

# The Economics of Topical Immunomodulators for the Treatment of Atopic Dermatitis

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## Abstract

Atopic dermatitis is a common, chronic, relapsing inflammatory skin disease frequently affecting infants and children. The worldwide prevalence of atopic dermatitis is estimated to be 5–20% of the paediatric population. First-line therapy has generally consisted of dry skin care, avoidance of triggers, application of topical corticosteroids, and administration of antihistamines and oral antibacterials. Topical corticosteroids improve the lesions of atopic dermatitis; however, concern on the part of physicians and patients regarding adverse effects has led to reluctance to utilise topical corticosteroids early and especially for prolonged periods. Topical immunomodulators (TIMs), including tacrolimus ointment and pimecrolimus cream, were recently introduced for the treatment of atopic dermatitis.

Clinical data show that TIMs are effective in atopic dermatitis, yet do not cause the significant adverse effects associated with topical corticosteroids. Questions remain regarding the place of TIMs as a treatment for atopic dermatitis and how to use them most effectively, from both therapeutic and pharmacoeconomic standpoints. Specifically, two major issues remain unresolved: (i) how TIMs measure up to other therapies, especially topical corticosteroids; and (ii) how members of the TIM drug class compare against each other.

Previous research has established that atopic dermatitis has a significant impact on quality of life (QOL) and carries a substantial economic burden. Some studies have also measured the utility of various atopic dermatitis disease states. While there is a need for further research, early economic studies provide evidence that TIMs positively affect the QOL of patients and families. In certain patients, TIMs may be cost effective and have an acceptable incremental cost utility compared with topical corticosteroids.

Making cost-effectiveness comparisons between tacrolimus and pimecrolimus is challenging because there are limited head-to-head comparative data. Given currently available efficacy data, the results of one study suggest that tacrolimus may be more cost effective than pimecrolimus in paediatric patients with moderate atopic dermatitis.

The full economic and QOL benefits of both agents are yet to be completely understood. The studies reviewed herein are the first to delineate the pharmacoeconomic benefits of TIMs in atopic dermatitis, and lay the foundation for future analyses. TIMs represent an exciting advance in the treatment of atopic dermatitis. Additional research will help determine the proper place of TIMs among the current array of therapeutic options for atopic dermatitis.

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Topical immunomodulators (TIMs), which include tacrolimus ointment and pimecrolimus cream, represent an exciting new therapy for atopic dermatitis. While multiple clinical trials have been conducted, clinical questions remain about how, where and when to use these agents to maximise their effectiveness. Healthcare decision-makers are also asking important economic questions concerning

the use of TIMs. Outstanding issues both from a clinical and an economic perspective include: (i) how TIMs compare with other therapies, especially topical corticosteroids; and (ii) how members of the TIM drug class compare against each other. The objective of this article is to review the studies performed to date that have examined the pharma-

coeconomic implications of TIMs for the treatment of atopic dermatitis.

To meet this objective, we performed a systematic review of clinical and pharmacoeconomic studies involving TIMs in the treatment of atopic dermatitis. This review focuses first on the clinical aspects of atopic dermatitis, including an evaluation of the clinical data on TIMs. We then turn our attention to economic considerations of atopic dermatitis, and to an in-depth review of the pharmacoeconomic research performed thus far on TIMs for the treatment of the disease. Methodology pertaining to our review of the clinical and pharmacoeconomic TIM literature is described within each appropriate section.

## 1. Atopic Dermatitis

### 1.1 Epidemiology

Atopic dermatitis is a common, chronic, relapsing inflammatory skin disease that most frequently affects infants and children. Worldwide, the prevalence of atopic dermatitis is estimated to be 5–20% of the paediatric population, depending upon locale. Approximately 10.9% of 6- to 7-year-olds in Australia and 14.7% in New Zealand have atopic dermatitis.<sup>[1]</sup> In another study, an estimated 16% of 7-year-olds in Denmark, Germany and Sweden were found to have the disease.<sup>[2]</sup> A recent US study in Oregon schoolchildren found the prevalence of atopic dermatitis in that population to be 6.8–17.2%, depending on the stringency of diagnostic criteria.<sup>[3]</sup> In Japan, another study determined that 19% of 7- to 9-year-olds had the disease.<sup>[4]</sup> Atopic dermatitis often resolves by early adolescence, but the disease can persist in adulthood. Disease prevalence across a non-elderly population was 2–4% in one study.<sup>[5]</sup>

### 1.2 Clinical Description

Although significant progress has been made in the understanding of atopic dermatitis in recent years, its cause remains largely unknown. The pathogenesis of the disease appears to be the result of a complex interrelationship of genetic, environmental, immunological and pharmacological factors.<sup>[6]</sup>

Atopic dermatitis is frequently seen in children with a personal history of respiratory allergy and/or a family history of atopic disease.<sup>[7]</sup> Histologically, atopic dermatitis is highlighted by spongiosis and increased infiltration of T cells, macrophages, Langerhans cells and eosinophils.<sup>[6]</sup>

Atopic dermatitis typically presents in early childhood, with onset before 5 years of age in approximately 90% of patients.<sup>[8]</sup> The most notable clinical symptoms of atopic dermatitis are cutaneous reactivity and intense pruritus that leads to a pattern of exacerbation by scratching. The disease typically follows a chronically relapsing time course. The skin of patients with acute atopic dermatitis is intensely pruritic, with erythematous papules that are associated with excoriations, vesiculations and serous exudate; weeping papules may become infected, especially when scratched. In subacute atopic dermatitis, the skin shows excoriated, erythematous, scaling papules, while patients with chronic atopic dermatitis have thickened skin with lichenification and fibrotic papules.<sup>[9]</sup> In infants and young children with atopic dermatitis, lesions commonly occur on the scalp, face and extensor surfaces of the extremities. Older children and adults typically have involvement of the flexor surfaces, neck, wrists and ankles.<sup>[10]</sup>

### 1.3 Treatment

Historically, patients seeking relief from atopic dermatitis have had few therapeutic options. At present, no curative therapy exists; rather, the therapeutic objectives for atopic dermatitis are to reduce signs and symptoms, prevent or reduce recurrences, provide long-term management by preventing exacerbation, and modify the course of the disease. Current therapy for atopic dermatitis is directed at hydrating the skin, reducing inflammation, and relieving symptoms such as pruritus and secondary sleep disturbance. First-line therapy has conventionally included moisturisation, avoidance of triggers, application of topical corticosteroids, and administration of antihistamines and antibacterials as appropriate.<sup>[11,12]</sup>

Topical corticosteroids have been the treatment cornerstone of atopic dermatitis for 40 years, and remain one of the most important treatments available for the condition.<sup>[13]</sup> Topical corticosteroids are effective in improving the lesions of atopic dermatitis via their anti-inflammatory properties, and they are easy to use. However, it is well known that prolonged use of these agents, particularly the more effective mid- to high-potency topical corticosteroids, is associated with adverse effects such as skin atrophy, striae, telangiectasia, hypopigmentation, rosacea, perioral dermatitis and acne. Systemic adverse effects, while rare, include adrenal suppression, cataracts, glaucoma, and growth retardation in children.<sup>[10,13]</sup> The potential for adverse effects is elevated in patients who have severe or long-standing disease, extensive body surface area involvement or facial lesions.<sup>[7]</sup> The more potent topical corticosteroids need to be especially avoided on regions of skin that are particularly thin and more susceptible to skin atrophy, such as the face and intertriginous areas. However, the efficacy of mid-potency topical corticosteroids is generally not sufficient to treat moderate-to-severe atopic dermatitis.<sup>[14]</sup>

The potential for adverse effects associated with corticosteroid use has always caused concern for physicians, patients and caregivers, leading to the reluctance to utilise topical corticosteroids for prolonged periods.<sup>[15]</sup> This is particularly problematic for patients with difficult-to-control atopic dermatitis, because few therapeutic options have been available for these patients. Oral corticosteroids have been used, but steroid-related adverse effects limit their use to short courses. Oral ciclosporin, a potent immunosuppressive drug that downregulates cytokine production via calcineurin inhibition, is effective in controlling atopic dermatitis,<sup>[16]</sup> but substantial concerns exist about the potential for systemic adverse effects such as nephrotoxicity, hypertension, gingival hyperplasia and tremor.<sup>[17]</sup> Ciclosporin is ineffective when applied topically, most likely as a result of poor absorption due to the size of the ciclosporin molecule.<sup>[18]</sup>

## 2. Topical Immunomodulators (TIMs)

### 2.1 Description

Recently, TIMs have been introduced for the treatment of atopic dermatitis. Tacrolimus ointment and pimecrolimus cream are the current members of this drug class. Similar to ciclosporin, TIMs inhibit calcineurin and, in doing so, block the local release of pro-inflammatory cytokines following T cell activation.<sup>[19]</sup> Unlike ciclosporin, however, tacrolimus and pimecrolimus are effectively absorbed into the skin.<sup>[7,20]</sup> Both tacrolimus and pimecrolimus have been approved in the US for the treatment of atopic dermatitis (table I). Tacrolimus ointment is indicated for short-term and intermittent long-term treatment of patients with moderate-to-severe atopic dermatitis in whom conventional therapy is not adequately effective, not advisable because of potential risks, or not tolerated. Pimecrolimus is similarly indicated, but for the treatment of patients with mild-to-moderate atopic dermatitis.

However, questions remain regarding the exact place of TIMs in the armamentarium for treatment of atopic dermatitis and how they can be used most effectively from both a clinical and pharmacoeconomic standpoint. Because of the previously mentioned limitations of conventional therapy, answering these questions is of particular interest to patients, providers and payers alike.

**Table I.** Comparison of tacrolimus and pimecrolimus formulations and indications

	Tacrolimus ointment	Pimecrolimus cream
Formulations	0.03% and 0.1%	1%
Indication	Moderate-to-severe atopic dermatitis	Mild-to-moderate atopic dermatitis
Age limitations	≥2 years of age	≥2 years of age
AWP/g <sup>a</sup>	\$US1.86 for 0.03%; \$US1.99 for 0.1%	\$US1.64

a Based on 100g tube at 2004 prices.<sup>[21]</sup>

**AWP** = average wholesale price.

## 2.2 Review of Clinical Trials of TIMs

### 2.2.1 Literature Search and Evaluation

We conducted a systematic search of the clinical trial literature assessing the efficacy and safety of TIMs as a treatment for atopic dermatitis. Our search focused on larger human trials published in English with at least 40 patients per treatment arm, although smaller human trials specifically designed to evaluate safety were also included. Studies of TIMs that were not conducted on patients with atopic dermatitis were excluded from review. Sources included MEDLINE, BIOSIS, Ingenta and MD Consult online databases up until June 2003, as well as abstracts from the 2003 American Academy of Dermatology annual meeting, the 2003 American Academy of Allergy, Asthma and Immunology annual meeting, and the Twentieth World Congress of Dermatology. From this search, approximately 20 pertinent studies were found, of which two (reports on long-term safety of tacrolimus ointment) were conference abstracts. Most studies included children as patients. Two trials (both involving pimecrolimus) studied infants. We evaluated the studies based on their study design, sample size, study endpoints, measurement tools and techniques, and reported clinical findings. This information is shown in table II for the most pertinent studies.

### 2.2.2 Efficacy of Tacrolimus

All of the major efficacy and safety studies evaluating tacrolimus were conducted on patients with moderate-to-severe atopic dermatitis, according to standard criteria. Most of the studies evaluated tacrolimus safety and efficacy compared with vehicle,<sup>[22-25]</sup> but one study compared tacrolimus with hydrocortisone acetate ointment<sup>[14]</sup> and one with hydrocortisone butyrate ointment.<sup>[26]</sup> Other studies were designed as long-term, open-label assessments of safety and efficacy.<sup>[27-30]</sup> The majority of these studies used a quantitative Physician's Global Evaluation (PGE) and the Eczema Area and Severity Index (EASI) as measures of efficacy of disease improvement.

Several large clinical studies involving tacrolimus ointment have been conducted, with the

purpose of measuring short- or long-term efficacy and safety of the drug in both the paediatric and adult atopic dermatitis patient population. As shown in table II, all of these studies demonstrated that tacrolimus 0.1% applied twice daily produced statistically significant improvement in moderate-to-severe atopic dermatitis compared with vehicle, with results being similar for children and adult patients.<sup>[22,23]</sup> The higher concentration (0.1%) tended to be more effective than the lower concentration (0.03%),<sup>[22,23]</sup> and no additional advantage was gained by using a 0.3% concentration.<sup>[24,25]</sup> Longer-term studies (up to 4 years) have found that tacrolimus ointment treatment maintains its efficacy over time when used for up to 1 week after clearance of the dermatitis.<sup>[27-30]</sup>

A pivotal phase III study of tacrolimus ointment 0.03% or 0.1% was conducted by Hanifin et al.,<sup>[22]</sup> involving two identical 12-week, randomised, double-blind, vehicle-controlled trials (RDBVCTs) in adult patients with moderate-to-severe atopic dermatitis (n = 632). Efficacy was evaluated on the basis of the PGE of clinical response at the end of twice-daily treatment (12 weeks or until approximately 1 week after complete clearance). Of the patients treated with tacrolimus, 56% had severe atopic dermatitis, with a mean body surface area (BSA) affected of 45%. Overall success rate ( $\geq 90\%$  improvement in disease status) was 27.5% for tacrolimus 0.03%, 36.8% for tacrolimus 0.1%, and 6.6% for vehicle; at least moderate improvement ( $\geq 50\%$  improvement in disease status) was seen in 61.6%, 72.7% and 19.8% of patients, respectively. Patients treated with tacrolimus 0.1% had a significantly higher success rate than patients treated with tacrolimus 0.03%. Patients treated with tacrolimus showed significantly greater improvement in secondary efficacy measures compared with vehicle-treated patients, including EASI scores, clinical scores of individual signs of atopic dermatitis, percentage of BSA affected, and patient's assessment of pruritus.

The largest study to date (n = 7341) is a 12-month, open-label, non-comparative, multicentre study in which both paediatric and adult atopic dermatitis patients applied tacrolimus 0.1% oint-

**Table II.** Overview of selected clinical trials of topical tacrolimus ointment (TAC) and topical pimecrolimus cream (PIM) in atopic dermatitis (AD). All outcome measures were versus baseline unless otherwise stated

Study	Design; treatment duration	No. of patients; indication	Outcome measure	Treatment	Results (% patients) <sup>a</sup>	Additional results and comments
<b>TAC ointment</b>						
<i>Shorter-term controlled trials</i>						
Hanifin et al. <sup>[22]</sup>	2 identical studies: db, r, vc; ≤12 wks	632 adults; MSAD	PGE success rate ≥90% improvement (≥50% improvement)	TAC 0.03% bid TAC 0.1% bid Vehicle bid	27.5* (61.6) 36.8*† (72.7) 6.6 (19.8)	TAC 0.1% and 0.03% also significantly improved secondary measures <sup>b</sup> vs vehicle
Paller et al. <sup>[23]</sup>	db, r, vc; ≤12 wks	351 children (2–15y); MSAD	PGE success rate ≥90% improvement (≥50% improvement)	TAC 0.03% bid TAC 0.1% bid Vehicle bid	35.9* (72.6) 40.7* (78.0) 6.9 (26.7)	TAC 0.1% and 0.03% also significantly improved secondary measures <sup>b</sup> vs vehicle
Boguniewicz et al. <sup>[24]</sup>	db, r, vc; 3wk	180 children (7–16y); MSAD	PGE success rate ≥75% improvement	TAC 0.03% bid TAC 0.1% bid TAC 0.3% bid Vehicle bid	69* 67* 70* 38	EASI scores also improved with TAC (72–81%) vs vehicle (26%)
Ruzicka et al. <sup>[25]</sup>	db, r, vc; 3wk	213 patients treated (13–60y); MSAD	Magnitude of decrease in severity score for erythema, oedema, pruritus (trunk, extremities)	TAC 0.03% bid TAC 0.1% bid TAC 0.3% bid Vehicle bid	66.7* 83.3* 75* 22.5	Similar results in head and neck area
Reitamo et al. <sup>[14]</sup>	db, r, mc; 3wk	560 children (2–15y); MSAD	PGE success rate ≥90% improvement	TAC 0.03% bid TAC 0.1% bid HCA 1%	38.5‡ 48.4†‡ 15.7	Improvement also seen on modified EASI (including pruritus): 55.2%, 60.2% and 36% with TAC 0.03%, TAC 0.1% and HCA, respectively. TAC concluded to be more efficacious than HCA
Reitamo et al. <sup>[26]</sup>	db, r, mc; 3wk	570 adults; MSAD	PGE success rate ≥90% improvement	TAC 0.03% bid TAC 0.1% bid HBA 0.1% bid	37.6 49.2† 51.4†	Improvement also seen on modified EASI (including pruritus): 53.0%, 63.5% and 63.9% with TAC 0.03%, TAC 0.1% and HBA, respectively. TAC 0.1% concluded to be similar in efficacy to HBA 0.1%
<i>Longer-term open-label studies</i>						
Kang et al. <sup>[27]</sup>	nc, open; ≤1y	255 children (2–15y); MSAD		TAC 0.1% bid	Effectiveness maintained with long-term daily use	Primarily a safety study
Reitamo et al. <sup>[28]</sup>	nc, open; ≤1y	245 <sup>c</sup> adults (≥18y); MSAD		TAC 0.1% bid	Effectiveness maintained with long-term daily use	Primarily a safety study

Continued next page

Table II. Contd

Study	Design; treatment duration	No. of patients; indication	Outcome measure	Treatment	Results (% patients) <sup>a</sup>	Additional results and comments
Hanifin et al. <sup>[29]d</sup>	nc, open; ≤49mo	391 children; MSAD	Magnitude of decrease in BSA% affected from baseline to 36mo	TAC 0.1% bid	Decrease from mean 32% to 11%	
Koo et al. <sup>[30]d</sup>	mc, nc, open; 1y	7341 children/adults; 96% MSAD	Magnitude of decrease in BSA% affected from baseline to 12mo	TAC 0.1% bid	Decrease from mean 33% to 9.4%	
<b>PIM cream</b>						
Wahn et al. <sup>[32]</sup>	db, r, vc; 1y	713 children (2–17y); MAD+	Success rate of no flares	PIM 1% bid ± CS <sup>e</sup> Vehicle ± CS <sup>e</sup>	50.8* 28.3	EASI scores also significantly lower with PIM. Fewer PIM recipients withdrew because of lack of efficacy (19.3% vs 57.8% with vehicle)
Kapp et al. <sup>[33]</sup>	db, r, vc; 1y	251 infants (3–23mo); MAD+	Success rate of no flares	PIM 1% bid ± CS <sup>e</sup> Vehicle ± CS <sup>e</sup>	56.9* 28.3	EASI scores, pruritus scores and caregiver assessments not significantly better with PIM. Fewer PIM recipients withdrew because of lack of efficacy (19.6% vs 63% with vehicle)
Eichenfield et al. <sup>[34]</sup>	Two identical studies: db, r, vc; 6wk	403 children (1–17y); MMAD	Success rate of L-IGA clearance or near clearance of AD	PIM 1% bid Vehicle bid	34.8* 18.4	EASI score reduced 44% with PIM relative to vehicle
Ho et al. <sup>[31]</sup>	6wk db then 20wk open	186 infants (3–23mo); MMAD	Success rate of L-IGA clearance or near clearance of AD in db phase	PIM 1% bid Vehicle bid	54.5* 23.8	PIM also produced significant improvements in secondary measures <sup>b</sup> versus vehicle. Recipients of vehicle swapped to PIM for open phase had similar improvement of AD
Luger et al. <sup>[35]</sup>	db, mc, r; ≤3wk	260 adults (>18y); MSAD	Success rate of ≥50% improvement, as determined by the patient	PIM 0.05% bid PIM 0.2% bid PIM 0.6% bid PIM 1% bid Vehicle bid BMV 0.1% bid (internal control)	Insignificant effect 32.6* 54.8* 53.3* 16.3 88.1	Dose-finding study. Dose-response relationship evident. All PIM significantly more effective than vehicle but BMV more effective than PIM. Greatest EASI improvement with BMV (88.2% median percentage change of EASI with BMV; 37.9–50.0% with PIM 1%)

a Unless otherwise stated.

b EASI, individual AD signs, % of BSA affected, patient-assessed pruritus scores<sup>[22,23]</sup> and caregiver assessments.<sup>[31]</sup>

c 245 patients completed the study; 68 completed at least 12 months.

d Reported as an abstract.

e Concomitant use of moderately potent topical corticosteroids permitted to treat acute disease flares.

**bid** = twice daily; **BSA** = body-surface area; **BMV** = betamethasone valerate cream; **CS** = corticosteroids; **db** = double blind; **EASI** = eczema area and severity index; **HBA** = hydrocortisone butyrate ointment; **HCA** = topical hydrocortisone acetate; **L-IGA** = Likert scale Investigator's Global Assessment; **MAD+** = atopic dermatitis of at least mild severity; **mc** = multicentre; **MMAD** = mild-to-moderate atopic dermatitis; **mo** = month; **MSAD** = moderate-to-severe atopic dermatitis; **nc** = non-comparative; **open** = open label; **PGE** = physician's global evaluation; **r** = randomised; **vc** = vehicle controlled; **wk** = week; **y** = years; \*  $p < 0.05$  vs vehicle; †  $p < 0.05$  vs tacrolimus 0.03%; ‡ significantly more effective vs HCA.

ment twice daily to affected areas until 1 week post-clearing. The results have not yet been published in full, but Koo et al.<sup>[30]</sup> in a recent abstract reported that the mean percentage of BSA affected decreased from 33% at baseline to 9.4% at month 12.

Two phase III, randomised, double-blind, multicentre 3-week studies were unique in that they compared the efficacy and safety of tacrolimus ointment with topical corticosteroids (table II).<sup>[14,26]</sup> One study concluded that tacrolimus 0.03% or 0.1% ointment was more efficacious than hydrocortisone acetate 1%, a mild topical corticosteroid, in paediatric patients with moderate-to-severe atopic dermatitis.<sup>[14]</sup> When compared with hydrocortisone butyrate 0.1% ointment, a mid-potency topical corticosteroid, tacrolimus 0.1% appeared to be very similar in terms of short-term efficacy for adult patients with moderate-to-severe atopic dermatitis.<sup>[26]</sup>

### 2.2.3 Efficacy of Pimecrolimus

Several of the clinical studies of pimecrolimus were randomised, double-blind, controlled trials (five efficacy studies,<sup>[31-35]</sup> and two safety studies<sup>[36,37]</sup>). Four of the studies used vehicle as the comparator<sup>[31-34]</sup> and one used vehicle and a topical corticosteroid.<sup>[35]</sup> Most studies used the Likert scale Investigator's Global Assessment (L-IGA) as the primary efficacy measure, and all studies reported EASI scores as an efficacy measure.

The studies showed pimecrolimus 1% cream twice daily produced significantly greater improvement in atopic dermatitis than vehicle when used for up to 1 year (table II). Unlike the vehicle-controlled tacrolimus studies, some studies of pimecrolimus allowed the concomitant use of moderately potent topical corticosteroids for the treatment of atopic dermatitis flares regardless of treatment group;<sup>[32,33]</sup> the significant effect of pimecrolimus versus vehicle in terms of success rate (measured as patients experiencing no flares) was still evident in these studies, but outcomes on secondary measures were less clear (table II).

As an example of the results achieved with pimecrolimus cream, Eichenfield et al.<sup>[34]</sup> reported pooled data from two identical, multicentre RDBVCTs comparing pimecrolimus 1% cream with

vehicle while disallowing the use of topical corticosteroids. The studies focused on children aged 1–17 years with mild-to-moderate atopic dermatitis (n = 403). Patients received either pimecrolimus 1% or vehicle cream twice daily on affected areas for up to 6 weeks. Of the patients treated with pimecrolimus, 30.0% had mild disease while 60.3% had moderate disease. Based on the primary efficacy measure (the L-IGA), pimecrolimus treatment resulted in clearance or near clearance of disease in 34.8% of patients at the end of the study versus 18.4% for vehicle. Among pimecrolimus-treated patients, 59.9% improved by one or more L-IGA scores, 36.0% remained the same, and 4.1% worsened. In comparison, 33.1% of vehicle-treated patients improved, 47.1% stayed the same, and 19.9% worsened. Pimecrolimus therapy also showed a 44% reduction in EASI scores relative to vehicle.

Luger et al.,<sup>[35]</sup> as part of a dose-finding study, found that pimecrolimus was not as effective as betamethasone valerate 0.1% cream, a mid-potency topical corticosteroid (table II).

### 2.2.4 Tolerability and Safety of TIMs

To date, the tolerability and safety profiles of TIMs have been favourable, with data available for tacrolimus for up to 4 years.<sup>[29]</sup> The most common adverse effects of tacrolimus and pimecrolimus are local reactions at the site of drug application, including the sensation of skin burning and, with tacrolimus, pruritus. These adverse effects usually resolve within the first few days of treatment and, in the clinical trial setting, have rarely resulted in discontinuation of therapy.<sup>[14,23,25-28,30-35,38]</sup> According to a study that analysed the pooled safety results of 1554 patients from five RDBVCTs, treatment with tacrolimus ointment (0.03% or 0.1%) does not increase the risk of cutaneous bacterial, viral or fungal infections in patients with atopic dermatitis, with the possible exception of folliculitis in adults.<sup>[39]</sup> One study reported a trend of a higher incidence of viral skin infection in pimecrolimus compared with vehicle recipients,<sup>[32]</sup> but other studies have not confirmed this.

Safety studies performed in rodents have raised the potential concern of photocarcinogenicity with

the TIMs, but the clinical relevance of this finding in humans is unknown; nevertheless, it may be advisable to minimise exposure of treated areas to sunlight as a precaution.<sup>[40,41]</sup> Blood levels of pimecrolimus or tacrolimus after topical application are generally below the level of quantitation, indicating minimal systemic absorption.<sup>[23,24,36,38,42]</sup>

The TIMs do not appear to cause the significant adverse effects commonly associated with topical corticosteroids, such as skin atrophy or telangiectasia.<sup>[23,27,37]</sup> When compared with corticosteroids in clinical trials, only skin burning and/or pruritus showed a significantly higher incidence in the tacrolimus treatment groups than in the corticosteroid group.<sup>[14,26]</sup>

### 2.2.5 Summary of Clinical Data for TIMs

Having reviewed the available clinical trial data for TIMs, a few observations can be made. The data show that TIMs as a class have a positive treatment effect on atopic dermatitis. Though further studies need to be conducted, data suggest that, compared with mid-potency topical corticosteroids, tacrolimus is approximately equivalent in efficacy,<sup>[26]</sup> while pimecrolimus appears to be less efficacious to similar agents.<sup>[35]</sup> Tacrolimus 0.1% ointment has also compared favourably with mometasone 0.1% ointment (a class II potent steroid) in the treatment of dyshidrotic hand eczema.<sup>[43]</sup> In addition, the adverse effect profiles of tacrolimus and pimecrolimus are favourable and, so far, treatment of atopic dermatitis with these drugs does not appear to carry the same concern for adverse effects as treatment with topical corticosteroids.

Beyond this, however, making comparisons between tacrolimus and pimecrolimus is challenging, as there are little head-to-head comparative data available. In most studies, differences in treatment protocols were significant, with two pimecrolimus trials allowing concomitant use of topical corticosteroids, while no tacrolimus trials allowed for this provision. The target patient populations were different as well, with tacrolimus ointment being used exclusively on patients with moderate or severe disease and pimecrolimus being used mainly in patients with mild or moderate disease. Furthermore,

the primary efficacy measure used in the tacrolimus trials (quantitative PGE of percentage improvement from baseline) was different from that used in the pimecrolimus trials (incidence of disease flares or Likert-scale based L-IGA of disease severity), which again prevents the possibility of direct comparison between the two TIMs. As discussed in section 4.4, secondary efficacy endpoints such as EASI scores may provide a means to compare the two products, although this is not without challenges.

Fortunately, the results of new multicentre, randomised, investigator-blinded studies directly comparing tacrolimus and pimecrolimus are emerging that will provide much-needed insights into the relative efficacy of TIMs.<sup>[44,45]</sup> In a study presented at the 2003 European Academy of Dermatology and Venereology, researchers found that in 198 paediatric patients with moderate-to-severe atopic dermatitis, tacrolimus 0.1% was significantly more effective than pimecrolimus 1% based on multiple endpoints.<sup>[46]</sup> These studies, and others like it, will prove valuable in determining the differences in safety and efficacy between these agents.

## 3. Economic Considerations of Atopic Dermatitis

### 3.1 Cost of Illness

While atopic dermatitis is certainly a common skin disorder, the perception exists among many that the disease is fairly benign and inexpensive, a minor dermatological condition that does not present any major problems for the family, patient or society.<sup>[47]</sup> In reality, however, atopic dermatitis is a condition that can be a major handicap, with considerable personal, social and financial burdens on the family and the community.<sup>[48]</sup> Atopic dermatitis is associated with substantial co-morbidities, including pruritus, impetigo, herpes simplex, nasopharyngitis and asthma.<sup>[5]</sup>

One study performed in 1990 conservatively suggested that the direct costs of atopic dermatitis were \$US364 million per year for the US paediatric population.<sup>[49]</sup> A more recent US study conducted from

the third-party payer perspective estimates the cost of illness to range from \$US0.9 billion to \$US3.8 billion per year nationally in 1997,<sup>[5]</sup> similar in cost to psoriasis,<sup>[50]</sup> emphysema<sup>[51]</sup> and epilepsy.<sup>[52]</sup> In the UK, yearly direct and indirect costs of atopic dermatitis were estimated at £46.9 million in 1995–96 for children aged 1–5 years<sup>[53]</sup> and £465 million overall (year of costing not reported),<sup>[54]</sup> and in Germany, similar costs are projected at DM7 billion (year of costing not reported).<sup>[55]</sup> An Australian study demonstrated that costs to both health services and families vary with disease severity,<sup>[56]</sup> with a range spent per year in 1997 of \$A1142 per patient with mild atopic dermatitis to \$A6099 per patient with severe disease.<sup>[48]</sup> Costs are high from the patient perspective as well. Fivenson et al.<sup>[57]</sup> estimated that total average annual burden of disease – including out-of-pocket expenses for such products as over-the-counter medications and household items, as well as days lost from work or school – totalled \$US609 per year per patient in 1997. Table III summarises the main characteristics and cost estimates from the studies mentioned above.

### 3.2 Impact of Atopic Dermatitis on Quality of Life (QOL)

The measurable burden of atopic dermatitis is not merely financial. Studies have shown that atopic dermatitis can have a major negative effect on a patient's quality of life (QOL), with a significant secondary effect on other family members.<sup>[58]</sup> An Australian study found that caring for a child with severe atopic dermatitis represents a greater stress on the family than caring for a child with type I diabetes mellitus. Besides the direct financial burden, caregivers attribute increased stress to sleep interruption and sleep deprivation, time missed from work for their child's healthcare, lost wages due to interruption of employment, and in cases of moderate-to-severe atopic dermatitis, being unable to work because of their child's disease.<sup>[56,59]</sup> In addition, parents commonly describe feelings of guilt, exhaustion, frustration and helplessness regarding their child's atopic dermatitis.<sup>[60]</sup> Atopic dermatitis may impair the patient's QOL by causing interrup-

tions to school or work, sleep deprivation, distractions related to physical discomfort, heightened self-consciousness due to appearance, decreased participation in social activities, disrupted sexual relationships, and distress over repeated treatments.<sup>[47,59,61-66]</sup>

Current treatment strategy is aimed at controlling rather than curing the disease. This reality increases the importance and relevance of measuring the QOL of patients and their families in order to make informed treatment decisions. To the patient with atopic dermatitis, the most important factor in choosing a therapy lies in determining which treatment improves QOL the most.<sup>[66]</sup> However, currently, there are no consensus guidelines on the correct use of QOL measurements in atopic dermatitis. While the most commonly used measurement instruments are the Dermatology Life Quality Index (DLQI)<sup>[67]</sup> and the Children's Dermatology Life Quality Index (CDLQI),<sup>[68]</sup> a recent review of QOL studies in atopic dermatitis found approximately 31 different scales that have been used in the past, ranging from general health measures to dermatology-specific and atopic dermatitis-specific instruments.<sup>[66]</sup>

### 3.3 Effect of TIMs on QOL

Only a few studies examining the impact of treatment with TIMs on the QOL of atopic dermatitis patients and caregivers have been conducted to date.

#### 3.3.1 Tacrolimus

Drake et al.<sup>[62]</sup> studied the QOL effects of tacrolimus ointment. The impact of tacrolimus 0.03% and 0.1% ointment was measured during three phase III, randomised, double-blind, multicentre studies during which patients were given either study drug or vehicle twice daily for 12 weeks or until 1 week after affected areas were completely cleared. Adults ( $\geq 16$  years old,  $n = 579$ ), children (5–15 years old,  $n = 178$ ) and toddlers (2–4 years old,  $n = 145$ ) with moderate-to-severe atopic dermatitis at baseline were included in the study. The investigators measured QOL using the DLQI for adults, CDLQI for children, and modified CDLQI (Toddler Survey) for toddlers. Assessments were

**Table III.** Summary of cost-of-illness studies for atopic dermatitis (AD)

Study	Country	Year of costing	Population studied	Perspective	Data source(s) for costs	Included costs	Cost findings (per year)
Kemp <sup>[48]</sup>	Australia	1997	48 infants and children with AD (Melbourne)	Societal	Questionnaires	Direct costs, out-of-pocket expenses, lost income	Mild: \$A1142 per patient Moderate: \$A3624 per patient Severe: \$A6099 per patient
Gieler et al. <sup>[55]</sup>	Germany	NA	148 AD patients (Marburg)	Societal	Questionnaires	Direct costs, out-of-pocket expenses, transportation, lost income	DM4827 per patient DM7 billion nationally
Emerson et al. <sup>[53]</sup>	UK	1995–96	290 children aged 1–5 years with AD (Nottingham)	Societal	Questionnaires to caregivers	Direct costs, out-of-pocket expenses, transportation, lost income	£79.59 per child £46.9 million nationally for 1- to 5-year olds
Herd et al. <sup>[54]</sup>	UK	NA	155 AD patients (West Lothian)	Societal	Questionnaires	Direct costs, out-of-pocket expenses, lost income	£250 per patient £465 million nationally
Ellis et al. <sup>[5]</sup>	US	1997	Large private managed care and state Medicaid claims databases	Third-party payer	Claims data	Direct medical costs covered by insurance for AD and co-morbidities	\$US580–1250 per patient \$US0.9–3.8 billion nationally
Fivenson et al. <sup>[57]</sup>	US	1997	962 AD patients (Detroit)	Societal	Claims data, questionnaires	Direct costs, out-of-pocket expenses, lost income	\$US609 per patient
Lapidus et al. <sup>[49]</sup>	US	1990	908 inpatient and outpatient visits for AD (Philadelphia)	Societal	Hospital billing data	Direct costs	\$US216 per visit \$US364 million nationally for paediatric population

NA = information not available.

conducted at baseline, week 3 and week 12 or end of study. For adults and toddlers, treatment with tacrolimus significantly improved QOL relative to vehicle across all QOL categories. For children, treatment with tacrolimus significantly improved QOL relative to vehicle across all categories except 'Personal Relationships', which showed no significant difference for 0.03% ointment.

### 3.3.2 Pimecrolimus

The QOL benefit of pimecrolimus has been investigated in a small number of studies.

Whalley et al.<sup>[69]</sup> reported results on parents' QOL obtained from two 26-week clinical trials conducted to evaluate the efficacy and safety of pimecrolimus 1% cream in paediatric patients with mild-to-moderate atopic dermatitis. In the two clinical trials, 403 patients aged 2–17 years received either pimecrolimus or vehicle twice daily on affected areas in a double-blind fashion for 6 weeks. Topical corticosteroids and emollients were used for disease flares. Patients were followed for an additional 20 weeks, during which time topical corticosteroids and emollients could be used. At 6 weeks, all patients receiving vehicle were switched to pimecrolimus. Of the 403 patients, 278 were aged <8 years, and it was in this latter group that parental QOL was assessed. The Parent's Index of QOL-Atopic Dermatitis (PIQoL-AD), an instrument designed to measure the QOL of parents of patients with atopic dermatitis aged ≤8 years, was used to capture QOL data. The instrument is a 28-item survey previously derived through in-depth qualitative interviews with parents of children with atopic dermatitis in the UK, The Netherlands and Italy.<sup>[70]</sup> In the QOL analysis of pimecrolimus,<sup>[69]</sup> the PIQoL-AD was used to assess QOL at baseline (n = 241), 6 weeks (n = 193) and 6 months (n = 161) for the parents of those aged ≤8 years. PIQoL-AD scores significantly improved over the first 6 weeks for both pimecrolimus and vehicle groups, although analysis of co-variance on PIQoL-AD scores showed that pimecrolimus improved PIQoL-AD scores significantly more than vehicle. After all patients were switched to pimecrolimus at week 6,

mean PIQoL-AD scores were the same for both groups at 6 months.<sup>[70]</sup>

In a longer study reported in an abstract,<sup>[71]</sup> an attempt to measure the QOL effect of pimecrolimus was performed as part of a 12-month RDBVCT<sup>[32]</sup> in paediatric patients aged 2–17 years with atopic dermatitis. According to the treatment protocol, patients were randomised to receive either pimecrolimus 1% twice daily or vehicle for their atopic dermatitis, and were allowed to use moderately potent topical corticosteroids and emollients for disease flares. Patients' QOL was measured using the CDLQI, and parents' QOL for children aged 0–8 years was assessed using the PIQoL-AD. Measurements were taken at baseline (n = 231), 6 weeks (n = 212), 6 months (n = 173) and 12 months (n = 141). At 6 weeks, 6 months and 12 months, using analysis of co-variance, a significant difference was seen between improvement in the pimecrolimus group compared with the control groups in CDLQI scores. Improvements in PIQoL-AD scores were significant in favour of pimecrolimus only at 6 months.<sup>[71]</sup>

The QOL benefit of pimecrolimus in infants with atopic dermatitis was reported in another abstract<sup>[72]</sup> as part of a 12-month RDBVCT<sup>[33]</sup> of similar design. Patients aged 2 months to 2 years again received either pimecrolimus 1% twice daily or vehicle treatment, along with topical corticosteroids for disease flares. The QOL of parents was measured using the PIQoL-AD at baseline (n = 154), 6 weeks (n = 137), 6 months (n = 119) and 12 months (n = 140). Statistically significant differences were found between treatment groups at 6 weeks, 6 months and 12 months using analysis of co-variance.<sup>[72]</sup>

### 3.3.3 Summary of QOL Data for the TIMs

The results of these initial studies discussed in section 3.3 provide evidence that TIMs have a measurable effect on the QOL of patients and family. However, questions remain about the full QOL benefit of both agents.

For tacrolimus, the study results by Drake et al.<sup>[62]</sup> show that tacrolimus ointment monotherapy improves the QOL of patients with moderate-to-severe atopic dermatitis in many domains up to 12

weeks after beginning treatment. The use of validated QOL instruments as tools for measurement is a strength of the study. Future analyses may choose to focus on differences in QOL benefit across disease severity and over longer periods of time. In addition, the potential benefit of tacrolimus treatment on the QOL of the family has not been studied, and the relative QOL benefit of tacrolimus ointment compared with other therapies such as topical corticosteroids is currently unknown.

The effect of pimecrolimus on QOL remains largely unmeasured. While one study suggests that pimecrolimus monotherapy benefits the QOL of caregivers of affected children up to 6 weeks after treatment initiation, nothing can be concluded about its QOL benefit to patients. The two 12-month studies described above evaluated the QOL improvement ostensibly achieved by pimecrolimus versus vehicle; however, the treatment protocol mandated the use of emollients and moderately potent topical corticosteroids for disease flares irrespective of treatment arm. Therefore, unfortunately, the impact on the QOL of patients and caregivers provided by pimecrolimus alone cannot be analysed.<sup>[66]</sup>

### 3.4 Utility in Atopic Dermatitis

Utility is a measure of QOL as expressed through individuals' preferences. The utility of a health state, e.g. moderate atopic dermatitis, is usually expressed as a value between two numbers: for example 0 and 1 (or 0 and 100), with 0 representing death and 1 (or 100) representing perfect health. Like QOL, utility can be particularly important to measure in disease areas such as atopic dermatitis, where treatment of disease often does not lead to decreased mortality, but rather to improved states of health.<sup>[73]</sup> The amount of benefit that a particular therapy provides in atopic dermatitis cannot be measured by the number of years of life gained, but rather by its overall effect on QOL. Health state utilities can be converted into QALYs as an effectiveness measure. What is important, then, is to accurately measure individuals' preferences regarding relevant health states in atopic dermatitis. Unfortunately, there are limited

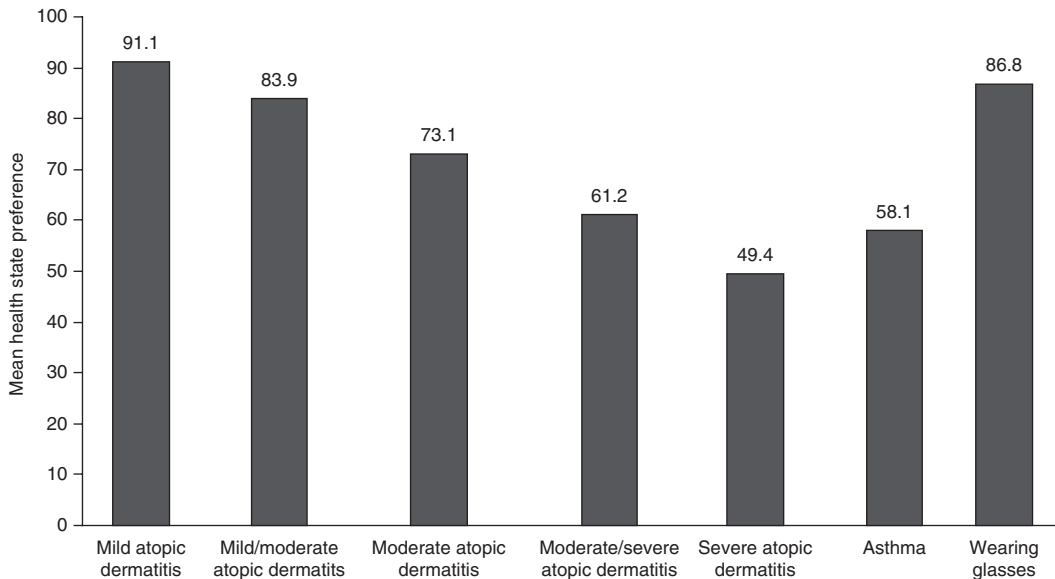
data available for health state utilities in patients with atopic dermatitis.<sup>[66,74]</sup>

The utility of atopic dermatitis was estimated in one European study by asking atopic dermatitis patients to indicate their preferences using three different methods: rating scale, time trade-off and standard gamble. These methods produced utilities of 0.73, 0.93 and 0.98, respectively. These health state utility estimates are unfortunately based on a small sample size ( $n = 132$ ), and disease severity was not evaluated or considered.<sup>[74]</sup> In a recent poster presentation, investigators described measuring preference scores for atopic dermatitis of increasing severity: mild, mild-to-moderate, moderate, moderate-to-severe and severe. Case scenarios representing each disease state were given to 3539 parents, who then rated on a visual analogue scale the health state descriptions for their child having the level of disease described. The resultant health state utility scores decreased with severity, ranging from 91.1 for mild to 49.4 for severe atopic dermatitis (figure 1). Strengths of this study included the large sample size, although the sample was unbalanced (93% of respondents were female, 90% white).<sup>[75]</sup>

## 4. Pharmacoeconomic Studies of TIMs

The next frontier in outcomes and economics research in atopic dermatitis lies in the development of methods and approaches for evaluating the cost effectiveness of current and emerging therapeutic alternatives. Previous research efforts have established that atopic dermatitis has a significant financial and QOL impact. As new therapies are introduced and treatment options increase, momentum is shifting towards the design and execution of studies that examine the cost effectiveness, cost utility and QOL impact of available treatment alternatives.

While the clinical evidence surrounding the safety and efficacy of TIMs in atopic dermatitis is compelling, payers and providers are still in the process of determining the place of TIMs within the armamentarium for treatment of atopic dermatitis. Outstanding issues are: (i) how TIMs compare with other therapies, especially topical corticosteroids; and (ii) how members of the TIM drug class (i.e.



**Fig. 1.** Mean health state preferences for varying severity of atopic dermatitis, showing steadily lower preferences with increasing disease severity. Adult survey participants ( $n = 3539$ ) were asked to imagine their children experiencing each of seven described scenarios and to score the health state descriptions on a visual analogue scale from 0 (death) to 100 (perfect health). Scenarios for wearing glasses and asthma were included to compare the preferences for atopic dermatitis health states with those for non-dermatological health states.<sup>[75]</sup>

tacrolimus and pimecrolimus) compare with each other. Rigorously conducted pharmacoeconomic research is crucial to illuminate these issues. Economic studies focusing on the benefit of TIMs have recently been performed, as data to enable these studies have become available.

#### 4.1 Literature Search and Evaluation

We performed a systematic literature search to identify original, published pharmacoeconomic studies that specifically examined the use of TIMs in the treatment of atopic dermatitis, including cost-of-illness, cost-benefit, cost-effectiveness and cost-utility analyses. Relevant citations through June 2003 were identified through the data sources identified in section 2.2.1. This search yielded the four original studies reviewed here, the characteristics of which are summarised in table IV.

We evaluated each study on the basis of methodological design, data sources, perspective, time horizon, and cost measurements. Two studies<sup>[77,78]</sup> were presented as conference posters (TIM cost-effectiveness analyses) and therefore did not contain full

methodological explanations. One of these appeared to employ a decision-analytic model, while the other utilised a Markov model (both posters relied on data from the same clinical trial). The other two studies were published cost-effectiveness analyses that employed Markov models to simulate therapeutic courses involving TIMs versus topical corticosteroids for moderate-to-severe atopic dermatitis,<sup>[76]</sup> and tacrolimus versus pimecrolimus for moderate atopic dermatitis.<sup>[79]</sup>

#### 4.2 Cost Effectiveness of TIMs versus Topical Corticosteroids

Ellis et al.<sup>[76]</sup> recently performed a cost-effectiveness analysis comparing the cost effectiveness of high-potency topical corticosteroids (HPTCs) with tacrolimus (0.03% and 0.1%) ointment for the treatment of moderate-to-severe atopic dermatitis in adults not responsive to or not well controlled with mid-potency topical corticosteroids. The study compared two different treatment protocols with HPTCs versus tacrolimus ointment monotherapy. The analysis was conducted from the third-party payer per-

**Table IV.** Characteristics of pharmacoeconomic studies of topical immunomodulators (TIMs) for the treatment of atopic dermatitis<sup>a</sup>

Study	Comparators	Study type	Publication type	Methodological approach	Outcomes data source(s)	Perspective	Cost measurements
Ellis et al. <sup>[76]</sup>	TAC vs HPTC	Cost effectiveness	Peer-reviewed journal	Markov model	Multiple clinical trials, expert panel	Third-party payer	Medication and physician visit costs
Ellis et al. <sup>[77]</sup>	PIM vs no PIM (usual care)	Cost utility	Abstract	NA	Single clinical trial	Societal <sup>b</sup>	Medication and physician visit costs
Verboom et al. <sup>[78]</sup>	PIM vs no PIM (usual care)	Cost effectiveness	Abstract	Markov model	Single clinical trial	Societal <sup>b</sup>	Medication costs
Abramovits et al. <sup>[79]</sup>	TAC vs PIM	Cost effectiveness	Peer-reviewed journal	Markov model	Multiple clinical trials, expert panel	Third-party payer	Medication and physician visit costs

a All studies had a time horizon of 1 year.

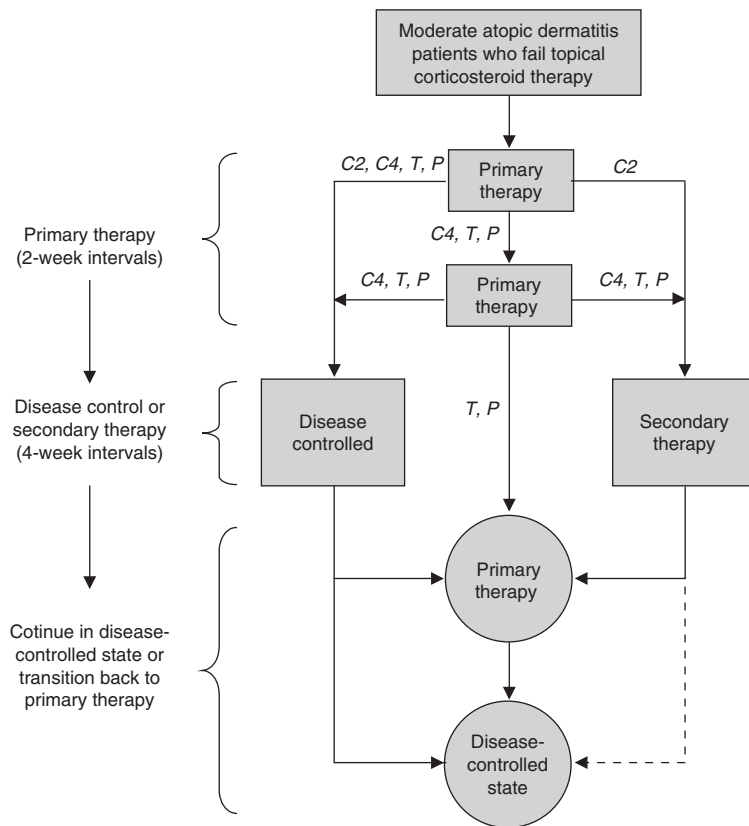
b Societal perspective was inferred from cost measurements, but was not stated by investigators.

**HPTC** = high-potency topical corticosteroids; **NA** = information not available; **PIM** = topical pimecrolimus cream; **TAC** = topical tacrolimus ointment.

spective over a 1-year period (2002) and focused on prescription drug and physician costs in US dollars. The study applied a Markov model to simulate the relapsing and remitting nature of the disease as well as treatment and response (figure 2).

Schematically, the model incorporated three different states that patients could be in: primary therapy, secondary therapy and disease-controlled. Simulated patients were assigned one of three primary treatment protocols: (i) HPTCs for 2 weeks; (ii) HPTCs for up to a maximum of 4 weeks; or (iii) tacrolimus ointment for 2 weeks at a time. On any of the three primary treatments, patients could achieve success at the end of 2 weeks and transition into a disease-controlled state. Because patients treated with HPTCs in the real world do not stay on them indefinitely due to potential adverse effects, HPTC-treated patients in the model who failed the 2- or 4-week primary therapy period automatically transitioned to secondary therapy. At the end of 4 weeks, patients receiving tacrolimus who failed treatment either received re-treatment with tacrolimus in 2-week intervals or transitioned to secondary therapy. The probability of patients remaining on tacrolimus was modelled after patient preferences that were reported in clinical trials.

All patients who failed the assigned primary therapy transitioned to treatment with second-line therapies for 4 weeks at a time. Based on the recommendations of a physician specialist panel, treatment success was considered to be >75% improvement in disease status from baseline. If primary or secondary treatment was successful, patients entered a disease-controlled, prescription-free treatment state for 4 weeks, i.e. 28 disease-controlled days (DCDs) at a time. Based on 4-week cycles, patients in the disease-controlled state could either remain in remission or relapse back to primary therapy. The probability of patients relapsing after entering the disease-controlled state was set at 50%, based on the results of a previous study involving topical corticosteroid therapy. In the base case, secondary treatment did not lead to treatment success, so patients returned to primary treatment; however, secondary treatment leading to treatment success (shown as



**Fig. 2.** Markov model used in two topical immunomodulator (TIM) cost-effectiveness studies. Ellis et al.<sup>[76]</sup> compared possible treatment regimens of high-potency topical corticosteroids (HPTCs) and tacrolimus. The model examined the random assignment of one of three primary therapy protocols for patients with moderate-to-severe atopic dermatitis who had failed treatment with mid-potency topical corticosteroids: HPTCs for 2 weeks (C2); HPTCs for 4 consecutive weeks (C4); and tacrolimus (0.03% and 0.1%) ointment for an indefinite period of time (T). Abramovits et al.<sup>[79]</sup> compared two primary therapy protocols – tacrolimus (T) 0.03% or pimecrolimus (P) 1% – for patients with moderate atopic dermatitis who had failed treatment with topical corticosteroids. Algorithms for both treatment arms were identical.

dashed lines in figure 2) was studied in a sensitivity analysis.

Dosage assumptions and efficacy data for tacrolimus were taken from pivotal clinical trials, and data for topical corticosteroids were derived from a meta-analysis of published clinical trials performed for class I and II HPTCs. Drug costs were based on the mean average wholesale price (AWP) for tacrolimus and several HPTCs. The secondary treatment costs were assumed to be \$US64 per week based on a possible treatment regimen consisting of oral antibacterials and mid-potency topical corticosteroids.

Running the model revealed that HPTCs, when limited to 2-week treatment cycles, were associated with the highest total costs (\$US1682 per year), least efficacy (185 DCDs per year), and the least favourable cost-effectiveness ratio (\$US9.08/DCD). HPTCs in 4-week treatment intervals and continuous tacrolimus ointment treatment were similar in total costs (\$US1317 vs \$1323), efficacy (194 vs 190 DCDs), and cost effectiveness (\$US6.80/DCD vs \$6.97/DCD). Primary drug costs were higher for patients treated with tacrolimus ointment (\$US727 vs \$US366 for 4-week HPTC patients) due to higher cost per gram and longer duration of continued treatment with tacrolimus. However, secondary

treatment costs were lower in the tacrolimus group (\$US162 vs \$US509 for 4-week HPTC patients), since patients treated with HPTCs more often required secondary treatment because of restrictions on the amount of time they could be receiving primary therapy. Sensitivity analyses performed on all variables showed that the model was sensitive to costs and efficacy of secondary therapy and the relapse rate of patients being treated with tacrolimus ointment.

The results of this study suggest that in atopic dermatitis patients with disease unresponsive to mid-potency topical corticosteroids, tacrolimus is more cost effective than HPTCs used at 2-week intervals, and similar in cost effectiveness to HPTCs used at 4-week intervals. Equally important, the model provides a framework that can be used as the basis for future analyses. However, the model has limitations. For example, the model as designed did not capture any costs related to adverse effects resulting from treatment with topical corticosteroids or tacrolimus. To be complete, future iterations of the model could include QOL measures or utilities to incorporate patients' preferences with regard to each health state. Another underlying assumption of the model is that HPTCs and tacrolimus are appropriate for use in all affected areas, while in reality the face and intertriginous areas would not necessarily be treatable using HPTCs and would require a different type of treatment (and potentially greater costs). Additionally, the model assigned patients exclusively to some form of monotherapy (i.e. HPTCs alone or tacrolimus ointment alone), whereas combination therapy may be more representative of many real-world treatment protocols.

#### 4.3 Cost Utility and Cost Effectiveness of TIMs in Atopic Dermatitis

A recent poster presentation by Ellis et al.<sup>[77]</sup> described an economic analysis performed from the societal perspective comparing the cost effectiveness of long-term management of paediatric patients with atopic dermatitis treated with pimecrolimus versus 'conventional therapy', which was defined as the control arm of the 12-month pimecrolimus

clinical trial.<sup>[32]</sup> In the clinical trial, paediatric patients aged 2–17 years were randomised to receive either pimecrolimus 1% cream twice daily or vehicle cream. In addition, patients in both treatment groups were treated with emollients for dry skin and mid-potency topical corticosteroids for disease flares. At baseline and at each subsequent month in the trial, patients were evaluated and assigned an L-IGA score, which rated the severity of atopic dermatitis on a Likert scale as 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), 4 (severe) or 5 (very severe). Based on these levels, the investigators appeared to have created a decision-analytic model, consisting of four possible disease severity states that patients could be found in: clear/almost clear, mild, moderate, and severe/very severe. Treatment costs were assigned to each severity level based on medication utilisation from the clinical trial as well as an assumption of frequency of physician visits. At each monthly evaluation interval, the percentage of patients in the trial with each disease severity level was quantified with half-cycle corrections. Utility values for each L-IGA severity level were obtained from an independent survey of parents.<sup>[75]</sup> All results were reported in US dollars, year 2002 values.

Total daily treatment costs (including medication and physician costs) associated with severity levels clear/almost clear, mild, moderate and severe/very severe were \$US1.03, \$US8.94, \$US16.37 and \$US4.67, respectively, for the pimecrolimus patient group and \$US0.92, \$US2.11, \$US4.47 and \$US5.61, respectively, for the control group.<sup>[77]</sup> The incremental cost-effectiveness ratio for treating patients with pimecrolimus versus conventional therapy was \$US34 108 per QALY. Sensitivity analyses performed by varying physician visit utilisation rates and health state utility values yielded a range of cost-effectiveness ratios from \$US24 354 to \$US56 615 per QALY. The investigators also asserted that in clinical practice approximately 80% of presenting patients would be between the ages of 2 and 6 years. Because these patients have approximately half the BSA of the average patient in the study, only 50% of the pimecrolimus cream would

be required, improving the incremental cost-effectiveness ratio to \$US16 580 per QALY.

A similar study was performed by Verboom et al.<sup>[78]</sup> (described in a recent poster presentation) and was based on the exact same clinical trial data<sup>[32]</sup> and utility scores.<sup>[75]</sup> It investigated the cost effectiveness of pimecrolimus cream from a societal perspective over 1 year (US dollars, year 2002 values). Again, according to the treatment protocol, patients were treated twice daily with pimecrolimus 1% or vehicle cream plus emollients for dry skin and mid-potency corticosteroids for acute disease flares. A Markov model was constructed, utilising four distinct disease states: none, mild, moderate and severe. Transitions could occur between all disease states, with a cycle time of 1 week. Transition probabilities were estimated from the study data. In the no-disease state, patients received no treatment except emollients, while in the mild and moderate disease states, patients additionally received either pimecrolimus or vehicle; patients in the severe disease state received emollients, pimecrolimus or vehicle, and topical corticosteroids. Only direct medication costs were captured. In the base case scenario, it was assumed that no patients actually dropped out of the model (although patients did drop out of the study).

Using a theoretical acquisition cost of £0.6/g for pimecrolimus cream, the cost-effectiveness ratio was £22 166 per QALY gained. Varying the costs by a factor of 0.5–1.25, the cost-effectiveness ratio ranged from £9498 to £28 500 per QALY gained. Recycling patients who had withdrawn from the study into the model yielded a cost effectiveness of £22 551, while completely excluding those who had withdrawn yielded a cost effectiveness of £5916.<sup>[78]</sup>

These two reviewed studies suggest that the incremental cost effectiveness of pimecrolimus cream, emollients and topical corticosteroids for flares over emollients and topical corticosteroids alone is \$US34 108 or £22 166 per QALY, values that are roughly equal to each other. Neither study attempted to capture costs other than those associated with medications and physician visits.

Although the previously described tacrolimus analysis,<sup>[76]</sup> as well as the above pimecrolimus studies,<sup>[77,78]</sup> examined treatment of atopic dermatitis with TIMs versus some form of topical corticosteroid, there were differences in underlying assumptions between the studies. In the tacrolimus analysis,<sup>[76]</sup> patients moved from primary to secondary therapy if their atopic dermatitis did not improve by at least 75%. In the pimecrolimus studies,<sup>[77,78]</sup> patients moved from either pimecrolimus or emollient therapy only if they had a disease flare, i.e. their atopic dermatitis became severe or very severe. Another difference is that the tacrolimus study did not utilise different disease severity states for atopic dermatitis as the cost-effectiveness analyses did, but instead focused on states representing various responses to therapy. These differences are reflective of the disparate approaches taken in the clinical studies involving tacrolimus compared with pimecrolimus and complicate any direct comparisons between study results.

The pimecrolimus studies<sup>[77,78]</sup> compared use of pimecrolimus with 'conventional therapy', defined as treatment with emollients only, except in the case of disease flares (severe disease) when mid-potency topical corticosteroids would be added. However, other conventional treatment protocols might involve less conservative use of topical corticosteroids. Future studies must explore real-world treatment patterns in order to improve applicability of results. Additional questions remain for both cost-effectiveness studies regarding how the patients who withdrew from the clinical trial should be accounted for, since a fairly large number of patients did so because of a lack of efficacy (19.6% in the pimecrolimus arm over the course of the 12-month study<sup>[32]</sup>). The fate of these patients and how they were accounted for in the models could significantly alter the cost-effectiveness numbers presented. Nevertheless, these studies represent the first attempts at describing the cost effectiveness of TIMs, and have laid a foundation for future analyses.

#### 4.4 Comparative Cost Effectiveness of Tacrolimus and Pimecrolimus in Atopic Dermatitis

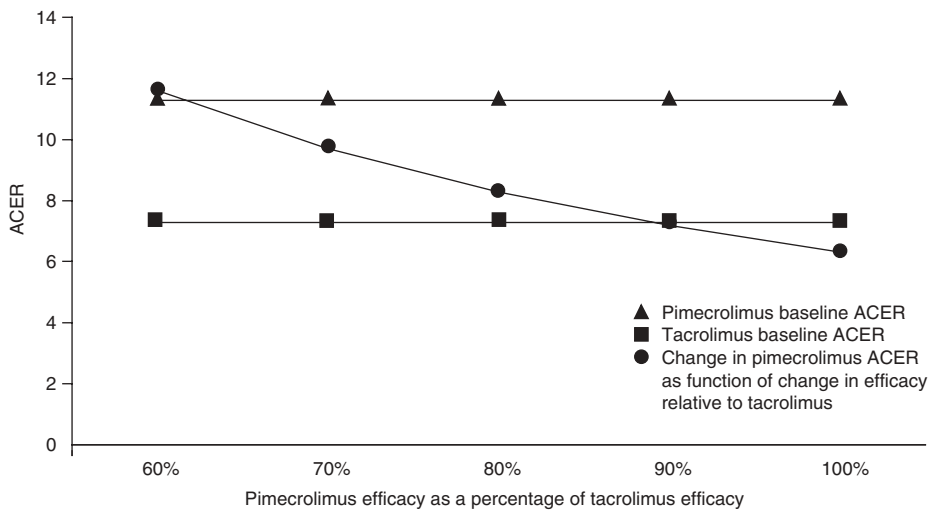
As mentioned previously, no head-to-head studies between tacrolimus and pimecrolimus have been conducted to allow direct comparisons of primary treatment efficacy. Currently, only one pharmacoeconomic study has attempted to compare the cost effectiveness of tacrolimus and pimecrolimus in the setting of atopic dermatitis.<sup>[79]</sup> The study's objective was to propose ways of comparing the efficacy and cost effectiveness of tacrolimus 0.03% ointment and pimecrolimus 1% cream as monotherapy for the treatment of paediatric patients with moderate atopic dermatitis inadequately controlled with topical corticosteroids. The analysis was conducted from the third-party payer perspective, considering only medication and physician costs, over a 1-year time horizon (in US dollars, year 2002 values). To determine the cost-effectiveness ratios for each treatment, the investigators utilised the same Markov model (figure 2) developed in the cost-effectiveness analysis of tacrolimus ointment versus HPTCs.

The model incorporated three alternative states pertaining to primary therapy (tacrolimus or pimecrolimus for 2 weeks), secondary therapy (mid-potency corticosteroids and antibacterials for 4 weeks), and disease control (prescription-free with no active treatment for 4 weeks). Patients receiving either therapy could have continuous treatment indefinitely. After every 2 weeks of primary treatment, if patients experienced treatment success they transitioned to the disease-controlled state. After 4 weeks of failing primary therapy, patients either received re-treatment with tacrolimus or pimecrolimus in 2-week intervals or transitioned to secondary therapy. Patients in a disease-controlled, treatment-free state continued in remission or relapsed back to primary treatment (evaluated every 4 weeks). In the base case, secondary treatment did not lead to treatment success, so patients returned to primary treatment; however, secondary treatment leading to treatment success (shown as dashed lines in figure 2) was studied in a sensitivity analysis.

Relative primary treatment efficacy was estimated based on existing outcomes reported in clinical trials of each respective treatment. Treatment success for tacrolimus and pimecrolimus was defined as 75% improvement in disease state from baseline. The rates of treatment success for tacrolimus were extracted directly from clinical trial data. However, the treatment success rates as defined were not directly known for pimecrolimus because clinical trials relied on the L-IGA, which is a measure of disease severity scored on a Likert scale. Therefore, the investigators relied on a comparison of reported EASI scores for each treatment population to calculate the treatment success rate of pimecrolimus indirectly. The EASI is a validated instrument for the assessment of severity and extent of atopic dermatitis.<sup>[80]</sup> The efficacy of tacrolimus 0.03% twice daily ( $\geq 75\%$  improvement from baseline) was estimated to be 36% at week 2 and 52% at week 4, versus 23% at week 2 and 32% at week 4 for pimecrolimus 1% twice daily. Medical resources costs were derived from fee schedules and product AWP. Other assumptions were based on opinions of a physician panel and from previously published reports.

The analysis found that total costs and efficacy over a 1-year period were \$US1 393 and 190 DCDs, respectively, for tacrolimus and \$US1 550 and 137 DCDs for pimecrolimus.<sup>[79]</sup> Primary drug costs were higher for tacrolimus than for pimecrolimus (\$US797 vs \$US786) due to its higher per-gram pricing; however, tacrolimus patients incurred lower costs on secondary treatment (\$US162 vs \$US236), as well as lower physician costs (\$US434 vs \$US529) because patients achieved better disease control and required fewer clinic visits. The average cost-effectiveness ratio was \$US7.34/DCD for tacrolimus and \$US11.34/DCD for pimecrolimus. Sensitivity analyses indicated that pimecrolimus would be cost effective only if its efficacy approached 90% that of tacrolimus (figure 3), or if the costs of the products were significantly different from their current AWP.

The study estimated that tacrolimus was roughly 40% more effective than pimecrolimus in patients with moderate atopic dermatitis, leading to more



**Fig. 3.** One-way sensitivity analysis of the effect of changes in the relative efficacy of tacrolimus compared with pimecrolimus on the average cost-effectiveness ratio (ACER) in patients with moderate atopic dermatitis (\$US; year 2002 values). At baseline, the ACER of tacrolimus was \$US7.34 per disease-controlled day (DCD), compared with \$US11.34 per DCD for pimecrolimus. As the efficacy rate of pimecrolimus approached that of tacrolimus, the ACER improved. At efficacy rates near 90% of that of tacrolimus, pimecrolimus became more cost effective than tacrolimus (reproduced from Abramovits et al.,<sup>[79]</sup> with permission).

DCDs and less time spent in secondary therapy. The results of the model suggested that for patients with moderate atopic dermatitis, tacrolimus may be more cost effective than pimecrolimus, given available data on efficacy. Depending on the method of calculation, investigators estimated that the efficacy of pimecrolimus was 60–75% of that of tacrolimus. Clearly, the EASI is not a direct measure of efficacy, but a surrogate. However, while it is impossible to prove relative efficacy, given the differences in the study design of the clinical trials, the present estimate is feasible.

The efficacy rate estimates were based on data from significantly different patient populations in terms of disease severity in the clinical trials; 61.5% of patients treated with tacrolimus had severe disease compared with only 9.7% of patients treated with pimecrolimus. Because patients with severe atopic dermatitis had a significantly lower rate of treatment success as reported in the Hanifin et al. phase III clinical trials,<sup>[22]</sup> and this effect was likely to have been experienced in paediatric patients with

more severe disease,<sup>[23]</sup> the treatment success rate for tacrolimus used in the study model (which focused on patients with moderate atopic dermatitis) was probably conservative.

Nevertheless, any attempt to infer relative efficacy has its limitations. Recent studies have drawn on head-to-head efficacy data. Very recently, two multicentre, randomised, investigator-blinded studies comparing the efficacy of topical tacrolimus and pimecrolimus have been completed.<sup>[44,45]</sup> Preliminary results support the suggestion that tacrolimus may be more efficacious than pimecrolimus, but details on study design and dosages compared are not yet available. When fully analysed and reported, the results from these studies will fill an important gap in the clinical data and undoubtedly be very useful in conducting future cost-effectiveness studies.

The cost-effectiveness study<sup>[79]</sup> just reviewed modelled TIM monotherapy in patients with moderate atopic dermatitis. As mentioned previously, treatment strategies combining TIMs with topical corticosteroids or other modalities may prove to be

important in clinical practice, although such protocols have yet to be elucidated in the clinical literature. More studies should be performed to further establish the cost effectiveness of TIMs in different atopic dermatitis patient populations, to include additional direct and indirect costs, and to incorporate available QOL data.

## 5. Conclusion

Future economic studies should focus on the comparison of the cost utility and cost effectiveness of TIMs with other available therapies as well as with each other. One potentially important variable that has not been measured seriously is the length of remission achieved through treatment with TIMs compared with topical corticosteroids or other therapeutic modalities. It is also important for future analyses to include not only estimates of direct costs, but also indirect costs such as out-of-pocket costs, loss of earnings or productivity, and transportation costs, as well as intangible costs from impaired QOL, which can be especially high in severe atopic dermatitis.<sup>[81,82]</sup>

To date, pharmacoeconomic studies on TIMs have not attempted to compare the costs associated with adverse effects. Information on the long-term adverse effect profile of TIMs will also be important to consider as such data become available. The favourable adverse effect profile of TIMs relative to other therapies represents a potential economic and QOL value that has yet to be measured.<sup>[81]</sup> However, it is difficult to gauge how large a benefit this actually represents.

Studies have shown that TIMs have a positive impact on the QOL of patients and caregivers.<sup>[62,69,71,72]</sup> However, studies to date have used vehicle as a treatment control or have allowed the simultaneous application of TIMs and topical corticosteroids, which make a serious comparison of QOL data concerning different treatment modalities impossible.<sup>[66]</sup> Head-to-head comparisons would facilitate the integration of QOL and other data into future analyses; while these are rare in the field of dermatology,<sup>[73]</sup> new studies that provide such data have begun to emerge.<sup>[44-46]</sup>

Clinical trials involving TIMs have demonstrated that these agents are safe and effective. In response to these findings, new treatment guidelines have begun to recognise TIMs as part of the overall treatment strategy for atopic dermatitis. One recently published algorithm suggested the use of TIMs as alternatives to topical corticosteroids in the setting of acute disease flares, as well as for maintenance therapy to prevent recurrence or disease progression.<sup>[12]</sup>

Ultimately, pharmacoeconomic data represent only one of several factors that will determine the appropriateness of prescribing tacrolimus ointment, pimecrolimus cream or other treatments such as topical corticosteroids in a given situation. The choice of therapy for atopic dermatitis is multidimensional and involves decision-making not only at the economic level, but also at the clinical and individual patient level. The severity of disease, age of the patient, areas of the body that are affected, past responses of the patient to specific therapies, potential for adverse effects, and patient attitudes (e.g. towards topical corticosteroids) are all factors to consider when attempting to choose the optimal treatment strategy for a particular patient.

TIMs represent an exciting new therapy for the treatment of atopic dermatitis, a disease that has high economic and QOL costs. Future studies will be required to answer remaining questions about how and when to use TIMs for the treatment of atopic dermatitis, for example whether TIMs are best used as monotherapy or in combination with other agents.<sup>[83]</sup> Hand in hand with these clinical questions are pharmacoeconomic issues of cost effectiveness. While a few economic analyses have been performed, with promising results, additional research will need to be conducted before the place of TIMs among therapeutic options is fully understood.

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