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Efficacy and tolerability of proactive treatment with topical corticosteroids and calcineurin inhibitors for atopic eczema: systematic review and meta-analysis of randomized controlled trials

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Summary

Background Long-term low-level topical anti-inflammatory therapy has been suggested as a new paradigm in the treatment of atopic eczema (AE).
Objectives To determine the efficacy and tolerability of topical corticosteroids and calcineurin inhibitors for flare prevention in AE.
Methods Systematic review of randomized controlled trials reporting efficacy of topical corticosteroids and/or topical calcineurin inhibitors for flare prevention in AE. Identification of relevant articles by systematic electronic searches (Cochrane Library, Medline) supplemented by hand search. Primary efficacy endpoint: proportion of participants experiencing at least one flare during proactive anti-inflammatory treatment. Relative risks (RRs) and corresponding 95% confidence intervals (CIs) were calculated and pooled by pharmaceutical agent using random-effects meta-analysis. Sensitivity analysis included meta-regression to explore the influence of study-specific covariates.
Results Nine articles reporting on eight vehicle-controlled trials were included. Three, four and one trial(s) evaluated proactive therapy with topical tacrolimus, fluticasone propionate and methylprednisolone aceponate, respectively. Each agent under study was more efficacious to prevent flares than vehicle. Meta-analysis suggested that topical fluticasone propionate (RR 0·46, 95% CI 0·38–0·55) may be more efficacious to prevent disease flares than topical tacrolimus (RR 0·78, 95% CI 0·60–1·00). Meta-regression indicated robustness of these findings. Proactive anti-inflammatory therapy was generally well tolerated. The trials identified, however, do not allow firm conclusions about long-term safety.
Conclusions Vehicle-controlled trials indicate efficacy of proactive treatment with tacrolimus, fluticasone propionate and methylprednisolone aceponate to prevent AE flares. Indirect evidence from vehicle-controlled trials suggests that twice weekly application of the potent topical corticosteroid fluticasone propionate may be more efficacious to prevent AE flares than tacrolimus ointment. Head to head trials should be conducted to confirm these results. Future studies are also needed to evaluate the long-term safety of proactive treatment of AE.

Atopic eczema (AE) is associated with considerable quality of life impairment and comorbidity, and imposes a significant economic burden.[1–7] Typically, the course of AE is chronically relapsing with periods of acute flares and remissions.[8] Based on findings that the skin of patients with AE has an impaired barrier function[9] and subclinical inflammatory infiltrate,[10] proactive treatment consisting of intensive topical anti-inflammatory therapy until visible skin lesions have cleared followed by continuous low-level use of topical anti-inflammatory agents to previously affected skin areas has been

suggested.[2,11,12] The primary goal of proactive anti-inflammatory treatment is to prevent AE flares, to improve and stabilize quality of life of affected patients, and to reduce the direct and indirect costs of AE in children and adults. Furthermore, it has been speculated that the use of proactive anti-inflammatory therapy early in infancy may modify the atopic march and help to reduce later sensitization to environmental allergens.[2]

We conducted a systematic review of randomized controlled trials (RCTs) to determine the efficacy and tolerability of proactive anti-inflammatory therapy with topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) for flare prevention in AE.

Materials and methods

Study design

We systematically reviewed all published RCTs to investigate the efficacy and tolerability of proactive topical anti-inflammatory therapy to prevent AE flares. All relevant procedures were fixed in a study protocol prior to the beginning of the literature search.

Eligibility criteria/identification of articles

All original articles reporting on RCTs to investigate the efficacy and tolerability of proactive topical anti-inflammatory therapy with TCS and/or TCI for flare prevention of AE against each other, symptomatic treatment, and/or placebo/vehicle were eligible. Proactive treatment was defined as the continuous low-level use of topical anti-inflammatory agents to previously affected skin areas after induction of remission.[2] To be eligible for the systematic review the proactive treatment phase had to be evaluated by means of an RCT irrespective of the study design in the previous remission induction regimen.

We undertook a systematic literature search in Medline and the Cochrane register of randomized controlled trials (CENTRAL), from inception to 14 August 2009, supplemented by hand search in the reference lists of review articles, treatment guidelines and included papers. Aiming for a very sensitive search strategy we searched for the term 'atopic dermatitis' and limited the search to studies with abstracts, conducted in humans, indexed as 'clinical trial' or 'randomized controlled trial'. No restrictions on language or participants' age were applied. Two investigators (J.S., L.v.K.) independently searched, reviewed and abstracted data. Disagreements were resolved by discussion between all authors.

Data abstraction

Data were abstracted using a standardized data abstraction form to summarize information on study design, study participants, study inclusion criteria, details of the treatment stabilization phase prior to proactive anti-inflammatory therapy, criteria to enter proactive phase (treatment maintenance) and details of proactive anti-inflammatory therapy. Originally, we planned to use change in symptoms, clinical signs and global disease severity as primary outcomes. However, these outcomes were not reported in most of the trials included. Following a discussion among all reviewers we chose the relapse rate (i.e. the proportion of participants experiencing at least one flare during proactive anti-inflammatory treatment) as the primary efficacy endpoint, as it may be easily interpreted and as it is consistently reported in all trials included. As secondary efficacy endpoints of the systematic review we aimed to abstract data on disease-free days (% days), time to first relapse (days), effects on quality of life, change in intensity/extent of disease based on a named outcome measure,[13] the effect of proactive treatment on the atopic march (sensitizations, incident asthma and rhinitis in children), treatment utilization, and financial cost. Data abstraction on the tolerability of treatments included the proportion of participants experiencing at least one adverse event, the most frequent adverse events, the number of serious adverse events, and the number/description of adverse events possibly related to the study drug. In studies evaluating proactive therapy with TCS we also extracted data on cutaneous (e.g. skin atrophy) and systemic adverse effects (e.g. adrenal suppression).

Study quality assessment

The methodological quality of each RCT included in the review was assessed independently by three investigators (J.S., L.v.K., C.A.) by means of the Cochrane Collaboration's tool for assessing risk of bias.[14] Disagreements were resolved by discussion between all authors.

Statistical analysis

If not reported, the primary efficacy endpoint – proportion of participants experiencing at least one flare during proactive anti-inflammatory treatment – was calculated from the data given in the paper. Relative risks (RRs) and corresponding 95% confidence intervals (CIs) were calculated. Qualitatively homogeneous trials were pooled by pharmaceutical agent using random-effects meta-analysis. Based on the pooled RR estimates the number needed to treat (NNT) and corresponding 95% CI were calculated separately for each intervention. To explore the robustness of our findings a set of sensitivity analyses was carried out. Sensitivity analysis included meta-regression to explore the role of potential sources of heterogeneity, e.g. key study factors such as age of participants, duration of induction of remission treatment, and study quality criteria. All meta-regression models were adjusted for the intervention under investigation. Publication bias was explored by regressing the study result (RR) on sample size adjusting for study intervention.[15] All analyses were carried out using STATA, version 10 (Stata Corp., College Station, TX, U.S.A.).

Results

We identified 1158 potentially eligible citations, and excluded 1136 articles after title/abstract review and another 13 articles after full-text review because they did not meet the eligibility criteria. Nine papers[11,12,16–22] met the predefined eligibility criteria and were included in the systematic review (Fig. 1).

Qualitative analysis

Table 1 summarizes information on the design and methodological characteristics of included studies. All studies were double-blind vehicle-controlled RCTs consisting of an initial treatment stabilization phase to induce remission followed by a proactive treatment phase to prevent new flares. The pharmaceutical agent under investigation was topical tacrolimus ointment (children: 0·03%; adults: 0·1%) in three studies summarized in four papers.[12,16,17,19] Paller *et al.*[16] and Breneman *et al.*[17] reported data from the same RCT with Paller *et al.*[16] summarizing the subgroup of paediatric patients and Breneman *et al.*[17] reporting on the total study population of adults and children. Four studies evaluated proactive therapy with topical fluticasone propionate 0·005% ointment[11,20,22] and/or fluticasone propionate 0·05% cream.[18,22] One study[21] compared proactive treatment with methylprednisolone aceponate 0·1% cream vs. vehicle. The efficacy and tolerability of topical tacrolimus and TCS was assessed over a period of 40–52 weeks and 16–20 weeks, respectively. Application of the anti-inflammatory agent under investigation not only to previously affected, but also to newly occurring sites was permitted in five studies,[11,12,17,21,22] not allowed in one study,[19] and unclear in two studies.[18,20] Table 2 provides a summary of participant characteristics of included trials. Four studies included both children and adults,[17,18,21,22] two studies only children,[19,20] and two studies only adults.[11,12] The sex distribution was similar across all trials (Table 2). The reporting of study outcomes and the choice of the primary outcome differed considerably between trials.

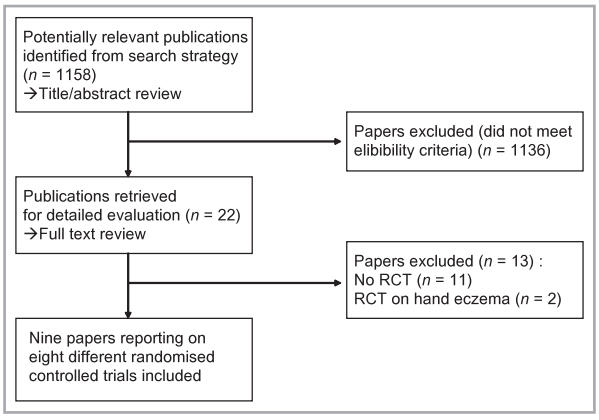

Fig 1. Flow of studies included. RCT, randomized controlled trial.

Table 3 details study results. Efficacy of proactive anti-inflammatory therapy to prevent disease flares was generally higher in trials using TCS compared with trials evaluating tacrolimus ointment. Compared with vehicle the RR (95% CI) for an AE flare during proactive treatment ranged between 0·61 (0·48–0·78) and 0·94 (0·76–1·16) for tacrolimus, between 0·38 (0·30–0·49) and 0·58 (0·33–1·02) for fluticasone propionate, and was 0·36 (0·21–0·62) for methylprednisolone aceponate. Although proactive treatment with tacrolimus was applied three times per week in the study by Breneman *et al.*,[17] the chance to experience at least one flare tended to be higher compared with the trials by Wollenberg *et al.*[12] and Thaçi *et al.*[19] in which proactive treatment with tacrolimus was used only twice a week (Table 3). Berth-Jones *et al.*[22] found proactive therapy with fluticasone propionate 0·05% cream to be significantly more efficacious than fluticasone propionate 0·005% ointment. The criteria to define a disease flare differed between trials (Table 3). Effects of proactive treatment on quality of life were generally only modest. The median time to first relapse ranged between 169 and 295 days with proactive tacrolimus ointment therapy and could not be estimated for proactive treatment with TCS, because < 50% of participants relapsed. Two tacrolimus studies observed a significantly higher proportion of disease-free days in the proactive treatment vs. control group[16,17] (Table 3). The amount of anti-inflammatory treatment utilized in the proactive and reactive treatment group was reported in only two studies[12,19] evaluating topical tacrolimus and in none of the studies evaluating TCS. In both studies, the median amount of tacrolimus ointment utilized tended to be higher under proactive vs. reactive treatment (272·5 vs. 100·8 g;[12] 249·8 vs. 69·6 g[19]). A subgroup analysis of the patients with moderate to severe AE included in the RCT by Wollenberg *et al.*[12] found proactive maintenance treatment with 0·1% tacrolimus ointment to be cost-effective, especially in patients with severe AE.[23] None of the RCTs included evaluated the effect of proactive treatment on the atopic march.

Methodological quality

Reporting of relevant information regarding sequence generation and allocation concealment was insufficient in the majority of trials included (Table 4). Blinding was reported as adequate in trials evaluating topical tacrolimus and unclear in trials assessing fluticasone propionate. In the study by Hanifin *et al.*[18] noncompliant patients withdrew which might have introduced bias in favour of proactive therapy with fluticasone propionate 0·05% cream. For further details on trial quality please refer to Table 4.

Quantitative results

The pooled RR (95% CI) of a disease flare during proactive therapy with topical tacrolimus ointment vs. vehicle and topical fluticasone propionate vs. vehicle was 0·775 (0·602–0·998) and 0·456 (0·382–0·545), respectively (Fig. 2). The

Table 1 Characteristics of studies included in the systematic review

Reference (first author)	Country	Study design	Inclusion criteria	Treatment stabilization phase	Criteria to enter maintenance phase	Numbers of patients included in stabilization and maintenance phase	Proactive treatment (treatment maintenance) phase		
							Proactive treatment	Control	Treatment of new lesions
Paller[16]	U.S.A.	db RCT	Age 2–15 years; IGA ≥ moderate	(a) 4 days tacrolimus 0·03% b.i.d. or alcometasone 0·05% b.i.d. (db) (b) ≤ 16 weeks tacrolimus 0·03% ointment b.i.d.	IGA clear or almost clear	206; 105 (51%)	40 weeks tacrolimus 0·03% 3 days per week once daily	Vehicle	Yes
Breneman[17]	U.S.A.	db RCT	Age ≥ 2 years; IGA ≥ moderate	(a) 4 days tacrolimus 0·03% b.i.d. or alcometasone 0·05% b.i.d. (db) (children)/triamcinolone 0·1% (adults) (b) ≤ 16 weeks tacrolimus 0·03% (children)/0·1% (adults) b.i.d.	IGA clear or almost clear	383; 197 (51%)	40 weeks tacrolimus 0·03% (children)/0·1% (adults) 3 days per week once daily	Vehicle	Yes
Wollenberg[12]	Europe	db RCT	Age ≥ 16 years; mild to severe AE[a]	≤ 6 weeks tacrolimus 0·1% b.i.d.	IGA clear or almost clear	257; 224 (87%)	12 months tacrolimus 0·1% ointment once daily on 2 days per week	Vehicle	Yes
Thaçi[19]	Europe	db RCT	Age 2–15 years; mild to severe AE[a]	≤ 6 weeks tacrolimus 0·03% b.i.d.	IGA clear or almost clear	267; 250 (94%)	12 months tacrolimus 0·03% ointment once daily on 2 days per week	Vehicle	No
van der Meer[11]	Nether-lands	db RCT	Age 15–50 years; moderate to severe AE (target lesion)	(a) 2 weeks fluticasone propionate 0·005% ointment once daily (b) 2 weeks fluticasone propionate 0·005% ointment once daily 4 days per week	Complete clearance or significant improvement	112; 54 (48%)	16 weeks fluticasone propionate 0·005% ointment on 2 consecutive days per week once daily on previously affected sites and on new lesions	Vehicle	Yes
Hanifin[18]	U.S.A., Canada	db RCT	Age 3 months–65 years; moderate to severe AE[a]	≤ 4 weeks fluticasone propionate 0·05% cream b.i.d.	IGA (almost) clear/marked clearing	372; 348 (94%)	4 weeks fluticasone propionate 0·05% cream once daily 4 days per week → 16 weeks fluticasone propionate 0·05% cream once daily on 2 days per week	Vehicle	Unclear
Glazenburg[20]	Europe	db RCT	Age 4–10 years; moderate to severe AE	≤ 4 weeks fluticasone propionate 0·005% ointment b.i.d.	TIS[32] < 2	90; 75 (83%)	16 weeks fluticasone propionate 0·005% ointment on two consecutive days per week once daily	Vehicle	Unclear

Table 1 Continued

Reference (first author)	Country	Study design	Inclusion criteria	Treatment stabilization phase	Criteria to enter maintenance phase	Numbers of patients included in stabilization and maintenance phase	Proactive treatment (treatment maintenance) phase		
							Proactive treatment	Control	Treatment of new lesions
Berth-Jones[22]	Europe	db RCT	Age 12–65 years; moderate to severe AE	4 weeks fluticasone propionate 0·005% ointment or fluticasone propionate 0·05% cream once or twice daily	TIS[32] < 2	376; 295 (78%)	16 weeks fluticasone propionate 0·005% ointment or 0·05% cream on two consecutive days per week once daily	Vehicle	Yes
Peserico[21]	Europe	db RCT	Age ≥ 12 years; IGA ≥ moderate	≤ 4 weeks methylprednisolone aceponate 0·1% cream once daily	IGA clear or almost clear	249; 221 (89%)	16 weeks methylprednisolone aceponate 0·1% cream on two consecutive days per week once daily	Vehicle	Yes

[a]According to grading by Rajka and Langeland.[33] db, double-blind; RCT, randomized controlled trial; IGA, Investigator Global Assessment; b.i.d., twice daily; AE, atopic eczema; TIS, Three Item Severity Score.[32]

corresponding NNT (95% CI) to prevent disease flares was 4 (3–587) for proactive therapy with tacrolimus ointment, 2 (2–2) for fluticasone propionate, and 2 (1–3) for methylprednisolone aceponate 0·1% cream. Sensitivity analysis indicated that fluticasone propionate 0·005% ointment was less effective than fluticasone propionate 0·05% cream to prevent AE flares [RR (95% CI) fluticasone propionate 0·005% ointment (n = 3)[11,20,22] 0·623 (0·491–0·792); fluticasone propionate 0·05% cream (n = 2)[18,22] 0·361 (0·287–0·454)]. Meta-regression analyses adjusting for the intervention under investigation suggested higher efficacy of proactive anti-inflammatory therapy with increasing duration of proactive anti-inflammatory therapy, i.e. when the proactive therapy was used for a longer overall period efficacy appeared to be better [β-coefficient (95% CI) per week: −0·024 (−0·043 to −0·0041) (P = 0·018)]. Application of the study drug not only to previously affected sites, but also to newly occurring lesions did not systematically influence the study results (P = 0·860). Efficacy of proactive therapy did not differ significantly between children and adults (P = 0·134) and none of the study quality criteria assessed had significant impact on the study results. There was no evidence for the presence of publication bias (P = 0·311).

Tolerability and safety of proactive anti-inflammatory therapy

Most frequent adverse events of proactive therapy with tacrolimus were burning of skin and other application site reactions (Table 5). The proportions of patients experiencing at least one adverse event were similar between tacrolimus ointment and vehicle. In total, four vs. zero cases of cancer were reported under proactive therapy with topical tacrolimus vs. vehicle.

In two trials investigating proactive therapy with TCS, viral and respiratory tract infections[20] and ear, nose and throat symptoms[18] tended to occur more frequently with topical fluticasone propionate compared with vehicle. Table 6 summarizes topical and systemic side-effects of proactive therapy with TCS. Skin atrophy or telangiectasia was not observed during proactive treatment with TCS. Hanifin *et al.*[18] found evidence for suppression of the hypothalamic–pituitary–adrenal axis in two of 44 children (4·5%). Two RCTs[11,20] did not observe adrenal suppression, and two RCTs[21,22] failed to report on systemic side-effects of proactive treatment with TCS (Table 6). In general, there was a shortcoming in the assessment of long-term side-effects of proactive treatment with TCS and TCI in the studies included.

Discussion

This systematic review indicates that proactive anti-inflammatory therapy with the TCS fluticasone propionate and methylprednisolone aceponate and the topical calcineurin inhibitor tacrolimus is more efficacious compared with vehicle to prevent AE flares. Meta-regression analysis indicated that the

Table 2 Summary of baseline characteristics (relates to maintenance phase assessing the efficacy of proactive treatment)

	Participants: (a) drug; (b) comparator				
Reference (first author)	n	Age (years), mean (SD)	% female	Diagnostic criteria	Main outcome measure of study
Paller[16]	(a) 68 (b) 37	(a) 7 (4) (b) 7 (4)	(a) 54 (b) 60	Hanifin and Rajka[34]	Number of disease-free days
Breneman[17]	(a) 125 (b) 72	(a) 23 (21) (b) 23 (19)	(a) 55 (b) 65	Hanifin and Rajka[34]	Number of disease-free days
Wollenberg[12]	(a) 116 (b) 108	(a) 31 (12) (b) 32 (12)	(a) 58 (b) 64	Hanifin and Rajka[34]	Number of flares requiring substantial therapeutic intervention[a]
Thaçi[19]	(a) 125 (b) 125	(a) 7 (4) (b) 7 (4)	(a) 54 (b) 50	Hanifin and Rajka[34]	Number of flares requiring substantial therapeutic intervention[a]
van der Meer[11]	(a) 23 (b) 31	Total 25 (NR)	Total 59	Hanifin and Rajka[34]	Mean change in SCORAD[36]
Hanifin[18]	(a) 229 (b) 119	Total 17 (16)	Total 58	NR	Relapse rate
Glazenburg[20]	(a) 39 (b) 36	(a) 6 (NR) (b) 6 (NR)	(a) 56 (b) 67	U.K. Working Party criteria[35]	Mean objective SCORAD[36] at end of study
Berth-Jones[22]	Cream: (a) 70 (b) 84 ointment: (a) 68 (b) 73	Total 29 (12)	Total 55	U.K. Working Party criteria[35]	Time to relapse
Peserico[21]	(a) 112 (b) 108	(a) 31 (15) (b) 31 (15)	(a) 59 (b) 70	NR	Time to relapse

[a]Use of tacrolimus 0·1% ointment for > 7 days. NR, not reported.

results obtained are robust and not systematically influenced by methodological trial quality.

The presented meta-analysis indicates that the potent topical corticosteroid fluticasone propionate may be more efficacious to prevent AE flares than tacrolimus ointment. However, due to the observed heterogeneity in trial methodology any inferences based on indirect evidence from vehicle-controlled trials regarding the comparative efficacy of proactive treatment with fluticasone propionate vs. tacrolimus ointment to prevent flares of AE should be made cautiously. Clearly, long-term head to head trials are needed before treatment recommendations can be made.

The trials evaluating proactive treatment with TCS were generally shorter than the trials investigating tacrolimus ointment. We do not believe that the shorter trial duration explains the observed superiority of topical fluticasone propionate vs. tacrolimus, because meta-analysis indicated a significant inverse relationship between efficacy and duration of proactive anti-inflammatory therapy. However, even though the maintenance phase of the studies evaluating the efficacy of proactive therapy with fluticasone propionate was 4–5 months, it is unclear if the benefit of twice weekly fluticasone therapy can be sustained for 1 year or more, or whether this treatment regimen will induce drug tolerance in the long run.[24]

Most trials used anti-inflammatory treatment not only on previously affected sites, but also for new AE lesions. This issue raised the question whether proactive anti-inflammatory treatment really did prevent existing sites of AE from flaring up again, or whether the observed efficacy is at least partly explained by early treatment of newly occurring sites of AE.[25] The presented meta-regression analysis suggests that the study results were not systematically influenced by treatment of newly occurring sites. However, we are aware that the limited number of studies included in the meta-regression analysis might have introduced limited statistical power.[26]

Interestingly, 0·05% fluticasone propionate cream appears to be more efficacious to prevent AE flares than 0·005% fluticasone propionate ointment. As previously discussed by Williams[25] this finding may be explained by the 10-fold difference in concentration of active ingredient in the cream. However, the different concentrations in the cream vs. ointment were specifically formulated to provide equivalent potency as determined by the established vasoconstrictor assay, but the assay may not accurately reflect clinical potency. This leads to the hypothesis that compliance might be better when using the cream formulation, but compliance was poorly reported in most studies.[25]

In total, four cases of incident cancer were observed under proactive therapy with topical tacrolimus. No cases of cancer were reported in vehicle groups of the tacrolimus trials and in active treatment and control groups of RCTs evaluating TCS. Most likely, the occurrence of cancers under proactive therapy with topical tacrolimus was a coincidence rather than related

Table 3 Summary of study results

Reference (first author)	Study results: (a) drug; (b) comparator						
	Relapse rate (main outcome of systematic review)						
	Definition of relapse	n/N (%) of patients experiencing ≥ 1 relapse	RR (95% CI) for relapse compared with placebo	Time to first relapse (days), median (95% CI)	Disease-free days, n/N (% days)	Change in intensity/extent of disease (based on named outcome measure, e.g. EASI, SCORAD)[a]	Change in quality of life (based on named outcome measure, e.g. DLQI, Skindex)[a]
Paller[16]	IGA ≥ mild	(a) 49/68 (72) (b) 27/37 (72)	0·99 (0·77–1·26)	(a) 116 (56–188) (b) 31 (29–113)	(a) 174/280 (62) (b) 107/280 (38)	NR	NR
Breneman[17]	IGA ≥ mild	(a) 77/124 (62) (b) 47/71 (66)	0·94 (0·76–1·16)	(a) 169 (113–225) (b) 43 (31–113)	(a) 177/280 (63) (b) 134/280 (48)	NR	NR
Wollenberg[12]	IGA ≥ mild for > 7 days despite treatment with tacrolimus 0·1% ointment b.i.d.	(a) 50/116 (43) (b) 76/108 (70)	0·61 (0·48–0·78)	(a) 142 (123; inestimable) (b) 15 (13–23)	NR	Median (range) EASI at beginning vs. end of proactive treatment: (a) 1·8 (0·0–22·2); 1·6 (0·0–33·7) (b) 2·0 (0·0–12·8); 3·2 (0·0–33·7)	Mean improvement in DLQI between study entry and end of proactive treatment: (a) 5·7 (b) 2·5
Thaçi[19]	IGA ≥ mild for > 7 days despite treatment with tacrolimus 0·1% ointment b.i.d.	(a) 62/125 (50) (b) 88/125 (70)	0·80 (0·62–1·04)	(a) 295 (178; inestimable) (b) 56 (35–120)	NR	NR	No difference in CDLQI between groups at end of study
van der Meer[11]	No explicit definition reported	(a) 9/23 (39) (b) 21/31 (68)	0·58 (0·33–1·02)	NR	NR	Mean difference in SCORAD change in favour of drug: 13 (3–24)	NR
Hanifin[18]	Modest clearing or less compared with study entry *plus* moderate to severe signs/symptoms of eczema	(a) 58/229 (25) (b) 79/119 (66)	0·38 (0·30–0·49)	(a) inestimable (b) 33 (NR) P < 0·001	NR	NR	NR
Glazenburg[20]	TIS[32] ≥ 3 at target lesion	(a) 17/39 (44) (b) 29/36 (81)	0·54 (0·37–0·80)	(a) inestimable (b) 18 (NR)	NR	Median (range) objective SCORAD at beginning vs. end of proactive treatment: (a) 3·6 (0–26); 10·7 (0–39) (b) 7·0 (0–24); 19·2 (0–38)	NR

Table 3 Continued

	Study results: (a) drug; (b) comparator						
	Relapse rate (main outcome of systematic review)						
Reference (first author)	Definition of relapse	*n*/*N* (%) of patients experiencing ≥ 1 relapse	RR (95% CI) for relapse compared with placebo	Time to first relapse (days), median (95% CI)	Disease-free days, *n*/*N* (% days)	Change in intensity/extent of disease (based on named outcome measure, e.g. EASI, SCORAD)[a]	Change in quality of life (based on named outcome measure, e.g. DLQI, Skindex)[a]
Berth-Jones[22]	TIS[32] ≥ 4 at target lesion	Cream: (a) 13/70 (19) (b) 54/84 (64) ointment: (a) 27/68 (40) (b) 41/73 (56)	Cream: 0·29 (0·17–0·48) ointment: 0·71 (0·50–1·01) total: 0·48 (0·36–0·74)	Cream: (a) inestimable (b) 43 (NR) ointment: (a) inestimable (b) 43 (NR)	NR	NR	NR
Peserico[21]	Need to intensify treatment from patient's perspective	(a) 15/112 (13) (b) 40/109 (37)	0·36 (0·21–0·62)	(a) inestimable (b) inestimable	NR	Mean EASI increase during proactive therapy: (a) 0·5 (b) 3·0	Change in DLQI during proactive therapy: (a) mean improvement 0·6 units (b) worsening 4·4–13·8 units

[a]Mean (95% CI) change compared with baseline. RR, relative risk; CI, confidence interval; EASI, Eczema Area and Severity Index; DLQI, Dermatology Life Quality Index; IGA, Investigator Global Assessment; NR, not reported; b.i.d., twice daily; CDLQI, Children's Dermatology Life Quality Index; TIS, Three Item Severity Score.[32]

Table 4 Summary of study quality (based on the Cochrane Collaboration's tool for assessing risk of bias)[14]

Reference (first author)	Sequence generation (low/high risk of bias or unclear?)	Allocation concealment (low/high risk of bias or unclear?)	Blinding (low/high risk of bias or unclear?)	Incomplete outcome data (low/high risk of bias or unclear?)	Selective outcome reporting (low/high risk of bias or unclear?)	Other bias (low/high risk of bias or unclear?)
Paller[16]	Unclear (NR)	Unclear (NR)	Low	Low	Unclear	Low
Breneman[17]	Unclear (NR)	Unclear (NR)	Low	Low	Unclear	Low
Wollenberg[12]	Unclear (NR)	Low	Low	Unclear	High (data on secondary outcomes NR)	Low
Thaçi[19]	Unclear (NR)	Low	Low	Unclear	High (data on secondary outcomes NR)	Low
van der Meer[11]	Unclear (NR)	Unclear (NR)	Unclear (NR)	Low	Unclear	Low
Hanifin[18]	Unclear (NR)	Unclear (NR)	Unclear (NR)	Low	Unclear	High: noncompliant patients withdrawn, unclear how missings were handled
Glazenburg[20]	Low	Unclear (NR)	Unclear (NR)	Low	Unclear	Unclear: compliance data NR
Berth-Jones[22]	Low	Unclear (NR)	Unclear	Low	Unclear	Low
Peserico[21]	High	Unclear (NR)	Low	Low	Unclear	Unclear: compliance data NR

NR, not reported.

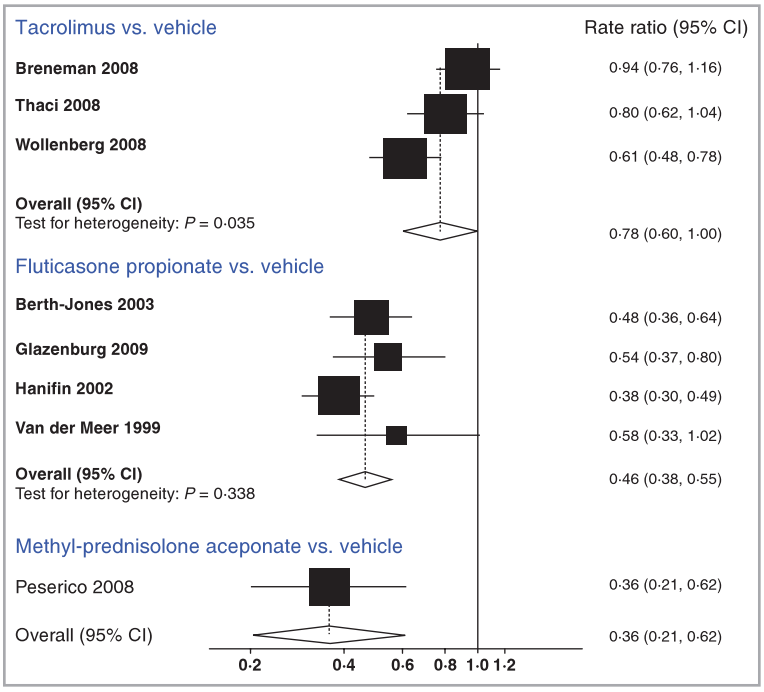

Fig 2. Forest plot (random-effects meta-analysis). CI, confidence interval.

to proactive treatment with tacrolimus ointment, as the cancers (liver cancer, prostate cancer, kidney cell cancer, cutaneous squamous cell carcinoma at a nontreated site) occurred only shortly after the initiation of study treatment. The investigators did not assess the cancers to be related to the treatment.

This systematic review also indicated that proactive therapy with fluticasone propionate might increase the risk for viral infections of the respiratory tract as well as ear, nose and throat symptoms. Another area of potential concern and further study is the finding that 4·5% of all children receiving proactive treatment with fluticasone propionate showed bio-

Table 5 Summary of adverse events

	Drug					Vehicle/comparator			
Reference (first author)	Name	% of participants with ≥ 1 adverse event	Most frequent adverse events	Number of serious adverse events	Number/ description of events possibly related	% of participants with ≥ 1 adverse event	Most frequent adverse events	Number of serious adverse events	Number/description of events possibly related
Paller[16]	Tacrolimus 0·03% ointment	12	Burning of skin, other application site reactions	NR	NR	11	Pruritus, burning of skin, skin infection (molluscum)	NR	NR
Breneman[17]	Tacrolimus 0·03% or 0·1% ointment	8	Burning of skin, other application site reactions	2 (death from liver cancer; skin cancer)	NR	9	Pruritus, burning of skin, skin infection (molluscum)	NR	NR
Wollenberg[12]	Tacrolimus 0·1% ointment	NR	Application site reactions; infections of skin	5 [prostate cancer; kidney cell cancer; cutaneous infection; NR (n = 2)]	47 (41%) had ≥ 1 related adverse event	NR	Application site reactions; infections of skin	3 [eczema herpeticum; NR (n = 2)]	38 (35%) had ≥ 1 related adverse event
Thaçi[19]	Tacrolimus 0·03% ointment	NR	Application site reactions; infections of skin, nasopharyngitis	7 [asthma (n = 2); bronchopneumonia; infected eczema; gastroenteritis; staphylococcal infection, eczema herpeticum]	40 (32%) had ≥ 1 related adverse event	NR	Application site reactions; infections of skin, nasopharyngitis	1 (sleep apnoea)	37 (30%) had ≥ 1 related adverse event
van der Meer[11]	Fluticasone propionate 0·005% ointment	NR	NR	NR	NR	NR	NR	NR	NR
Hanifin[18]	Fluticasone propionate 0·05% cream	31	Ear, nose, throat symptoms	NR	1 (acne)	24	Ear, nose, throat symptoms	NR	0
Glazenburg[20]	Fluticasone propionate 0·005% ointment	45	Viral infection, upper respiratory tract and enteral infections	None (no details reported)	2	14	Enteral infections	None	1 (no details reported)

Table 5 Continued

Reference (first author)	Drug					Vehicle/comparator				
	Name	% of participants with ≥ 1 adverse event	Most frequent adverse events	Number of serious adverse events	Number/ description of events possibly related	% of participants with ≥ 1 adverse event	Most frequent adverse events	Number of serious adverse events	Number/description of events possibly related
Berth-Jones[22]	Fluticasone propionate 0·005% ointment/0·05% cream	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
Peserico[21]	Methylprednisolone aceponate 0·1% cream	15	NR	None	None	24	NR	2 (no details reported)	None

[a]Adverse events not reported by treatment group. NR, not reported.

chemical signs of adrenal suppression in the study by Hanifin *et al.*[18] Although the studies included in this systematic review did not find any evidence for skin atrophy from twice weekly application of TCS, prolonged application of potent steroids to nonlesional skin might lead to skin atrophy, striae and systemic side-effects.[27] Large independent long-term studies such as registries are clearly indicated to clarify the safety and tolerability of long-term proactive anti-inflammatory therapy with TCS and TCI.

Our study followed *a priori* defined procedures which also met current methodological criteria for adequately performing a systematic review of RCTs.[26] Despite all the efforts undertaken, we cannot guarantee that we identified all relevant articles on the issue.

The reporting of study outcomes, the choice of the primary and secondary outcomes, and the definition of a flare differed considerably between trials. While some studies used score thresholds or changes in severity scores to define a disease flare, others applied behavioural definitions, such as the use of rescue therapy (Table 3). Although we believe that the occurrence of a flare may be defined either way, the observed heterogeneity in the definition of a flare might have to some extent accounted for the observed indirect differences in the relapse rates between topical tacrolimus and TCS. We are not aware of any studies that were primarily designed to develop a definition of a 'flare' in AE.[28] This is clearly an issue for future research. As pointed out by systematic research[13,28,29] the lack of standardization of outcomes methodology in eczema trials is a significant threat to evidence-based dermatology. One recent research initiative to overcome these shortcomings in the future was an international Delphi exercise involving consumers, clinical experts, journal editors and regulatory agencies to identify a preliminary core set of outcomes for eczema trials.[30] Following this consensus, a measurement for long-term control of flares, disease symptoms, and physician-assessed clinical signs should be assessed in future eczema trials.[30]

The initial anti-inflammatory treatment for stabilization of eczema differed considerably between trials and has to be considered another source of heterogeneity (Table 1). To explore whether the initial stabilization treatment affects long-term effectiveness of proactive treatment is an important issue for future research.

The study populations generally consisted of patients with moderate to severe AE recruited in secondary or tertiary care. Caution should therefore be exercised in generalizing the results of this meta-analysis to primary care where most cases of AE are mild and relapses occur less frequently.[31] It should also be noted that the presented results are generalizable only to the subset of patients responding to initial induction of remission by daily application of topical anti-inflammatory agents.

In summary, vehicle-controlled trials indicate efficacy of proactive treatment with tacrolimus, fluticasone propionate and methylprednisolone aceponate to prevent AE flares.

The meta-analysis yielded indirect evidence from vehicle-controlled trials suggesting that twice weekly application of

Table 6 Assessment of skin atrophy and adverse systemic steroid effects (e.g. adrenal suppression) in trials evaluating proactive corticosteroid therapy

Reference (first author)	Method used for assessment of skin atrophy	Results of skin atrophy assessment: (a) proactive steroid therapy[a]; (b) vehicle/comparator	Methods used for assessment of adrenal suppression	Results of assessment of adverse systemic steroid effects: (a) proactive steroid therapy; (b) vehicle/comparator
van der Meer[11]	Biopsies from lesional skin; assessment of skin atrophy visually subjectively on 4-point Likert scale and objectively using an interactive image analysis by blinded pathologists	No evidence of skin atrophy in 32 biopsies [13 from steroid group (95% CI 0–23%); 19 from vehicle group (95% CI 0–16%)] taken at the end of the proactive treatment	Serum cortisol level	No change in geometric mean cortisol levels at baseline and end of maintenance treatment in both groups
Hanifin[18]	Visual assessment for signs of skin atrophy	No evidence for atrophy of treated sites (95% CI 0–1%); one case of sudden onset of axillary striae (untreated site; graded as unrelated to study treatment)	Cosyntropin stimulation test to assess HPA axis function[b]	(a) Evidence of possible adrenal suppression in 2/44 children (b) no evidence of adrenal suppression
Glazenburg[20]	Visual assessment for signs of skin atrophy	No evidence for atrophy (95% CI 0–8%); one case of local pre-atrophy (telangiectasia) in each treatment group	Assessment of urinary overnight cortisol/creatinine ratios	No evidence for adverse effects on cortisol/creatinine ratios
Berth-Jones[22]	Visual assessment for signs of skin atrophy	No new visual signs of skin atrophy observed in either group during maintenance phase (95% CI 0–2%); 3 cases of visual signs of skin atrophy in stabilization phase	Not investigated	
Peserico[21]	Visual assessment for signs of skin atrophy	No new visual signs of skin atrophy observed in either group (95% CI 0–3%)	Not investigated	

[a]95% CI was calculated according to the '3 in n' rule.[37] [b]Possible adrenal suppression defined as poststimulation cortisol level < 18 μg dL^{-1}. CI, confidence interval; HPA, hypothalamic–pituitary–adrenal.

the potent topical corticosteroid fluticasone propionate may be more efficacious to prevent AE flares than tacrolimus ointment. However, head to head trials comparing fluticasone propionate against tacrolimus ointment should be conducted to confirm these results and adequately assess possible long-term side-effects of proactive anti-inflammatory treatment. Additionally, clinical registries should be established to further clarify the effectiveness, cost-effectiveness and long-term safety of different proactive anti-inflammatory treatment regimens.

What's already known about this topic?

- Atopic eczema (AE) is an important dermatological condition in terms of prevalence, impact on quality of life, and financial burden.
- Proactive long-term continuous low-level topical anti-inflammatory therapy has been suggested as a new paradigm to prevent AE flares.

What does this study add?

- This systematic review identified eight randomized controlled trials consistently indicating that proactive topical therapy with fluticasone propionate (n = 4), tacrolimus (n = 3) and methylprednisolone aceponate (n = 1) more efficaciously prevents flares than vehicle.
- Twice weekly application of topical fluticasone propionate appears to be more efficacious to prevent AE flares than tacrolimus ointment.
- Proactive treatment was generally well tolerated. Future studies should evaluate the long-term safety of long-term low-level anti-inflammatory therapy.

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