

Comparative Effectiveness of Topical Calcineurin Inhibitors in Adult Patients with Atopic Dermatitis

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Abstract

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by extreme pruritis and lichenified papules and plaques that may begin in or persist into adulthood. Topical corticosteroids are first-line prescription therapy for AD; they are efficacious and have a well established safety profile. The topical calcineurin inhibitors tacrolimus and pimecrolimus were approved by the US FDA in 2000 and 2001, respectively, as second-line topical therapy for AD. This review evaluates the available studies on the comparative effectiveness, safety, cost, and impact on quality of life of topical corticosteroids and topical calcineurin inhibitors for the treatment of adult AD.

Tacrolimus was found to be as effective as class III–V topical corticosteroids for AD of the trunk and extremities, and more effective than low-potency class VI or VII corticosteroids for AD of the face or neck. Pimecrolimus was less effective than both tacrolimus and low-potency topical corticosteroids for moderate to severe AD. The short-term safety studies found that, compared with topical corticosteroid-treated adults, patients treated with topical calcineurin inhibitors had an increased frequency of application-site reactions, an equivalent infection risk, and a decreased risk of skin atrophy. The long-term safety of topical calcineurin inhibitors remains under investigation. Currently published studies that evaluated the comparative cost and quality-of-life effects compared tacrolimus with less potent topical corticosteroids despite the availability of equivalent potency corticosteroids. Further cost and quality-of-life studies are needed that compare topical calcineurin inhibitors with stronger classes of topical corticosteroids over longer time periods.

The available clinical trials data do not suggest an efficacy advantage for topical calcineurin inhibitors over topical corticosteroids in adults with AD of the trunk and extremities, and there is not yet adequate evidence to support topical calcineurin inhibitors as first-line therapy for adult AD.

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by extreme pruritis and lichenified papules and plaques that commonly occur on extensor surfaces in children and in skin flexures in adults. Although AD has a higher prevalence in children, the disorder may begin in or persist into adulthood, with an estimated 1–3% worldwide prevalence in adults.^[1] Since their introduction in the 1950s, topical corticosteroids have been first-line prescription therapy for AD.^[2] In 2000 and 2001, respectively, the topical calcineurin inhibitors (TCIs) tacrolimus and pimecrolimus were approved by the US FDA for the treatment of AD in patients who were unresponsive to, intolerant of, or unsuitable for topical corticosteroid therapy.^[3,4] Initial studies compared the TCIs with an emollient vehicle, providing evidence of their efficacy and short-term safety but no data on their comparative efficacy and safety with each other or with established topical corticosteroid therapy.^[5–7] Subsequent studies have evaluated the comparative effectiveness of TCIs. We review studies that compared the effectiveness, safety, cost, and impact on quality of life (QOL) of the TCIs with that of topical corticosteroids.

We systematically reviewed all available studies on the comparative effectiveness of TCIs and topical corticosteroids in adults with atopic dermatitis. Studies that evaluated cost effectiveness, safety, and impact on quality of life were also included. All available sources, including randomized trials, observational and non-randomized studies, modeling analyses, and database studies, were included. A standardized electronic literature search was performed using MEDLINE (until March 2011) and the keywords '(atopic AND [eczema OR dermatitis])' AND '(tacrolimus OR pimecrolimus)'. We limited the literature search to papers on humans. Additional papers were identified by hand searching the reference lists of review articles on atopic dermatitis. Exclusion criteria included no original data reported, studies not carried out in humans, studies not carried out in adults, and vehicle-controlled trials. Recorded data from the selected studies included the year of publication, study design, study population, treatments evaluated, measured endpoints, study outcome, and adverse effects.

1. Standard Atopic Dermatitis Therapy in Adults

Both topical corticosteroids and TCIs fall within a standard treatment hierarchy for adults with AD. Individuals with AD

have an impaired skin permeability barrier, which allows for increased transepidermal water loss, allergen penetration, and microbial introduction.^[8] The first step in AD treatment is to enhance the skin's barrier function with topical emollients and to control environmental factors that cause flares, including dust mites, foods, skin infections, emotional distress, xerosis, and high temperatures.^[2,9] In addition to emollient therapy, xerosis can be improved by reducing excessive bathing, using tepid water and mild soap, and air humidification.^[10] Cutaneous infections can be controlled with topical or systemic antibacterial therapy.

If flare avoidance and skin emollients fail to control AD, topical therapy is the next treatment option. The mainstay of topical therapy is topical corticosteroids; however, corticosteroid-associated adverse effects limit their use to discontinuous flare therapy. The established adverse effects of topical corticosteroids include tachyphylaxis, systemic absorption leading to insulin resistance and suppression of endogenous cortisol production, cutaneous atrophy with the development of striae, telangiectasias and dyspigmentation, and perioral dermatitis.^[11] TCIs are approved as second-line topical therapy for AD.

For patients who are resistant to topical therapy, phototherapy is the next treatment option. Psoralen and UVA and narrow-band UVB are both effective AD therapy, but carry an increased risk of skin cancer and photoaging.^[11] Widespread disease or recalcitrant local disease that interferes with the patient's QOL may be treated with systemic immunomodulatory agents, including corticosteroids, cyclosporine (cyclosporin), methotrexate, azathioprine, and mycophenolate mofetil.^[12] More rarely used therapeutic options include interferon- γ , intravenous immunoglobulin, phosphodiesterase inhibitors, leukotriene inhibitors, and thalidomide.

2. Mechanism of Action of Topical Calcineurin Inhibitors

The TCIs tacrolimus and pimecrolimus are immunomodulatory molecules that are naturally produced by *Streptomyces* bacteria.^[13] The TCIs were developed for use as immunosuppressive medications in organ transplant recipients to prevent rejection. Subsequently, it was discovered that, when applied topically, they could penetrate inflamed skin. In AD, the topical application of TCIs is designed to suppress cutaneous immune

cells without inducing systemic adverse effects, including nephrotoxicity and hypertension.

The TCIs target three cell types implicated in AD pathogenesis: T cells, mast cells, and dendritic cells.^[13] T-cell activation relies on the transcription of pro-inflammatory cytokines, including interleukin-2. The transcription of these cytokines is triggered when nuclear factor of activated T cells (NF-AT) is dephosphorylated by calcineurin and translocates to the nucleus.^[11] The TCIs inhibit calcineurin-dependent dephosphorylation of NF-AT. As a result, NF-AT is unable to translocate to the nucleus and induce cytokine transcription that would activate T cells. In addition, both TCIs decrease mast-cell activation and tacrolimus decreases the absolute number and the stimulatory capacity of epidermal dendritic cells.

3. Comparative Effectiveness

Several studies have attempted to evaluate the comparative effectiveness of pimecrolimus, tacrolimus, and topical corticosteroids in the treatment of AD. No study has directly compared the three agents, but studies have compared the two TCIs with each other and each calcineurin inhibitor with topical corticosteroids of different potency classes. Topical corticosteroids discussed below are referred to by the US potency classification system, where class I corticosteroids are the most potent and class VII corticosteroids are the weakest. In the UK and elsewhere, only four potency classes are recognized and the numeric potency classification is reversed, with class IV corticosteroids as the most potent and class I corticosteroids as the weakest.

3.1 Tacrolimus Compared with Pimecrolimus

One randomized, investigator-blinded study sponsored by the manufacturer of tacrolimus evaluated the comparative effectiveness of tacrolimus 0.1% ointment with pimecrolimus 1.0% cream in adult patients with mild to very severe AD (table I).^[16] Although the study compared the use of the two topical therapies in AD patients with a wide range of disease severity, tacrolimus is approved only for patients with moderate to severe disease and pimecrolimus is approved only for patients with mild to moderate disease.^[3,4] Two separately published sub-analyses compared the effectiveness of the two agents in a subset of study patients with moderate to very severe AD^[15] and in patients with moderate AD.^[14] The study findings comparing the efficacy of tacrolimus with pimecrolimus in patients with mild AD have not been published. In all three published analyses, tacrolimus was found to be more effective than pi-

mecrolimus, as measured by improvement in the Eczema Area and Severity Index (EASI) at 6 weeks. In the combined analysis, the clinical response was faster in tacrolimus-treated patients, with significantly greater improvement in the tacrolimus group than in the pimecrolimus group at week 1.

In summary, the published results support the conclusion that tacrolimus is more effective and elicits a faster clinical response than pimecrolimus in patients with moderate to very severe AD and in a mixed population of AD patients with mild to very severe disease. No conclusions can be drawn regarding the comparative effectiveness of the two agents in patients with mild AD or for use longer than 6 weeks.

3.2 Tacrolimus Compared with Topical Corticosteroids

One study evaluated the comparative effectiveness of tacrolimus 0.03% ointment in adult patients with moderate to severe AD and found it to be less effective than both tacrolimus 0.1% ointment and a class V topical corticosteroid.^[21] Seven studies have evaluated whether tacrolimus 0.1% ointment is more effective than standard corticosteroid therapy in adult patients with moderate to severe AD (table I).^[17-23] Five of the studies were sponsored by the manufacturer of tacrolimus.^[17-21] Two studies limited their analysis to AD of the head and neck.^[18,23] Of the five studies that were not limited to the head and neck, three were randomized, double-blind, controlled trials,^[17,20,21] and two were randomized, open-label trials.^[19,22] They compared tacrolimus 0.1% ointment with class V, class III, and a combination of class II–VII topical corticosteroids. Three studies compared tacrolimus with class V topical corticosteroids using various treatment durations.^[17,20,21] In one of these studies, tacrolimus showed equivalent clinical improvement, as measured by median EASI score, to topical corticosteroids after 1 year.^[17] Two studies found that tacrolimus was more effective than class V topical corticosteroids after 6 months, but only Reitamo et al.^[20] found tacrolimus to be more effective at 3 months.^[17,20] No difference in treatment efficacy between groups, as measured by improvement in modified EASI score, was observed after only 3 weeks in the third study.^[21] Tacrolimus 0.1% ointment was compared with class III topical corticosteroids in one 3-week study.^[22] Class III topical corticosteroids and tacrolimus led to equal clinical improvement, as measured by physician's global assessment, at 3 weeks. There are no data on the long-term effectiveness of tacrolimus relative to class III corticosteroids, and no studies have evaluated tacrolimus compared with potent class I or II topical corticosteroids. The remaining study compared tacrolimus with a variety of topical corticosteroids ranging in strength from class VII to class II.^[19] After

Table I. Comparative effectiveness of tacrolimus (TAC) 0.1% ointment, pimecrolimus (PIM) 1.0% cream, and topical corticosteroids (TCs) in adults with atopic dermatitis (AD)

Year	Study	Study design (duration)	Adult population	TCs	TC class	Body area	Outcome measure	Results	p-Value
TAC compared with PIM									
2008	Abramovits et al. ^[14]	r, ib (6 wk)	Moderate AD	N/A	N/A	All affected areas	EASI	Greater EASI improvement in TAC patients (59% vs 43% reduction)	0.01
2007	Fleischer et al. ^[15]	r, ib (6 wk)	Moderate to very severe AD	N/A	N/A	All affected areas	EASI	Greater EASI improvement in TAC patients (57% vs 39% reduction)	0.0002
2005	Paller et al. ^[16]	r, ib (6 wk)	Mild to very severe AD	N/A	N/A	All affected areas	EASI	Greater EASI improvement in TAC patients (54% vs 35% reduction)	<0.0001
TAC compared with TCs									
2010	Mandelin et al. ^[17]	r, db (12 mo)	Moderate to severe AD	HCT A 1% ointment HCT B 0.1% ointment	VII V	Face, neck Trunk, extremities	EASI	For combined analysis, greater EASI improvement in TAC patients at 6 mo, no difference at 3 or 12 mo. For head and neck, greater EASI improvement at 6 and 12 mo	≤0.05 at 6 mo (combined analysis); ≤0.01 at 6 mo, ≤0.05 at 12 mo (head and neck)
2009	Doss et al. ^[18]	r, db (3 wk)	Moderate to severe AD, intolerant of or unresponsive to conventional therapy	FP 0.005% ointment	III	Face	% with ≥60% mLEASI decrease	Greater response rate in TAC patients (93% vs 88% with ≥60% mLEASI reduction)	0.03
2008	Neumann et al. ^[19]	r, op (6–20 mo)	Moderate AD	Class II–VII	II–VII	All	EASI, BSA	No difference between groups	
2005	Reitamo et al. ^[20]	r, db (6 mo)	Moderate to severe AD	HCT B 0.1% ointment	V	Trunk, extremities	% with ≥60% mEASI decrease	For combined analysis, greater response rate in TAC patients at 3 and 6 mo (73% vs 52% at 3 mo)	<0.001 at 3 and 6 mo
2002	Reitamo et al. ^[21]	r, db (3 wk)	Moderate to severe AD	HCT A 1% ointment HCT B 0.1% ointment	VII V	Face, neck All areas	mEASI	No difference between TAC and TC groups (63.5% vs 63.9% reduction, respectively)	
1997	FK506 Ointment Study Group ^[22]	r, op (3 wk)	Moderate to severe AD	BMV 0.12% ointment	III	Trunk, extremities	Physician's global severity	No difference between TAC and TC groups (95.5% vs 91.5% with moderate or greater improvement, respectively)	

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Table I. Contd

Year	Study	Study design (duration)	Adult population	TCs	TC class	Body area	Outcome measure	Results	p-Value
1997	FK506 Ointment Study Group ^[23]	r, op (1 wk)	Moderate to severe AD	AMD 0.1%	VI	Head, neck	Physician's global severity	Greater proportion of TAC patients with marked or greater improvement	<0.001
PIM compared with TCs									
2004	Luger et al. ^[24]	r, db (13 mo)	Moderate to severe AD	HCT A 1% cream	VII	Face, neck, and intertriginous areas	EASI	TCs more effective at all timepoints (d 8, d 22, 7 mo, 13 mo)	≤0.006
				TRC 0.1% cream	VI	Trunk, extremities			
2001	Luger et al. ^[25]	r, db (3 wk)	Moderate to severe AD	BMV 0.1% cream	V	Trunk, extremities	EASI	Greater EASI improvement in TC patients	<0.05

AMD=alclometasone dipropionate; **BMV**=betamethasone valerate; **BSA**=body surface area; **db**=double-blind; **EASI**=Eczema Area and Severity Index; **FP**=fluticasone propionate; **HCT A**=hydrocortisone acetate; **HCT B**=hydrocortisone butyrate; **ib**=investigator-blind; **mEASI**=modified Local Eczema Area and Severity Index; **N/A**=not applicable; **r**=randomized; **op**=open-label; **TRC**=triamcinolone acetate.

11 months of treatment, no difference in effectiveness, as measured by EASI or body surface area (BSA) improvement, was noted.

Based on these studies, tacrolimus 0.1% ointment appears equally effective to mid to high potency class III–V corticosteroids in the treatment of AD. Given that no data on treatment longer than 1 year exist, we can not compare the long-term treatment efficacy of these agents.

Three randomized studies (two double-blind and one open-label) compared treatment for AD limited to the head and neck.^[17,18,23] In all three studies, patients treated with tacrolimus showed greater improvement than patients treated with topical corticosteroids. In two studies, tacrolimus showed greater clinical improvement, as measured by the modified Local Eczema Area and Severity Index (mLEASI) and physician estimates of global severity, than low-potency (class VI and VII) topical corticosteroids at 1 week, 6 months, and 1 year.^[17,23] In the third study, tacrolimus led to greater mLEASI improvement than a class III topical corticosteroid after 3 weeks in patients who were resistant to or intolerant of conventional therapy.^[18] These studies support the conclusions that tacrolimus is more effective than low-potency corticosteroids for AD of the face and neck and that tacrolimus is an effective second-line therapy for corticosteroid-resistant or intolerant patients. No studies have compared tacrolimus with medium-potency corticosteroids for facial AD in a population without previously demonstrated topical corticosteroid resistance.

3.3 Pimecrolimus Compared with Topical Corticosteroids

Two randomized, double-blind, controlled studies have compared the efficacy of pimecrolimus with topical corticosteroids in adults with moderate to severe AD without limitations on affected body areas (table I).^[24,25] One of the trials was funded by the manufacturer of pimecrolimus.^[24] A medium-potency, class V topical corticosteroid and low-potency, class VI and VII topical corticosteroids were used as comparative treatments in the studies. Both found that pimecrolimus was less effective than topical corticosteroids at all timepoints evaluated, from 1 week up to 13 months. Pimecrolimus is less effective than topical corticosteroids for the treatment of moderate to severe AD.

4. Safety

When evaluating a new immunosuppressive medication, safety concerns are of high priority. The long-term safety of TCIs remains a controversial issue that awaits a final resolution. Phase I, II, and III trials were designed to assess the efficacy and short-term safety of TCIs by documenting acute-onset events,

including anaphylaxis, irritation, pain, and other localized reactions.^[26] However, these early trials did not evaluate the long-term medication safety. Following US FDA approval, sporadic malignancy-related events were reported among individuals using TCIs, including 22 cases of lymphoma and 9 cutaneous malignancies. Reported systemic absorption of TCIs and an established link between high drug concentrations and malignancies in animal models raised concern about a possible cancer risk associated with TCI use. In January 2005, the FDA recommended approval of a 'black-box' warning on tacrolimus and pimecrolimus, which was approved in January 2006.^[27]

Although the long-term post-marketing studies of TCIs are ongoing, epidemiologic studies have found no link between TCI use and the occurrence of lymphoma or non-melanoma skin cancers (NMSC).^[28] In a case-control study, Arellano et al.^[29] evaluated the association between topical immunosuppressants and lymphoma in a cohort of patients with AD. They replicated the previously established 2.5-fold increase in lymphoma risk in AD patients.^[30,31] However, they did not find an increased risk of lymphoma among users of TCIs or topical corticosteroids. Although it is difficult to disentangle the effects of disease severity from drug effects, severity of AD was the main factor associated with increased lymphoma risk in their analysis. An additional case-control study evaluated the association between TCI use and the risk of NMSC^[32] and found that TCI use was not associated with an increased risk of NMSC. After completion of post-marketing surveillance studies evaluating longer drug exposure periods, it will be important to confirm these findings.

Although not designed to evaluate the long-term safety of tacrolimus, pimecrolimus, and topical corticosteroids, a number of studies have evaluated the comparative short-term safety and tolerability of these agents.

4.1 Tacrolimus Compared with Pimecrolimus

The randomized, investigator-blind trial that compared tacrolimus with pimecrolimus in adult patients with mild to very severe AD found that local application-site reactions were the most common adverse effect observed during the 6-week trial (table II).^[16] Individuals treated with tacrolimus ointment had significantly more application-site burning during the first week of treatment than individuals treated with pimecrolimus. 11.4% of tacrolimus-treated individuals experienced application-site burning compared with 4.9% of pimecrolimus-treated individuals. However, after 1 week of treatment, there was no difference in the frequency of application-site reactions. There was no significant difference in the frequency of application-site pruritis, pain, erythema or skin infections, acne, or herpes simplex

between the two treatment groups. No study has compared the adverse effects of the two calcineurin inhibitors beyond 6 weeks of treatment. In sub-analyses of patients with either moderate or moderate to very severe AD, no significant difference in application-site reactions or other adverse events was observed, although there was a trend towards increased application-site reactions in the tacrolimus-treated groups.^[14,15]

In summary, the available short-term safety data support an increased frequency of application-site reactions with tacrolimus compared with pimecrolimus that diminish in severity after 1 week of topical use.

4.2 Tacrolimus Compared with Topical Corticosteroids

Six randomized controlled trials found that patients treated with tacrolimus experienced more skin burning at the application site than those treated with topical corticosteroids.^[17,18,20-23] Local application-site reactions were generally mild to moderate and improved over time. Alcohol intolerance, skin tingling, hyperesthesia, and herpes simplex were also reported more often in the tacrolimus group by Reitamo et al.^[20] Despite a significant increase in herpes infections among tacrolimus-treated patients in the above-mentioned study, infection rates among patients treated with tacrolimus ointment did not significantly differ from those observed in patients treated with topical corticosteroids in all other studies. A retrospective study compared the rates of herpes simplex and eczema herpeticum infections during periods of corticosteroid and tacrolimus use in the same individuals, allowing each participant to act as his or her own control and eliminating differences between comparison populations.^[33] In this study, the rates of herpes simplex and eczema herpeticum infections did not differ with the use of tacrolimus or topical corticosteroids.

Unlike topical corticosteroids, tacrolimus is not associated with skin atrophy or thinning. Class V topical corticosteroid use led to skin atrophy in four participants after 6–12 months of treatment whereas no events associated with skin atrophy were reported for tacrolimus-treated patients.^[17,20] No atrophy-related adverse effects were reported in the studies with shorter follow-up periods. A randomized, double-blind, controlled trial designed to compare the effects of topical tacrolimus with a class III corticosteroid on skin thickness and collagen synthesis in healthy adult volunteers and patients with moderate to severe AD found that topical corticosteroids reduced collagen synthesis and decreased skin thickness whereas tacrolimus 0.1% ointment had no atrophic effects.^[34]

In summary, the short-term safety studies found that, compared with topical corticosteroid-treated adults, tacrolimus-

Table II. Comparative short-term safety of tacrolimus 0.1% ointment, pimecrolimus 1.0% cream, and topical corticosteroids (TCs) in adults with atopic dermatitis

Year	Study	Application-site reactions	Infection	Skin atrophy
Tacrolimus compared with pimecrolimus				
2008	Abramovits et al. ^[14]	Trend towards increased burning with tacrolimus, not significant	No difference	None reported
2007	Fleischer et al. ^[15]	No difference	No difference	None reported
2005	Paller et al. ^[16]	More burning with tacrolimus up to 1 week	No difference	None reported
Tacrolimus compared with TCs				
2010	Mandelin et al. ^[17]	Increased incidence of burning with tacrolimus	No difference	Signs of atrophy in two TC-treated patients
2009	Doss et al. ^[18]	Increased incidence of application-site reactions with tacrolimus	No difference	None reported
2006	Hashizume et al. ^[33]	N/A	No difference in HSV or EH	N/A
2005	Reitamo et al. ^[20]	More skin tingling, hyperesthesia, burning with tacrolimus	Increased HSV with tacrolimus	Signs of atrophy in two TC-treated patients
2002	Reitamo et al. ^[21]	Increased burning and pruritis with tacrolimus	No difference	None reported
1997	FK506 Ointment Study Group ^[22]	Increased irritation with tacrolimus	No difference	None reported
1997	FK506 Ointment Study Group ^[23]	Increased irritation with tacrolimus	No difference	None reported
1998	Reitamo et al. ^[34]	N/A	N/A	TCs reduced collagen synthesis and skin thickness; tacrolimus did not
Pimecrolimus compared with TCs				
2004	Luger et al. ^[24]	More application-site reactions with pimecrolimus	No difference, although increased infections if TCs used on >30% BSA	Striae in three TC-treated patients after 4–9 mo of treatment
2001	Luger et al. ^[25]	More burning with pimecrolimus	No difference	None reported
2001	Queille-Roussel et al. ^[35]	N/A	N/A	Significant decrease in skin thickness from 8 d onward with TCs. Epidermal thinning at 4 wk with TCs

BSA=body surface area; **EH**=eczema herpeticum; **HSV**=herpes simplex virus; **N/A**=not applicable.

treated patients have an increased frequency of application-site reactions, an equivalent infection risk, and a decreased risk of skin atrophy with up to 1 year of use.

4.3 Pimecrolimus Compared with Topical Corticosteroids

Two randomized, double-blind, controlled trials found a greater frequency of skin burning at the application site with pimecrolimus than with class V, VI, or VII topical corticosteroids.^[24,25] Luger et al.^[24] evaluated the safety of pimecrolimus compared with a class VII corticosteroid for the face and a class VI corticosteroid for the trunk and extremities. Although they observed no difference in the incidence of bacterial, fungal, herpes simplex, herpes zoster, or molluscum infections between all patients in the pimecrolimus- and corticosteroid-

treated groups, patients with a >30% BSA affected by AD treated with topical corticosteroids had significantly more skin infections than participants treated with pimecrolimus.

Two studies have evaluated the effects of pimecrolimus and topical corticosteroids on skin atrophy.^[24,35] Luger et al.^[24] observed skin striae in three topical corticosteroid-treated patients after 13 months of treatment; no patients treated with pimecrolimus developed striae. An additional randomized, double-blind, controlled trial compared the effects of pimecrolimus with topical corticosteroids on skin thickness in healthy adult participants. In healthy volunteers, class IV or class V corticosteroids significantly decreased skin thickness as measured by ultrasound and epidermal thickness on histology whereas pimecrolimus did not induce skin atrophy.^[35]

Compared with topical corticosteroids, pimecrolimus has an increased frequency of application-site reactions and is significantly less likely to induce skin thinning.^[24,25,35] Patients with a >30% BSA treated with topical corticosteroids may have an increased risk of skin infections compared with pimecrolimus-treated patients.

5. Quality of Life

Two published studies have compared the effects of tacrolimus with topical corticosteroids on QOL measures and patient satisfaction in adults with AD. The European Tacrolimus Ointment Study, which found that tacrolimus was more effective than a class V topical corticosteroid after 6 months in adult patients with moderate to severe AD,^[20] also collected data on patient QOL that was published separately.^[36] The study was financially supported by the manufacturer of tacrolimus. QOL was measured using the Short Form-36, a generic health survey that is not specialized for dermatologic disease or AD. Eight functional domains are evaluated on a 1–100 scale. After 6 months, tacrolimus-treated patients showed statistically greater improvements in seven of the eight QOL domains and in overall physical and mental summary scores than corticosteroid-treated patients. Although the differences were statistically significant, the difference between the absolute improvements in the two treatment groups was small. On the 100-point scale, tacrolimus-treated patients improved by one more point than corticosteroid-treated patients on the physical summary score at the end of treatment. On the mental-summary score, tacrolimus-treated patients had an average of 2.6 points of improvement over corticosteroid-treated patients.

A second study compared patient satisfaction with tacrolimus and a class V topical corticosteroid during a 2-week open-label trial.^[37] Participants used the TCI on one half of their body and the corticosteroid on the other half for the duration of the trial. At the end of the trial, patients reported greater satisfaction with topical corticosteroids than with tacrolimus.

No published studies have compared the effects of tacrolimus with pimecrolimus or pimecrolimus with topical corticosteroids on QOL measures.

6. Cost Effectiveness

6.1 Tacrolimus Compared with Pimecrolimus

Two studies compared the cost effectiveness of tacrolimus and pimecrolimus in adults with AD.^[38,39] The study by Taneja et al.,^[38] funded by the manufacturer of tacrolimus, used a

Markov cohort model and data from a 2005 clinical trial that demonstrated superior efficacy of tacrolimus versus pimecrolimus in adult patients with mild to very severe AD.^[16] Despite pimecrolimus being indicated solely for patients with mild to moderate AD, they compared the cost effectiveness of the two agents in this mixed-severity population over 6 weeks. During the 42 days of treatment, they found that AD-related drug therapy costs were similar between the tacrolimus and pimecrolimus treatment groups but that the expected costs of AD-related outpatient visits were lower for tacrolimus-treated patients. The overall costs of AD-related care were \$US44.87 lower for patients receiving tacrolimus (\$US501.27 vs \$US546.14 for pimecrolimus).

Delea et al.^[39] conducted an observational, retrospective study, funded by the manufacturer of pimecrolimus, using an administrative-claims database to evaluate the relative costs of AD-related medical care in patients prescribed pimecrolimus cream or tacrolimus ointment. Disease-severity information was not available in the database, and the authors did not match for or adjust based on disease severity. The study found slightly reduced AD-related utilization and costs in the pimecrolimus-treated group, amounting to less than \$US100 per year. However, the results of this analysis may be confounded by differences in disease severity between the two treatment groups.

6.2 Tacrolimus Compared with Topical Corticosteroids

Three studies compared the cost effectiveness of tacrolimus with topical corticosteroids in adults with AD.^[36,40,41] Two of these studies were based on data from the 2005 randomized controlled trial by Reitamo et al.^[20] that compared the efficacy of tacrolimus with low- to medium-potency corticosteroids in adults with moderate to severe AD.^[36,40] Based on the superior efficacy of tacrolimus in the clinical trial, Hjelmgren et al.^[40] estimated that AD patients treated with tacrolimus would have more AD-free weeks per year. Tacrolimus treatment was determined to be more cost effective with a lower cost per quality-adjusted life year (QALY) gained than low- to medium-potency topical corticosteroids. Poole et al.^[36] used QOL data obtained in the same trial to estimate the relative QOL benefit from tacrolimus compared with class V corticosteroids. They calculated the incremental cost per QALY gained with tacrolimus treatment, found it to be below the current accepted willingness-to-pay threshold, and determined that tacrolimus was cost effective.

A 2003 study sponsored by the manufacturer of tacrolimus compared the cost effectiveness of treatment with tacrolimus compared with high-potency corticosteroid therapy in adult

patients with moderate to severe AD who were previously unresponsive to or not well controlled with mid-potency topical corticosteroids.^[41] Using a Markov cohort model, they determined that tacrolimus was more cost effective than high-potency corticosteroids used in 2-week cycles and equally cost effective to high-potency topical corticosteroids used in 4-week cycles in this patient population. However, there were a number of unsupported assumptions and flaws in this analysis. Because no published data are available comparing tacrolimus with high-potency topical corticosteroids, the authors conducted a meta-analysis to estimate the efficacy of corticosteroids and then decreased the efficacy estimate by 15% based on the opinion of a physician panel that the clinical response to topical corticosteroids decreases with extended use. Based on the panel's opinion, the model was also designed such that the probability of relapsing was higher if patients had been most recently treated with corticosteroids rather than tacrolimus. The efficacy of tacrolimus was estimated based on published clinical trials and remained unadjusted. The study was later criticized for the unnecessary twice-daily treatment with high-potency topical corticosteroids when once daily is optimal and for using a mid-strength corticosteroid and an oral antibacterial agent as secondary treatment. In the model, patients taking tacrolimus could be treated indefinitely, a treatment strategy that was later advised against by the FDA.

6.3 Pimecrolimus Compared with Topical Corticosteroids

One study evaluated the cost effectiveness of pimecrolimus compared with topical corticosteroids among adults with AD. Pitt et al.^[42] used a Markov state-transition model to evaluate the comparative cost utility of pimecrolimus and topical corticosteroids. The comparison topical corticosteroid regimen allowed for escalation of treatment from low- to medium- and high-potency corticosteroids. They found that topical corticosteroids were more cost effective than regimens that incorporated pimecrolimus either as a first- or second-line treatment. However, for patients who were unable or unwilling to use topical corticosteroids, the authors found that pimecrolimus was cost effective compared with emollient-only regimens at normal levels of willingness-to-pay for QALY gained from treatment. The probability of recurrence was the same for the pimecrolimus- and corticosteroid-treated participants and the probability of successful treatment was determined based on a systematic review of randomized controlled trials.

7. Discussion

In the established treatment for adult AD, TCIs are used as second-line topical therapy in patients who are resistant to,

intolerant of, or unsuitable for topical corticosteroid therapy. Topical corticosteroids have been the mainstay of AD treatment for more than 50 years. The safety profile and efficacy of topical corticosteroids is well established. The TCIs provide a treatment option without the risk of cutaneous atrophy or systemic absorption leading to hypothalamic-pituitary-adrenal axis suppression. However, their long-term safety has not been studied, and their efficacy is not superior to equivalent-potency topical corticosteroids, with one exception: tacrolimus is more effective than low-potency class VI or VII topical corticosteroids for AD of the face and neck. The face, neck, and intertriginous areas are particularly sensitive to corticosteroid atrophy and the prolonged use of higher potency corticosteroids is not recommended in these regions. On the trunk and extremities, tacrolimus is as effective as class III–V topical corticosteroids. A study that compares tacrolimus with potent class I or II corticosteroids has not been conducted and would be valuable.

Further studies on the comparative safety, cost, and effects on QOL of the TCIs and topical corticosteroids would provide additional helpful information. As previously discussed, the need for long-term post-marketing studies of TCIs is necessary to evaluate long-term safety. Although current analyses do not support a causative role of TCIs in the development of lymphoma or cutaneous malignancies, these findings must be confirmed in patients with longer drug-exposure periods and extended follow-up. QOL studies that compare TCIs with stronger classes of topical corticosteroids over longer time periods and that employ a dermatology-specific QOL tool, such as the Dermatology Life Quality Index (DLQI),^[43] or an AD-specific tool, such as the Quality of Life Index – Atopic Dermatitis (QoLIAD),^[44] could provide additional insight. Similarly, comparative cost studies could benefit from TCI comparisons with stronger classes of topical corticosteroids over longer time periods in which the comparison populations are matched for disease severity. The cost per gram of tacrolimus and pimecrolimus is currently much higher than that of generic topical corticosteroids and it is likely that a study comparing the treatment cost of tacrolimus with high-potency topical corticosteroids without an arbitrary decrease in the efficacy of topical corticosteroids would find the topical corticosteroids more cost-effective AD treatment than tacrolimus. However, the cost analyses will likely change when generic equivalents of the TCIs are available and their cost per gram decreases.

8. Conclusion

The available clinical trial data do not suggest an efficacy advantage for the TCIs over topical corticosteroids in adults

with AD of the trunk and extremities, and the long-term safety profile of TCIs remains under investigation. There is not yet adequate evidence to support TCIs as first-line therapy for adult AD. However, the superior efficacy of tacrolimus relative to low-potency topical corticosteroids for AD of the face and neck may warrant its consideration as a first-line agent for facial AD if and when long-term safety studies confirm no treatment-associated malignancies.

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