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Review Article

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

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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.
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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-reference 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.

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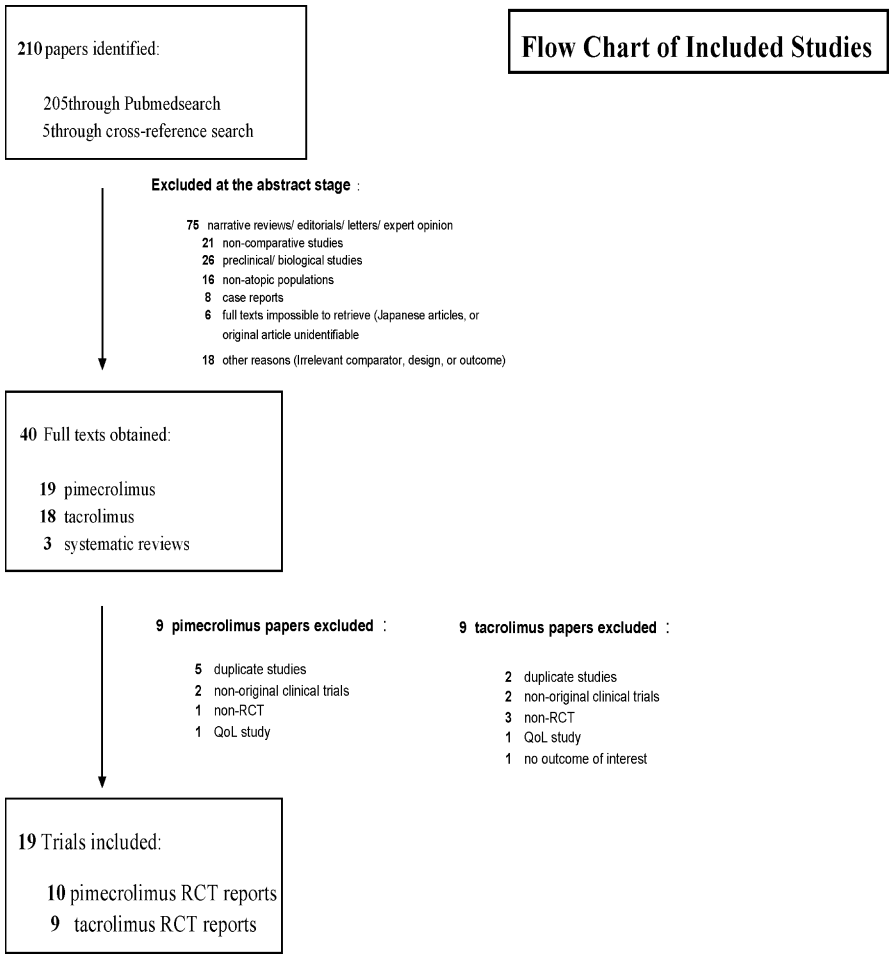

Fig. 1. Flow chart of included studies.

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 ≤ 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.

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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.

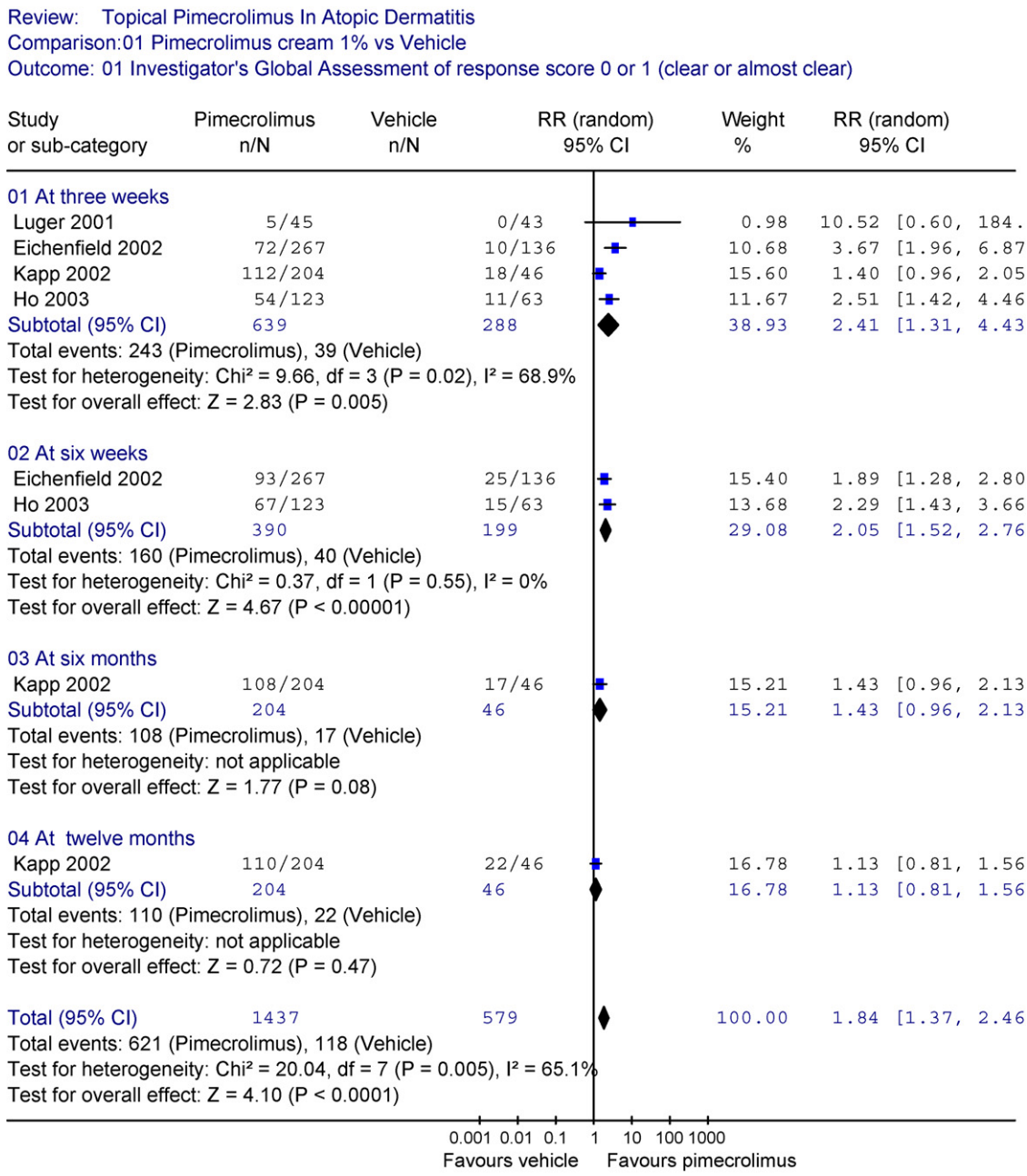

Fig. 2. Comparison between the effect of Pimecrolimus cream 1% and vehicle on the Investigator's Global Assessment of response.

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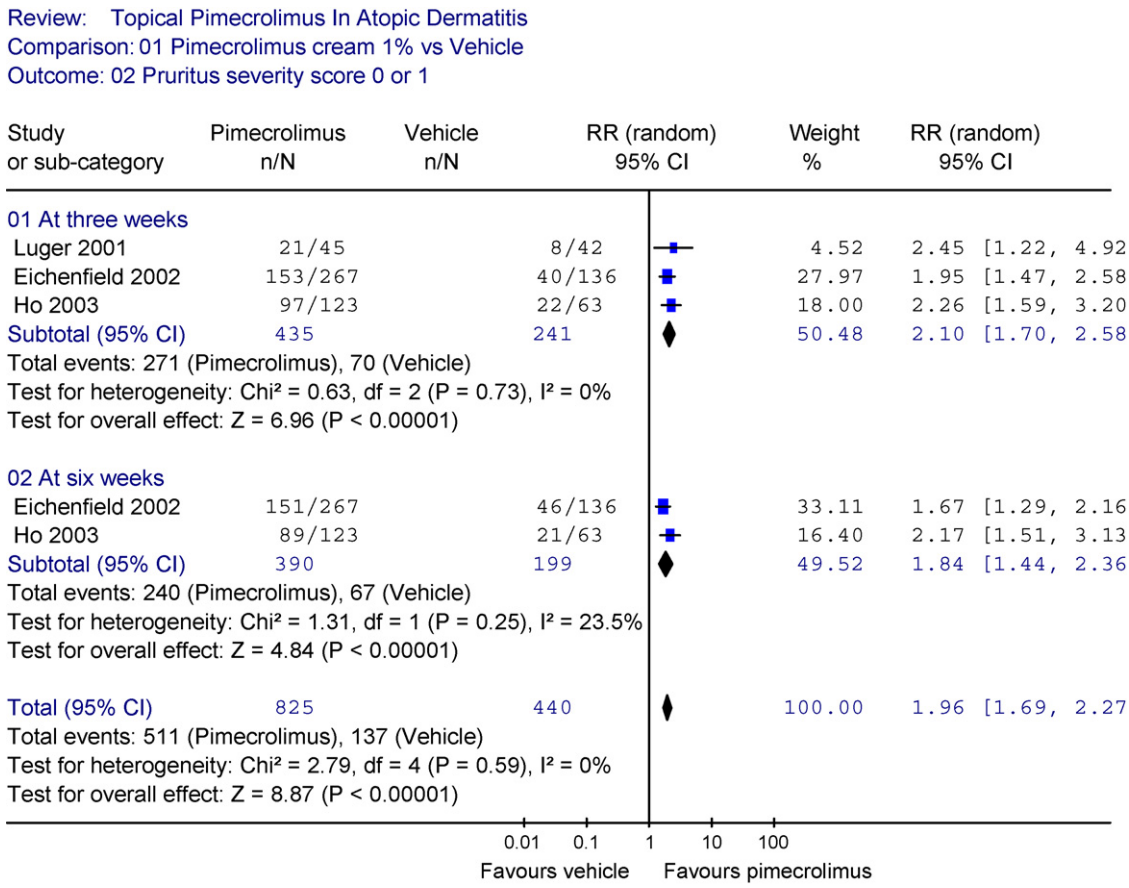

Fig. 3. Comparison between the effect of Pimecrolimus cream 1% and vehicle on Pruritis Severity Score.

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.

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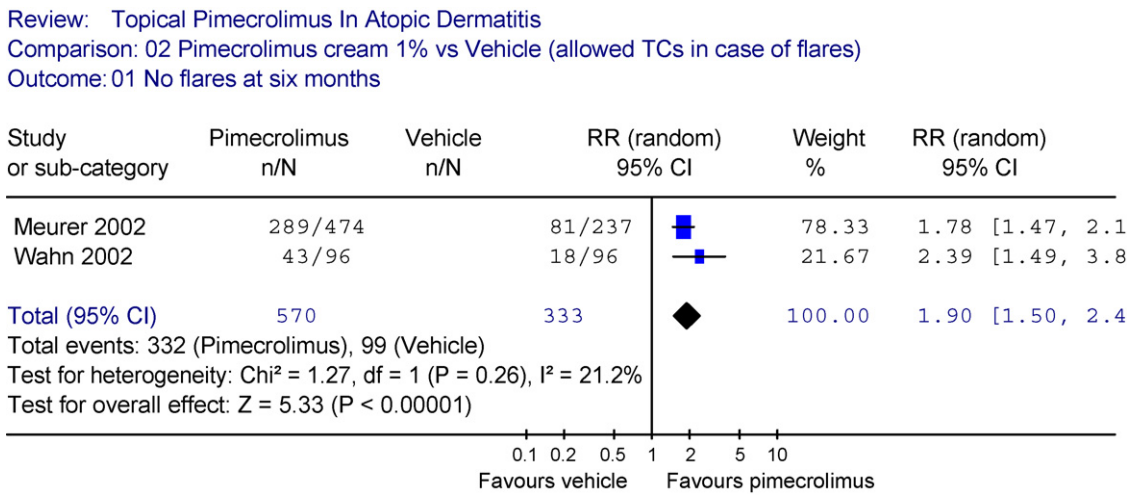

Fig. 4. Comparison between the effect of Pimecrolimus cream 1% and vehicle on flares of atopic dermatitis at six months.

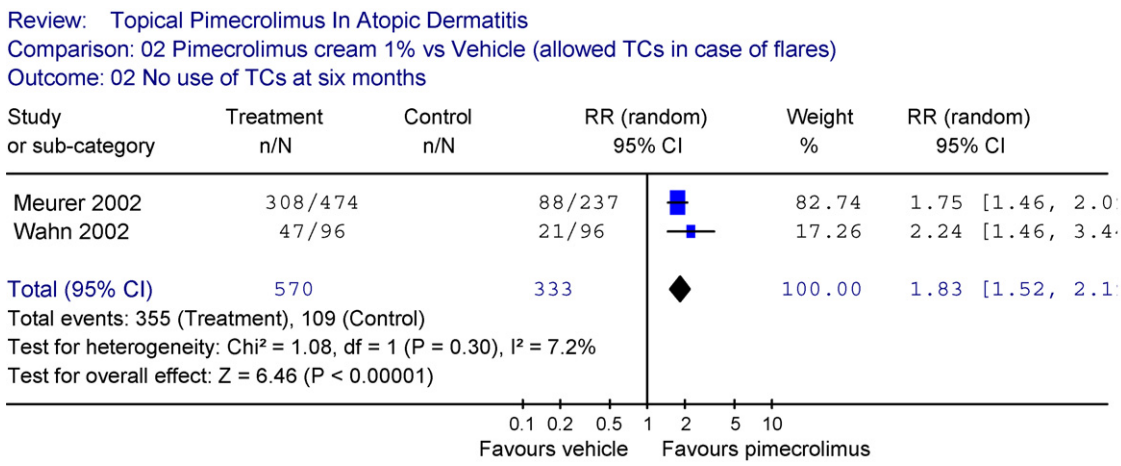

Fig. 5. Comparison between the effect of Pimecrolimus cream 1% and vehicle without the use of TCs at six months.

($p = 0.00001$ 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

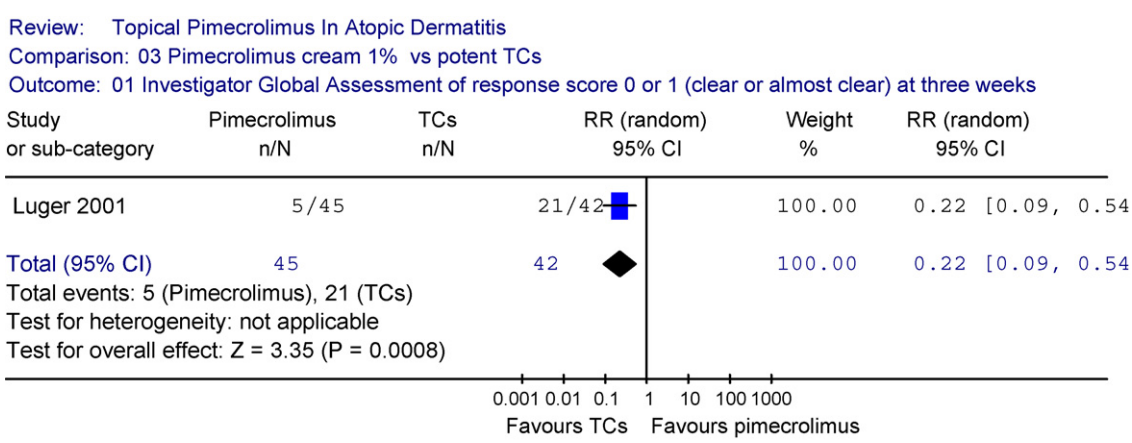

Fig. 6. Comparison between the effect of Pimecrolimus cream 1% and potent TCs on the Investigator's Global Assessment of response.

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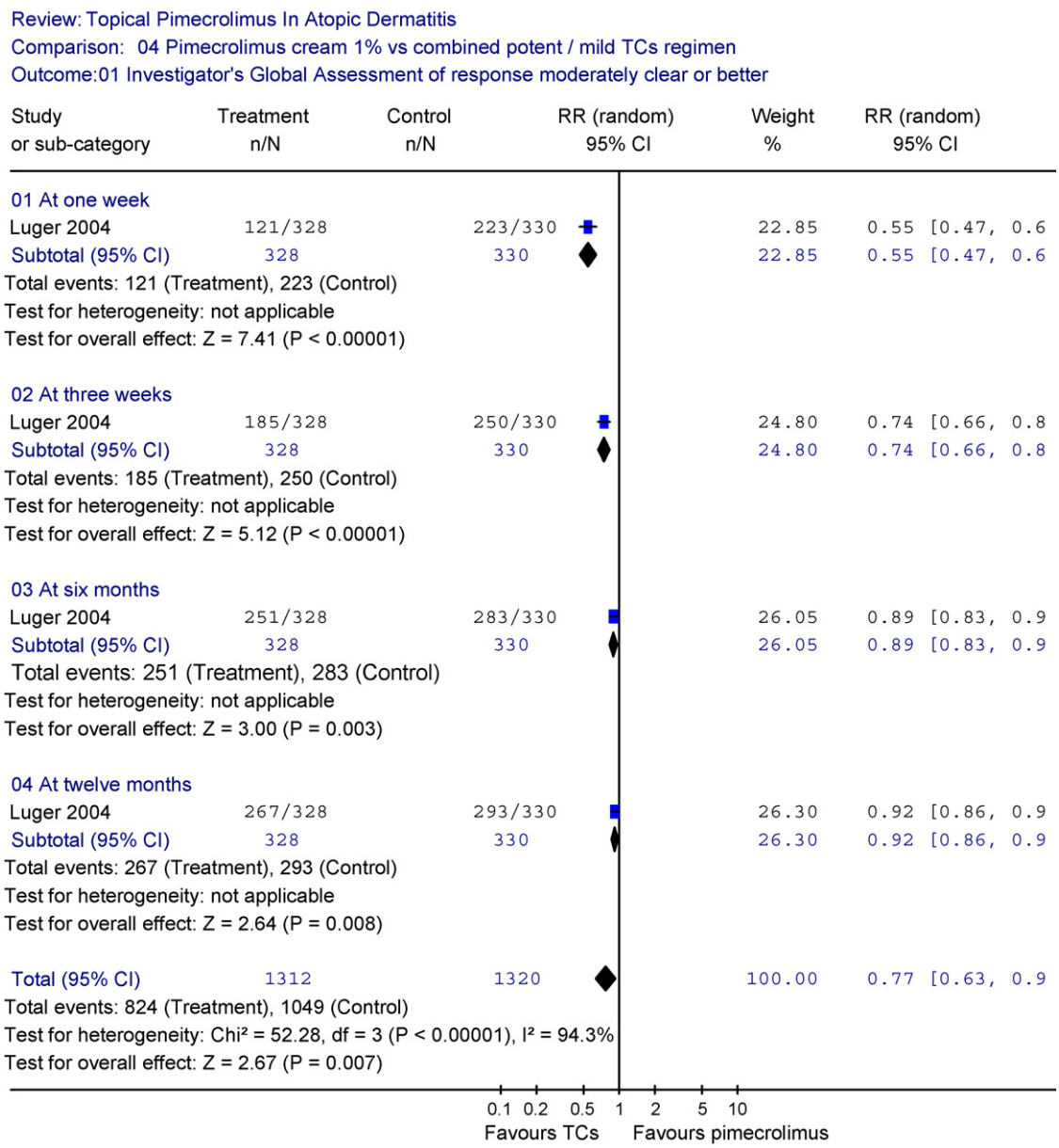

Fig. 7. Comparison between the effect of Pimecrolimus cream 1% and combined potent/mild TCs regimen on the Investigator's Global Assessment of response.

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

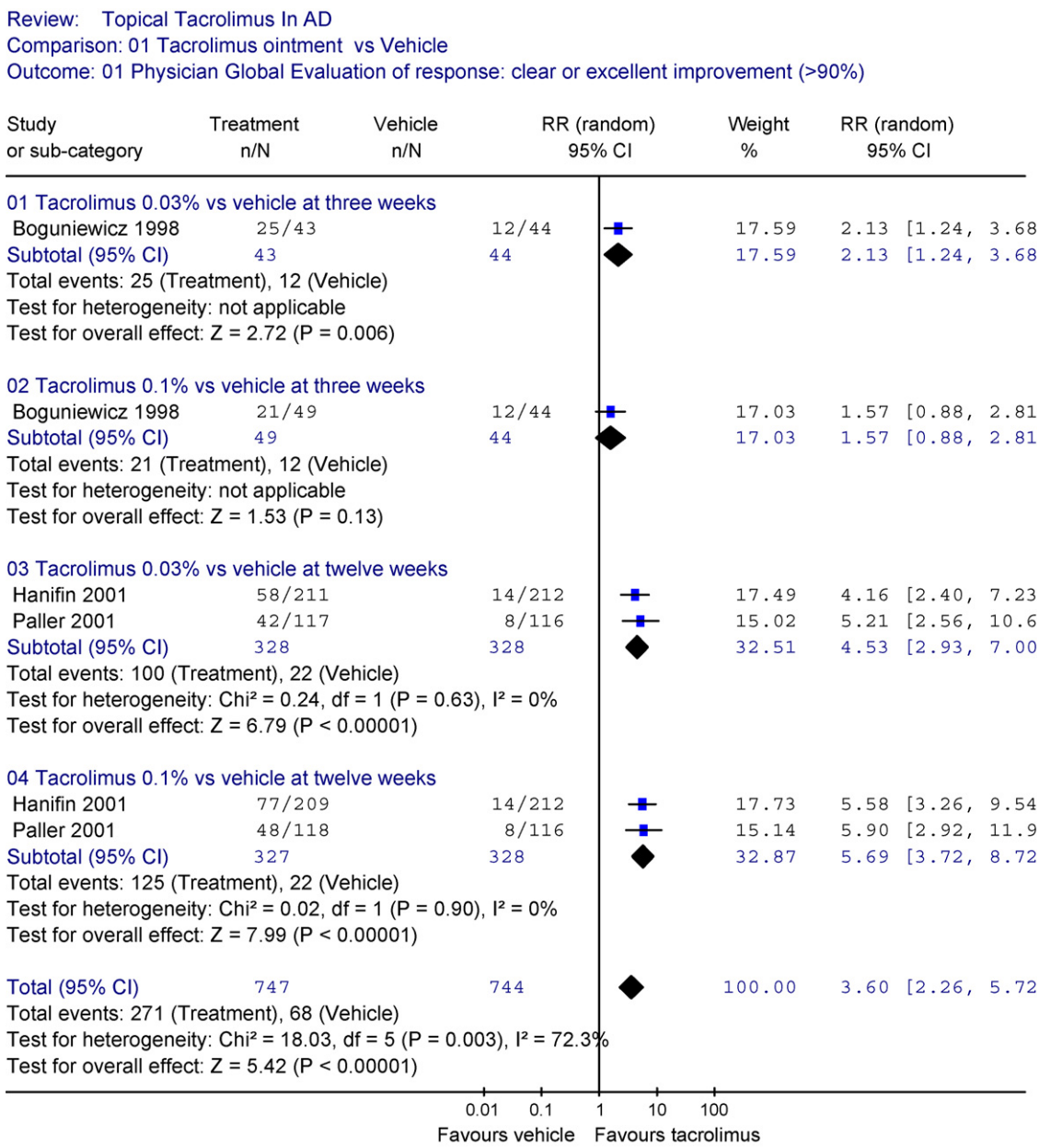

Fig. 8. Comparison between the effect of Tacrolimus ointment and vehicle on Physician Global Evaluation of Response.

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

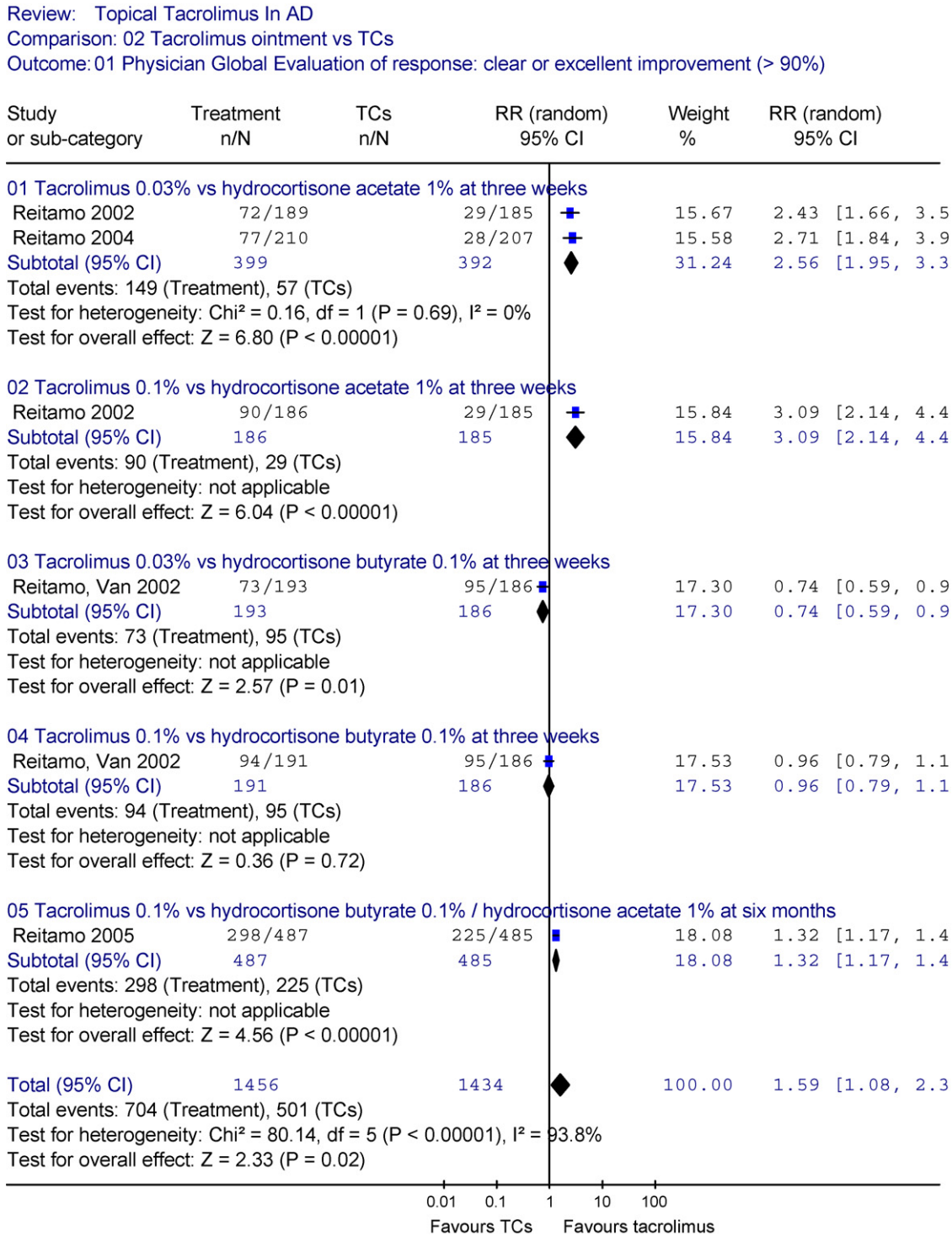

Fig. 9. Comparison between the effect of Tacrolimus ointment and TCs on Physician Global Evaluation of Response.

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).

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