

Systematic Review on the Efficacy, Safety, and Cost-Effectiveness of Topical Calcineurin Inhibitors in Atopic Dermatitis

Brian Keng Yong Chia, MBBS (Hons), MRCP (UK), MMed (Int Med)
and Hong Liang Tey, MBBS, MRCP (UK), MRCPS (Glasg), GDGM, FAMS

Background: Topical calcineurin inhibitors (TCIs) are widely used as an alternative to topical corticosteroids (TCSs) in treating of atopic dermatitis, but their risk versus benefit compared with TCSs remains unclear.

Objective: We performed a systematic review of the efficacy, safety, and cost-effectiveness of TCI compared with TCS and emollients.

Methods: Published meta-analysis, systematic reviews, and individual studies from January 2005 to January 2015 on the comparative efficacy, safety, and cost-effectiveness of TCI against emollients and TCS were included.

Results: Tacrolimus is comparable to TCS in efficacy, safety profile, and cost-effectiveness. Pimecrolimus has a similar safety profile compared with TCS, emollients, and tacrolimus. It is superior to emollients but inferior to TCS and tacrolimus in efficacy and cost-effectiveness. The association of tacrolimus with malignancy remains uncertain.

Conclusions: Tacrolimus is an efficacious and cost-effective alternative to TCS, but its benefits need to be weighed against its still uncertain risk for malignancy. Pimecrolimus is appropriate for mild atopic dermatitis when TCS or tacrolimus is unsuitable.

Atopic dermatitis (AD) is a chronic, pruritic, relapsing inflammatory skin disorder occurring most commonly during childhood. Most commonly, AD is treated topically with topical corticosteroids (TCSs)^{1–3} as the anti-inflammatory agent. However, TCS can have prominent adverse effects (AEs), including skin atrophy, striae, and, when applied to the eyes, cataracts and glaucoma.

Topical calcineurin inhibitors (TCIs) are macrolactam immunomodulators⁴ devoid of steroidal AEs. They were introduced in 2000 to 2001 and are currently commercially available as tacrolimus and pimecrolimus. Topical calcineurin inhibitors are thought to exert their immunosuppressive effects by inhibiting the activation of T lymphocytes and thereby decreasing the production of proinflammatory cytokines.⁵

Topical calcineurin inhibitors are currently widely used in dermatology for eczema and off-label treatment of numerous conditions, such as vitiligo⁶ and psoriasis.⁷ They are, however, not used routinely because they are expensive, long-term safety data are lacking, and their risks versus benefits compared with standard

therapy (TCS) are still not well established. In this systematic review, we aimed to compare the efficacy, safety, and cost-effectiveness of TCIs with TCS in the treatment of AD.

METHODOLOGY

A literature search was performed through 5 electronic databases as follows: PubMed, Embase, Cochrane, Database of Abstract of Reviews of Effects (DARE), and National Health Service (NHS) Centre for Reviews and Dissemination (CRD). The main key words used were “atopic dermatitis” or “eczema” and “calcineurin inhibitor” or “tacrolimus” or “pimecrolimus.” We confined our initial search to systematic reviews and meta-analyses published in English between January 2005 and January 2015. All results were assessed independently by 2 reviewers, and the most relevant and recent publications containing the outcome measure of interest were reported. Further literature search was also performed to locate any new studies published between the submission date of this study and the publication date of the systematic review or meta-analysis.

RESULTS

Comparative Efficacy and Safety of TCIs

We assessed the comparative efficacy and safety of TCIs against the current standard of care. The comparisons between tacrolimus

From the National Skin Centre, Singapore.

Address reprint requests to Hong Liang Tey, MBBS, MRCP (UK), MRCPS (Glasg), GDGM, FAMS, National Skin Centre, 1 Mandalay Rd, Singapore 308205, Singapore. E-mail: teyhongliang111@yahoo.com.

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(0.03% and 0.1%) versus TCS, pimecrolimus versus vehicle and TCS, as well as tacrolimus ointment versus pimecrolimus cream will be presented here. Topical corticosteroids are classified based on their potencies using a vasoconstrictive assay. The 2 most widely used classifications are the United Kingdom⁸ and United States⁹ systems; the former will be used in this article as most of the relevant studies used this classification. This system uses a 4-point scale, with class I being mild TCS and class IV being very potent TCS.

Comparing Tacrolimus With TCS

A number of systematic reviews have been performed comparing the efficacy and safety of tacrolimus against TCS, and the most recent one by Svensson et al in 2011 will be reported here. Further literature search performed using PubMed, Embase, Cochrane, DARE, and NHS CRD did not identify any new randomized controlled trials (RCTs) published between January 2011 and January 2015.

Comparative Efficacy of Tacrolimus Versus TCS

The systematic review included a total of 17 RCTs^{10–25} involving both children (n = 2383) and adults (n = 2849). A summary of the inclusion and exclusion criteria and the methodological quality is provided in Table 1.

Eleven publications compared tacrolimus with class I/II TCS.^{10,11,14–19,22,24,25} For outcome measures using the Physician's Global Evaluation of Clinical Response (PGECR) or the Physician's Global Evaluation of Skin Condition, 6 publications showed that tacrolimus was more efficacious than TCS,^{10,11,14,16–18} 1 publication reported superior efficacy with TCS compared with 0.03% tacrolimus,²⁴ whereas 1 publication reported similar efficacy between 0.1% tacrolimus and TCS (although both were superior to 0.03% tacrolimus).¹⁵ Using the eczema area and severity index (EASI) or modified EASI (mEASI) as the outcome measure, 4 publications found greater efficacy with tacrolimus,^{10,14,16,17} 2 publications reported better results with TCS compared with 0.03% tacrolimus,^{19,24} and 1 publication found no significant differences.¹⁵

The concentration of 0.1% tacrolimus was shown to be more efficacious in the reduction of affected body surface area (BSA) compared with TCS in 4 studies^{10,14,16,17} and equally efficacious in 1 study.¹⁵ The concentration of 0.03% tacrolimus, on the other hand, was found to be less efficacious than TCS in 3 studies.^{18,19,24} Improvement of pruritus was greater with tacrolimus than TCS in 3 publications,^{11,15,16} similar between TCS and 0.1% tacrolimus in 2 publications,^{15,17} and greater with TCS than 0.03% tacrolimus in 2 publications.^{10,19}

Only 5 of the 11 aforementioned trials were suitable for meta-analysis. In 2 of the studies that had pediatric populations,^{10,16} PGECR scores were significantly in favor of tacrolimus over TCS (relative risk [RR], 3.09; 95% confidence interval [CI], 2.14–4.45 and RR, 2.57; 95% CI, 1.96–3.37, respectively). In 2 studies^{14,15} that used PGECR scores in their adult populations, there was no

significant difference between 0.1% tacrolimus and TCS (RR, 0.95; 95% CI, 0.78–1.16 and RR, 1.35; 95% CI, 0.86–2.12, respectively). With regards to tacrolimus 0.03%, PGECR scores with use of TCS were superior in a study involving adults¹⁵ and another in children²⁴ (RR, 0.73; 95% CI, 0.58–0.92 and RR, 0.20; 95% CI, 0.05–0.76, respectively).

TABLE 1. Summary of the Inclusion and Exclusion Criteria and Methodological Quality of the Study by Svensson et al²⁶

Inclusion criteria	
Types of studies	RCTs regardless of blinding status Crossover trials with adequate washout (2 wk) between treatment period Prospective and comparative studies
Types of participants	Both adults and children (of any age and race) with a symptomatic diagnosis of AD according to a clinical practitioner (any severity at baseline)
Types of interventions	At least 1 tacrolimus ointment arm (all doses) and at least 1 TCS comparator arm (all doses/potencies) Combination therapy where the additional therapy was nonpharmacological and was identical between study arms
Efficacy outcome measures	Percentage BSA affected EASI mEASI mLEASI Intensity of pruritus IGADA Sleep 100 mm VAS PGECR
Safety outcome measures	Withdrawals due to adverse events Withdrawals due to skin burning
Exclusion criteria	
Types of studies	Single-arm extension studies to RCTs Non-randomized controlled clinical trial Cohort study Observational Case control Case study
Types of participants	Nil
Types of interventions	Pimecrolimus or vehicle
Methodological quality	
Allocation	All trials claim to be randomized, but no description was found in 5 studies and was unclear in another 4.
Blinding	Ten studies double-blinded, 2 studies investigator blinded, 4 studies open-label or included an open-label period, blinding status unclear in 1 study

mLEASI, local mEASI; IGADA, Investigator's Global AD Assessment; VAS, visual analog scale.

Six trials compared tacrolimus with class III TCS.^{11–13,20,21,23} The concentration of 0.1% tacrolimus was shown to be superior to fluticasone propionate with respect to mEASI,²¹ local mEASI,¹² and PGECR score,¹² but it was not significantly different with regard to BSA.²³ There was a trend toward greater improvement of the Physician's Global Evaluation of Skin Condition scores with tacrolimus compared with TCS,¹¹ but there was no significant difference in pruritus scores.^{11,12,20,23} No meta-analyses were possible because of the heterogeneity of the study designs. There were no trials comparing tacrolimus with class IV TCS.

Comparison of AEs Between Tacrolimus and TCS

Comparing tacrolimus with class I/II TCS, the withdrawal rates due to AEs were generally low across all studies, and there was no significant difference between both arms.^{10,15–17,19}

The commonest report was that AE was a skin irritation at the application site, and this was more frequent with tacrolimus than TCS.^{10,11,15,17–19,22,24} Skin burning was more frequent with both 0.03% and 0.1% tacrolimus^{10,15–19,22,24} compared with TCS (RR, 3.49; 95% CI, 2.33–5.24 and RR, 4.59; 95% CI, 3.10–6.78, respectively). However, the burning sensation was generally mild to moderate in severity and decreased over time.^{10,11,15–17} The comparative incidence of skin atrophy was not reported in this review.

Comparing tacrolimus with class III/IV TCS,^{11,12,20,21} there was no significant difference in withdrawals due to AEs, but there was a higher risk for skin burning with tacrolimus (RR, 5.59; 95% CI, 2.69–11.63 and RR, 3.00; 95% CI, 1.21–7.43, respectively).

Comparing Pimecrolimus With Vehicle

The comparative efficacy and safety of pimecrolimus against vehicle and TCS is best addressed by the systematic review by Ashcroft et al²⁷ in 2009. Further literature search using PubMed, Embase, Cochrane, DARE, and NHS CRD to identify new studies published between January 2009 and January 2015 did not yield any results. A total of 31 RCTs were included. A summary of the inclusion and exclusion criteria and methodological quality is provided in Table 2.

Comparative Efficacy of Pimecrolimus Versus Vehicle

In studies using Investigator's Global Assessment (IGA) as the outcome measure, pimecrolimus was shown to be superior to vehicle in achieving clear or almost clear eczema after therapy at 2 weeks (RR, 2.00; 95% CI, 1.06–3.76),²⁸ 3 weeks (RR, 2.72; 95% CI, 1.84–4.03),^{29–32} and 6 weeks (RR, 2.03; 95% CI, 1.50–2.74).^{29,30} Pimecrolimus was also shown to be superior to vehicle in achieving clear or almost clear eczema in patients with facial eczema after therapy at 1 week, 3 weeks, and 6 weeks of treatment (RR, 2.94; 95% CI, 1.31–6.61; RR, 3.02; 95% CI, 1.72–5.29; and RR, 2.88; 95% CI, 1.76–4.72, respectively).³³ However, in patients who had previously not responded to prednicarbate, a class II TCS, there was

no significant difference between pimecrolimus and vehicle (RR, 6.19; 95% CI, 0.36–107.66).³⁴

In studies using participant-rated or caretaker-rated clinical response (PGA) as the outcome measure, pimecrolimus was shown to be more efficacious than vehicle in achieving complete or well-controlled eczema after treatment at 3 weeks (RR, 1.88; 95% CI, 1.33–2.67)³² and 6 weeks (RR, 2.65; 95% CI, 1.74–4.04).³⁰ However, in patients who did not respond to pretrial prednicarbate, there was no significant difference between pimecrolimus and vehicle (RR, 1.29; 95% CI, 0.56–2.59).³⁴

In terms of achieving mild or absent pruritus, pimecrolimus was significantly more effective than vehicle at 1 week (RR, 1.89; 95% CI, 1.51–2.35),^{30,31,35} 3 weeks (RR, 2.02; 95% CI, 1.69–2.42),^{29–32} and 6 weeks (RR, 1.82; 95% CI, 1.48–2.25)^{29,30} based on pooled results from 3 trials. Pimecrolimus was similarly more effective than vehicle for patients with facial eczema after 1 week (RR, 1.81; 95% CI, 1.32–2.50), 3 weeks (RR, 1.85; 95% CI, 1.39–2.47), and 6 weeks (RR, 2.02; 95% CI, 1.49–2.73) of treatment.³³ However, in patients who had previously failed pretrial prednicarbate, there was no significant difference between pimecrolimus and vehicle (RR, 1.11; 95% CI, 0.47–2.60).³⁴

Only 3 trials^{36–38} examined the difference in the impact on quality of life (QoL) between pimecrolimus and vehicle. One trial³⁸ used the Parent's Index of Quality of Life in Atopic Dermatitis score and included a 6-week RCT period and a 20-week open-label trial period. At the end of the RCT, pimecrolimus was shown to result in a significantly improved QoL compared with vehicle ($P = 0.023$), but this difference was not sustained in the latter period. One vehicle-controlled trial³⁶ used the Children's Dermatology Life Quality Index and demonstrated improved scores with pimecrolimus, although there was no significant change from baseline in both groups ($P = 0.12$). The third trial³⁷ used the QoL in Parents of Children with Atopic Dermatitis score and demonstrated that pimecrolimus resulted in a significantly improved QoL from baseline ($P < 0.05$).

Comparison of AEs Between Pimecrolimus and Vehicle

In the 22 trials^{29–35,38–51} comparing pimecrolimus with vehicle, the reported AEs were generally mild. The most common AEs were skin infection and application site reactions. From the pooled results of these trials, pimecrolimus was associated with significantly fewer withdrawals (RR, 0.40; 95% CI, 0.27–0.58) both from a lack of efficacy (RR, 0.21; 95% CI, 0.11–0.41) and occurrence of AEs (RR, 0.43; 95% CI, 0.19–0.97). There were no significant differences between pimecrolimus and vehicle in their frequency of overall AEs (RR, 0.92; 95% CI, 0.82–1.02), bacterial skin infections (RR, 0.13; 95% CI, 0.01–1.12), and skin burning (RR, 1.40; 95% CI, 0.90–2.18) (pooled results from 4,^{29,31,41} 1,³⁰ and 5^{30–32,35,41} vehicle-controlled trials, respectively).

TABLE 2. Summary of the Inclusion and Exclusion Criteria and Methodological Quality of the Study by Ashcroft et al²⁷

Inclusion criteria	
Types of studies	RCTs Crossover trials Within-participant studies
Types of participants	Anyone diagnosed by a medical practitioner using standardized diagnostic criteria such as the Hanifin and Rajka or the United Kingdom work group criteria Anyone diagnosed by a dermatologist using the terms <i>atopic eczema</i> or <i>eczema</i>
Types of interventions	Trials comparing topical pimecrolimus 1% twice daily with vehicle Trials comparing topical pimecrolimus 1% twice daily with TCSs Trials comparing topical pimecrolimus 1% twice daily with topical tacrolimus
Efficacy outcome measures	Investigator-rated clinical response (proportion of participants whose eczema was rated by the investigator as clear or almost clear) Participant-rated or caretaker-rated clinical response (proportion of participants who rated their eczema as well controlled or completely controlled and the proportion of participants who rated their eczema as better or much better) Improvement in pruritus (proportion of participants experiencing mild or absent pruritus) No flare of eczema (proportion of participants not experiencing flares of eczema during treatment) No rescue medication (proportion of participants not using TCSs as rescue medications during treatment) Improvement in QoL
Safety outcome measures	Proportion of participants experiencing any adverse events Proportion of participants experiencing any skin infections Proportion of participations experiencing bacterial skin infections Proportion of participations experiencing viral skin infections Proportion of participations experiencing skin burning Proportion of participations experiencing skin thinning
Exclusion criteria	
Types of studies	Non-randomized controlled clinical trial Combined analysis or reanalysis
Types of participants	Patients not having the condition of AD
Types of interventions	Oral medications Unlicensed dosage used for medication (pimecrolimus 4 times daily)

TABLE 2. (Continued)

Methodological quality	
Allocation	Only 5 (16.1%) of the 31 included trials reported adequate allocation concealment. Only 7 (22.6%) of 31 trials described using a computerized system or telephoning a controlled randomization system to automate the assignment of treatment and reported the ratio or blocks of allocation.
Blinding	Four (12.9%) of the 31 trials were investigator blinded, and the other 27 trials (87.1%) were double-blind. Only 9 (33.3%) of the 27 trials that were double-blinded reported on the methods used to ensure the blinding of outcome assessment
Follow-up and exclusions	Loss to follow-up rate ranged from 0%–44% with withdrawal rate of more than 20% in 15 trials (48.4%).
Selective reporting	Only 16 trials (51.6%) reported the criteria used for diagnosing eczema. A total of 21 trials (67.7%) stated that the baseline severities of eczema were comparable between the different treatment groups.

Comparing Pimecrolimus With TCS

Comparative Efficacy of Pimecrolimus Versus TCS

Using the IGA as the end point, a 12-month trial⁵² comparing pimecrolimus and 0.1% triamcinolone acetone (a class II TCS) in adults with moderate to severe eczema showed that pimecrolimus was significantly less effective in achieving clear to almost clear eczema at 1 week (RR, 0.52; 95% CI, 0.45–0.61), 3 weeks (RR, 0.75; 95% CI, 0.67–0.83), 6 months (RR, 0.89; 95% CI, 0.83–0.96), and 12 months (RR, 0.92; 95% CI, 0.86–0.98) of treatment.

In terms of PGA measurement, a comparative trial between pimecrolimus and 0.1% betamethasone valerate³¹ (a class II TCS) found pimecrolimus to be significantly less effective in achieving moderately clear or better eczema at 3 weeks (RR, 0.61; 95% CI, 0.45–0.81).

In both the aforementioned trials,^{31,52} pimecrolimus was shown to have significantly fewer participants achieving mild or absent pruritus at 1 week (RR, 0.51; 95% CI, 0.34–0.75), 3 weeks (RR, 0.58; 95% CI, 0.41–0.81), and 12 months (RR, 0.47; 95% CI, 0.38–0.58).

Comparison of Adverse Events Between Pimecrolimus and TCS

When comparing pimecrolimus with 0.1% triamcinolone acetone, Luger et al³¹ in 2001 found no significant difference in overall withdrawals (RR, 2.18; 95% CI, 0.60–7.88), withdrawals due to lack of efficacy (RR, 4.67; 95% CI, 0.23–94.61), and withdrawals due to AEs (RR, 2.80; 95% CI, 0.30–25.88). However,

in 2004, Luger et al⁵² found pimecrolimus to be associated with significantly more overall withdrawals (RR, 2.45; 95% CI, 1.98–3.03), withdrawals due to lack of efficacy (RR, 4.43; 95% CI, 3.01–6.54), and withdrawals due to AEs (RR, 5.63; 95% CI, 2.20–14.41).

In both studies,^{31,52} the risk for skin burning was found to be significantly higher with pimecrolimus (RR, 2.38; 95% CI, 1.66–3.40 and RR, 5.13; 95% CI, 1.93–3.66, respectively). Although the 2001 study³¹ found the risk for any AE to be higher with pimecrolimus (RR, 1.57; 95% CI, 1.07–2.30), the 2004 study⁵² showed no significant difference (RR, 1.07; 95% CI, 0.98–1.17) between the 2 arms.

Comparing Pimecrolimus With Tacrolimus

Comparative Efficacy of Pimecrolimus Versus Tacrolimus

Using IGA to assess efficacy, there was no significant difference between pimecrolimus and 0.03% tacrolimus in achieving clear or almost clear eczema after 1 week (RR, 0.91; 95% CI, 0.63–1.31), 3 weeks (RR, 0.82; 95% CI, 0.58–1.15), and 6 weeks (RR, 0.84; 95% CI, 0.69–1.02) of treatment.^{53,54} Although pimecrolimus was not significantly different from 0.1% tacrolimus in achieving clear or almost clear eczema after 1 week of treatment (RR, 0.85; 95% CI, 0.53–1.34), it was significantly less effective at 3 weeks (RR, 0.56; 95% CI, 0.41–0.77) and 6 weeks (RR, 0.58; 95% CI, 0.46–0.74) of treatment.⁵⁴

In terms of achieving mild or absent pruritus, 1 trial⁵⁴ showed that there was no significant difference between pimecrolimus and 0.03% tacrolimus at 1 week (RR, 0.80; 95% CI, 0.62–1.04) and 6 weeks (RR, 0.92; 95% CI, 0.73–1.17) of treatment, but pimecrolimus was significantly less effective in achieving mild or absent pruritus at 3 weeks (RR, 0.78; 95% CI, 0.61–0.99).

Comparison of Adverse Events Between Pimecrolimus and Tacrolimus

Comparing pimecrolimus and 0.03% tacrolimus, there was no significant difference in the overall withdrawal rate (RR, 1.94; 95% CI, 0.54–6.98), but pimecrolimus was associated with significantly higher withdrawal rates due to lack of efficacy (RR, 3.45; 95% CI, 1.23–9.71) and AEs (such as skin infections and skin burning) (RR, 8.19; 95% CI, 1.50–44.73).

Comparing pimecrolimus and 0.1% tacrolimus, there was no significant difference in the overall withdrawal rate (RR, 1.18; 95% CI, 0.91–1.52) and withdrawal rate due to AEs (such as skin infections and skin burning) (RR, 1.01; 95% CI, 0.43–2.41). However, there was a significantly higher withdrawal rate because of lack of efficacy (RR, 2.37; 95% CI, 1.10–5.08) with pimecrolimus.⁵⁴

Long-Term Safety of TCIs

In 2006, the US Food and Drug Administration issued a public health advisory and “black box” warning on the risk for malignancy with the use of TCIs. This was prompted by animal

carcinogenicity studies, small number of case reports, and the increased risk for cancer observed in posttransplant patients receiving systemic calcineurin inhibitors.⁵⁵ The risk for malignancy associated with TCIs is best addressed by the systematic review by Tennis et al.⁵⁶ Further literature search using PubMed, Embase, Cochrane, DARE, and NHS CRD to identify new studies published between March 2011 and January 2015 did not yield any results.

Risk for Lymphoproliferative Diseases With the Use of TCIs Versus TCS

Four studies had addressed the risk for lymphomas with use of TCIs compared with TCS. Hui et al⁵⁷ reported an increased risk for cutaneous lymphomas in eczema patients with the use of tacrolimus (hazards ratio, 5.44; 95% CI, 2.51–11.79) but not pimecrolimus (hazards ratio, 2.32; 95% CI, 0.89–6.07) compared with patients who were not exposed to TCIs. On the other hand, Schneeweiss et al⁵⁸ reported an increased risk for cutaneous lymphomas with the use of tacrolimus (RR, 2.82; 95% CI, 1.08–7.39), pimecrolimus (RR, 2.89; 95% CI, 1.32–6.32), and TCS (RR, 2.10; 95% CI, 1.01–4.33) when compared with the general population. Arellano et al⁵⁹ in 2007 reported no increased risk with the use of pimecrolimus (odds ratio [OR], 0.8; 95% CI, 0.4–1.6) or tacrolimus (OR, 0.8; 95% CI, 0.4–1.7) compared with patients unexposed to TCIs. However, a significant increased risk was noted with increased severity of AD (OR, 2.4; 95% CI, 1.5–3.8), use of oral steroids (OR, 1.5; 95% CI, 1.0–2.4), and high-dose TCS or TCI use (OR, 2.3; 95% CI, 1.17–4.51). This finding was further corroborated by Arellano et al⁶⁰ in 2009, who found an increased risk for lymphoma with TCS use compared with non-TCS users (OR, 1.96; 95% CI, 1.62–2.37). In this study, however, the number of patients exposed to TCI was insufficient to study any association between TCIs and TCS.^{58,60}

Risk for Skin Cancers With the Use of TCIs

In a questionnaire-based case-control study,⁶¹ the use of TCIs was not associated with increased risk for nonmelanoma skin cancers (OR, 0.5; 95% CI, 0.4–0.7), a finding consistent with data from animal models.^{62–64} However, a confounder may be the selective prescription of TCIs to patients least likely to develop skin cancer. With regards to melanoma, Hui et al⁵⁷ found a negative association with the use of both tacrolimus (RR, 0.3; 95% CI, 0.1–0.8) and pimecrolimus (RR, 0.7; 95% CI, 0.4–1.3). Similarly, the results may have been confounded by the selective prescription of TCIs.

Cost-Effectiveness of TCIs

The comparative cost-effectiveness of TCIs was assessed as follows: tacrolimus with TCS, pimecrolimus with vehicle and TCS, and tacrolimus with pimecrolimus.

A total of 9 studies^{65–73} evaluating the cost-effectiveness of TCIs were identified. Of these, 3 studies were excluded as they compared proactive against reactive therapy and were not relevant

to this review. Of the remainder, Garside et al⁶⁵ compared both tacrolimus and pimecrolimus against TCS, Hjelmgren et al⁶⁷ compared tacrolimus against TCS, and 2 studies by Abramovits et al⁶⁸ and Taneja et al⁶⁹ compared tacrolimus against pimecrolimus in pediatric and adult populations, respectively. The findings of these studies will be reported later. Both the last 2 studies evaluated the cost-effectiveness of pimecrolimus against vehicle. The study by Pitt et al⁶⁶ will be presented later as it evaluated the cost-effectiveness of pimecrolimus against vehicle in both adults and children, and included efficacy data synthesized from multiple trials.^{29,31,38,49,74} In contrast, the study by Ellis et al⁷⁵ analyzed the cost-effectiveness of pimecrolimus only in adolescents aged 2 to 17 years and included efficacy data based on a single trial.⁴⁹

All 5 studies presented used the Markov model in the analysis of cost-effectiveness.

In the 3 studies^{65–67} comparing TCIs against TCS, the time horizon of the models was 1 year in adults and 14 years in children. The number of cohorts independently modeled ranged from 2 to 8. The characteristics of these 3 studies are summarized in Table 3.

In the 2 studies^{68,69} that compared tacrolimus against pimecrolimus, the time horizon was 1 year in children and 6 weeks in adults. Both studies modeled a single cohort. The shorter time horizon and fewer modeled cohorts in the 2 studies comparing tacrolimus against pimecrolimus could be due to the paucity of data regarding the comparative efficacy of tacrolimus against pimecrolimus. The characteristics of these 2 studies are summarized in Table 4.

The incremental cost-effectiveness ratio (ICER) is the ratio of the change in costs to incremental benefits of a therapeutic intervention.⁷⁶ We consider a value below £30,000 per quality-adjusted life year (QALY) gained, in accordance with the United Kingdom NHS, to be cost-effective.

Comparative Cost-Effectiveness of TCIs Versus TCS

Three studies^{65–67} (2 from the United Kingdom and 1 from Sweden) are reported below.

Comparative Cost-Effectiveness of Pimecrolimus Versus Emollients

For children with mild to moderate eczema, pimecrolimus was more cost-effective than emollients, with an ICER of between £9684 (~US \$14,561) and £11,909 (~US \$17,908). For adults with mild to moderate eczema, pimecrolimus was similarly more cost-effective than emollients, with an ICER of between £16,646 (~US \$25,031) and £16,856 (~US \$25,346).

Comparative Cost-Effectiveness of Pimecrolimus Versus TCS

For both children and adults with mild to moderate eczema affecting either the face or body, pimecrolimus costs more and

conferred fewer QALYs compared with TCS, both as the first-line and second-line treatment.

Comparative Cost-Effectiveness of Tacrolimus Versus TCS

For children with moderate to severe body eczema, using tacrolimus was cost-effective both as first-line and second-line therapy (ICER of £9083 [~US \$13,658] and £14,175 [~US \$21,315], respectively). In contrast, for children with moderate to severe facial eczema, tacrolimus was not cost-effective both as the first-line (ICER of £35,669 [~US \$53,635], slightly higher than the NHS threshold) and second-line treatment. This was surprising, considering the low ICER in adults (see below).

For adults with moderate to severe body eczema, tacrolimus was cost-effective as second-line therapy with an ICER of £7828 (~US \$11,771). When used as first-line therapy, however, the ICER was £37,362 (~US \$56,181), marginally above the NHS threshold. For adults with moderate to severe facial eczema, tacrolimus was cost-effective as first-line therapy (ICER of £11,882 [~US \$17,867]) but not second-line therapy. This contrasting result was attributed to the similar levels of QALYs conferred by tacrolimus when used as both first-line and second-line therapies, which resulted in greater incremental QALYs in the former when low-potency steroids were the main comparators and lower increment in the latter when midpotency steroids and oral antibiotics were the main comparators.

Comparative Cost-Effectiveness of Tacrolimus Ointment Versus Pimecrolimus Cream

The comparison of cost-effectiveness between tacrolimus ointment and pimecrolimus cream was studied in both children⁶⁸ and adults⁶⁹ and is reported below.

Comparative Cost-Effectiveness of Tacrolimus Versus Pimecrolimus in Children

Abramovits et al⁶⁸ included pediatric patients with moderate AD inadequately controlled by TCS. The costs of treatment with 0.03% tacrolimus and pimecrolimus over a 1-year period were US \$1393 and US \$1550, respectively. Although the primary drug cost was higher for tacrolimus (US \$797) compared with pimecrolimus (US \$786), patients treated with tacrolimus achieved better disease control and required fewer clinic visits, incurring lower costs on secondary treatments (US \$162 vs US \$236) and consultations (US \$434 vs US \$529).

The use of tacrolimus resulted in 190 disease-controlled days (DCDs) over a 1-year period compared with 137 DCDs with the use of pimecrolimus. Overall, tacrolimus was more cost-effective compared with pimecrolimus (US \$7.37/DCD vs US \$11.34/DCD).

Comparative Cost-Effectiveness of Tacrolimus Versus Pimecrolimus in Adults

Taneja et al⁶⁹ included patients 16 years and older who had mild to very severe AD. The total costs of treatment estimated over

TABLE 3. Summary of Study Characteristics and Incremental Cost-Effectiveness Ratios in Cost-Effectiveness Analyses of TCIs Versus Topical Steroids (the Standard of Care)

	Garside et al ⁶⁵ (United Kingdom Study)	Pitt et al ⁶⁶ (United Kingdom Study)	Hjelmgren et al ⁶⁷ (Swedish Study)			
Study population	Children (2 years and older) with mild to severe AD		Adolescents and adults aged 14 years and older			
	Adults (16 years and older) with mild to severe AD					
Comparators	Topical tacrolimus and pimecrolimus against TCSs	Topical pimecrolimus against TCSs and emollients	Topical tacrolimus ointment against TCSs			
Model	Markov model based on 8 separate cohorts (children with mild to moderate facial eczema, children with mild to moderate body eczema, children with moderate to severe facial eczema, children with moderate to severe body eczema, adults with mild to moderate body eczema, adults with mild to moderate facial eczema, adults with moderate to severe facial eczema, and adults with moderate to severe body eczema)	Markov model based on 4 separate cohorts (children with mild to moderate facial eczema, children with mild to moderate body eczema, adults with mild to moderate body eczema, and adults with mild to moderate facial eczema)	Markov model based on 2 separate cohorts (adults with moderate eczema and adults with severe eczema)			
Time horizon	Modeled over 1 year in adults (to capture cyclical response and relapse nature of eczema) Modeled over 14 years in children (to incorporate possibility of disease resolution) Ratio of the expected costs of AD-related care to the QALYs		Modeled over 1 year with a cycle of 3 weeks (to capture cyclical response and relapse nature of eczema)			
Assessment of cost-effectiveness						
Measures of efficacy	Utility values were estimated for each treatment state (disease controlled, mild, moderate, or severe atopic eczema)	Utility values estimated for each health state (disease controlled, mild, and moderate atopic eczema)	Disease severity was estimated based on erythema and population QoL weight was estimated for each health state (virtually cleared, moderate, severe first-line therapy, severe second-line therapy)			
Perspective	Health care provider (United Kingdom NHS)		Health care provider (Swedish health care sector)			
Summary of the ICER values (in pounds per QALY)						
	Mild to moderate AD		Moderate to severe AD			
			Children		Adults	
	Children	Adults	Facial	Body	Facial	Body
Topical pimecrolimus against emollients	£9684 (~\$14,561) to £11,909 (~\$17,908)	£16,646 (~\$25,031) to £16,856 (~\$25,346)	Not examined in trials			
Topical pimecrolimus against TCSs	TCSs cost less and conferred more QALYs		Not examined in trials			
Topical pimecrolimus against TCSs (first-line)	Not examined in trials		£35,669 (~\$53,635)	£9083 (~\$13,658)	£11,882 (~\$17,867)	£37,362 (~\$56,181)
Topical tacrolimus against TCSs (second-line)	Not examined in trials		TCSs cost less and conferred more QALYs	£14,175 (~\$21,315)	TCSs cost less and conferred more QALYs	£7828 (~\$11,771)

TABLE 4. Characteristics of Studies on Cost-Effectiveness of Topical Tacrolimus Versus Pimecrolimus

Abramovits et al⁶⁹	
Study population	Pediatric patients with moderate AD
Comparators	Topical 0.03% tacrolimus ointment against pimecrolimus cream
Model	Generic Markov model applied to single cohort
Time horizon	Modeled over 1 year (52 wk) with a cycle length of 4 weeks except for the primary treatment state (2 or 4 wk depending on likelihood of treatment success)
Assessment of cost-effectiveness	Ratio of the expected costs of AD-related care to the number of DCDs
Measures of efficacy	Treatment success defined as 75% improvement in disease state from baseline Treatment efficacy estimated based on existing outcomes reported in clinical trials of each respective treatment Treatment success rates for pimecrolimus not directly known as clinical trials relied on IGA scored on a Likert scale Comparison of EASI scores used to estimate treatment efficacy indirectly
Perspective	Health care provider (United States)
Taneja et al⁷⁰	
Study population	Adult patients aged older than 16 years with mild to very severe AD
Comparators	Topical 0.1% tacrolimus ointment against pimecrolimus cream
Model	Generic Markov model applied to single cohort
Time horizon	Modeled over 42 d (6 wk)
Assessment of cost-effectiveness	Ratio of the expected costs of AD-related care to the number of days of resolved AD
Measures of efficacy	IGADA score was used to determine transition between states. IGADA score of "mild," "moderate," "severe," or "very severe" defined as "active AD" IGADA score of "clear" or "almost clear" defined as "resolved AD"
Perspective	Health care provider (United States)

IGADA, Investigator's Global AD Assessment.

42 days were similar between 0.1% tacrolimus and pimecrolimus (US \$214.31 vs US \$216.02). However, patients treated with tacrolimus had 4.9 fewer days of active AD compared with patients treated with pimecrolimus (total of 30 vs 34.9 days). Overall, tacrolimus, with higher clinical efficacy, demonstrated greater cost-effectiveness.

DISCUSSION

Overall, the efficacy of 0.1% tacrolimus was similar to or greater than that of class I-II TCS, whereas the efficacy of 0.03% tacrolimus ointment was less than that of class I/II TCS. There was no significant difference in the AEs between tacrolimus and TCS except

for the increased incidence of skin burning. Compared with TCS (standard of care), tacrolimus was cost-effective in moderate to severe body eczema in children as both first-line and second-line therapies but not in moderate to severe facial eczema. In contrast, in adults with moderate to severe facial eczema, tacrolimus was cost-effective as the first-line therapy. In adults with moderate to severe body eczema, tacrolimus was cost-effective only as the second-line therapy.

The efficacy of pimecrolimus was greater than vehicle in controlling the signs and symptoms of AD except in patients who had previously failed to respond to moderately potent (class II) TCS. However, pimecrolimus was significantly less effective than moderately potent or potent TCS. With regard to overall AEs, there was no significant difference between pimecrolimus and vehicle or TCS. However, pimecrolimus was associated with a higher risk for skin burning compared with TCS. With regard to cost-effectiveness, pimecrolimus was more cost-effective compared with emollients in the treatment of mild to moderate AD but was less cost-effective compared with TCS in the treatment of both body and facial eczema in both adults and children.

With regard to the risk for malignancy with use of TCIs, postmarketing surveillance and epidemiological data remain unclear.^{56,77–79} In the studies performed,^{58–60} it was difficult to disentangle the effect of drugs used from the effect of AD itself. Topical calcineurin inhibitors have been shown not to be associated with development of skin cancers. However, the risk of development of lymphoproliferative diseases is a concern and requires further evaluation and monitoring.

Comparing pimecrolimus and 0.03% tacrolimus, there was no significant difference in efficacy in controlling the signs and symptoms of AD. On the other hand, pimecrolimus was less efficacious compared with 0.1% tacrolimus. With regard to AEs, both pimecrolimus and tacrolimus were well tolerated, with no significant difference in overall withdrawal rates. In terms of cost-effectiveness, tacrolimus was superior to pimecrolimus in the treatment of both adults and children with AD.

CONCLUSIONS AND RECOMMENDATIONS

Based on the aforementioned findings, tacrolimus is an efficacious and cost-effective alternative to TCS in the treatment of AD in both children and adults. However, the benefits of tacrolimus use need to be weighed against the still uncertain risk for malignancy development. Pimecrolimus, on the other hand, is appropriate in patients with mild AD in whom treatment with TCS or tacrolimus is not suitable.

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