enhances clinical effectiveness of an optimized formulation of triamcinolone acetonide in atopic dermatitis. Int J Dermatol 2001;40:232-6.
81. Chapman MS, Schachner LA, Breneman D, Boguniewicz M, Gold MH, Shull T, et al. Tacrolimus ointment 0.03% shows efficacy and safety in pediatric and adult patients with mild to moderate atopic dermatitis. J Am Acad Dermatol 2005;53: S177-85.
82. Charney P, Leibsohn E. Atopic dermatitis: treatment with topical betamethasone dipropionate. Cutis 1975;16:739-41.
83. Clement E, Lucas T. Fluocinolone acetonide solution in the therapy of atopic dermatitis. Cutis 1967;3:377-8.
84. Czarnowicki T, Dohlman AB, Malik K, Antonini D, Bissonnette R, Chan TC, et al. Effect of short-term liver X receptor activation on epidermal barrier features in mild to moderate atopic dermatitis: a randomized controlled trial. Ann Allergy Asthma Immunol 2018;120:631-40.e11.
85. Dahnhardt D, Bastian M, Dahnhardt-Pfeiffer S, Buchner M, Folster-Holst R. Comparing the effects of proactive treatment with tacrolimus ointment and mometasone furoate on the epidermal barrier structure and ceramide levels of patients with atopic dermatitis. J Dermatolog Treat 2021;32:721-9.
86. Das SP, Mowla MR, Baura DP, Jahangir SM, Khan I. Efficacy and safety of 0.1% tacrolimus ointment versus 0.05% clobetasone butyrate ointment in childhood atopic dermatitis. Forum Dermatologicum 2020;6:33-9.
87. De Belilovsky C, Roo-Rodriguez E, Baudouin C, Menu F, Chadoutaud B, Msika P. Natural peroxisome proliferator-activated receptor-alpha agonist cream demonstrates similar therapeutic response to topical steroids in atopic dermatitis. J Dermatolog Treat 2011;22:359-65.
88. Del Rosso JQ, Bhambri S. Daily application of fluocinonide 0.1% cream for the treatment of atopic dermatitis. J Clin Aesthet Dermatol 2009;2:24-32.
89. Doss N, Kamoun MR, Dubertret L, Cambazard F, Remitz A, Lahfa M, et al. Efficacy of tacrolimus 0.03% ointment as second-line treatment for children with moderate-to-severe atopic dermatitis: evidence from a randomized, double-blind non-inferiority trial vs. fluticasone 0.005% ointment. Pediatr Allergy Immunol 2010;21:321-9.
90. Doss N, Reitamo S, Dubertret L, Fekete GL, Kamoun MR, Lahfa M, et al. Superiority of tacrolimus 0.1% ointment compared with fluticasone 0.005% in adults with moderate to severe atopic dermatitis of the face: results from a randomized, double-blind trial. Br J Dermatol 2009;161:427-34.
91. Dou X, Liu LL, Xie ZQ, Chen LJ, Li L, Feng SY, et al. The impact of tacrolimus ointment on health-related quality of life of Chinese adult and pediatric patients with atopic dermatitis. J Clin Dermatol 2006;35:50-2.
92. Draelos Z, Nayak A, Pariser D, Shupack JL, Chon K, Abrams B, et al. Pharmacokinetics of topical calcineurin inhibitors in adult atopic dermatitis: a randomized, investigator-blind comparison. J Am Acad Dermatol 2005;53:602-9.
93. Drake LA, Fallon JD, Sober A. Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. The Doxepin Study Group. J Am Acad Dermatol 1994;31:613-6.
94. Eichenfield LF, Lucky AW, Boguniewicz M, Langley RG, Cherill R, Marshall K, et al. Safety and efficacy of pimecrolimus (ASM 981) cream 1% in the treatment of mild and moderate atopic dermatitis in children and adolescents. J Am Acad Dermatol 2002;46:495-504.
95. Eichenfield LF, Miller BH. Cutivate Lotion Study Group. Two randomized, double-blind, placebo-controlled studies of fluticasone propionate lotion 0.05% for the treatment of atopic dermatitis in subjects from 3 months of age. J Am Acad Dermatol 2006;54:715-7.
96. Foelster Holst R, Reitamo S, Yankova R, Worm M, Kadurina M, Thaci K, et al. The novel protease inhibitor SRD441 ointment is not effective in the treatment of adult subjects with atopic dermatitis: results of a randomized, vehicle-controlled study. Allergy 2010;65:1594-9.
97. Fowler J, Johnson A, Chen M, Abrams K. Improvement in pruritus in children with atopic dermatitis using pimecrolimus cream 1. Cutis 2007;79:65-72.
98. Francis NA, Ridd MJ, Thomas-Jones E, Shepherd V, Butler CC, Hood K, et al. A randomised placebo-controlled trial of oral and topical antibiotics for children with clinically infected eczema in the community: the ChildRen with Eczema, Antibiotic Management (CREAM) study. Health Technol Assess 2016;20(i-xxiv):1-84.
99. Fukuie T, Hirakawa S, Narita M, Nomura I, Matsumoto K, Tokura Y, et al. Potential preventive effects of proactive therapy on sensitization in moderate to severe childhood atopic dermatitis: a randomized, investigator-blinded, controlled study. J Dermatol 2016;43:1283-92.
100. Furue M, Kitahara Y, Akama H, Hojo S, Hayashi N, Nakagawa H, et al. Safety and efficacy of topical E6005, a phosphodiesterase 4 inhibitor, in Japanese adult patients with atopic dermatitis: results of a randomized, vehicle-controlled, multicenter clinical trial. J Dermatol 2014;41:577-85.
101. Gao Y, Li Y, Tan Y, Liu W, Zou Y, Ouaddi S, et al. Novel cannabidiol aspartame combination treatment (JW-100) significantly reduces ISGA score in atopic dermatitis: results from a randomized double-blinded placebo-controlled interventional study. J Cosmet Dermatol 2021;21:1647-50.

102. Gehring W, Gloor M. Treatment of the atopic dermatitis with a water-in-oil emulsion with or without the addition of hydrocortisone—results of a controlled double-blind randomized study using clinical evaluation and bioengineering methods. Zeitschrift fur Hautkrankheiten 1996;71:554-60.
103. Gelmetti C, Grimalt R, Del Campo G, Caputo R. Tolerability and efficacy of topical budesonide in the treatment of atopic dermatitis in pediatric age. Giornale Italiano di Dermatologia e Venereologia 1994;129:XIII-XVII.
104. GlaxoSmithKline. Randomised, double-blind, placebo-controlled study of topical GW842470X formulation in adult patients with moderate atopic dermatitis. Available at: https://www.clinicaltrialsregister.eu/ctr-search/rest/download/result/attachment/2005-005430-12/1/14677. Accessed December 23, 2022.
105. Glazenburg EJ, Wolkerstorfer A, Gerretsen AL, Mulder PG, Oranje AP. Efficacy and safety of fluticasone propionate 0.005% ointment in the long-term maintenance treatment of children with atopic dermatitis: differences between boys and girls? Pediatr Allergy Immunol 2009;20:59-66.
106. Gollnick H, Kaufmann R, Stough D, Heikkila H, Andriano K, Grinienko A, et al. Pimecrolimus cream 1% in the long-term management of adult atopic dermatitis: prevention of flare progression. A randomized controlled trial. Br J Dermatol 2008;158:1083-93.
107. Gooderham M, Kircik L, Ziras M, Lee M, Kempers S, Draelos Z, et al. The safety and efficacy of roflumilast cream 0.15% and 0.05% in atopic dermatitis: phase II proof-ofconcept study. Br J Dermatol 2021;184:e69.
108. Granlund H, Remitz A, Kyllonen H, Lauerma AI, Reitamo S. Treatment of lichenified atopic eczema with tacrolimus ointment. Acta Derm Venereol 2001;81:314-5.
109. Handa S, Chandrasengaran A, Kanwar AJ, Mahajan R. Comparing the effectiveness of topical fluticasone 0.05% cream versus topical tacrolimus 0.1% ointment in pediatric atopic dermatitis: A randomized controlled trial. Indian J Paediatr Dermatol 2022;23:111-5.
110. Hanifin J, Gupta AK, Rajagopalan R. Intermittent dosing of fluticasone propionate cream for reducing the risk of relapse in atopic dermatitis patients. Br J Dermatol 2002;147:528-37.
111. Hanifin JM, Ellis CN, Frieden IJ, Folster-Holst R, Stein Gold LF, Secci A, et al. OPA-15406, a novel, topical, nonsteroidal, selective phosphodiesterase-4 (PDE4) inhibitor, in the treatment of adult and adolescent patients with mild to moderate atopic dermatitis (AD): a phase-II randomized, double-blind, placebo-controlled study. J Am Acad Dermatol 2016;75:297-305.
112. Hanifin JM, Ling MR, Langley R, Breneman D, Rafal E. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part I, efficacy. J Am Acad Dermatol 2001;44:S28-38.
113. Hebert AA, Cook-Bolden FE, Basu S, Calvarese B, Trancik RJ. Desonide Hydrogel Study Group. Safety and efficacy of desonide hydrogel 0.05% in pediatric subjects with atopic dermatitis. J Drugs Dermatol 2007;6:175-81.
114. Hindley D, Galloway G, Murray J, Gardener L. A randomised study of "wet wraps" versus conventional treatment for atopic eczema. Arch Dis Child 2006;91:164-8.
115. Ho VC, Gupta A, Kaufmann R, Todd G, Vanaclocha F, Takaoka R, et al. Safety and efficacy of nonsteroid pimecrolimus cream 1% in the treatment of atopic dermatitis in infants. J Pediatr 2003;142:155-62.
116. Hoeger PH, Lee KH, Jautova J, Wohlrab J, Guettner A, Mizutani G, et al. The treatment of facial atopic dermatitis in children who are intolerant of, or dependent on, topical corticosteroids: a randomized, controlled clinical trial. Br J Dermatol 2009;160:415-22.
117. Hofman T, Cranswick N, Kuna P, Boznanski A, Latos T, Gold M, et al. Tacrolimus ointment does not affect the immediate response to vaccination, the generation of immune memory, or humoral and cell-mediated immunity in children. Arch Dis Child 2006;91:905-10.
118. Hoybye S, Balk Moller S, De Cunha Bang F, Ottevanger V, Veien NK. Continuous and intermittent treatment of atopic dermatitis in adults with mometasone furoate versus hydrocortisone 17-butyrate. Curr Ther Res Clin Exp 1991;50:67-72.
119. Hung SH, Lin YT, Chu CY, Lee CC, Liang TC, Yang YH, et al. Staphylococcus colonization in atopic dermatitis treated with fluticasone or tacrolimus with or without antibiotics. Ann Allergy Asthma Immunol 2007;98:51-6.
120. Iraji F, Farhadi S, Faghihi G, Mokhtari F, Basiri A, Jafari-Koshki T, et al. Efficacy of topical azathioprine and betamethasone versus betamethasone-only emollient cream in 2-18 years old patients with moderate-to-severe atopic dermatitis: a randomized controlled trial. Adv Biomed Res 2015;4:228.
121. Janmohamed SR, Oranje AP, Devillers AC, Rizopoulos D, van Praag MCG, Van Gysel D, et al. The proactive wet-wrap method with diluted corticosteroids versus emollients in children with atopic dermatitis: a prospective, randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol 2014;70:1076-82.
122. Jorizzo J, Levy M, Lucky A, Shavin J, Goldberg G, Dunlap F, et al. Multicenter trial for long-term safety and efficacy comparison of 0.05% desonide and 1% hydrocortisone ointments in the treatment of atopic dermatitis in pediatric patients. J Am Acad Dermatol 1995;33:74-7.
123. Kaplan RJ, Daman L, Rosenberg EW, Feigenbaum S. Topical use of caffeine with hydrocortisone in the treatment of atopic dermatitis. Arch Dermatol 1978;114:60-2.
124. Kapp A, Papp K, Bingham A, Folster-Holst R, Ortonne JP, Potter PC, et al. Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. J Allergy Clin Immunol 2002;110:277-84.
125. Katas H, Mohd Amin MCI, Siddique MI, Sarfraz M, Chohan TA, Jamil A. Clinical insights into topically applied multipronged nanoparticles in subjects with atopic dermatitis. Journal of Drug Delivery Science and Technology 2021;65:102744.
126. Kaufmann R, Bieber T, Helgesen AL, Andersen BL, Luger T, Poulin Y, et al. Onset of pruritus relief with pimecrolimus cream 1% in adult patients with atopic dermatitis: a randomized trial. Allergy 2006;61:375-81.
127. Kaufmann R, Folster-Holst R, Hoger P, Thaci D, Loffler H, Staab D, et al. Onset of action of pimecrolimus cream 1% in the treatment of atopic eczema in infants. J Allergy Clin Immunol 2004;114:1183-8.
128. Kempers S, Boguniewicz M, Carter E, Jarratt M, Pariser D, Stewart D, et al. A randomized investigator-blinded study comparing pimecrolimus cream 1% with tacrolimus ointment 0.03% in the treatment of pediatric patients with moderate atopic dermatitis. J Am Acad Dermatol 2004;51:515-25.
129. Kim BS, Howell MD, Sun K, Papp K, Nasir A, Kuligowski ME, et al. Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. J Allergy Clin Immunol 2020;145:572-82.
130. Kimball AB, Gold MH, Zib B, Davis MW. Clobetasol Propionate Emulsion Formulation Foam Phase III Clinical Study Group. Clobetasol propionate emulsion formulation foam 0.05%: review of phase II open-label and phase III randomized controlled trials in steroid-responsive dermatoses in adults and adolescents. J Am Acad Dermatol 2008;59:448-54, 454.e1.
131. Kirkup ME, Birchall NM, Weinberg EG, Helm K, Kennedy CT. Acute and maintenance treatment of atopic dermatitis in children—two comparative studies with fluticasone propionate (0.05%) cream. J Dermatolog Treat 2003;14:141-8.
132. Korting HC, Zienicke H, Braun-Falco O, Bork K, Milbradt R, Nolting S, et al. Modern topical glucocorticoids and anti-infectives for superinfected atopic eczema: do prednicarbate and didecyldimethylammoniumchloride form a rational combination? Infection 1994;22:390-4.
133. Lassus A. Clinical comparison of alclometasone dipropionate cream 0.05% with hydrocortisone butyrate cream 0.1% in the treatment of atopic dermatitis in children. J Int Med Res 1983;11:315-9.
134. Lassus A. Alclometasone dipropionate cream 0.05% versus clobetasone butyrate cream 0.05%. A controlled clinical comparison in the treatment of atopic dermatitis in children. Int J Dermatol 1984;23:565-6.
135. Lawlor F, Black AK, Greaves M. Prednicarbate 0.25% ointment in the treatment of atopic dermatitis: a vehicle-controlled double-blind study. J Dermatolog Treat 1995;6:233-5.
136. Lebrun-Vignes B, Legrain V, Amoric J-C, Taïeb A. Comparative study of efficacy and effect on plasma cortisol levels of micronized desonide cream 0.1 p. 100 versus betamethasone dipropionate cream 0.05 p. 100 in the treatment of childhood atopic dermatitis [in French]. Ann Dermatol Venereol 2000;127:590-5.
137. Lebwohl M. Efficacy and safety of fluticasone propionate ointment, 0.005%, in the treatment of eczema. Cutis 1996;57:62-8.
138. Lebwohl M. A comparison of once-daily application of mometasone furoate 0.1% cream compared with twice-daily hydrocortisone valerate 0.2% cream in pediatric atopic dermatitis patients who failed to respond to hydrocortisone: mometasone furoate study group. Int J Dermatol 1999;38:604-6.
139. Lee HJ, Park CO, Lee JH, Lee KH. The antipruritic effect of topical doxepin cream in patients with atopic dermatitis. Korean Journal of Dermatology 2006;44:309-14.
140. Lee SJ, Woo S, Ahn SH, Lim DK, Hong JY, Park JH, et al. Functional interpretation of metabolomics data as a new method for predicting long-term side effects: treatment of atopic dermatitis in infants. Sci Rep 2014;4:7408.
141. Lee YW, Won CH, Jung K, Nam HJ, Choi G, Park YH, et al. Efficacy and safety of PAC-14028 cream—a novel, topical, nonsteroidal, selective TRPV1 antagonist in patients with mild-to-moderate atopic dermatitis: a phase IIb randomized trial. Br J Dermatol 2019;180:1030-8.
142. Lembo C, Patruno C, de Leonibus C, Panariello L, Lembo S, Ayala F. Topical erythromycin in atopic dermatitis. Annali Italiani di Dermatologia Allergologica Clinica e Sperimentale 2011;65:113-8.
143. Leo HL, Bender BG, Leung SB, Tran ZV, Leung DY. Effect of pimecrolimus cream 1% on skin condition and sleep disturbance in children with atopic dermatitis. J Allergy Clin Immunol 2004;114:691-3.
144. Lessard R, Labelle JL. Evaluation of desoximetasone 0.25% emollient cream in atopic dermatitis. Curr Ther Res Clin Exp 1980;27:247-54.

145. Leung DY, Hanifin JM, Pariser DM, Barber KA, Langley RG, Schlievert PM, et al. Effects of pimecrolimus cream 1% in the treatment of patients with atopic dermatitis who demonstrate a clinical insensitivity to topical corticosteroids: a randomized, multicentre vehicle-controlled trial. Br J Dermatol 2009;161:435-43.
146. Levy AL, Sheehan M, Roberts R. Tacrolimus cream 0.03% is safe and effective in the treatment of mild to moderate atopic dermatitis in adults. J Allergy Clin Immunol 2005;115:S103.
147. Liang Y, Liu L, Wang S, Zhao Z, Ma L, Xiang X, et al. Efficacy and safety of 0.03% tacrolimus ointment in the long-term intermittent maintenance treatment of atopic dermatitis in children: a multicenter randomized controlled clinical trial. Zhonghua Pifuke Zazhi 2019;52:519-24.
148. Lisante TA, Nunez C, Zhang P. Efficacy and safety of an over-the-counter 1% colloidal oatmeal cream in the management of mild to moderate atopic dermatitis in children: a double-blind, randomized, active-controlled study. J Dermatolog Treat 2017;28:659-67.
149. Liu L, Ong G. A randomized, open-label study to evaluate an intermittent dosing regimen of fluticasone propionate 0.05% cream in combination with regular emollient skin care in reducing the risk of relapse in pediatric patients with stabilized atopic dermatitis. J Dermatolog Treat 2018;29:501-9.
150. Liu LL, Gong Y, Zhang JZ, Cal L, Sun QN, Ma DL, et al. A multi-center, randomized, double-blind, parallel, vehicle controlled study on the moderate to severe eczema patients with the treatment of clobetasone butyrate cream. J Clin Dermatol 2014;43:402-5.
151. Liu LL, Ren WJ, Dou X, Wang BX, Ma DL, Li HJ, et al. Pimecrolimus cream 1% for the treatment of atopic dermatitis in Chinese children and adults: a multicenter, randomized, double-blind, parallel-group, vehicle-controlled trial. Zhonghua Pifuke Zazhi 2007;40:34-7.
152. Liu Y, Zhou Q, Dai W, Wang S, Liang Y, Li Y, et al. Is antibiotics prescription needed in infants with topical corticosteroids treatment for moderate-to-severe atopic dermatitis? Dermatol Ther 2020;33:e14215.
153. Luger T, Van Leent EJ, Graeber M, Hedgecock S, Thurston M, Kandra A, et al. SDZ ASM 981: an emerging safe and effective treatment for atopic dermatitis. Br J Dermatol 2001;144:788-94.
154. Luger TA, Lahfa M, Folster-Holst R, Gulliver WP, Allen R, Molloy S, et al. Long-term safety and tolerability of pimecrolimus cream 1% and topical corticosteroids in adults with moderate to severe atopic dermatitis. J Dermatolog Treat 2004;15:169-78.
155. Maloney JM, Morman MR, Stewart DM, Tharp MD, Brown JJ, Rajagopalan R. Clobetasol propionate emollient 0.05% in the treatment of atopic dermatitis. Int J Dermatol 1998;37:142-4.
156. Marchesi E, Rozzoni M, Pini P, Cainelli T. Comparative study of mometasone furoate and betamethasone dipropionate in the treatment of atopic dermatitis. Giornale Italiano di Dermatologia e Venereologia 1994;129:IX-XII.
157. Matheson R, Kempers S, Breneman D, Draelos Z, Johnson CE, Loss R, et al. Hydrocortisone butyrate 0.1% lotion in the treatment of atopic dermatitis in pediatric subjects. J Drugs Dermatol 2008;7:266-71.
158. Meurer M, Eichenfield LF, Ho V, Potter PC, Werfel T, Hultsch T. Addition of pimecrolimus cream 1% to a topical corticosteroid treatment regimen in paediatric patients with severe atopic dermatitis: a randomized, double-blind trial. J Dermatolog Treat 2010;21:157-66.
159. Meurer M, Folster-Holst R, Wozel G, Weidinger G, Junger M, Brautigam M, et al. Pimecrolimus cream in the long-term management of atopic dermatitis in adults: a six-month study. Dermatology 2002;205:271-7.
160. Miller DW, Koch SB, Yentzer BA, Clark AR, O'Neill J, Fountain J, et al. An over-the-counter moisturizer is as clinically effective as, and more cost-effective than, prescription barrier creams in the treatment of children with mild-to-moderate atopic dermatitis: a randomized, controlled trial. J Drugs Dermatol 2011;10:531-7.
161. Mudaliyar VR, Pathak A, Dixit A, Kumar SS. An open-label prospective study to compare the efficacy and safety of topical fluticasone versus tacrolimus in the proactive treatment of atopic dermatitis. Dermatol Pract Concept 2020;10:e2020094.
162. Murrell DF, Calvieri S, Ortonne JP, Ho VC, Weise-Riccardi S, Barbier N, et al. A randomized controlled trial of pimecrolimus cream 1% in adolescents and adults with head and neck atopic dermatitis and intolerant of, or dependent on, topical corticosteroids. Br J Dermatol 2007;157:954-9.
163. Nakagawa H, Nemoto O, Igarashi A, Nagata T. Efficacy and safety of topical JTE-052, a Janus kinase inhibitor, in Japanese adult patients with moderate-to-severe atopic dermatitis: a phase II, multicentre, randomized, vehicle-controlled clinical study. Br J Dermatol 2018;178:424-32.
164. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Kabashima K, Oda M, et al. Delgocitinib ointment in pediatric patients with atopic dermatitis: a phase 3, randomized, double-blind, vehicle-controlled study and a subsequent open-label, long-term study. J Am Acad Dermatol 2021;85:854-62.
165. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Kaino H, Nagata T. Delgocitinib ointment, a topical Janus kinase inhibitor, in adult patients with moderate to severe atopic dermatitis: a phase 3, randomized, double-blind, vehicle-controlled study and an open-label, long-term extension study. J Am Acad Dermatol 2020;82:823-31.
166. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Oda M, Kabashima K, et al. Phase 2 clinical study of delgocitinib ointment in pediatric patients with atopic dermatitis. J Allergy Clin Immunol 2019;144:1575-83.
167. Nakagawa H, Nemoto O, Yamada H, Nagata T, Ninomiya N. Phase 1 studies to assess the safety, tolerability and pharmacokinetics of JTE-052 (a novel Janus kinase inhibitor) ointment in Japanese healthy volunteers and patients with atopic dermatitis. J Dermatol 2018;45:701-9.
168. Nemoto O, Hayashi N, Kitahara Y, Furue M, Hojo S, Nomoto M, et al. Effect of topical phosphodiesterase 4 inhibitor E6005 on Japanese children with atopic dermatitis: results from a randomized, vehicle-controlled exploratory trial. J Dermatol 2016;43:881-7.
169. Neumann E, Amtage D, Bruckner-Tuderman L, Mockenhaupt M. A single-center open-label long-term comparison of tacrolimus ointment and topical corticosteroids for treatment of atopic dermatitis. J Dtsch Dermatol Ges 2008;6:548-53.
170. Niemeyer-van der Kolk T, van der Wall H, Hogendoorn GK, Rijneveld R, Luijten S, van Alewijk D, et al. Pharmacodynamic effects of topical omiganan in patients with mild to moderate atopic dermatitis in a randomized, placebo-controlled, phase II trial. Clin Transl Sci 2020;13:994-1003.
171. Nilsson EJ, Henning CG, Magnusson J. Topical corticosteroids and Staphylococcus aureus in atopic dermatitis. J Am Acad Dermatol 1992;27:29-34.
172. Nolting S. Treatment with topical corticosteroids in severe or resistant dermatoses [in German]. Derm Beruf Umwelt 1985;33:140-4.
173. Nolting S, Glowania HJ, Grunder K, Jablonski K, Donhauser G, Stalleicken D. Therapy of atopical eczema in children. Results of a controlled study with the topical corticosteroid preparations Mometason and Prednikarbat. Der Kinderarzt 1991;22:1689-97.
174. Novartis. Confirmatory study in adult patients with atopic dermatitis. 2005. Available at: https://www.novctrd.com/ctrdweb/trialresult/trialresults/pdf?trialResultId=1999. Accessed December 23, 2022.
175. Novartis. Confirmatory study in pediatric patients with atopic dermatitis. 2005. Available at: https://www.novctrd.com/ctrdweb/trialresult/trialresults/pdf?trialResultId=1997. Accessed December 23, 2022.
176. Novartis A. 6-month, randomized, multicenter, parallel-group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of pimecrolimus 1% cream twice daily vs standard of care in the management of mild to severe atopic dermatitis in adults. 2005. Available at: https://www.novctrd.com/ctrdweb/trialresult/trialresults/pdf?trialResultId=1462. Accessed December 23, 2022.
177. Novartis. A 26-week, randomized, multicenter, parallel-group, double-blind, vehicle-controlled study to evaluate the incidence of atopic dermatitis flares when pimecrolimus cream 1% is used at the first signs and/or symptoms of atopic dermatitis and its safety and tolerability in adults 18 years of age and older. 2005. Available at: https://www.novctrd.com/ctrdweb/trialresult/trialresults/pdf?trialResultId=1954. Accessed December 23, 2022.
178. Ohba F, Matsuki S, Imayama S, Matsuguma K, Hojo S, Nomoto M, et al. Efficacy of a novel phosphodiesterase inhibitor, E6005, in patients with atopic dermatitis: an investigator-blinded, vehicle-controlled study. J Dermatolog Treat 2016;27:467-72.
179. Ono R, Yagi M, Shoji A, Fujita K, Yoshida M, Ports WC, et al. Phase 1 study of crisaborole in Japanese healthy volunteers and patients with atopic dermatitis. J Dermatol 2020;47:25-32.
180. Onumah N, Kircik L. Pimecrolimus cream and tacrolimus ointment in the treatment of atopic dermatitis: a pilot study on patient preference. J Drugs Dermatol 2013;12:1145-8.
181. Otsuki M, Kawashima M, Shibata Y, Nakagawa H, Harada S. Efficacy and safety of FK506 (tacrolimus) ointment in children with atopic dermatitis-phase III double-blinded comparison with vehicle ointment. Journal of Clinical Therapeutics & Medicines 2003;19:569-95.
182. Paller A, Eichenfield LF, Leung DY, Stewart D, Appell M. A 12-week study of tacrolimus ointment for the treatment of atopic dermatitis in pediatric patients. J Am Acad Dermatol 2001;44:S47-57.
183. Paller AS, Lebwohl M, Fleischer AB Jr, Antaya R, Langley RG, Kirsner RS, et al. Tacrolimus ointment is more effective than pimecrolimus cream with a similar safety profile in the treatment of atopic dermatitis: results from 3 randomized, comparative studies. J Am Acad Dermatol 2005;52:810-22.
184. Paller AS, Nimmagadda S, Schachner L, Mallory SB, Kahn T, Willis I, et al. Fluocinolone acetonide 0.01% in peanut oil: therapy for childhood atopic dermatitis, even in patients who are peanut sensitive. J Am Acad Dermatol 2003;48:569-77.
185. Paller AS, Tom WL, Lebwohl MG, Blumenthal RL, Boguniewicz M, Call RS, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal

phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. J Am Acad Dermatol 2016;75:494-503.e6.
186. Papp K, Szepietowski JC, Kircik L, Toth D, Eichenfield LF, Leung DYM, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: results from 2 phase 3, randomized, double-blind studies. J Am Acad Dermatol 2021;85:863-72.
187. Parikh-Das A, Moreira L. A clinical trial to determine the therapeutic benefit of an investigational over-the-counter cream on dry, itchy skin of adults and children with atopic dermatitis. J Am Acad Dermatol 2017;76:AB10.
188. Park CW, Kim BJ, Lee YW, Won C, Park CO, Chung BY, et al. Asivatrep, a TRPV1 antagonist, for the topical treatment of atopic dermatitis: a phase III, randomized, vehicle-controlled study (CAPTAIN-AD). J Allergy Clin Immunol 2021;149:1340-7.
189. Patrizi A, Capitanio B, Neri I, Giacomini F, Sinagra JL, Raone B, et al. A double-blind, randomized, vehicle-controlled clinical study to evaluate the efficacy and safety of MAS063DP (ATOPICLAIR) in the management of atopic dermatitis in paediatric patients. Pediatr Allergy Immunol 2008;19:619-25.
190. Patrizi A, Raone B, Neri I, Gurioli C, Carbonara M, Cassano N, et al. Randomized, controlled, double-blind clinical study evaluating the safety and efficacy of MD2011001 cream in mild-to-moderate atopic dermatitis of the face and neck in children, adolescents and adults. J Dermatolog Treat 2016;27:346-50.
191. Pei AY, Chan HH, Ho KM. The effectiveness of wet wrap dressings using 0.1% mometasone furoate and 0.005% fluticasone proprionate ointments in the treatment of moderate to severe atopic dermatitis in children. Pediatr Dermatol 2001;18:343-8.
192. Peppers J, Paller AS, Maeda-Chubachi T, Wu S, Robbins K, Gallagher K, et al. A phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of atopic dermatitis. J Am Acad Dermatol 2019;80:89-98.e3.
193. Perala M, Ahola M, Mikkola T, Pelkonen AS, Remitz A, Makela MJ. Young children with moderate-to-severe atopic dermatitis can be treated safely and effectively with either topical tacrolimus or mild corticosteroids. Acta Paediatr 2020;109:550-6.
194. Peserico A, Stadtler G, Sebastian M, Fernandez RS, Vick K, Bieber T. Reduction of relapses of atopic dermatitis with methylprednisolone aceponate cream twice weekly in addition to maintenance treatment with emollient: a multicentre, randomized, double-blind, controlled study. Br J Dermatol 2008;158:801-7.
195. Prado de Oliveira ZN, Cucé LC, Arnone M. Comparative evaluation of efficacy, tolerability and safety of 0.1% topical momethasone furoate and 0.05% desonide in the treatment of childhood atopic dermatitis. An Bras Dermatol 2002;77:25-33.
196. Queille C, Pommarede R, Saurat JH. Efficacy versus systemic effects of six topical steroids in the treatment of atopic dermatitis of childhood. Pediatr Dermatol 1984;1:246-53.
197. Rahman MF, Nandi AK, Kabir S, Kamal M, Basher MS, Banu LA. Topical tacrolimus versus hydrocortisone on atopic dermatitis in paediatric patients: a randomized controlled trial. Mymensingh Med J 2015;24:457-63.
198. Rahman MF, Rashid MM, Sikder AU, Akhtar N, Banu LA, Wahab MA, et al. Efficacy of topical tacrolimus in atopic dermatitis. Journal of Pakistan Association of Dermatologists 2008;18:84-92.
199. Rajka G, Avrach W, Gartner L, Overgaard-Petersen H. Mometasone furoate 0.1% fatty cream once daily versus betamethasone valerate 0.1% cream twice daily in the treatment of patients with atopic and allergic contact dermatitis. Curr Ther Res Clin Exp 1993;54:23-9.
200. Ramsay CA, Savoie JM, Gilbert M, Gidon M, Kidson P. The treatment of atopic dermatitis with topical fusidic acid and hydrocortisone acetate. J Eur Acad Dermatol Venereol 1996;7:S15-22.
201. Reitamo S, Harper J, Bos JD, Cambazard F, Bruijnzeel-Koomen C, Valk P, et al. 0.03% Tacrolimus ointment applied once or twice daily is more efficacious than 1% hydrocortisone acetate in children with moderate to severe atopic dermatitis: results of a randomized double-blind controlled trial. Br J Dermatol 2004;150:554-62.
202. Reitamo S, Ortonne JP, Sand C, Cambazard F, Bieber T, Folster-Holst R, et al. A multicentre, randomized, double-blind, controlled study of long-term treatment with 0.1% tacrolimus ointment in adults with moderate to severe atopic dermatitis. Br J Dermatol 2005;152:1282-9.
203. Reitamo S, Van Leent EJ, Ho V, Harper J, Ruzicka T, Kalimo K, et al. Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone acetate ointment in children with atopic dermatitis. J Allergy Clin Immunol 2002;109:539-46.
204. Rubio-Gomis E, Martinez-Mir I, Morales-Olivas FJ, Martorell-Aragones A, Palop-Larrea V, Bernalte-Sese A, et al. Fluticasone in mild to moderate atopic dermatitis relapse: a randomized controlled trial. Allergol Immunopathol (Madr) 2018;46:378-84.
205. Ruzicka T, Bieber T, Schopf E, Rubins A, Dobozy A, Bos JD, et al. A short-term trial of tacrolimus ointment for atopic dermatitis. European Tacrolimus Multicenter Atopic Dermatitis Study Group. N Engl J Med 1997;337:816-21.
206. Ryu YS, Choi SW, Kim TY, Kim HO, Kim CW. Comparison of the safety and efficacy of mometasone furoate cream 0.1% and fluocortin butylester cream 0.75% in the treatment of atopic dermatitis. Journal of Korean Society for Clinical Pharmacology and Therapeutics 1997;5:205-11.
207. Saeki H, Baba N, Ito K, Yokota D, Tsubouchi H. Difamilast, a selective phosphodiesterase 4 inhibitor, ointment in paediatric patients with atopic dermatitis: a phase III randomized double-blind, vehicle-controlled trial. Br J Dermatol 2022;186:40-9.
208. Saeki H, Baba N, Oshiden K, Abe Y, Tsubouchi H. Phase 2, randomized, double-blind, placebo-controlled, 4-week study to evaluate the safety and efficacy of OPA- 15406 (difamilast), a new topical selective phosphodiesterase type-4 inhibitor, in Japanese pediatric patients aged 2-14 years with atopic dermatitis. J Dermatol 2020;47:17-24.
209. Saeki H, Ito K, Yokota D, Tsubouchi H. Difamilast ointment in adult patients with atopic dermatitis: a phase 3 randomized, double-blind, vehicle-controlled trial. J Am Acad Dermatol 2022;86:607-14.
210. Saeki H, Kawashima M, Sugaya S, Oshiden K, Tsubouchi H. Efficacy and safety of topical OPA-15406, a new phosphodiesterase 4 inhibitor, in Japanese patients with atopic dermatitis for 8 weeks: a phase 2, randomized, double-blind, placebo-controlled study. J Dermatol 2019;46:672-9.
211. Salavec M, Bučková H. First experiences with 1% pimecrolimus cream therapy in prevention of atopic eczema flares in children. Cesko-Slovenska Dermatologie 2004;79:3-7.
212. Sanabria-Silva E, Laterza AM, Tamayo L, Ruiz-Maldonado R. Evaluation of rebound phenomenon in children with atopic dermatitis treated with topical corticosteroids [in Spanish]. Dermatol Rev Mex 1991;35:84-9.
213. Savin RC. Betamethasone dipropionate in psoriasis and atopic dermatitis. Conn Med 1976;40:5-7.
214. Schachner LA, Lamerson C, Sheehan MP, Boguniewicz M, Mosser J, Raimer S, et al. Tacrolimus ointment 0.03% is safe and effective for the treatment of mild to moderate atopic dermatitis in pediatric patients: results from a randomized, double-blind, vehicle-controlled study. Pediatrics 2005;116:e334-42.
215. Schneider L, Hanifin J, Boguniewicz M, Eichenfield LF, Spergel JM, Dakovic R, et al. Study of the atopic march: development of atopic comorbidities. Pediatr Dermatol 2016;33:388-98.
216. Sears HW, Bailer JW, Yeadon A. Efficacy and safety of hydrocortisone buteprate 0.1% cream in patients with atopic dermatitis. Clin Ther 1997;19:710-9.
217. Siegfried E, Korman N, Molina C, Kianifard F, Abrams K. Safety and efficacy of early intervention with pimecrolimus cream 1% combined with corticosteroids for major flares in infants and children with atopic dermatitis. J Dermatolog Treat 2006;17:143-50.
218. Sigurgeirsson B, Boznanski A, Todd G, Vertruyen A, Schuttelaar ML, Zhu X, et al. Safety and efficacy of pimecrolimus in atopic dermatitis: a 5-year randomized trial. Pediatrics 2015;135:597-606.
219. Sigurgeirsson B, Ho V, Ferrandiz C, Andriano K, Grinienko A, Jimenez P, et al. Effectiveness and safety of a prevention-of-flare-progression strategy with pimecrolimus cream 1% in the management of paediatric atopic dermatitis. J Eur Acad Dermatol Venereol 2008;22:1290-301.
220. Sikder MAU, Al Mamun S, Khan RM, Chowdhury AH, Khan HM, Hoque MM. Topical 0.03% tacrolimus ointment, 0.05% clobetasone butyrate cream alone and their combination in older children with atopic dermatitis—an open randomized comparative study. Journal of Pakistan Association of Dermatologists 2005;15:304-12.
221. Smitt JHS, Winterberg DH, Oosting J. Treatment of atopic dermatitis with topical corticosteroids in children. Efficacy and systemic effects of triamcinolone acetonide and alclometasone dipropionate. Eur J Dermatol 1993;3:549-52.
222. Stander S, Metz M, Ramos FM, Maurer M, Schoepke N, Tsianakas A, et al. Antipruritic effect of sertaconazole 2% cream in atopic dermatitis subjects: a prospective, randomized, double-blind, vehicle-controlled, multi-centre clinical trial of efficacy, safety and local tolerability. Acta Derm Venereol 2016;96:792-6.
223. Sugarman JL, Parish LC. Efficacy of a lipid-based barrier repair formulation in moderate-to-severe pediatric atopic dermatitis. J Drugs Dermatol 2009;8:1106-11.
224. Takeuchi S, Saeki H, Tokunaga S, Sugaya M, Ohmatsu H, Tsunemi Y, et al. A randomized, open-label, multicenter trial of topical tacrolimus for the treatment of pruritis in patients with atopic dermatitis. Ann Dermatol 2012;24:144-50.
225. Tan WP, Suresh S, Tey HL, Chiam LY, Goon AT. A randomized double-blind controlled trial to compare a triclosan-containing emollient with vehicle for the treatment of atopic dermatitis. Clin Exp Dermatol 2010;35:e109-12.
226. Thaci D, Reitamo S, Gonzalez Ensenat MA, Moss C, Boccaletti V, Cainelli T, et al. Proactive disease management with 0.03% tacrolimus ointment for children

with atopic dermatitis: results of a randomized, multicentre, comparative study. Br J Dermatol 2008;159:1348-56.
227. Tharp MD. A comparison of twice-daily and once-daily administration of fluticasone propionate cream, 0.05%, in the treatment of eczema. Cutis 1996; 57:19-26.
228. Thomas KS, Armstrong S, Avery A, Po AL, O'Neill C, Young S, et al. Randomised controlled trial of short bursts of a potent topical corticosteroid versus prolonged use of a mild preparation for children with mild or moderate atopic eczema. BMJ 2002;324:768.
229. Tiplica GS, Boralevi F, Konno P, Malinauskiene L, Kaszuba A, Laurens C, et al. The regular use of an emollient improves symptoms of atopic dermatitis in children: a randomized controlled study. J Eur Acad Dermatol Venereol 2018;32:1180-7.
230. Torok HM, Maas-Irslinger R, Slayton RM. Clocortolone pivalate cream 0.1% used concomitantly with tacrolimus ointment 0.1% in atopic dermatitis. Cutis 2003;72:161-6.
231. Ulrich R, Andresen I. Treatment of acute episodes of atopic dermatitis. Double-blind comparative study with 0.05% halometasone cream versus 0.25% prednicarbate cream [in German]. Fortschr Med 1991;109:741-4.
232. Van Delrey ML, Geller M, Azulay RD. Estudo duplo-cego sobre a eficacia e a seguranca do creme de alcometasoma no tratamento de dermatite atopica. An Bras Dermatol 1983;58:177-80.
233. Van Der Meer JB, Glazenburg EJ, Mulder PG, Eggink HF, Coenraads PJ. The management of moderate to severe atopic dermatitis in adults with topical fluticasone propionate. The Netherlands Adult Atopic DermatitisStudy Group. Br J Dermatol 1999;140:1114-21.
234. Vanderploeg DE. Betamethasone dipropionate ointment in the treatment of psoriasis and atopic dermatitis: a double-blind study. South Med J 1976;69:862-3.
235. Vernon HJ, Lane AT, Weston W. Comparison of mometasone furoate 0.1% cream and hydrocortisone 1.0% cream in the treatment of childhood atopic dermatitis. J Am Acad Dermatol 1991;24:603-7.
236. Wahn U, Bos JD, Goodfield M, Caputo R, Papp K, Manjra A, et al. Efficacy and safety of pimecrolimus cream in the long-term management of atopic dermatitis in children. Pediatrics 2002;110:e2.
237. Wang F, Cao GL, Qi SL, Zhang XT, Zhang XQ. Clinical observation of calcipotriol betamethasone ointment in the treatment of chronic eczema. J Clin Dermatol 2014;43:179-81.
238. Wang JB, Jin HZ, Liu YH. Clinical observation on the efficacy of fluticasone propionate cream and ointment in the treatment of eczema. Chinese Journal of Dermatology 1995;28:128-9.
239. Wollenberg A, Reitamo S, Atzori F, Lahfa M, Ruzicka T, Healy E, et al. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. Allergy 2008;63:742-50.
240. Wu SH, Chen XQ, Liu B, Wu HJ, Dong L. Efficacy and safety of 15(R/S)-methyllipoxin A4 in topical treatment of infantile eczema. Br J Dermatol 2013;168:172-8.
241. Yawalkar SJ, Schwerzmann L. Double-blind, comparative clinical trials with halobetasol propionate cream in patients with atopic dermatitis. J Am Acad Dermatol 1991;25:1163-6.
242. Zhang JD, Chen M, Yang HJ. Clinical efficacy of heparinoid cream combined with 0.05% fluticasonepropionate cream for the treatment of chronic eczyme. J Clin Dermatol 2014;43:368-9.
243. Zuberbier T, Heinzerling L, Bieber T, Schauer U, Klebs S, Brautigam M. Steroid-sparing effect of pimecrolimus cream 1% in children with severe atopic dermatitis. Dermatology 2007;215:325-30.
244. Rafanelli A, Rafanelli S, Stanganelli I, Marchesi E. Mometasone furoate in the treatment of atopic dermatitis in children. J Eur Acad Dermatol Venereol 1993;2:225-30.
245. Bleehen SS, Chu AC, Hamann I, Holden C, Hunter JA, Marks R. Fluticasone propionate 0.05% cream in the treatment of atopic eczema: a multicentre study comparing once-daily treatment and once-daily vehicle cream application versus twice-daily treatment. Br J Dermatol 1995;133:592-7.
246. GlaxoSmithKline. Four Week Multicentre, Double Blind Study to Compare Safety and Efficacy With an OD and BD Administration of Fluticasone Propionate 0.005% Ointment in the Treatment of Atopic Eczema. 1995. Report 135L, Protocol no. GL/FLT/002. Unpublished report.
247. Koopmans B, Andersen BL, Mørk NJ, Austad J, Suhonen R, Roders GA. Multicentre randomized double-blind study of Locoid Lipocream fatty cream twice daily versus Locoid Lipocream once daily and Locobase once daily. J Dermatolog Treat 1995;6:103-6.
248. Richelli C, Piacentini GL, Sette L, Bonizzato MC, Andreoli A, Boner AL. Clinical efficacy and tolerability of clobetasone-17-butyrate 0.5% lotion in children with atopic dermatitis. Curr Ther Res Clin Exp 1990;47:413-7.
249. Wolkerstorfer A, Strobos MA, Glazenburg EJ, Mulder PGH, Oranje AP. Fluticasone propionate 0.05% cream once daily versus clobetasone butyrate 0.05% cream twice daily in children with atopic dermatitis. J Am Acad Dermatol 1998;39:226-31.
250. Pena J, Zameza PA, Pixley JN, Remitz A, Feldman SR. A comparison of topical corticosteroids and topical calcineurin inhibitors for the treatment of atopic dermatitis. J Allergy Clin Immunol Pract 2023;11:1347-59.
251. Bognanni A, Chu DK, Rank MA, Bernstein J, Ellis AK, Golden D, et al. Topical corticosteroids for chronic rhinosinusitis with nasal polyposis: GRADE systematic review and network meta-analysis. J Allergy Clin Immunol 2022;150: 1447-59.
252. Guyatt GH, Juniper EF, Walter SD, Griffith LE, Goldstein RS. Interpreting treatment effects in randomised trials. BMJ 1998;316:690-3.
253. Johnston BC, Thorlund K, Schunemann HJ, Xie F, Murad MH, Montori VM, et al. Improving the interpretation of quality of life evidence in meta-analyses: the application of minimal important difference units. Health Qual Life Outcomes 2010;8:116.
254. Chu DK, Llop-Guevara A, Walker TD, Flader K, Goncharova S, Boudreau JE, et al. IL-33, but not thymic stromal lymphopoietin or IL-25, is central to mite and peanut allergic sensitization. J Allergy Clin Immunol 2013;131: 187-200.e1-8.
255. Al-Obaydi S, Craig TJ, Al-Shaikhly T. Racial and ethnic disparities in the treatment of patients with atopic dermatitis in the United States: a retrospective matched cohort study. J Allergy Clin Immunol Pract 2023;11:2602-4.e1.
256. Corbett M, Allen A, Bobo N, Foggs MB, Fonacier LS, Gupta R, et al. Proposed solutions by the American College of Allergy, Asthma, and Immunology and advocacy experts to address racial disparities in atopic dermatitis and food allergy. Ann Allergy Asthma Immunol 2023;130:392-6.e2.
257. Croce EA, Levy ML, Adamson AS, Matsui EC. Reframing racial and ethnic disparities in atopic dermatitis in Black and Latinx populations. J Allergy Clin Immunol 2021;148:1104-11.
258. Davis CM, Apter AJ, Casillas A, Foggs MB, Louisias M, Morris EC, et al. Health disparities in allergic and immunologic conditions in racial and ethnic underserved populations: a Work Group Report of the AAAAI Committee on the Underserved. J Allergy Clin Immunol 2021;147:1579-93.
259. Davis CM, Flohr C, Gupta MR, Koplin JJ. Managing atopic dermatitis in patients with skin of color. J Allergy Clin Immunol Pract 2023;11:1376-83.
260. Martinez A, de la Rosa R, Mujahid M, Thakur N. Structural racism and its pathways to asthma and atopic dermatitis. J Allergy Clin Immunol 2021;148:1112-20.
261. Ogbogu PU, Capers Q 4th, Apter AJ. Disparities in asthma and allergy care: what can we do? J Allergy Clin Immunol Pract 2021;9:663-9.
262. Capozza K, Vastrup A, Proctor A, Roberts A, Picozza M, Manion R, et al. The sound of silence: where are the voices of patients in eczema guideline development? Br J Dermatol 2022;187:1005-6.
263. Thibau IJ, Loiselle AR, Latour E, Foster E, Smith Begolka W. Past, present, and future shared decision-making behavior among patients with eczema and caregivers. JAMA Dermatol 2022;158:912-8.
264. Capozza K, Funk M, Hering M, Lang J, Merhand S, Manion R, et al. Patients' and caregivers' experiences with atopic dermatitis-related burden, medical care, and treatments in 8 countries. J Allergy Clin Immunol Pract 2023;11:264-73.e1.
265. Capozza K, Gadd H, Kelley K, Russell S, Shi V, Schwartz A. Insights from caregivers on the impact of pediatric atopic dermatitis on families: "I'm tired, overwhelmed, and feel like I'm failing as a mother." Dermatitis 2020;31:223-7.
266. Schunemann HJ, Brennan S, Akl EA, Hultcrantz M, Alonso-Coello P, Xia J, et al. The development methods of official GRADE articles and requirements for claiming the use of GRADE—a statement by the GRADE guidance group. J Clin Epidemiol 2023;159:79-84.
267. Green C, Colquitt JL, Kirby J, Davidson P. Topical corticosteroids for atopic eczema: clinical and cost effectiveness of once-daily vs. more frequent use. Br J Dermatol 2005;152:130-41.