Review Article

Topical calcineurin inhibitors in atopic dermatitis: A systematic review and meta-analysis

Mohammad Maged. Y. El-Batawy, Manal A.-W. Bosseila *,
Heba M. Mashaly, Vanessa Suzan G.A. Hafez

Department of Dermatology, Faculty of Medicine, Cairo University, Egypt

ARTICLE INFO

ABSTRACT

Objectives: To build a critical appraisal of the available literature to evaluate the effectiveness of topical calcineurin inhibitors in treatment of atopic dermatitis (AD), in comparison to topical corticosteroids (TCs) and/or placebo.

Review methods: Design: systematic review and meta-analysis. *Data sources*: electronic search of MEDLINE Pubmed along the last 10 years (1997–2006). *Study selection*: randomized control trials of TCIs reporting efficacy outcomes, in comparison to TCs or vehicle (placebo) or both. *Data synthesis*: of **210** articles, 19 studies were included, 10 for tacrolimus and 9 for pimecrolimus, involving **7378** patients of whom **2771** applied tacrolimus, **1783** applied pimecrolimus, and **2824** were controls. Both drugs were significantly more effective than a vehicle. However, two long-term trials comparing demonstrated the value of pimecrolimus in reduction of flares and steroid-sparing effect after 6 months. Compared to TCs, both 0.1% and 0.03% tacrolimus ointments were as effective as moderate potency TCs, and more effective than a combined steroid regimen. Tacrolimus was more effective than mild TCs.

Conclusions: TCIs in AD are more effective than placebo. Although less effective than TCs, pimecrolimus has its value in long-term maintenance and as a steroid-sparing agent in AD, whenever used early enough, at first appearance of erythema and/or itching. In treatment of moderate to severe AD, topical tacrolimus is as effective as moderately potent TCs, and more effective than mild preparations. Chronic AD lesions of the face and flexures are the most justified indication for topical calcineurin inhibitors.

Contents

* Corresponding author at: 37 Str. Hadaek El-Ahram, Giza, Egypt. Tel.: +2 0102412964.
  E-mail address: manalbosseila@yahoo.com (Manal A.-W. Bosseila).

1. Introduction

Atopic dermatitis (AD) is one of the most common chronic diseases of childhood [1] that may persist in adulthood with distinctive clinical features and disease course [2]. Treatment should be tailored to an individual's needs, bearing in mind age, sex, social conditions, sites of involvement and severity. Choice of therapy should reflect an understanding of the underlying immune abnormalities of this complex chronic skin disease [3]. First-line therapy has generally consisted of care for dry skin, avoidance of triggers, application of topical corticosteroids (TC), topical antiseptics and administration of oral antibacterials and sedating antihistamines [4].

Corticosteroids continue to be one of the main pillars of dermatological therapy of atopic dermatitis. However, their use is limited by local and systemic adverse effects. Cutaneous complications such as striae, atrophy, and telangiectasia limit the long-term use of these agents. Tachyphylaxis is also one of the clinical concerns. Application on large surface areas, especially in infants, carries the risk of percutaneous systemic absorption, resulting in hypothalamic pituitary axis suppression [3,5].

An enormous demand for anti-inflammatory agents not belonging to the corticosteroid group is increasing [6]. In the last few years the therapeutic arsenal for AD has expanded with two distinct groups of drugs: topical immunomodulators and leukotriene inhibitors [6].

Tacrolimus (FK 506) and pimecrolimus (ASM 981) are topical immunomodulators classified as calcineurin inhibitors. They belong to this group of substances with a high capacity to inhibit T lymphocyte activation. Although they also act on other cells playing a role in AD (mastocytes, Langerhans' cells, B lymphocytes), their action on T lymphocytes seems to be the most important [6,7,8]. Questions remain regarding the place of topical calcineurin inhibitors (TCIs) as a treatment for AD and how to use them most effectively, from both therapeutic and pharmacoeconomic standpoints [4].

The aim of this work was to build a critical appraisal of the available literature to evaluate the effectiveness of topical tacrolimus and pimecrolimus in the treatment of atopic dermatitis, in comparison to topical corticosteroids and/or placebo. This study was designed in the form of a systematic review and meta-analysis.

2. Methodology

The methods used to carry out this systematic review adhered to the guidelines stated by the Centre of Research and Dissemination (CRD) report for carrying out systematic reviews. The items of the report were adapted to meet the quality requirements for reports of systematic reviews and meta-analyses, as summarized by the QUOROM statement check list according to Moher et al. [9].

2.1. Search strategy

Our data sources included: electronic database (1997–2006), available through MEDLINE Pubmed, Bibliographies (cross-refer-

ence search). *Documentation*: search terms included: dermatitis, atopic, eczema, calcineurin, tacrolimus, pimecrolimus. *Bibliographic management*: All retrieved references were saved on special software, *Reference Manager* (version 11).

2.2. Study selection

The abstracts collected by the above mentioned search strategy were first screened for identification of the relevant trials. Full texts of these articles were retrieved through the official site of the Egyptian Universities Library (www.eul.edu.eg), accessible through the computer laboratory of the National Institute of Laser Enhanced Sciences (NILES). The trials were examined for inclusion or exclusion according to the criteria described below.

2.2.1. Inclusion criteria
Patients: atopic dermatitis patients, all age groups, including children aged less than 2 years, and all ethnic groups. *Intervention*: topical pimecrolimus and/or tacrolimus. *Comparator*: topical corticosteroids and/or placebo. *Outcome*: effectiveness outcomes. *Study design*: randomized controlled trials (RCTs), only the original clinical trials.

2.2.2. Exclusion criteria included
Studies on other types of eczema, case reports, case series, and non-randomized studies, cost-effectiveness studies, studies published in languages other than English, French or German, studies not reporting patient relevant outcomes, Quality of Life studies (QoL) studies, studies only available as abstracts, studies reporting safety outcomes only, duplicate studies and animal models studies. Fig. 1 (Flow chart) shows the sequence of steps in the process of study selection.

2.3. Data extraction

Data from the retrieved trials were extracted and tabulated in a Data Extraction Sheet. The trials used different scales to rate the degree of improvement. Therefore, we defined our outcomes of interest for effectiveness according to the most commonly used ones across all trials.

Primary outcomes were Investigator Global Assessment (IGA) of AD and Physician Global Evaluation score (PGE). Secondary outcomes were Patient Global assessment of feeling better, Pruritus severity score, frequency of flares of AD and steroid-sparing effect.

The effectiveness outcome was dichotomized in terms of "*treatment success*", where for pimecrolimus, it was defined as the proportion of patients who were rated by the investigator as *clear* or *almost clear*. This was equivalent to IGA score 0 or 1. As for tacrolimus, treatment success was defined as the proportion of patients who achieved at least 90% improvement from baseline, described in the trials as reaching *clear* state or *excellent improvement*, as rated by the Physician Global Evaluation score.

For extraction of trials' results, the number of patients in each outcome of interest was reported as an actual number, and when necessary, recalculated on an intention-to-treat (ITT) basis.
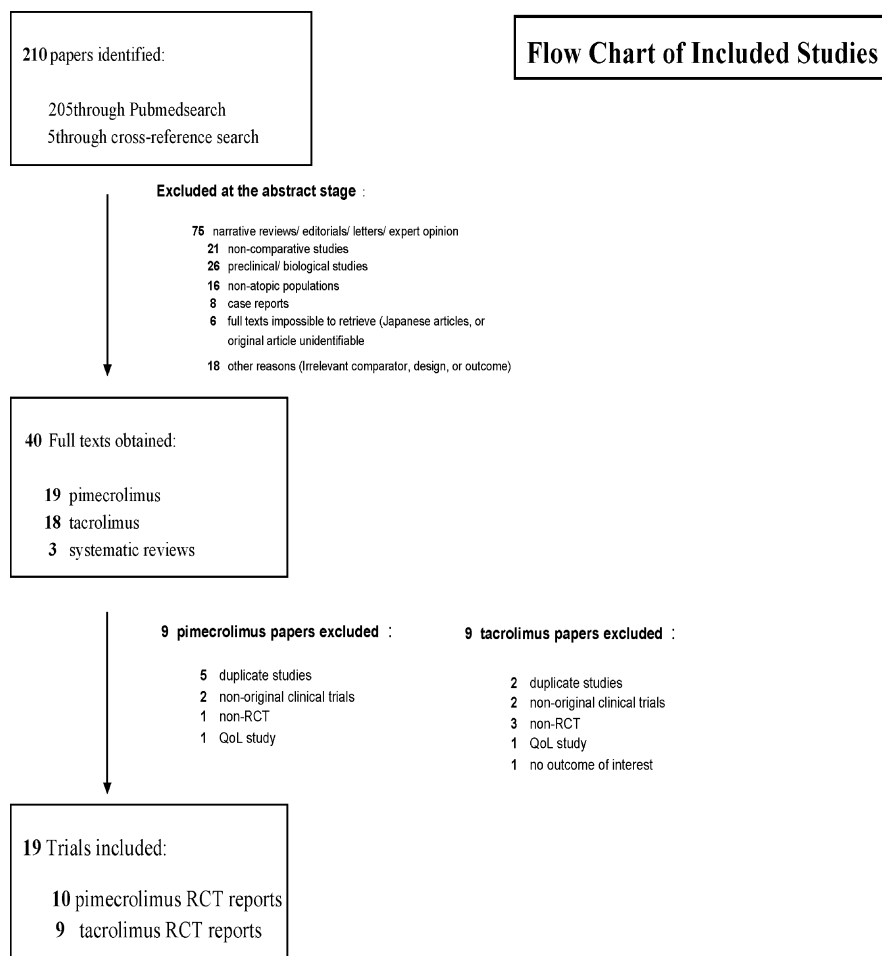
Fig. 1. Flow chart of included studies.

2.4. Validity (quality) assessment

2.4.1. Internal validity

All studies were evaluated as regards the criteria of internal validity which included, appropriate randomization and allocation concealment, double blinding and whether intention-to-treat analysis and power calculation were performed.

2.4.2. External validity

Studies were given a rating of *high generalisability* if there was a detailed description of the following criteria, and *low generalisability* if there was little informative description. Criteria of external validity included timing, duration and location of the study, age of participants, co-morbidity, inclusion and exclusion criteria, concomitant treatment, washout periods and length of follow-up.

2.5. Data analysis (synthesis)

Data from Extraction Sheets of included studies were entered into the Cochrane collaboration's software for systematic reviews and meta-analysis, the *Review Manager* (*version 4.2.8*), to allow the process of computerized data analysis. Dichotomous data were summarized as rate ratios (relative risks, RR) and combined by using a random effects meta-analytic model, as developed by Cochrane (1954) [10]. Results were presented with 95% confidence interval. Heterogeneity statistics were computed to test the agreement of the individual trial results with the combined meta-analytic summary, using chi-square. All analyses were

considered significant when the confidence interval did not include the value one, which means a *p*-value $\leq$0.05.

3. Results

The applied search strategy identified 210 articles, of which 191 were excluded. Nineteen randomized controlled trials (RCTs) were included: 10 for pimecrolimus, and 9 for tacrolimus, with a total of 7378 patients involved in the trials. The included studies used topical corticosteroids or vehicle as a comparator. Vehicle is the base of the cream or ointment without the active ingredient; thus it was used as a placebo.

3.1. Pimecrolimus studies

3.1.1. Characteristics of included studies

The characteristics of included studies are elaborated in Table 1, 10 RCTs were included, involving a total of **2959** patients, of which **1783** applied pimecrolimus cream, **804** were in the vehicle control group, and only **372** were in the TCs control group. The age groups involved were as follows: three studies included infants aged 3–23 months old, two studies included children and adolescents aged 2–17 years old and five studies included adults aged $\geq$18 years old.

3.1.2. Quality (validity) of included studies

According to the predefined criteria of external validity, only five out of the ten trials were judged to have high

Table 1
Characteristics of included pimecrolimus studies.

Study	Setting	Participants	Interventions	Outcomes	Severity of AD	Definition of AD
1. Ho [27]	Six weeks DB, followed by 20 weeks open label	186 infants (3–23 months)	Pimecrolimus 1% twice daily.[a] Vehicle (DB phase)	IGA; EASI; Pruritus score; Primary care giver's global assessment of disease control	Mild to moderate	Seymour et al. [31]
2. Kapp [12]	Twelve months DB	251 infants (3–23 months)	Pimecrolimus 1% twice daily[a]. Vehicle	Incidence of flares at 6 months; IGA; EASI; Pruritus score; Primary care giver's global assessment of disease control	Mild to very severe	Seymour et al. [31]
3. Kaufmann [28]	Four weeks DB, followed by 12 weeks open label, followed by 4 weeks follow up	196 infants (3–23 months)	Pimecrolimus 1% twice daily[a]. Vehicle	Onset of effectiveness; Incidence of flares at EOS; EASI; IGA; Caregiver's assessment of pruritus severity and sleep loss	Mild to very severe	Seymour et al. [31]
4. Eichen–field [29]	Pooled data of 2 RCTs of identical design; 6 weeks DB	403 children and adolescents (1–17 years)	Pimecrolimus 1% twice daily[a]. Vehicle	IGA; EASI; Pruritus score; Patient's global assessment of disease control	Mild to moderate	Williams et al. [32]
5. Wahn [13]	Twelve months DB	711 children and adolescents (2–17 years)	Pimecrolimus 1% twice daily[a]. Vehicle	Incidence of flares at 6 and 12 months; TCs requirement; Time to first flare; IGA; EASI	Moderate to very severe	Williams et al. [32]
6. Kaufmann [28]	One week DB, followed by 5 weeks open label	198 adults (18–81 years)	Pimecrolimus 1% twice daily[a]. Vehicle	Time to 1st pruritus relief; Pruritus severity score; IGA	Mild to moderate	Seymour et al. [31]
7. Luger [11]	Three weeks DB, 6 arms trial	130 adults (≥18 years)	Pimecrolimus 0.05%, 0.2%, 0.6% and 1% twice daily[a]. 0.1% betamethasone-17-valerate[a]. Vehicle	Adapted EASI; Pruritus score; Patient's self assessment of disease control	Moderate to severe	Hanifin and Rajka [33]
8. Luger [15]	Twelve months DB	658 adults (18–79 years)	Pimecrolimus 1%[a]. 0.1% triamcinolone acetonide (trunk and limbs), + 1% hydrocortisone acetate (face, neck, flexures)	Incidence of skin infections; Application site reactions; EASI; IGA; Remission incidence; Recurrence incidence	Moderate to severe	Williams et al. [32]
9. Meurer [14]	Six months DB	192 adults (≥18 years)	Pimecrolimus 1% twice daily[a]. Vehicle	Incidence of flares; TCs requirement; IGA; EASI; Pruritus score; Patient's global assessment of disease control	Moderate to severe	Rajka and Langland criteria [34]
10. Van Leent [30]	Three weeks DB	34 adults	Pimecrolimus 1% twice daily or once daily[a]. Vehicle	ADSI	Moderate to severe	Hanifin and Rajka [33]

[a] Versus *TCs*: topical corticosteroids; *DB*: double blind; *IGA*: Investigator's Global Assessment of Atopic Dermatitis; *ADSI*: atopic dermatitis severity index; *EASI*: eczema area severity index.

generalisability. All studies, except one [11] were sponsored from Novartis.

3.1.3. Pooled analysis

The studies were grouped according to their main outcomes of interest. Figs. 2–9 illustrate forest plots of these pooled analyses.

3.1.3.1. Vehicle controlled studies (Figs. 2–9).

- Comparison 1—pimecrolimus cream 1% versus vehicle

Outcome 01: *Investigator's Global Assessment of AD, score 0 or 1 (clear or almost clear)* (Fig. 2). Pimecrolimus cream 1% was found significantly more effective than vehicle, as measured by Investigator's Global Assessment at three weeks ($p = 0.005$), and at six weeks ($p < 0.00001$). One trial on infants with mild to very severe AD [12] found no significant difference

between both groups at 6 months ($p = 0.08$) and at 12 months ($p = 0.47$).

Outcome 02: *Pruritus severity score 0 or 1* (Fig. 3). Pimecrolimus cream 1% was found significantly more effective than vehicle as assessed by the pruritus severity score at three weeks (RR 2.10, 95% CI 1.7–2.58) ($p < 0.00001$), and similarly at six weeks (RR 1.84, 95% CI 1.44–2.36) ($p < 0.00001$).

- Comparison 2—pimecrolimus cream 1% versus vehicle with allowed TCs in case of flares

Outcome 01: *No flares at 6 months* (Fig. 4). Application of pimecrolimus cream 1% regularly for 6 months resulted in significantly fewer flares of AD, as demonstrated by two long-term studies [13,14] RR 1.90, 95% CI 1.5–2.41) ($p < 0.00001$). Both trials allowed the use of moderately potent TCs as a rescue medication in case of uncontrolled flares. These studies had strong validity and high generalisability.

Review: Topical Pimecrolimus In Atopic Dermatitis
Comparison: 01 Pimecrolimus cream 1% vs Vehicle
Outcome: 01 Investigator's Global Assessment of response score 0 or 1 (clear or almost clear)

Study or sub-category	Pimecrolimus n/N	Vehicle n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 At three weeks					
Luger 2001	5/45	0/43		0.98	10.52 [0.60, 184.]
Eichenfield 2002	72/267	10/136		10.68	3.67 [1.96, 6.87]
Kapp 2002	112/204	18/46		15.60	1.40 [0.96, 2.05]
Ho 2003	54/123	11/63		11.67	2.51 [1.42, 4.46]
Subtotal (95% CI)	639	288		38.93	2.41 [1.31, 4.43]
Total events: 243 (Pimecrolimus), 39 (Vehicle)					
Test for heterogeneity: Chi² = 9.66, df = 3 (P = 0.02), I² = 68.9%					
Test for overall effect: Z = 2.83 (P = 0.005)					
02 At six weeks					
Eichenfield 2002	93/267	25/136		15.40	1.89 [1.28, 2.80]
Ho 2003	67/123	15/63		13.68	2.29 [1.43, 3.66]
Subtotal (95% CI)	390	199		29.08	2.05 [1.52, 2.76]
Total events: 160 (Pimecrolimus), 40 (Vehicle)					
Test for heterogeneity: Chi² = 0.37, df = 1 (P = 0.55), I² = 0%					
Test for overall effect: Z = 4.67 (P < 0.00001)					
03 At six months					
Kapp 2002	108/204	17/46		15.21	1.43 [0.96, 2.13]
Subtotal (95% CI)	204	46		15.21	1.43 [0.96, 2.13]
Total events: 108 (Pimecrolimus), 17 (Vehicle)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 1.77 (P = 0.08)					
04 At twelve months					
Kapp 2002	110/204	22/46		16.78	1.13 [0.81, 1.56]
Subtotal (95% CI)	204	46		16.78	1.13 [0.81, 1.56]
Total events: 110 (Pimecrolimus), 22 (Vehicle)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.72 (P = 0.47)					
Total (95% CI)	1437	579		100.00	1.84 [1.37, 2.46]
Total events: 621 (Pimecrolimus), 118 (Vehicle)					
Test for heterogeneity: Chi² = 20.04, df = 7 (P = 0.005), I² = 65.1%					
Test for overall effect: Z = 4.10 (P < 0.0001)					

0.001 0.01 0.1 1 10 100 1000
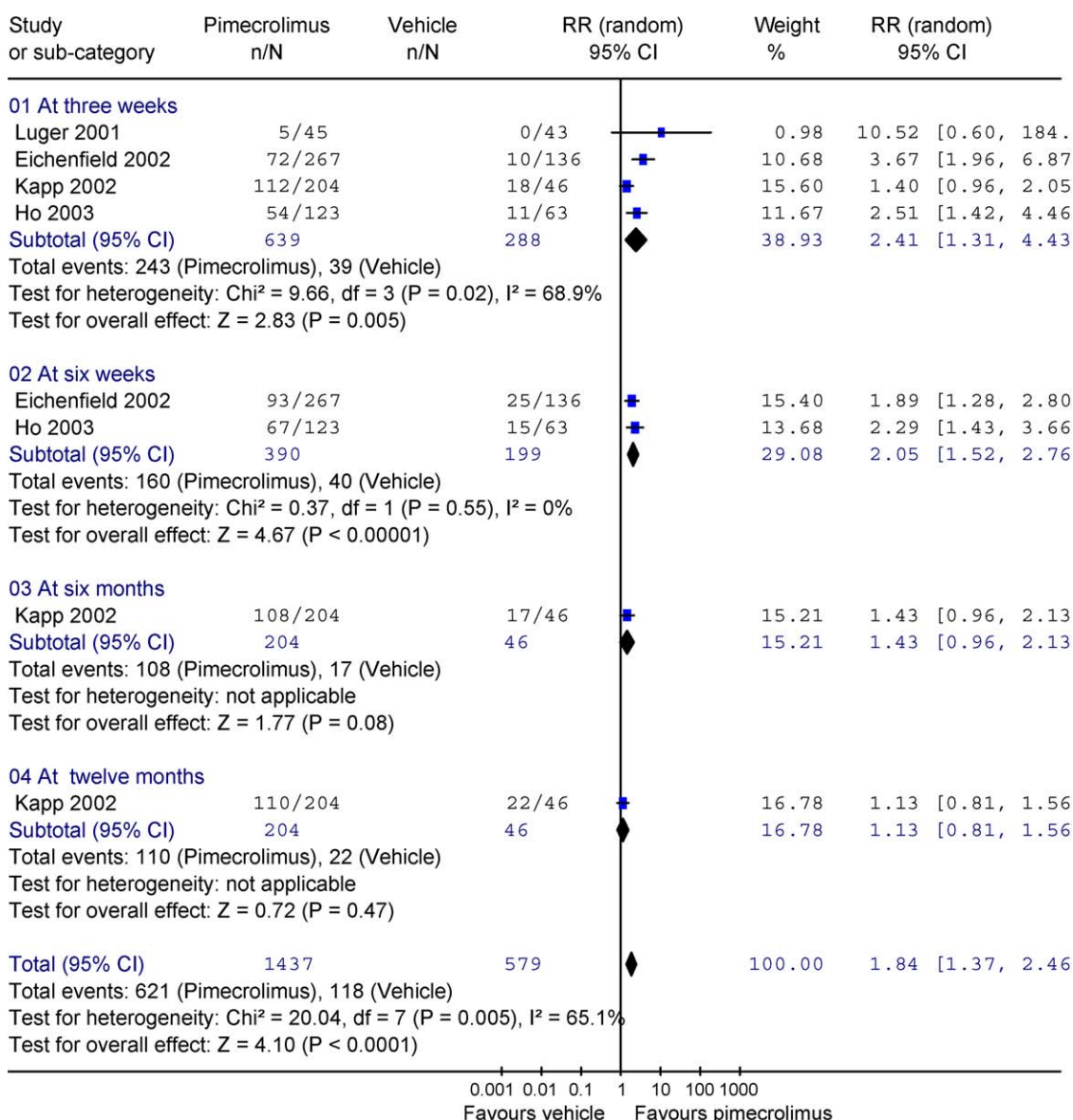Favours vehicle   Favours pimecrolimus

Fig. 2. Comparison between the effect of Pimecrolimus cream 1% and vehicle on the Investigator's Global Assessment of response.

Review: Topical Pimecrolimus In Atopic Dermatitis
Comparison: 01 Pimecrolimus cream 1% vs Vehicle
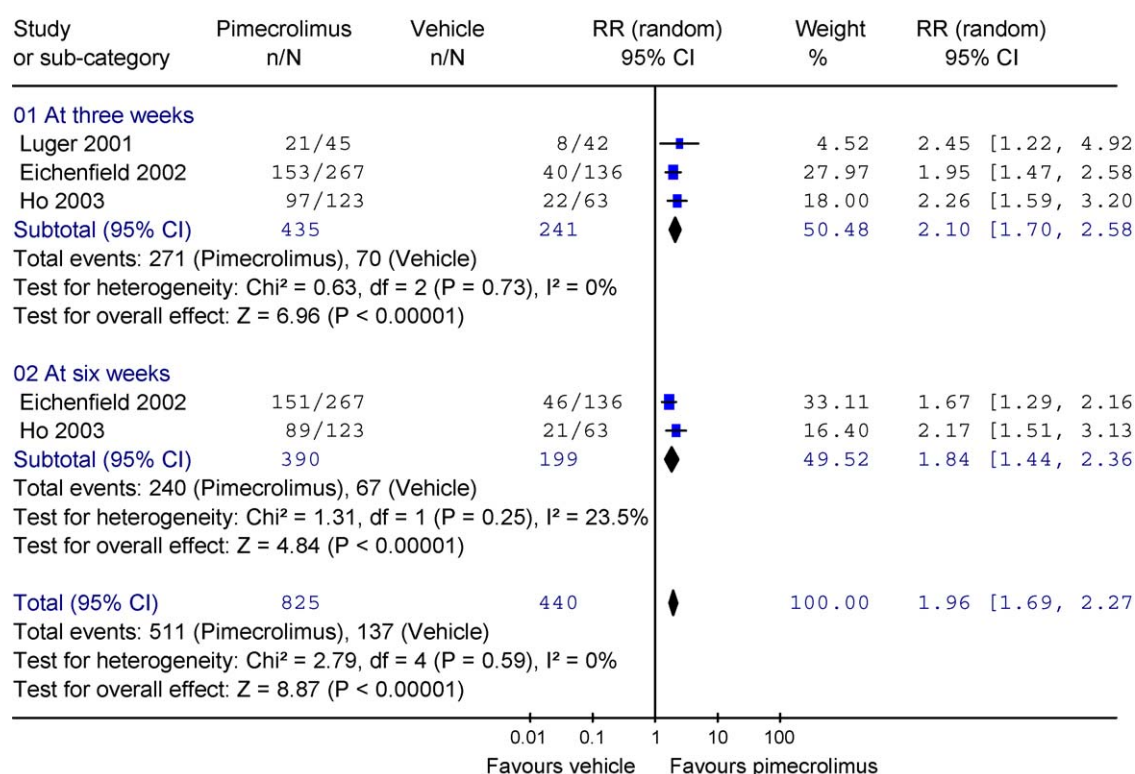Outcome: 02 Pruritus severity score 0 or 1

Study or sub-category	Pimecrolimus n/N	Vehicle n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 At three weeks					
Luger 2001	21/45	8/42		4.52	2.45 [1.22, 4.92
Eichenfield 2002	153/267	40/136		27.97	1.95 [1.47, 2.58
Ho 2003	97/123	22/63		18.00	2.26 [1.59, 3.20
Subtotal (95% CI)	435	241		50.48	2.10 [1.70, 2.58

Total events: 271 (Pimecrolimus), 70 (Vehicle)
Test for heterogeneity: Chi² = 0.63, df = 2 (P = 0.73), I² = 0%
Test for overall effect: Z = 6.96 (P < 0.00001)

02 At six weeks					
Eichenfield 2002	151/267	46/136		33.11	1.67 [1.29, 2.16
Ho 2003	89/123	21/63		16.40	2.17 [1.51, 3.13
Subtotal (95% CI)	390	199		49.52	1.84 [1.44, 2.36

Total events: 240 (Pimecrolimus), 67 (Vehicle)
Test for heterogeneity: Chi² = 1.31, df = 1 (P = 0.25), I² = 23.5%
Test for overall effect: Z = 4.84 (P < 0.00001)

Total (95% CI)	825	440		100.00	1.96 [1.69, 2.27

Total events: 511 (Pimecrolimus), 137 (Vehicle)
Test for heterogeneity: Chi² = 2.79, df = 4 (P = 0.59), I² = 0%
Test for overall effect: Z = 8.87 (P < 0.00001)

```
         0.01   0.1    1    10   100
         Favours vehicle  Favours pimecrolimus
```

Fig. 3. Comparison between the effect of Pimecrolimus cream 1% and vehicle on Pruritis Severity Score.

Outcome 02: *No use of TCs at 6 months* (Fig. 5). Regular application of pimecrolimus cream 1% for 6 months was found to reduce significantly the rate of use of TCs, as demonstrated by the same two long-term studies of strong validity [13,14] (RR 1.83, 95% CI 1.52–2.19) ($p < 0.00001$).

3.1.3.2. Studies with TCs control (comparative effectiveness).

- Comparison 3—pimecrolimus cream 1% versus potent TCs

  Outcome: *Investigator's Global Assessment of AD, score 0 or 1 (clear or almost clear) at three weeks* (Fig. 6). One trial only [11] compared pimecrolimus cream 1% with betamethasone-17-valerate 0.1% cream in moderate to severe AD, and reported on the proportion of patients clear or almost clear at three weeks. The potent TCs was found to be significantly more effective than pimecrolimus (RR 0.22, 95% CI 0.09–0.54) ($p = 0.0008$).
- Comparison 4—pimecrolimus cream 1% versus combined potent-and-mild TCs regimen

  Outcome: *Investigator's Global Assessment of AD, moderately clear or better* (Fig. 7). A single 1-year duration trial [15] compared pimecrolimus cream 1% with a combined treatment regimen of triamcinolone acetonide 0.1% cream (on trunk and limbs), and hydrocortisone acetate (HCA) 1% cream (on face and flexures). On basis of the proportion of patients moderately clear or better, the combined TCs regimen was found significantly more effective than pimecrolimus after treatment for one week ($p < 0.00001$), three weeks ($p < 0.00001$), 6 months ($p = 0.003$), but treatment groups did not differ significantly at the end of treatment (12 months, $p = 0.008$) (RR 0.77, 95% CI 0.63–0.93).

3.2. Tacrolimus studies

3.2.1. Characteristics of included studies

The characteristics of included studies are elaborated in Table 2, nine RCTs were included, involving a total of **4419** patients, of which **2771** applied tacrolimus cream, **585** were control in the vehicle group, and **1063** were in the TCs control group. The age groups involved were as follows five studies included children with ages ranging between 2 and 17 years old. The other four studies included adolescents and adults in age range between 13 and 79 years. No trials were performed on infants younger than 2 years old.

3.2.2. Quality (validity) of included studies

According to the predefined criteria of external validity, only two out of the nine trials were judged to have high generalisability. All studies, except one [16], were sponsored from Fujisawa.

3.2.3. Pooled analysis

The pooled extracted results of all combinable tacrolimus studies were grouped according to their main outcomes of interest. Figs. 8 and 9 illustrate forest plots of these pooled analyses.

- Comparison 1—tacrolimus ointment versus vehicle

  Outcome: *Physician's Global Evaluation of response clear or excellent improvement ($>90\%$)* (Fig. 8). One of three studies [17] compared both tacrolimus ointment concentrations, 0.03% and 0.1%, to vehicle for three weeks in children. The 0.03% ointment was found to be more effective than vehicle (RR 2.13, 95% CI 1.24–3.68) ($p = 0.006$), but this was not the case for the 0.1% ointment ($p = 0.13$). The two other studies [18,19] compared both concentrations to vehicle for a longer duration, 12 weeks. Tacrolimus 0.03% and 0.1% were significantly more effective

Table 2
Characteristics of included tacrolimus studies.

Study	Setting	Participants	Interventions	Outcomes	Severity of AD	Definition of AD
1. Bogunie-wicz [17]	Three weeks, 4 arms DB	180 children (7–16 years)	Tacrolimus 0.03%, 0.1%, and 0.3% twice daily[a]. Vehicle	PGE; mEASI; Patient's assessment of global response and of pruritus; Duration of remission	Moderate to severe	Hanifin and Rajka [33]
2. Paller [18]	Twelve weeks, 3 arms DB	351 children (2–15 years)	Tacrolimus 0.03%, and 0.1% twice daily[a]. Vehicle	PGE; EASI; %BSA affected; Physician assessment of signs of AD; Patient's assessment of overall response and pruritus	Moderate to severe	Hanifin and Rajka [33]
3. Schachner [16]	Six weeks, 2 arms DB	317 children (2–15 years)	Tacrolimus 0.03% twice daily[a]. Vehicle	IGADA; EASI; %BSA affected; Patient's assessment of itch	Mild to moderate	Hanifin and Rajka [33]
4. Reitamo [21]	Three weeks, 3 arms DB	560 children (2–15 years)	Tacrolimus 0.03%, and 0.1% twice daily[a]. Hydrocortisone acetate 1%	mEASI mean area under the curve as percent of baseline; PGE	Moderate to severe	Hanifin and Rajka [33]
5. Reitamo [22]	Three weeks, 3 arms DB	624 children (2–15 years)	Tacrolimus 0.03% twice daily, and once daily[a]. Hydrocortisone acetate 1%	mEASI; EASI; PGE; Response rate; Patient's assessment of global response, of itch, and of quality of sleep; %BSA affected	Moderate to severe	Hanifin and Rajka [33]
6. Ruzicka [35]	Three weeks, 4 arms DB	213 adolescents and adults (13–60 years)	Tacrolimus 0.03%, 0.1%, and 0.3% twice daily[a]. Vehicle	PGE; Individual signs of AD	Moderate to severe	Hanifin and Rajka [33]
7. Hanifin [20]	Pooled data of 2 RCTs of identical design; 12 weeks DB 3 arms	632 adults (15–79 years)	Tacrolimus 0.03%, and 0.1% twice daily[a]. Vehicle	PGE; EASI; %BSA affected; individual signs of AD; Patient's assessment of pruritus;	Moderate to severe	Hanifin and Rajka [33]
8. Reitamo [23]	Six months, 2 arms DB	972 adults (≥18 years)	Tacrolimus 0.1% twice daily[a]. Hydrocortisone butyrate 0.1% (trunk and extremities), hydrocortisone acetate 0.1% (face and neck)	Response rate; EASI; mEASI; PGE; Patient's assessment of global response, of itch, and of quality of sleep; %BSA affected	Moderate to severe	Hanifin and Rajka [33]
9. Reitamo, Van Leent [23]	Three weeks, 3 arms DB	570 adults (16–70 years)	Tacrolimus 0.03%, and 0.1% twice daily[a]. Hydrocortisone-17-butyrate 0.1%	mEASI mean area under the curve as percent of baseline; PGE	Moderate to severe	Hanifin and Rajka [33]

EOS: end-of-study; *ADSI*: atopic dermatitis severity index; *TCs*: topical corticosteroids; *DB*: double blind.

[a] Versus: *PGE*: Physician's global evaluation of treatment response; *EASI*: eczema area severity index of atopic dermatitis; *mEASI*: modified EASI; *IGADA*: Investigator Global Atopic Dermatitis Assessment; *AD*: atopic dermatitis; *%BSA*: percent of body surface area affected.

Review: Topical Pimecrolimus In Atopic Dermatitis
Comparison: 02 Pimecrolimus cream 1% vs Vehicle (allowed TCs in case of flares)
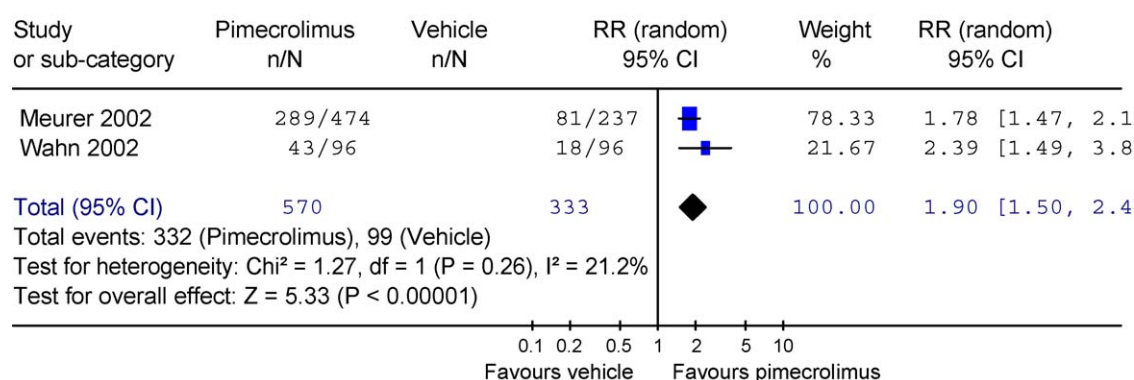Outcome: 01 No flares at six months

Study or sub-category	Pimecrolimus n/N	Vehicle n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Meurer 2002	289/474	81/237		78.33	1.78 [1.47, 2.1
Wahn 2002	43/96	18/96		21.67	2.39 [1.49, 3.8
Total (95% CI)	570	333		100.00	1.90 [1.50, 2.4

Total events: 332 (Pimecrolimus), 99 (Vehicle)
Test for heterogeneity: Chi² = 1.27, df = 1 (P = 0.26), I² = 21.2%
Test for overall effect: Z = 5.33 (P < 0.00001)

0.1 0.2 0.5 1   2   5 10
Favours vehicle   Favours pimecrolimus

Fig. 4. Comparison between the effect of Pimecrolimus cream 1% and vehicle on flares of atopic dermatitis at six months.

Review: Topical Pimecrolimus In Atopic Dermatitis
Comparison: 02 Pimecrolimus cream 1% vs Vehicle (allowed TCs in case of flares)
Outcome: 02 No use of TCs at six months

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Meurer 2002	308/474	88/237		82.74	1.75 [1.46, 2.0
Wahn 2002	47/96	21/96		17.26	2.24 [1.46, 3.4
Total (95% CI)	570	333		100.00	1.83 [1.52, 2.1

Total events: 355 (Treatment), 109 (Control)
Test for heterogeneity: Chi² = 1.08, df = 1 (P = 0.30), I² = 7.2%
Test for overall effect: Z = 6.46 (P < 0.00001)

0.1 0.2 0.5 1   2   5 10
Favours vehicle   Favours pimecrolimus
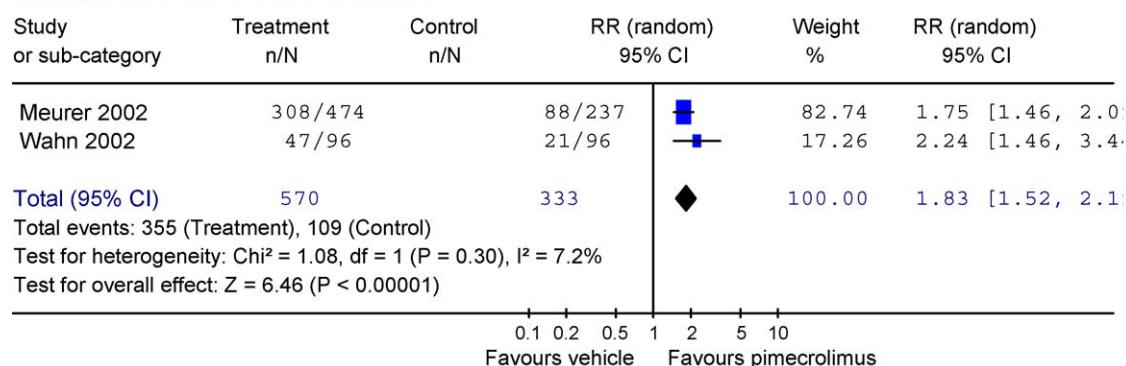
Fig. 5. Comparison between the effect of Pimecrolimus cream 1% and vehicle without the use of TCs at six months.

(p = 0.00001 in both). One was in children and the other in adults. The global comparison was in favor of tacrolimus (RR 3.6, 95% CI 2.26–5.72) (p = 0.00001).

• Comparison 2—tacrolimus ointment versus TCs ointment

   Outcome: Physician's Global Evaluation of response clear or excellent improvement (>90%) (Fig. 9).

○ *Mild TCs*: Two studies [20,21] compared tacrolimus 0.03% and 0.1% ointments with 1% hydrocortisone acetate which were

significantly more effective than the mild TC at three weeks. The corresponding rate ratios were (RR 2.56, 95%CI 1.95–3.36) and (RR 3.09, 95%CI 2.14–4.45). p-Values were the same for both: (p = 0.00001). Reitamo 2004 study [21] was judged as a highly valid one.

○ *Moderate TCs*: One trial, also highly valid [22], compared tacrolimus different concentrations to a moderate potency TC: 0.1% hydrocortisone butyrate (HCB) ointment, in adults with

Review: Topical Pimecrolimus In Atopic Dermatitis
Comparison: 03 Pimecrolimus cream 1% vs potent TCs
Outcome: 01 Investigator Global Assessment of response score 0 or 1 (clear or almost clear) at three weeks

Study or sub-category	Pimecrolimus n/N	TCs n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Luger 2001	5/45	21/42		100.00	0.22 [0.09, 0.54
Total (95% CI)	45	42		100.00	0.22 [0.09, 0.54

Total events: 5 (Pimecrolimus), 21 (TCs)
Test for heterogeneity: not applicable
Test for overall effect: Z = 3.35 (P = 0.0008)

0.001 0.01 0.1 1   10 100 1000
Favours TCs   Favours pimecrolimus

Fig. 6. Comparison between the effect of Pimecrolimus cream 1% and potent TCs on the Investigator's Global Assessment of response.

Review: Topical Pimecrolimus In Atopic Dermatitis
Comparison: 04 Pimecrolimus cream 1% vs combined potent / mild TCs regimen
Outcome:01 Investigator's Global Assessment of response moderately clear or better
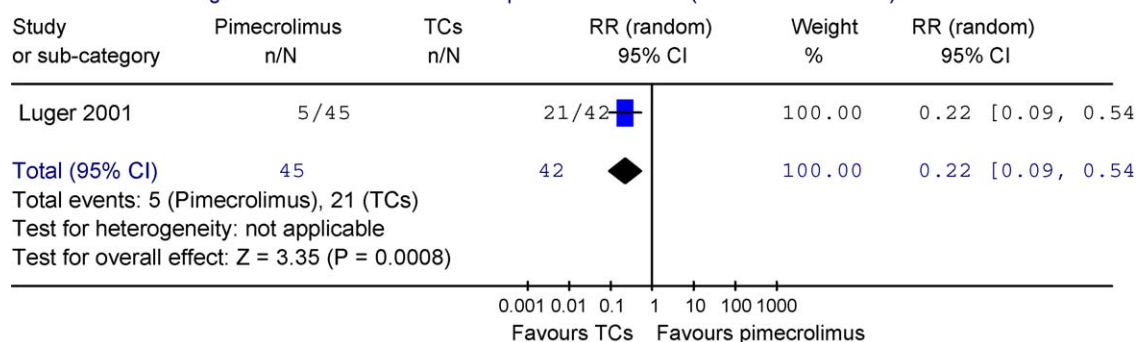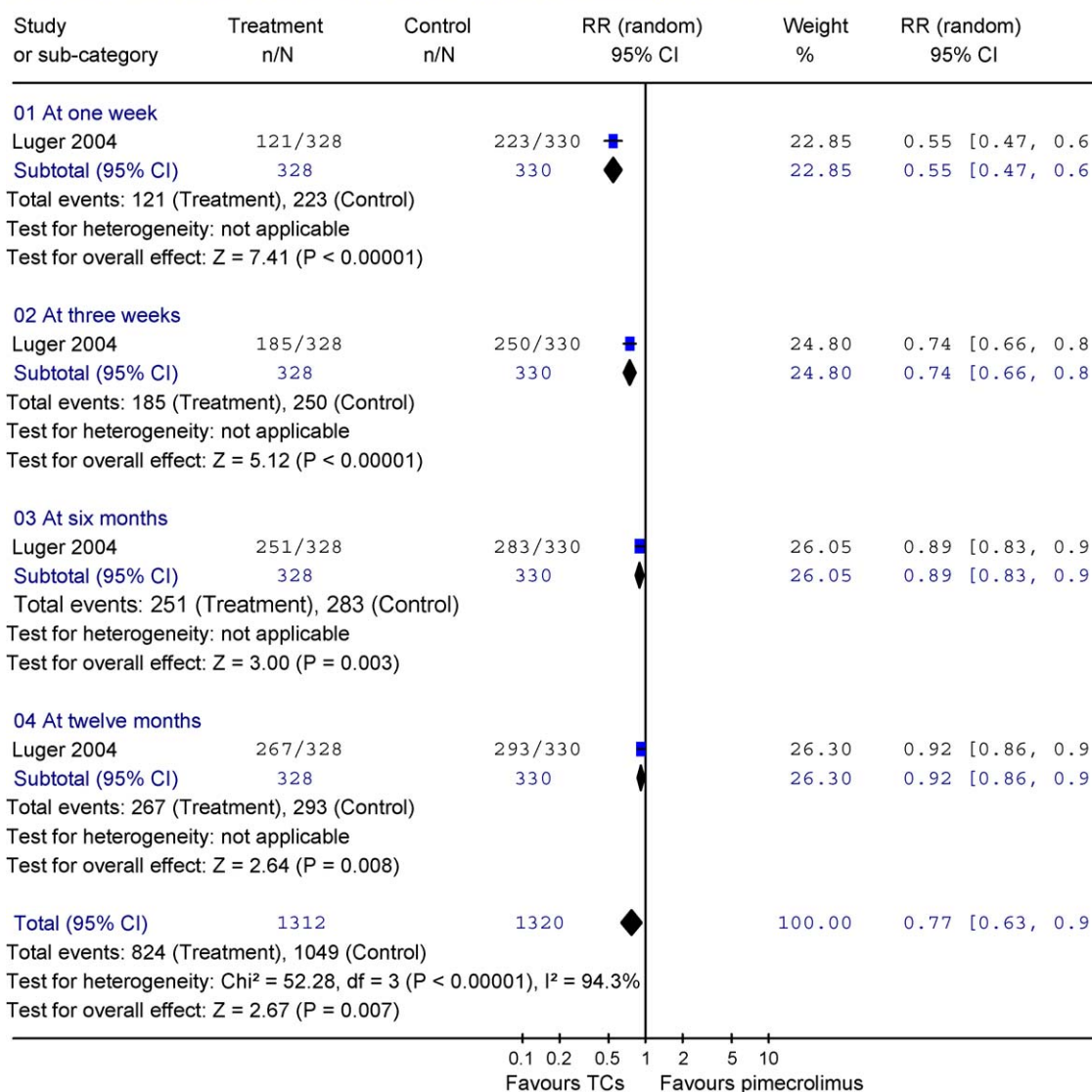
Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 At one week					
Luger 2004	121/328	223/330		22.85	0.55 [0.47, 0.6
Subtotal (95% CI)	328	330		22.85	0.55 [0.47, 0.6
Total events: 121 (Treatment), 223 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 7.41 (P < 0.00001)					
02 At three weeks					
Luger 2004	185/328	250/330		24.80	0.74 [0.66, 0.8
Subtotal (95% CI)	328	330		24.80	0.74 [0.66, 0.8
Total events: 185 (Treatment), 250 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 5.12 (P < 0.00001)					
03 At six months					
Luger 2004	251/328	283/330		26.05	0.89 [0.83, 0.9
Subtotal (95% CI)	328	330		26.05	0.89 [0.83, 0.9
Total events: 251 (Treatment), 283 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 3.00 (P = 0.003)					
04 At twelve months					
Luger 2004	267/328	293/330		26.30	0.92 [0.86, 0.9
Subtotal (95% CI)	328	330		26.30	0.92 [0.86, 0.9
Total events: 267 (Treatment), 293 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 2.64 (P = 0.008)					
Total (95% CI)	1312	1320		100.00	0.77 [0.63, 0.9
Total events: 824 (Treatment), 1049 (Control)					
Test for heterogeneity: Chi² = 52.28, df = 3 (P < 0.00001), I² = 94.3%					
Test for overall effect: Z = 2.67 (P = 0.007)					

0.1 0.2 0.5 1 2 5 10
Favours TCs   Favours pimecrolimus

Fig. 7. Comparison between the effect of Pimecrolimus cream 1% and combined potent/mild TCs regimen on the Investigator's Global Assessment of response.

moderate to severe AD. Tacrolimus 0.03% was significantly less effective than this TC (RR 0.74, 95%CI 0.59–0.93) ($p = 0.01$), whereas tacrolimus 0.1% was as effective ($p = 0.72$).
○ *Combined moderate-and-mild TCs*: Tacrolimus 0.1% was superior to a combined TCs regimen of 0.1% hydrocortisone butyrate ointment applied to the trunk and arms, and 1% hydrocortisone acetate ointment applied to the face and flexures, in case of moderate to severe AD in adults. The study [23] was judged to be highly valid.

4. Discussion

This systematic review and meta-analysis was undertaken to assess how the effectiveness of TCIs measures up to topical corticosteroids and/or placebo. In this systematic review, the overall comparison between pimecrolimus and vehicle favored pimecrolimus. Pimecrolimus cream 1% was found to be more effective than vehicle in AD, at three and six weeks. However, in one study with long-term management of patients no significant

difference was found between both groups in treatment response at 6 and 12 months [12]. It was noticed that the longer the patients remained on therapy the less often study medication had to be used to maintain disease control. This denotes that sustained regular use of emollients sparingly can control AD, as would pimecrolimus application.

It should be noted that the population included in this pooled analysis ranged from infants to adults, and that the severity of cases ranged between mild and very severe AD. This means that all age groups and grades of severity showed the same results.

Although less effective than topical corticosteroids, pimecrolimus seems to have its value in long-term maintenance and steroid-sparing effect in atopic dermatitis, whenever used early enough, at first appearance of erythema and/or itching. In moderate to severe AD of children, adolescents and adults, application of pimecrolimus cream 1% regularly for 6 months resulted in significantly fewer flares of AD and significant reduction of the rate of use of topical corticosteroids. Furthermore, two long-term studies proved that those benefits of pimecrolimus

Review: Topical Tacrolimus In AD
Comparison: 01 Tacrolimus ointment vs Vehicle
Outcome: 01 Physician Global Evaluation of response: clear or excellent improvement (>90%)

Study or sub-category	Treatment n/N	Vehicle n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Tacrolimus 0.03% vs vehicle at three weeks					
Boguniewicz 1998	25/43	12/44		17.59	2.13 [1.24, 3.68
Subtotal (95% CI)	43	44		17.59	2.13 [1.24, 3.68
Total events: 25 (Treatment), 12 (Vehicle)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 2.72 (P = 0.006)					
02 Tacrolimus 0.1% vs vehicle at three weeks					
Boguniewicz 1998	21/49	12/44		17.03	1.57 [0.88, 2.81
Subtotal (95% CI)	49	44		17.03	1.57 [0.88, 2.81
Total events: 21 (Treatment), 12 (Vehicle)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 1.53 (P = 0.13)					
03 Tacrolimus 0.03% vs vehicle at twelve weeks					
Hanifin 2001	58/211	14/212		17.49	4.16 [2.40, 7.23
Paller 2001	42/117	8/116		15.02	5.21 [2.56, 10.6
Subtotal (95% CI)	328	328		32.51	4.53 [2.93, 7.00
Total events: 100 (Treatment), 22 (Vehicle)					
Test for heterogeneity: Chi² = 0.24, df = 1 (P = 0.63), I² = 0%					
Test for overall effect: Z = 6.79 (P < 0.00001)					
04 Tacrolimus 0.1% vs vehicle at twelve weeks					
Hanifin 2001	77/209	14/212		17.73	5.58 [3.26, 9.54
Paller 2001	48/118	8/116		15.14	5.90 [2.92, 11.9
Subtotal (95% CI)	327	328		32.87	5.69 [3.72, 8.72
Total events: 125 (Treatment), 22 (Vehicle)					
Test for heterogeneity: Chi² = 0.02, df = 1 (P = 0.90), I² = 0%					
Test for overall effect: Z = 7.99 (P < 0.00001)					
Total (95% CI)	747	744		100.00	3.60 [2.26, 5.72
Total events: 271 (Treatment), 68 (Vehicle)					
Test for heterogeneity: Chi² = 18.03, df = 5 (P = 0.003), I² = 72.3%					
Test for overall effect: Z = 5.42 (P < 0.00001)					

```
           0.01  0.1   1   10  100
        Favours vehicle  Favours tacrolimus
```
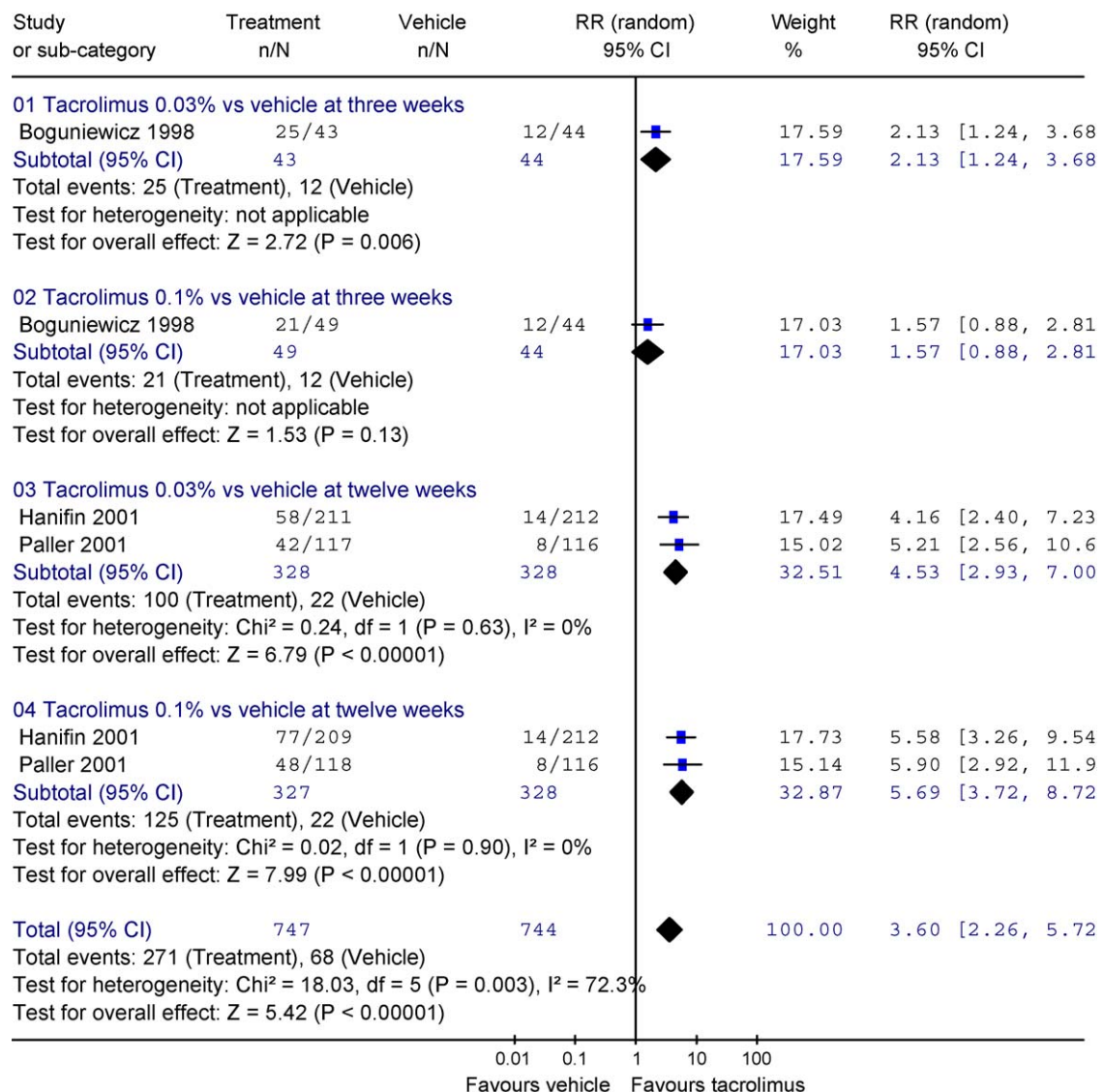
Fig. 8. Comparison between the effect of Tacrolimus ointment and vehicle on Physician Global Evaluation of Response.

were sustained for 12 months, providing evidence that long-term treatment with pimecrolimus leads to better control of AD [13,14].

In this systematic review, a commonly used potent topical corticosteroid, betamethasone valerate, was found to be significantly more effective than pimecrolimus in treatment of moderate to severe AD of adults at three weeks. This finding was supported by a recent systematic review [24] which concluded that topical moderate and potent corticosteroids are significantly more effective than topical pimecrolimus in the treatment of different types of eczema including AD. Also in our systematic review, a combination of potent-and-mild TCs for 1 year was found to be more effective than pimecrolimus. Based on these data, pimecrolimus seems to have no value in replacement of TCs in the short-term treatment of AD, but it can find its place in long-term maintenance for prevention of flares of the disease and for its assumed steroid-sparing effect.

This systematic review agrees with that of Luger et al. [15] in their statement that one possible therapeutic outcome in the future could be a treatment paradigm, which would combine the

safety advantages of pimecrolimus and the efficacy advantages of TCs, e.g. using pimecrolimus for the face and intertriginous areas in infants and children to avoid the possible risk of using TCs in such sensitive sites, whereas TCs can be used to control flares as soon as they occur on other sites.

Pooled analysis of tacrolimus trials showed that 0.03% ointment was more effective than vehicle at three weeks, and the 0.1% ointment was equal in effectiveness to vehicle. Both 0.03% and 0.1% tacrolimus were significantly more effective than vehicle after 12 weeks. The global comparison favored tacrolimus. In another systematic review [25], a comparison between tacrolimus 0.03% and 0.1% for 3 weeks was done to estimate the incremental effect of the higher concentration in adults and children populations. An overall effect slightly favorable to 0.1% was observed, in adults but not in children. This suggests that the use of concentrations higher than 0.03% does not provide additional benefits in children on short-term therapy.

In this systematic review, comparison to a commonly used mild topical corticosteroid, hydrocortisone acetate, showed that both

Review: Topical Tacrolimus In AD
Comparison: 02 Tacrolimus ointment vs TCs
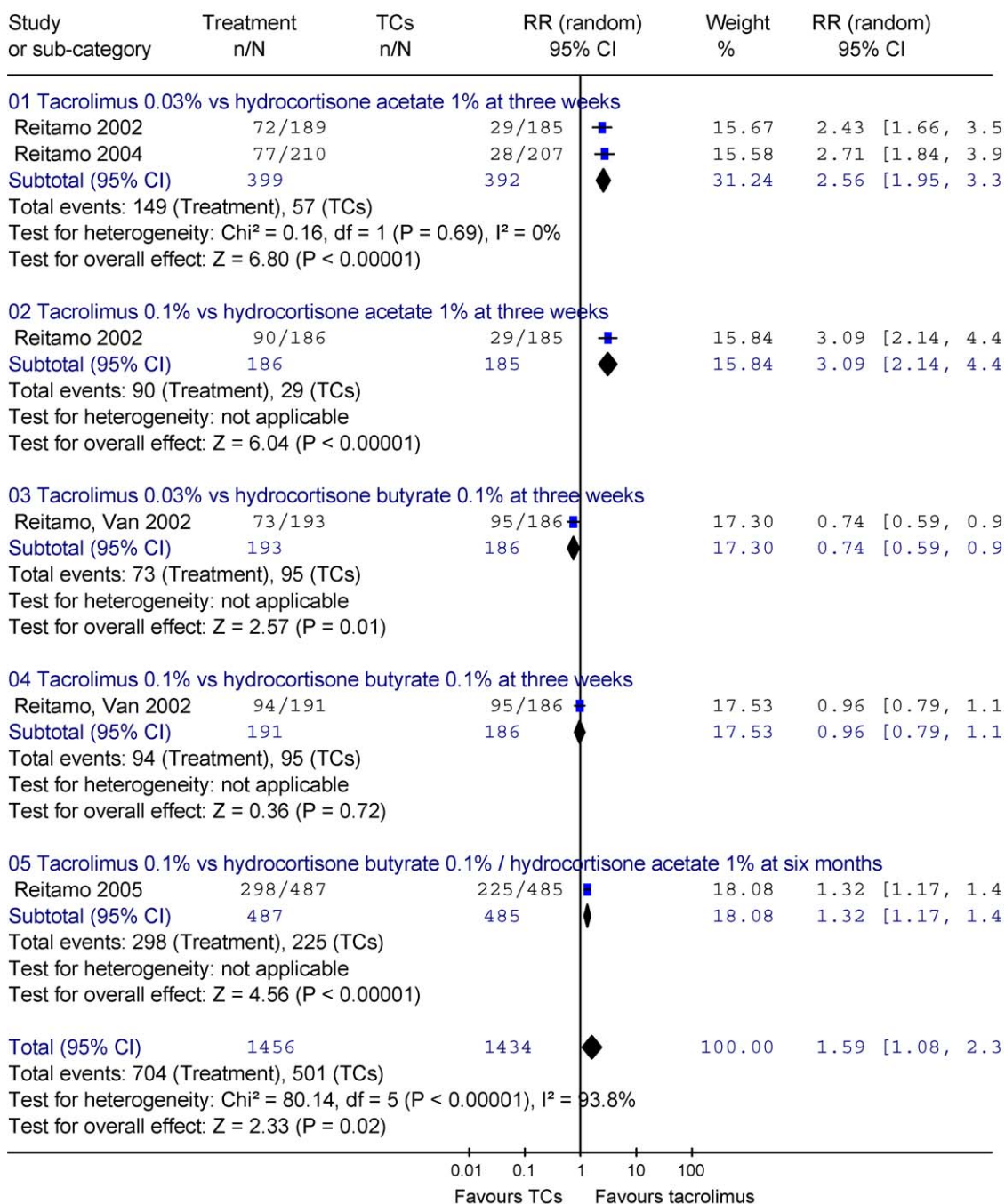Outcome: 01 Physician Global Evaluation of response: clear or excellent improvement (> 90%)

Study or sub-category	Treatment n/N	TCs n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Tacrolimus 0.03% vs hydrocortisone acetate 1% at three weeks					
Reitamo 2002	72/189	29/185		15.67	2.43 [1.66, 3.5
Reitamo 2004	77/210	28/207		15.58	2.71 [1.84, 3.9
Subtotal (95% CI)	399	392		31.24	2.56 [1.95, 3.3
Total events: 149 (Treatment), 57 (TCs)					
Test for heterogeneity: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%					
Test for overall effect: Z = 6.80 (P < 0.00001)					
02 Tacrolimus 0.1% vs hydrocortisone acetate 1% at three weeks					
Reitamo 2002	90/186	29/185		15.84	3.09 [2.14, 4.4
Subtotal (95% CI)	186	185		15.84	3.09 [2.14, 4.4
Total events: 90 (Treatment), 29 (TCs)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 6.04 (P < 0.00001)					
03 Tacrolimus 0.03% vs hydrocortisone butyrate 0.1% at three weeks					
Reitamo, Van 2002	73/193	95/186		17.30	0.74 [0.59, 0.9
Subtotal (95% CI)	193	186		17.30	0.74 [0.59, 0.9
Total events: 73 (Treatment), 95 (TCs)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 2.57 (P = 0.01)					
04 Tacrolimus 0.1% vs hydrocortisone butyrate 0.1% at three weeks					
Reitamo, Van 2002	94/191	95/186		17.53	0.96 [0.79, 1.1
Subtotal (95% CI)	191	186		17.53	0.96 [0.79, 1.1
Total events: 94 (Treatment), 95 (TCs)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.36 (P = 0.72)					
05 Tacrolimus 0.1% vs hydrocortisone butyrate 0.1% / hydrocortisone acetate 1% at six months					
Reitamo 2005	298/487	225/485		18.08	1.32 [1.17, 1.4
Subtotal (95% CI)	487	485		18.08	1.32 [1.17, 1.4
Total events: 298 (Treatment), 225 (TCs)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 4.56 (P < 0.00001)					
Total (95% CI)	1456	1434		100.00	1.59 [1.08, 2.3
Total events: 704 (Treatment), 501 (TCs)					
Test for heterogeneity: Chi² = 80.14, df = 5 (P < 0.00001), I² = 93.8%					
Test for overall effect: Z = 2.33 (P = 0.02)					

```
        0.01   0.1    1    10   100
        Favours TCs    Favours tacrolimus
```

Fig. 9. Comparison between the effect of Tacrolimus ointment and TCs on Physician Global Evaluation of Response.

tacrolimus concentrations (0.1% and 0.03%) are more effective in short-term therapy of moderate to severe AD in children. On the other hand, a comparison to moderate TCs in adults with moderate to severe AD showed that tacrolimus 0.03% was significantly less effective, whereas tacrolimus 0.1% was equal in effectiveness.

By contrast, tacrolimus 0.1% was proved superior to a combined TC regimen of moderate and mild potencies in a large number of patients with moderate to severe AD, after 6 months of treatment. These two different evaluations of 0.1% tacrolimus potency in relation to moderate TCs, where it was found equal to it alone but

superior to it when combined to another TC of mild potency, can be probably explained by the difference in duration of included studies. The first one was of three weeks duration, while the second one extended to 6 months. Based on limited data available about tacrolimus effectiveness in comparison to TCs, we think that both 0.03% and 0.1% tacrolimus ointment can be used with success in long-term treatment of moderate to severe AD in adults.

Moreover, a highly valid study proved that the application of 0.03% tacrolimus ointment once daily, in children with moderate AD, has a similar effect to the licensed twice daily application. This

would be expected to reduce the degree of exposure to medication, and to increase the patient's compliance [21].

Therefore, in the treatment of moderate to severe AD, topical tacrolimus was found to be as effective as moderately potent topical corticosteroids, and more effective than mild preparations.

5. Conclusion

This study concludes that pimecrolimus is superior in efficacy than vehicle but equivalent to mildly potent topical steroids, and less effective than moderately potent TCs. On the other hand, tacrolimus is more effective than mild TCs and equally effective to moderately potent topical steroids. Based on this we suggest that pimecrolimus could be used in milder cases of AD, or in long-term maintenance for prevention of flares of the disease and for its assumed steroid-sparing effect. Tacrolimus can be reserved for moderate to severe cases of AD, and can be used as first line therapy instead of topical corticosteroids.

5.1. Strengths and limitations

In contrast to an earlier systematic review [26], we aimed to include RCTs on infants. We were encouraged by the availability and quality of these studies which, in our opinion, were necessary to inform practitioners. This review also tried not to underestimate the inappropriateness of using topical corticosteroids on certain skin areas, aiming to make a balanced analysis, taking at equal consideration both patients needs and scientific evidence rules.

One limitation of our study is that a source of bias could not be avoided, as only published trials were retrieved, owing to the lack of access to certain search operators, e.g. the Cochrane Library (Publication bias).

References

[1] Thestrup-Pedersen K. Tacrolimus treatment of atopic eczema/dermatitis syndrome. Curr Opin Allergy Clin Immunol 2003;3:359–62.
[2] Meurer M, Wozel G. The treatment of atopic dermatitis in adults with topical calcineurin inhibitors. Hautarzt 2003;54(5):424–31.
[3] Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. Health Technol Assess 2000;4:1–191.
[4] Abeck D, Strom K. Optimal management of atopic dermatitis. Am J Clin Dermatol 2000;1(1):41–6.
[5] Charman CR, Morris AD, Williams HC. Topical corticosteroid phobia in patients with atopic eczema. Br J Dermatol 2000;142:931–6.
[6] Ortiz De Frutos FJ. New horizons in the treatment of atopic dermatitis. Allergol Immunopathol (Madr) 2002;30(3):134–40.
[7] Breuer K, Werfel T, Kapp A. Safety and efficacy of topical calcineurin inhibitors in the treatment of childhood atopic dermatitis. Am J Clin Dermatol 2005;6(2):65–77.
[8] Novak N, Kwiek B, Bieber T. The mode of topical immunomodulators in the immunological network of atopic dermatitis. Clin Exp Dermatol 2005;30(2):160–4.
[9] Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of reporting of meta-analyses. Lancet 1999;354:1896–900.
[10] Cochrane W. The combination of estimates from different experiments. Biometrics 1954;10:101–29.
[11] 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 Deratol 2001;144(m4):788–94.
[12] 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(2):277–84.
[13] 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;10(1 Pt I):e2.
[14] Meurer M, Folster-Holst R, Wozel G, Weidinger G, Junger M, Brautigam M. Pimecrolimus cream in the long-term management of atopic dermatitis in adults: a six-month study. Dermatology 2002;205(3):271–7.
[15] Luger TA, Lahfa M, Folster-Holst R, Gulliver WP, Alien 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 Dermatol Treat 2004;15(3):169–78.
[16] Schachner LA, Lamerson C, Sheehan MP, Boguniewicz M, Mosser J, Rainier 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(3):e334–42.
[17] 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(4Pt l):637–44.
[18] 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(1 Suppl.):S47–57.
[19] 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(1 Suppl.):S28–38.
[20] Reitamo S, Rustin M, Ruzicka T, Cambazard F, Kalimo K, Friedmann PS, et al. Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone butyrate ointment in adult patients with atopic dermatitis. J Allergy Clin Immunol 2002;109(3):547–55.
[21] 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(3):554–62.
[22] 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(3):539–46.
[23] 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 a treatment with 0.1% tacrolimus ointment in adults with moderate to severe atopic dermatitis. Br J Dermatol 2005;152(6):1282–9.
[24] Ashcroft DM, Chen LC, Garside R, Stein K, Williams HC. Topical pimecrolimus for eczema. Cochrane Database Syst Rev 2007;4:CD005500.
[25] Hidalgo BP, Knight T, Burls A. A systematic review of effectiveness and cost effectiveness of tacrolimus ointment for topical treatment of atopic dermatitis. http://rep.bham.ac.uk/pdfs/2003/atopic_dermatitis.pdf.
[26] Garside R, Stein K, Castelnuovo E, Pitt M, Ashcroft D, Dimmock P, et al. The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation. Health Technol Assess 2005;1–230.
[27] 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(2):155–62.
[28] 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(3):375–81.
[29] 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(4):495–504.
[30] Van Leent EJ, Graber M, Thurston M, Wagenaar A, Spuls PI, Bos JD. Effectiveness of the ascomycin macrolactam SDZ ASM 981 in the topical treatment of atopic dermatitis. Arch Dermatol 1998;134(7):805–9.
[31] Seymour J, Keswick B, Hanifin J, et al. Clinical effects of diaper types on the skin of normal infants and infants with atopic dermatitis. J Am Acad Dermatol 1987;17:988–97.
[32] Williams H, Burney P, Pembroke A, Hay RJ. The UK Working Party's diagnostic criteria for atopic dermatitis: III. Independent hospital validation. Br J Dermatol 1994;131:406–16.
[33] Hanifin J, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol 1980;92:44–7.
[34] Rajka G, Langland T. Grading of the severity of atopic dermatitis. Acta Derm Venereol Suppl (Stock) 1989;144:13–4.
[35] 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(12):816–21.