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Two topical calcineurin inhibitors for the treatment of atopic dermatitis in pediatric patients: A meta-analysis of randomized clinical trials

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Two new topical immunomodulators, pimecrolimus cream and tacrolimus ointment for atopic dermatitis (AD) in pediatric patients, have provided alternatives to topical corticosteroids without the associated adverse events. Objective: To evaluate the efficacy and safety of tacrolimus ointment and pimecrolimus cream for the treatment of AD in pediatric patients. Methods: MEDLINE, Embase, the CNKI and Cochrane Library databases were searched up to December 2008. Additional data sources were manual searches of abstract proceedings and personal contact with investigators and pharmaceutical companies. Two investigators assessed the quality of trials with unified tables independently. Disagreements on validity assessment were resolved through discussion or consultation with the third author. Quality analysis of methodology was evaluated according to the Jadad scale, including randomization, blinding and patients' discontinuation. Results: Twenty trials involving 6288 infants and children with AD met the inclusion criteria. More patients using tacrolimus had a good response than those in control groups including vehicle, 1% hydrocortisone acetate and 1% pimecrolimus, the corresponding OR were (4.56; 95%CI: 2.80 to 7.44), (3.92; 95% CI: 2.96 to 5.20) and (1.58; 95% CI: 1.18 to 2.12). The effect difference between 0.03% tacrolimus and 0.1% tacrolimus ointments was not statistically significant (OR = 0.90; 95% CI: 0.55 to 1.48). The incidence of adverse events of tacrolimus ointment or pimecrolimus cream was similar to the vehicle. The major adverse events were burning and pruritus. Conclusions: Both tacrolimus ointment and pimecrolimus cream are safe and effective in the treatment of AD in pediatric patients. Tacrolimus ointments were superior to pimecrolimus cream.
Key words: *atopic dermatitis, children, meta-analysis, pimecrolimus, tacrolimus.*

INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease that often presents with flares and can be complicated by recurrent skin infections [1, 2]. Onset is within the first year of life in 60% of cases and within the first 5 years in 80–90% (3,4). AD is a major public health problem worldwide with a lifetime prevalence in children of 10–20% [5, 6]. Acute and subacute skin lesions are often seen in children and are characterized by intensely pruritic erythematous papules associated with excoriation and serous exudate. Chronic AD is characterized by lichenification, papules, and excoriations. At all stages of this disease, patients usually have dry lacklustre skin. The distribution and skin reaction pattern varies according to the patient's age and disease activity. During infancy, AD is generally more acute and mainly affects the face, scalp, and extensor surfaces of the extremities. In older children and in those who have longstanding skin disease, the patient develops lichenification and localization of the rash to the flexural folds of the extremities. Chronic hand eczema can be the primary manifestation of many adults with AD [7]. Two forms of AD have been delineated, including an extrinsic form associated with IgE-mediated sensitization involving 70–80% of patients and an intrinsic form without IgE-mediated sensitization involving 20–30% of the patients [7, 8]. Both forms of AD have associated eosinophilia.

Successful management of AD requires a multipronged approach involving skin care, identification and elimination of flare factors, and anti-inflammatory treatment [4]. Traditionally, the treatment of AD included the frequent use of emollients and the intermittent use of topical corticosteroids to control acute flares. Corticosteroids, although effective, may be associated with several local and systemic adverse events, such as thinning of the skin and adrenal gland suppression. Patients' fears about the safety profile of topical corticosteroids also have important implications for adherence to treatment, and knowledge on differentiating weak preparations from strong preparations is poor [9, 10]. Two new topical immunosuppressive preparations, tacrolimus ointment and pimecrolimus cream, were developed to provide alternatives to topical corticosteroids without the associated adverse events. They work by inhibiting calcineurin in the skin, which regulates the activity of several transcription factors that control cell division and trigger the early stages of T-cell activation [11].

The treatment of AD involves a combination of preventive measures and an individualized therapeutic regimen. Randomized controlled trials (RCTS) are especially important in assessing the effects of treating AD because of the substantial placebo effect in this disease [7]. As a result of the difference in the clinical manifestation of AD between children and adults, the treatment result also has a big difference [11]. Based on

published RCTs, we made a systematic review on the efficacy and adverse effects of tacrolimus ointment and pimecrolimus cream in treating pediatric AD.

METHODS

Searches

Searches were conducted to identify all published RCTS. There was no language restriction for the search. An effort was made to translate non-English articles into English for inclusion. The following databases were searched for relevant studies: Ovid: http://gateway.ovid.com/; The Cochrane Library (Issue 4, 2008); Embase (1974 — Dec 2008); MEDLINE (1966 — Dec 2008): http://www.ncbi.nlm.nih. gov/entrez/query.fcgi?DB=pubmed); National Knowledge Infrastructure (CNKI) (1979 — Dec 2008): http://www.cnki.net/index.htm. Key words: (Tacrolimus OR FK506 OR Protopic OR Pimecrolimus OR ASM 981 OR Elidel) AND atopic dermatitis. Additional data sources were manual searches of abstract proceedings and personal contact with investigators and pharmaceutical companies.

Inclusion criteria

All pediatric patients (< 18 years of age) with a diagnosis of AD on the basis of reliable criteria.

Intervention

Locally applied tacrolimus ointment or pimecrolimus cream with placebo or other medicines as controls.

Outcomes

The primary outcomes were the investigators' global assessment (IGA) or the physician's global evaluation (PGE). Secondary outcomes were the eczema area and severity index (EASI) or the modified EASI (mEASI), quality of life (QoL) and adverse events.

The PGE is an efficacy scale of clinical response. It is commonly used to measure the improvement of AD through treatment and represents the physician's overall evaluation of clinical response, with improvement from 0% (worse) to 100% (totally cleared). Inpublished clinical trials with these kinds of patients, the most commonly reported outcomes were: (i) ⩾ 90% (excellent); (ii) 75–89% (marked); and (iii) 50–74% (moderate) improvement. An additional efficacy scale was the IGA score. It represents an overall evaluation of dermatitis performed by the investigator at each visit. IGA scores utilize a six-point scale, ranging from 0 (clear) to 5 (very severe disease). IGA scores measure disease severity based on morphology, without referring back to the baseline state. PGE ⩾ 90% or IGAJ ⩽ one response were enrolled in the meta-analysis.

Data extraction

A meta-analysis model was used in this study, as reported previously by Moher et al. [12]. Two investigators assessed the quality of trials with unified tables independently. Any disagreements on validity assessment were resolved through discussion or consultation with the third author. Quality analysis of methodology was evaluated according to the Jadad scale, including randomization, blinding and patients' discontinuation. The Jadad scale scores from 1 to 5, where 1 or 2 indicates poor in quality and 3–5 indicates high quality [13].

Statistical analysis

Statistical analysis was performed with Review Manager Software (RevMan 4.2.8, Cochrane Collaboration). Heterogeneity of results between each trial was tested by the chi-squared test ($p > 0.1$, $I^2 < 50\%$). Meta-analysis was done using the fixed effect model if there was no heterogeneity among subgroups, otherwise using the randomized effect model. Comparison of the effects between two groups was expressed by odds ratio (OR) and its 95% confidence interval (95% CI).

RESULTS

Trial flow

A total of 88 relative studies published between 1998 and 2008 were found, in which 50 were excluded (different research purposes or an adult study) through reading titles and abstracts; 38 full texts were therefore obtained for further evaluation. From these 38 articles, 17 were rejected because of data redundancy, the research goal being different and the use of combination therapy [14–30]; finally, 21 articles met all entry criteria and were included in the study [31–51]. The 20 studies (21 articles) involving 6288 enrolled infants and children were all double-blind RCTs. All trials were of a high quality (Jadad score ⩾ 3), in which 19 articles were in English and two were in Chinese. Details are listed in Table I.

Efficacy

0,03% tacrolimus ointment versus 0.1% tacrolimus ointment. Table IIA shows three trials (702 children) directly comparing 0.03% tacrolimus ointment with 0.1% tacrolimus ointment. Two of the trials reported on the proportions of patients with a PGE ⩾ 90% at 3 weeks and found no significant difference in response between the strengths of the tacrolimus ointments (pooled OR 1.04; 95% CI: 0.39 to 2.80) [31, 34]. Another trial reported on the proportions of patients with an IGA ⩽ 1 at 12 weeks and found no significant difference between the strengths of the tacrolimus ointments (OR 0.82; 95% CI: 0.48 to 1.48) [33].

Tacrolimus versus vehicle. Table IIB shows four trials (943 children) directly comparing tacrolimus ointments with a vehicle. Two trials reported on the proportion of patients with a PGE ⩾ 90% at 3 weeks (OR 4.98; 95% CI: 2.58 to 9.61) [31, 37]. One trial reported on the proportion of patients with an IGA ⩽ 1 at 6 weeks (OR 2.95; 95% CI: 1.84 to 4.74) [38]. Another trial reported on the proportion of patients with a PGE ⩾ 90% at 12 weeks (OR 7.56; 95% CI: 3.36 to 17.02) [33]. The 0.03% tacrolimus ointment was significantly more effective than the vehicle. There were two trials directly comparing 0.03% tacrolimus, 0.1% tacrolimus and a vehicle control. One trial reported on the proportion of patients with a PGE ⩾ 90% at 3 weeks (OR 2.00; 95% CI: 0.84 to 4.78) (31). The other trial reported on the proportion of patients with an IGA ⩽ 1 at 12 weeks (OR 9.26; 95% CI: 4.13 to 20.74) [33]. The 0.1% tacrolimus ointment was significantly more effective than the vehicle. Four articles reported that the improvement percentage from baseline (by reduction in EASI score) was significantly greater for the tacrolimus ointment-treated groups than for vehicle ($p < 0.001$)/(Table III) [31, 33, 37, 38].

For children and toddlers, the 0.1% tacrolimus ointment group exhibited statistically significant improvements from baseline at the end of treatment compared with the vehicle ointment group for all QoL scores ($p < 0.05$). Compared with the vehicle group, improvements in the 0.1% tacrolimus ointment group were very substantial in the aspects of symptoms and feelings, sleep, and treatment. The 0.03% tacrolimus ointment group demonstrated significant QoL improvements in both children and toddlers at the end of treatment compared with the vehicle control group for all QoL scores ($p < 0.05$), with the exception of the personal relationships scale in children. Differences between the tacrolimus ointment groups were not statistically significant among children and toddlers [32]. However, another trial reported that there was a difference between children and toddlers for QoL improvement. Among children, the tacrolimus ointment group demonstrated significant improvement compared to the vehicle control group

Table I. Characteristics of RCTs

Study	*n*	Age (years)	Criteria	Severity of AD	Intervention, control	Duration	Outcomes
Boguniewicz, 1998 [31]	180	7–16	Hanifin [52]	Moderate to severe	0.03% tacrolimus, 0.1% and 0.3% twice daily; vehicle	18 centers, 3 weeks	PGE, EASE
Drake, 2001 [32]	145–138[a]	2–4	Hanifin [52]	Moderate to severe	0.03% tacrolimus and 0.1% twice daily; vehicle	Multicenter, 12 weeks	QoL
	178–169[a]	5–15	Hanifin [52]	Moderate to severe	0.03% tacrolimus and 0.1% twice daily; vehicle	Multicenter, 12 weeks	QoL
Paller, 2001 [33]	351	2–15	Hanifin [52] and Rajka [53]	Moderate to severe	0.03% tacrolimus and 0.1% twice daily; vehicle	23 centers in the United States, 12 weeks	PGE, EASI
Reitamo, 2002 [34]	560	2–15	Hanifin [52] and Rajka [53]	Moderate to severe	0.03% tacrolimus and 0.1% twice daily; hydrocortisone acetate 1%	Multicenter, 3 weeks	IGA, mEASI
Reitamo, 2004 [35]	624	2–15	Hanifin [52] and Rajka [53]	Moderate to severe	0.03% tacrolimus once or twice daily; hydrocortisone acetate 1%	42 centers in 11 European countries, 3 weeks	PGE, mEASI
Kempers, 2004 [36]	141	2–17	Bernard [54], IGA	Moderate	0.03% tacrolimus twice daily; 1% pimecrolimus	19 centers in the United States, 6 weeks	IGA
Liu, 2005 [37]	139	2–17	Williams [55] and Rajka [53]	Moderate to severe	0.03% tacrolimus twice daily; placebo	Five centers in China, 3 weeks	PGE, EASI
Schachner, 2005 [38]	317	2–15	Hanifin [52] IGA	Mild to moderate	0.03% tacrolimus twice daily; vehicle	Multicenter, 6 weeks	IGA, EASI
Paller, 2005 [39]	425	2–15	Hanifin [52] IGA	Mild	0.03% tacrolimus twice daily; 1% pimecrolimus	Three multicenter, 4 weeks	IGA, EASI
Paller, 2005 [39]	225	2–15	Hanifin [52] IGA	Moderate to severe	0.1% tacrolimus twice daily; 1% pimecrolimus	Three multicenter, 4 weeks	IGA, EASI
Dou, 2006 [40]	21	2–4	Williams [55] and Rajka [53]	Moderate to severe	0.03% tacrolimus twice daily; vehicle	Six centers in China, 3 weeks	QoL
	104	5–17	Williams [55] and Rajka [53]	Moderate to severe	0.03% tacrolimus twice daily; vehicle	Six centers in China, 3 weeks	QoL
Bieber, 2007 [41]	265	2–15	IGA	Moderate to severe	0.03% tacrolimus twice daily; 0.1% methylprednisolone aceponate	25 centers in Germany, Italy and Spain	IGA, EASI, QoL, pruritus, sleep
Eichenfield, 2002 (42) and Whalley, 2002 [43]	403	1–17	Williams [55] IGA	Mild to moderate	1% pimecrolimus twice daily; vehicle	11 centers in the United States, 6 weeks	IGA, EASI, QoL, pruritus
Wahn, 2002 [44]	713/711[a]	2–17	Williams [55] IGA	Mild to severe	1% pimecrolimus twice daily; corticosteroids	53 centers in 13 countries, 1 year	IGA, EASI
Kapp, 2002 [45]	251–250[a]	3–23 months	Seymour [56] IGA	Severe	1% pimecrolimus twice daily; corticosteroids	41 centers in eight countries, 1 year	IGA, EASI, pruritus
Ho, 2002 [46]	186	3–23 months	Seymour [56] IGA	Mild to moderate	1% pimecrolimus twice daily; vehicle	25 centers in Australia, Brazil, Canada, Germany, South Africa, and Spain, 6 weeks	IGA, EASI, pruritus
Breuer, 2004 [47]; Kaufmann, 2004 [48]; Staab, 2005 [49]	196–195[a]	3–23 months	Seymour [56] IGA	Mild to severe	1% pimecrolimus twice daily; vehicle	19 centers in Germany, 4 weeks	IGA, EASI, QoL, pruritus, sleep
Eichenfield, 2005 [50]	589	3 months to 17 years	Williams [55] IGA	Mild to moderate	1% pimecrolimus twice daily; vehicle	Three centers, 6 weeks	IGA, EASI
Siegfried, 2006 [51]	275–272[a]	3 months to 11 years	Williams [55] IGA	Mild to severe	1% pimecrolimus twice daily; vehicle	35 centers in the United States, 6 months	IGA, EASI, flare

[a] — Randomized/ITT (intent-to-treat); PGE — physician's global evaluation; EASI = eczema area and severity index; QoL = quality of life; IGA = investigators' global assessment; mEASI = modified EASI.

Table II. Comparison of PGE ⩾ 90% or IGA ⩽ 1 in RCTs between tacrolimus ointment and controls

IIA

Study or sub-category	Tacrolimus 0.03% n/N	Tacrolimus 0.1% n/N	Weight %	OR (random) 95% CI
01. Tacrolimus 0.03% vs Tacrolimus 0.1% at 3 weeks				
Boguniewicz, 1998	25/43	21/49	22,27	1,85 (0,81; 4,24)
Reitamo, 2002	72/189	89/186	42,20	0,67 (0,44; 1,01)
Subtotal (95% CI)	232	235	64,47	1,04 (0,39; 2,80)
Total events: 97 (Tacrolimus 0.03%), 110 (Tacrolimus 0.1%) Test for heterogeneity: $\chi^2 = 4.63$, df = 1 ($p = 0.03$), $I^2 = 78.4\%$ Test for overall effect: Z = 0.08 ($p = 0.93$)				
02. Tacrolimus 0.03% vs Tacrolimus 0.1% at 12 weeks				
Paller, 2001	42/117	48/118	35,53	0,82 (0,48; 1,38)
Subtotal (95% CI)	117	118	35,53	0,82 (0,48; 1,38)
Total events: 42 (Tacrolimus 0.03%), 48 (Tacrolimus 0.1%) Test for heterogeneity: not applicable Test for overall effect: Z = 0.75 ($p = 0.45$)				
Total (95% CI)	349	353	100,00	0,90 (0,55; 1,48)
Total events: 139 (Tacrolimus 0.03%), 158 (Tacrolimus 0.1%) Test for heterogeneity: $\chi^2 = 4.63$, df = 2 ($p = 0.10$), $I^2 = 56.8\%$ Test for overall effect: Z = 0.41 ($p = 0.68$)				

IIB

Study or sub-category	Tacrolimus n/N	Vehicle n/N	Weight %	OR (random) 95% CI
01. Tacrolimus 0.03% vs vehicle at 3 weeks				
Boguniewicz ,1998	25/43	12/44	14,84	3,70 (1,51; 9,10)
Liu, 2005	28/70	6/69	13,79	7,00 (2,67; 18,36)
Subtotal (95% CI)	113	113	28,63	4,98 (2,58; 9,61)
Total events: 53 (Tacrolimus), 18 (Vehicle) Test for heterogeneity: $\chi^2 = 0.90$, df = 1 ($p = 0.34$), $I^2 = 0\%$ Test for overall effect: Z = 4.79 ($p < 0.00001$)				
02. Tacrolimus 0.03% vs vehicle at 6 weeks				
Schachner, 2005	80/158	41/159	23,28	2,95 (1,84; 4,74)
Subtotal (95% CI)	158	159	23,28	2,95 (1,84; 4,74)
Total events: 80 (Tacrolimus), 41 (Vehicle) Test for heterogeneity: not applicable Test for overall effect: Z = 4.49 ($p < 0.00001$)				
03. Tacrolimus 0.03% vs vehicle at 12 weeks				
Paller, 2001	42/117	8/116	16,35	7,56 (3,36; 17,02)
Subtotal (95% CI)	117	116	16,35	7,56 (3,36; 17,02)
Total events: 42 (Tacrolimus), 8 (Vehicle) Test for heterogeneity: not applicable Test for overall effect: Z = 4.89 ($p < 0.00001$)				
04. Tacrolimus 0.1% vs vehicle at 3 weeks				
Boguniewicz, 1998	21/49	12/44	15,29	2,00 (0,84; 4,78)
Subtotal (95% CI)	49	44	15,29	2,00 (0,84; 4,781)
Total events: 21 (Tacrolimus), 12 (Vehicle) Test for heterogeneity: not applicable Test for overall effect: Z = 1.56 ($p = 0.12$)				
05. Tacrolimus 0.1% vs vehicle at 12 weeks				
Paller, 2001	48/118	8/116	16,44	9,26 (4,13; 20,74)
Subtotal (95% CI)	118	116	16,44	9,26 (4,13; 20,74)
Total events: 48 (Tacrolimus), 8 (Vehicle) Test for heterogeneity: not applicable Test for overall effect: Z = 5.41 ($p < 0.00001$)				
Total (95% CI)	555	548	100,00	4,56 (2,80; 7,44)
Total events: 244 (Tacrolimus), 87 (Vehicle) Test for heterogeneity: $\chi^2 = 11.86$, df = 5 ($p = 0.04$), $I^2 = 57.9\%$ Test for overall effect: Z = 6.08 ($p < 0.00001$)				

Table II.

IIC

Study or sub-category	Tacrolimus n/N	Glucocorticosteroids n/N	Weight %	OR (fixed) 95% CI
01. 0.03% tacrolimus ointment vs 1% hydrocortisone acetate at 3 weeks				
Reitamo, 2002	72/189	29/185	50,33	3,31 (2,02; 5,42)
Reitamo, 2004	77/210	28/206	49,67	3,68 (2,26; 5,99)
Subtotal (95% CI)	399	391	100,00	3,49 (2,47; 4,94)
Total events: 149 (Tacrolimus), 57 (Glucocorticosteroids) Test for heterogeneity: $\chi^2 = 0.09$, df = 1 ($p = 0.76$), $I^2 = 0\%$ Test for overall effect: Z = 7.07 ($p < 0.00001$)				
02. 0.1% tacrolimus ointment vs 1% hydrocortisone acetate at 3 weeks				
Reitamo, 2002	89/186	29/185	100,00	4,94 (3,02; 8,05)
Subtotal (95% CI)	186	185	100,00	4,94 (3,02; 8,05)
Total events: 89 (Tacrolimus), 29 (Glucocorticosteroids) Test for heterogeneity: not applicable Test for overall effect: Z = 6.39 ($p < 0.00001$)				
03. 0.03% tacrolimus ointment vs 0.1% methylprednisolone aceponate at 3 weeks				
Bieber, 2007	40/136	48/129	100,00	0,70 (0,42; 1,17)
Subtotal (95% CI)	136	129	100,00	0,70 (0,42; 1,17)
Total events: 40 (Tacrolimus), 48 (Glucocorticosteroids) Test for heterogeneity: not applicable Test for overall effect: Z =1.34 ($p = 0.18$)				

Table III. Eczema area and severity index (EASI) of RCTs

Study	Intervention	EASI (%)	*p*
Boguniewicz, 1998 [31]	0,03% tacrolimus 0,1% tacrolimus Vehicle	72[a] 77[a] 26[a]	< 0,001
Paller, 2001 [33]	0,03% tacrolimus 0,1% tacrolimus Vehicle	/ / /	< 0,001
Liu, 2005 [37]	0,03% tacrolimus Placebo	/ /	< 0,001
Schachner, 2005 [38]	0,03% tacrolimus Vehicle	54,8 20,8	< 0,001
Reitamo, 2002 [34]	0,03% tacrolimus 0,1% tacrolimus 1% hydrocortisone acetate	55,2[a] 60,2[a] 36,0[a]	< 0,001
Reitamo, 2004 [35]	0,03% tacrolimus 1% hydrocortisone acetate	76,7[a] 47,2[a]	< 0,001
Bieber, 2007 [41]	0,03% tacrolimus 0,1% methylprednisolone aceponate	85,3 89,7	= 0,0667
Paller, 2005 [39]	0,1% tacrolimus 1% pimecrolimus	67,2 56,4	= 0,04
Eichenfield, 2002 [42]	1% pimecrolimus Vehicle	47 -1	< 0,001
Ho, 2003 [46]	1% pimecrolimus Vehicle	81,6 25	< 0,001
Kaufmann, 2004 [48]	1% pimecrolimus Vehicle	71,5 19,4	< 0,001
Eichenfield, 2005 [50]	1% pimecrolimus Vehicle	/ /	< 0,001
Siegfried, 2006 (1 w) [51]	1% pimecrolimus Vehicle	34 3	< 0,001

[a] — Modified EASI; / — No reported data.

for all QoL scales ($p < 0.05$), and among toddlers there was no significant improvement in the tacrolimus ointment group in the QoL scale compared to the vehicle group ($p > 0.05$) [40].

Tacrolimus ointment versus mild topical corticosteroids. Table IIC shows two trials comparing tacrolimus ointment with 1% hydrocortisone acetate in 1161 children with moderate to severe atopic dermatitis [34, 35]. Both 0.03% and 0.1% tacrolimus ointments were significantly more effective than 1% hydrocortisone acetate on the basis of the proportion of patients with a PGE ⩾ 90% or an IGA ⩽ 1 at 3 weeks; the corresponding OR were 3.49 (95% CI: 2.47 to 4.94) and 4.94 (95% CI: 3.02 to 8.05). Two articles reported that the improvement percentage from baseline (by reduction in EASI score) was significantly greater for the tacrolimus ointment-treated groups than for the 1% hydrocortisone acetate group ($p < 0.001$) [34, 35].

1% pimecrolimus cream versus vehicle. Table IVA shows six trials (1645 children) directly comparing pimecrolimus cream with a vehicle. The 1% pimecrolimus cream was significantly more effective than the vehicle (OR 3.21; 95% CI: 2.48 to 4.14). Four trials reported that 1% pimecrolimus cream remained significantly more effective than vehicle after 6 weeks (OR 2.80; 95% CI: 2.11 to 3.73) [42, 46, 50]. Another trial (195 infants) found a significant difference between the proportions of patients IGA ⩽ 1 at 4 weeks (OR 9.69; 95% CI: 4.12 to 22.83) [47]. The latest vehicle-controlled trials (272 children) found a significant difference between the proportions of patients with an IGA ⩽ 1 at 1 week (OR 2.78; 95% CI: 1.18 to 6.54), and pimecrolimus cream resulted in significantly fewer children with a flare of AD at 6 months (51.9%) [51]. Five articles reported that the improvement percentage from baseline (by reduction in EASI score) was significantly greater for the 1% pimecrolimus cream-treated groups than for the vehicle ($p < 0.001$) (shown in Table III) [42, 46, 48, 50, 51].

Infants (n = 196) with mild to severe atopic eczema were randomized 2:1, double-blind, to receive either 1% pimecrolimus cream or the corresponding vehicle (bid) for 4 weeks, followed by a 12-week open-label phase and a 4-week treatment-free follow-up period. The parents' QoL was measured at baseline and at the end of the double-blind phase, using the QoL questionnaire for parents of children with AD; thus data presented here refers to the initial 4-week treatment phase only. After 4 weeks of double-blind treatment, an increase in the mean percentage change from baseline in the eczema area and severity index of 71.5% was observed with 1% pimecrolimus cream compared with 19.4% with the vehicle. The increase in efficacy was paralleled by the following mean percentage changes from baseline in the five domains of the questionnaire in 1% pimecrolimus cream and vehicle, respectively: psychosomatic well-being: 14.6% vs 6.2%; effects on social life: 6.7% vs 2.3%; confidence in medical treatment: 10.0% vs 3.7%; emotional coping: 16.1% vs 6.5%; acceptance of disease: 19.6% vs 7.0%. Analysis of the dependent variable difference from baseline and the covariate baseline value revealed values of $p < 0.05$ for all five domains, despite the very short duration of the study. It is concluded that improvements in atopic eczema in infants achieved by treatment with 1% pimecrolimus cream have a significant beneficial effect on the QoL of parents [49].

Table IV. Comparison of PGE ⩾ 90% or IGA ⩽ 1 in RCTs between pimecrolimus cream and controls

IVA

Study or sub-category	Pimercrolimus n/N	Vehicle n/N	Weight %	OR (fixed) 95% CI
01. Pimecrolimus 1% vs vehicle in infants and children at 1 weeks				
Siegfried, 2006	34/181	7/91	10,34	2,78 (1,18; 6,54)
Subtotal (95% CI)	181	91	10,34	2,78 (1,18; 6,54)
Total events: 34 (Pimecrolimus), 7 (Vehicle) Test for heterogeneity: not applicable Test for overall effect: Z = 2.34 ($p = 0.02$)				
02. Pimecrolimus 1% vs vehicle in infants at 4 weeks				
Breuer, 2004	69/129	7/66	5,89	9,69 (4,12; 22,83)
Subtotal (95% CI)	129	66	5,89	9,69 (4,12; 22,83)
Total events: 69 (Pimecrolimus), 7 (Vehicle) Test for heterogeneity: not applicable Test for overall effect: Z = 5.20 ($p < 0.00001$)				
03. Pimecrolimus 1% vs vehicle in infants and children at 6 weeks				
Eichenfield, 2002	93/267	25/136	29,49	2,37 (1,44; 3,92)
Ho, 2003	67/123	15/63	12,34	3,83 (1,94; 7,56)
Eichenfield, 2005 (1)	95/211	26/110	25,67	2,65 (1,58; 4,44)
Eichenfield, 2005 (2)	65/179	14/89	16,27	3,05 (1,60; 5,83)
Subtotal (95% CI)	780	398	83,78	2,80 (2,11; 3,73)
Total events: 320 (Pimecrolimus), 80 (Vehicle) Test for heterogeneity: $\chi^2 = 1.35$, df = 3 ($p = 0.72$), $I^2 = 0\%$ Test for overall effect: Z = 7.08 ($p < 0.00001$)				
Total (95% CI)	555	353	100,00	3,21 (2,48; 4,14)
Total events: 423 (Pimecrolimus), 94 (Vehicle) Test for heterogeneity: $\chi^2 = 8.71$, df = 5 ($p = 0.12$), $I^2 = 42.6\%$ Test for overall effect: Z = 8.92 ($p < 0.00001$)				

Table IV.

IVB

Study or sub-category	Pimercrolimus n/N	Corticosteroids n/N	Weight %	OR (fixed) 95% CI
01. Pimecrolimus 1% vs corticosteroids in 6 months				
Kapp, 2002	108/204	17/46	17,29	1,92 (0,99; 3,71)
Wahn, 2002	289/474	120/237	82,71	1,52 (1,11; 2,09)
Subtotal (95% CI)	678	283	100,00	1,59 (1,20; 2,11)
Total events: 397 (Pimecrolimus), 137 (Corticosteroids) Test for heterogeneity: $\chi^2 = 0.39$, df = 1 ($p = 0.53$), $I^2 = 0\%$ Test for overall effect: Z = 3.21 ($p = 0.001$)				
02. Pimecrolimus 1% vs corticosteroids in 12 months				
Kapp, 2002	110/204	22/46	21,96	1,28 (0,67; 2,42)
Wahn, 2002	162/474	67/237	78,04	1,32 (0,94; 1,85)
Subtotal (95% CI)	678	283	100,00	1,31 (0,97; 1,77)
Total events: 272 (Pimecrolimus), 89 (Corticosteroids) Test for heterogeneity: $\chi^2 = 0.01$, df = 1 ($p = 0.93$), $I^2 = 0\%$ Test for overall effect: Z = 1.75 ($p = 0.08$)				

1% pimecrolimus cream versus potent corticosteroid (trunk) and mild corticosteroid (face). Table IVB shows two trials (711 children, aged 2–17 years; 250 infants, aged 3–23 months) comparing 1% pimecrolimus cream with a combined treatment regimen of 0.1% triamcinolone acetonide (trunk and limbs) and 1% hydrocortisone acetate (face, neck and intertriginous areas). The 1% pimecrolimus cream was no more significantly effective than 1% hydrocortisone acetate on the basis of the proportion of patients with an IGA ⩽ 1 at 6 months and at 12 months the corresponding OR were 1.59 (95% CI: 1.20 to 2.11) and 1.31 (95% CI: 0.97 to 1.77) [44, 45].

1% pimecrolimus cream versus 0.03% or 0.1% tacrolimus ointments. Table V shows one trial comparing 0.03% tacrolimus ointment against 1% pimecrolimus cream (425 children with mild AD); no significant difference was found in the proportion of children with an IGA ⩽ 1 at 4 weeks (OR 1.28; 95% CI: 0.78 to 1.88) [39]. The other trial compared 0.03% tacrolimus ointment against 1% pimecrolimus cream (141 children with moderate AD);

Table. V. Comparison of PGE ⩾ 90% or IGA ⩽ 1 in RCTs between tacrolimus ointment and pimecrolimus cream

Исследование или подкатегория	Tacrolimus n/N	Pimercrolimus n/N	Weight %	OR (fixed) 95% CI
01. Tacrolimus 0.03% vs pimecrolimus 1% at 4 weeks				
Paller, 2005	97/208	88/217	64,39	1,28 (0,87; 1,88)
Subtotal (95% CI)	208	217	64,39	1,28 (0,87; 1,88)
Total events: 97 (Tacrolimus), 88 (Pimecrolimus) Test for heterogeneity: not applicable Test for overall effect: Z = 1.26 ($p = 0.21$)				
02. Tacrolimus 0.03% vs pimecrolimus 1% at 6 weeks				
Kempers, 2004	42/70	30/71	16,69	2,05 (1,05; 4,01)
Subtotal (95% CI)	70	71	16,69	2,05 (1,05; 4,01)
Total events: 42 (Tacrolimus), 30 (Pimecrolimus) Test for heterogeneity: not applicable Test for overall effect: Z = 2.10 ($p = 0.04$)				
03. Tacrolimus 0.1% vs pimecrolimus 1% at 4 weeks				
Paller, 2005	36/112	20/113	18,92	2,20 (1,18; 4,12)
Subtotal (95% CI)	112	113	18,92	2,20 (1,18; 4,12)
Total events: 36 (Tacrolimus), 20 (Pimecrolimus) Test for heterogeneity: not applicable Test for overall effect: Z = 2.48 (P = 0.01)				
Total (95% CI)	390	401	100,00	1,58 (1,18; 2,12)
Total events: 175 (Tacrolimus), 138 (Pimecrolimus) Test for heterogeneity: $\chi^2 = 2.81$, df = 2 ($p = 0.25$), $I^2 = 28.8\%$ Test for overall effect: Z = 3.08 ($p = 0.002$)				

a significant difference was found in the proportion of children with an IGA ⩽ 1 at 6 weeks (OR 2.05; 95% CI: 1.05 to 4.01) [36]. The latest trial in comparing 0.03% tacrolimus ointment against 1% pimecrolimus cream (225 children with moderate to severe AD) showed a significant difference in the proportion of children with an IGA ⩽ 1 at 6 weeks (OR 2.20; 95% CI: 1.18 to 4.12) too [39]. One article reported that the improvement percentage from baseline (by reduction in EASI score) was significantly greater for the tacrolimus ointment-treated groups than for the 1% pimecrolimus cream group (p = 0.04) (shown in Table III) [39].

Safety

The safety data are summarized in Table VI, with incidence rates of common adverse events presented as reported in the original studies. The incidence of adverse events of 0.03% tacrolimus ointment was 15–84%; 29 cases withdrew because of adverse events (eight trials) [31, 33–39, 41]. The incidence of adverse events of 0.1% tacrolimus ointment was 13–39%; 11 cases withdrew (four trials) [31, 33, 34, 39]. The incidence of adverse events of 1% imecrolimus cream was 5–86%; 27 cases withdrew because of adverse events (seven trials) [36, 39, 42, 47, 48, 50, 51]. The major adverse events included burning and pruritus.

Discussion

Four earlier reviews (11,58–60) in RCTs gathered from 1998 to 2004 had no distinct adult and child to carry out the pooling analysis. However, these studies were not adequately powered to detect a significant difference in the efficacy and safety for pediatric patients. To our knowledge, this study represents the most comprehensive evidence-based review of topical tacrolimus and pimecrolimus in the treatment of pediatric AD to date, with data on 2056 pediatric patients (between 2 and 17 years of age) treated with tacrolimus from nine RCTs (eight articles) and 2169 pediatric patients (between 3 months and 17 years of age) treated with pimecrolimus from 10 RCTs (nine articles). In general, significantly more patients in 0.03% or 0.1% tacrolimus have a PGE ⩾ 90% or an IGA ⩽ one response than control groups, including vehicle (OR = 4.56; 95% CI: 2.80 to 7.44), 1% hydrocortisone acetate (OR = 3.92; 95% CI: 2.96 to 5.20) and 1% pimecrolimus (OR = 1.58; 95% CI: 1.18 to 2.12), which was statistically significant. The effect difference between 0.03% tacrolimus and 0.1% tacrolimus ointments

Table VI. Adverse events and withdrawn RCTs

Study	Intervention	AE/% (n/N)	Withdrawn		
			AE	LE	Other
Boguniewicz, 1998 [31]	0,03% tacrolimus	49 (21/43)	0	1	1
	0,1% tacrolimus	33 (16/49)	1	0	4
	Vehicle	27 (12/44)	2	4	1
Paller, 2001 [33]	0,03% tacrolimus	/	6	4	13
	0,1% tacrolimus	/	3	5	9
	Vehicle	/	9	46	10
Liu, 2005 [37]	0,03% tacrolimus	33 (23/70)	7[a]	–	–
	Placebo	38 (26/69)	6[a]	–	–
Schachner, 2005 [38]	0,03% tacrolimus	37 (58/158)	7	4	18
	Vehicle	45 (72/159)	12	20	29
Reitamo, 2002 [34]	0,03% tacrolimus	43 (81/189)	3	0	0
	0,1% tacrolimus	39 (72/186)	3	0	0
	1% Hydrocortisone acetate	21 (39/185	4	0	0
Reitamo, 2004 [35]	0,03% tacrolimus	73 (153/210)	8	4	9
	1% Hydrocortisone acetate	52 (107/207)	6	17	18
Kempers, 2004 [36]	0,03% tacrolimus	84 (59/70)	1	0	2
	1% pimecrolimus	86 (61/71)	5	3	5
Paller, 2005 [39]	0,03% tacrolimus	15 (32/208)	0	4	43
	1% pimecrolimus	17 (36/217)	10	13	33
Paller, 2005 [39]	0,1% tacrolimus	13 (14/112	4	6	26
	1% pimecrolimus	20 (23/113)	5	11	27
Bieber, 2007 [41]	0,03% tacrolimus	17 (23/136)	4	0	2
	0,1% methylprednisolone aceponate	12 (16/129)	0	0	2
Wahn, 2002 [44]	1% pimecrolimus: 6 m	25 (117/474)	/	42	72
	12 m	8 (39/474)		59	91
	Corticosteroids: 6 m	19 (44/237)	/	65	49
	12 m	5 (12/237)		72	50
Kapp, 2002 [45]	1% pimecrolimus: 6 m	/	/	19	13
	12 m	–	–	21	29
	Corticosteroids: 6 m	/	/	14	2
	12 m	–	–	15	3

Table VI.

Eichenfield, 2002 [42]	1% pimecrolimus	44 (117/267)	5	7	18
	Vehicle	43 (58/136)	4	21	9
Ho, 2003 [46]	1% pimecrolimus	75 (92/123)	/	8	6
	Vehicle	65 (41/63)	/	26	4
Breuer, 2004 [47] and Kaufmann, 2004 [48]	1% pimecrolimus	64 (83/130)	2	5	6
	Vehicle	61 (40/66)	1	23	1
Eichenfield, 2005 [50]	1% pimecrolimus	9 (19/211) Caucasian	0	0	0
		6 (10/179) non-Caucasian	–	–	–
	Vehicle	9 (10/110) Caucasian	0	0	0
		10 (9/89) non-Caucasian	–	–	–
Siegfried, 2006 [51]	1% pimecrolimus	10 (18/183)	0	7	28
	Vehicle	2 (2/92)	0	13	13

[a] — No described reason; AE — Adverse events; LE — lack of efficacy; / — No reported data.

was not statistically significant for PGE ⩾ 90% or IGA ⩽ 1 (OR = 0.90; 95% CI: 0.55 to 1.48). Overall, tacrolimus ointment or pimecrolimus cream had a significantly greater relative reduction in the EASI score than the vehicle and 1% hydrocortisone acetate ($p < 0.001$). Only one trial had the comparison between 0.1% tacrolimus and 1% pimecrolimus, showing a significant difference in favor of 0.1% tacrolimus over 1% pimecrolimus ($p = 0.04$). The incidence of adverse events of tacrolimus ointment or pimecrolimus cream was similar to vehicle. The major adverse events were burning and pruritus. Clinical data about the application of tacrolimus ointment in infants were not found.

AD primarily occurred in infants and children. In those patients, onset was more frequent and clinical symptoms were more severe compared with adult patients. Therefore the clinical data from the childhood stage and adult stage may have some heterogeneity. To avoid bias, we collected the data specially aimed at pediatric patients, and searched more widely than the earlier studies (11,57–59). At last, 18 RCTs between 1998 and 2006 were identified, pooling analysis was carried out and a dependable result was acquired. The 0.03% tacrolimus ointment appeared to be as effective as 0.1% tacrolimus. The tacrolimus ointments (0.03% and 0.1%) were superior to 1% hydrocortisone acetate and 1% pimecrolimus, and 1% pimecrolimus was superior to triamcinolone acetonide 0.1% (trunk and limbs) and hydrocortisone acetate 1% (face, neck, and intertriginous areas).

The 19 RCTs were of high quality and were all sponsored by Fujisawa or Novartis, so there is a possibility of positive bias of remittive effects in the original literature, which could result in evaluation bias of remittive effects in this systematic review. Therefore, the results of this systematic review should be integrated with doctors' experiences and actual clinical conditions as a guide to clinical practice after careful thinking. The results should now be tested by more large-scale clinical trials.

Declaration of interest. The authors and this study were autonomous and had no conflict of interest with Fujisawa or Novartis.

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