
Cost-effectiveness analysis of tacrolimus ointment versus high-potency topical corticosteroids in adults with moderate to severe atopic dermatitis

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Background: Few cost-effectiveness analyses have been conducted on topical therapies for atopic dermatitis.

Objective: We sought to compare cost-effectiveness of high-potency topical corticosteroids (HPTCs) and tacrolimus ointment for the treatment of moderate to severe atopic dermatitis for patients who are not responsive to or not well controlled with mid-potency topical corticosteroids.

Methods: A Markov model represented the cyclic nature of atopic dermatitis. Clinical outcomes were derived from published literature. "Efficacy" was defined as disease-controlled days on which patients experienced a greater than 75% improvement in their disease. Resource use and changes in management were on the basis of opinions of a physician panel; secondary treatment was an oral antibiotic with topical corticosteroids. Sensitivity analyses were conducted for all variables.

Results: The model was sensitive to duration of continuous treatment with HPTCs. HPTCs, when limited to 2-week treatment cycles, were associated with the highest total costs (\$1682 per year) and the least efficacy (185 disease-controlled days). HPTCs in 4-week treatment intervals and tacrolimus ointment were similar in total costs and efficacy (\$1317 vs \$1323 for 194 vs 190 disease-controlled days, respectively). Although primary drug costs were higher for patients treated with tacrolimus ointment, patients treated with regimens of HPTCs incurred higher secondary drug costs.

Conclusion: In the base case analyses, tacrolimus ointment was more cost-effective than HPTCs administered in 2-week treatment cycles, and similar in cost-effectiveness to 4-week cycles of HPTCs. (J Am Acad Dermatol 2003;48:553-63.)

Atopic dermatitis (AD) is a common skin disorder, causing inflammation and pruritus in 5% to 15% of adults and children in the United States.^{1,2} Economic studies have shown the financial impact of AD to be substantial. Treatment of the pediatric AD population was estimated to be

\$364 million in the United States in 1990, and \$721 million in the United Kingdom in 1996.^{3,4} Our cost-of-illness study from a third-party payer perspective estimated expenditures of \$0.9 to \$3.8 billion for nonelderly people with private insurance or Medicaid in the United States in 1998.⁵ AD has the potential

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Supported by Fujisawa Healthcare Inc.

Disclosure: All physician authors were compensated for their time serving on the advisory board for this work. Ms Prendergast is an employee of Fujisawa Healthcare Inc. Dr Ellis and Mr Tong are consultants to Fujisawa Healthcare Inc. Drs Ellis, Drake, Abramo-

vits, Boguniewicz, Daniel, Lebwohl, and Whitaker-Worth have been investigators for clinical trials sponsored by Fujisawa Healthcare Inc. Drs Drake, Abramovits, Boguniewicz, Stevens, and Whitaker-Worth have been compensated by Fujisawa Healthcare Inc for speaking engagements. Dr Stevens has received a research grant from Fujisawa Pharmaceutical Co Ltd.

Accepted for publication August 5, 2002.

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doi:10.1067/mjd.2003.240

Abbreviations used:

AD:	atopic dermatitis
AWP:	average wholesale price
DCDs:	disease-controlled days
DFDs:	disease-free days
HPTCs:	high-potency topical corticosteroids
QALYs:	quality-adjusted life years

to affect quality of life, schooling and productivity, and out-of-pocket expenses. The annual costs per patient were estimated at more than \$4600 when medical, hospital, direct, and indirect costs were considered.⁶

Historically, low-potency and mid-potency topical corticosteroids have been the most widely used topical first-line therapies for AD.⁷ However, in moderate to severe AD, use of a high-potency topical corticosteroid (HPTC) is often necessary. There are concerns regarding the long-term chronic use of HPTCs because of the increased risk of side effects such as skin atrophy, infection, cataracts, glaucoma, hypothalamic-pituitary-adrenal axis suppression, and Cushing's syndrome.⁸⁻¹¹

Additional therapies may include psoralen plus ultraviolet A (PUVA), other UV, systemic corticosteroids, and cyclosporine. Because of the potential for significant adverse effects, these generally are used only in severe cases of AD that are unresponsive to topical therapies.^{12,13}

Tacrolimus ointment (Protopic, Fujisawa Healthcare Inc, Deerfield, Ill) is a new therapeutic option, a topical immunomodulator indicated for the treatment of moderate to severe AD. It has been shown to be a safe and effective therapy for the treatment of AD in adults and in children as young as 2 years.^{14,15} In multicenter, phase III studies, tacrolimus ointment demonstrated prolonged response and minimal side effects.^{16,17}

The objective of this study was to conduct a computerized cost-effectiveness analysis of topical therapies for the treatment of AD. Mathematic models are commonly used to assess the relative effectiveness and cost-effectiveness of alternative treatment strategies. The results may be used to guide policy decisions, to inform clinicians, or to assist in the design of future clinical studies.¹⁸ This study compares 2 different treatment protocols with HPTCs to tacrolimus ointment, each as a monotherapy, for the treatment of moderate to severe AD in adult patients unresponsive to or not well controlled with mid-potency topical corticosteroids. Outcomes and costs are combined to assess relative cost-effectiveness of treatment with HPTCs or tacrolimus.

DESIGN AND METHODS**Markov model**

This study was conducted according to published standards for accepted methods in cost-effectiveness studies.^{19,20} The analysis was conducted from the third-party payer perspective during a 1-year period. Published fee schedules and prices were used to standardize all health care cost estimates.

Patients with AD often transition through periods of remission and relapse. This study applied a Markov model^{21,22} chosen over a chronologically structured decision analytic model because it is able to represent more accurately the cyclic, recursive nature of AD. Markov models simulate how patients might experience periods of remission and recurrence, and treatment and response. In the Markov model, patients are assigned to one of various states, each representing a different situation with its own costs and clinical results. Markov models have been used to study the cost-effectiveness of treating psoriasis.^{23,24}

Model construction

The model was developed on the basis of input from all physician authors, who are experienced in the treatment of patients with AD. The model was designed to compare 2 primary therapies, namely HPTCs (Table I) administered using 2 different treatment cycles and tacrolimus ointment (Fig 1). This model examined an adult population because it focused on HPTCs, which normally are not used in pediatric patients. The Markov model randomly assigned simulated patients to their treatment group. Model software was used (DATA, Version 3.5, Tree-age Software, Williamstown, Mass).

The base case Markov analysis was performed using the initial data input from a literature review and physician panel opinion. Subsequently, sensitivity analyses were performed to determine the effect of changing certain variables in the model. In the base case, the main differences between primary treatments were their efficacy, drug costs, and limits on duration of use. The safety profile of tacrolimus ointment allowed for long-term use, whereas the potential for side effects restricted the duration of use of HPTCs either to 2 or 4 weeks of continuous therapy. The regimen of the primary treatment groups was intentionally similar with no crossover to avoid bias.

Each treatment group incorporated 3 alternative Markov states: (1) primary treatment in which patients were treated either with HPTCs or tacrolimus ointment for 2 weeks at a time (up to a maximum of 2 or 4 consecutive weeks for treatment with HPTCs); (2) secondary treatment in which patients were

Table I. Class I/II high-potency topical steroids and prices per gram

Topical steroid	Available generically?*	Sample branded name	Mean AWP per gram†
Amcinonide‡	No	Cyclocort	\$1.15
Betamethasone	Yes	Diprosone/Diprolene	\$0.63
Augmented formulation	No	Diprolene AF	\$1.82
Clobetasol	Yes	Temovate	\$1.22
Desoximetasone§	Yes	Topicort	\$1.23
Diflorasone	No	Psorcon	\$1.66
Fluocinonide‡	Yes	Lidex	\$0.68
Halcinonide	No	Halog	\$1.48
Halobetasol	No	Ultravate	\$1.62
Mometasone‡	No	Elocon	\$1.29

*Both branded and generic formulations were included in the meta-analysis.

†On the basis of average of generic and branded AWP.

‡Only in ointment form to achieve high potency.

§Only in ointment and gel forms to achieve high potency.

treated with second-line therapies for 4 weeks at a time; or (3) disease-controlled, prescription-free treatment in which the disease was well controlled and was not actively treated with prescription pharmaceuticals for 4 weeks at a time.

After every 2 weeks of primary treatment, if patients experienced a greater than 75% improvement, they transitioned to a disease-controlled, prescription-free state. If they did not improve by 75% after 2 weeks, they would transition to secondary therapy (patients in the HPTC 2-week group) or continue on primary therapy for 2 more weeks (patients in the HPTC 4-week or tacrolimus group). Patients on 4-week HPTC treatment who did not experience greater than 75% improvement after 4 continuous weeks of treatment were forced into secondary treatment. At the end of 4 weeks, patients undergoing tacrolimus treatment who were not improved by 75% received retreatment with tacrolimus in 2-week intervals or transitioned to secondary therapy. Patients in the disease-controlled, prescription-free state continued in that state, or relapsed and returned to primary treatment. The probabilities of patients transitioning to the various states, and the time spent in each state, were calculated as described below.

Because the model aimed to compare the cost-effectiveness of treatment with HPTCs and tacrolimus ointment, crossover among primary treatment assignments was not permitted. Furthermore, there were more data on outcomes of each treatment as a monotherapy; for use in combination, outcome data were lacking.

Costs of treatment

Because the study was conducted from the third-party payer perspective, the analysis focused on

prescription drug and physician costs. It did not address costs related to over-the-counter medications because the third-party payer generally would not incur these costs. The analysis did not include direct, nonmedical costs such as transportation expenses, nor did it address indirect costs (eg, productivity, time lost seeking treatment, quality of life). In addition, the costs of long-term side effects and adverse events were not included because the analysis was limited to 1 year.

Treatment outcomes

Cost-effectiveness analysis requires the identification and selection of a measurement of treatment efficacy. For example, in quality of life studies, a widely accepted measure is quality-adjusted life years. However, there are inconsistent standards regarding the measurement and reporting of treatment efficacy in AD. Some studies have defined “efficacy” using disease-free days.²⁵ However, in a chronic, relapsing, and remitting disease such as AD, the term “disease-free” is subjective and can be misleading.

This study defined “treatment success” (ie, efficacy of treatment) using the disease-controlled day (DCD). DCDs represented days in which patients did not require primary prescription topical therapy. The study considered patients to be disease-controlled if they achieved a greater than 75% improvement on the basis of physician global assessment of disease.

In the base case model of this study, DCDs were accumulated only in the disease-controlled, prescription-free state. However, control of the disease also could have occurred during primary or secondary therapy. The impact of intratreatment DCDs on

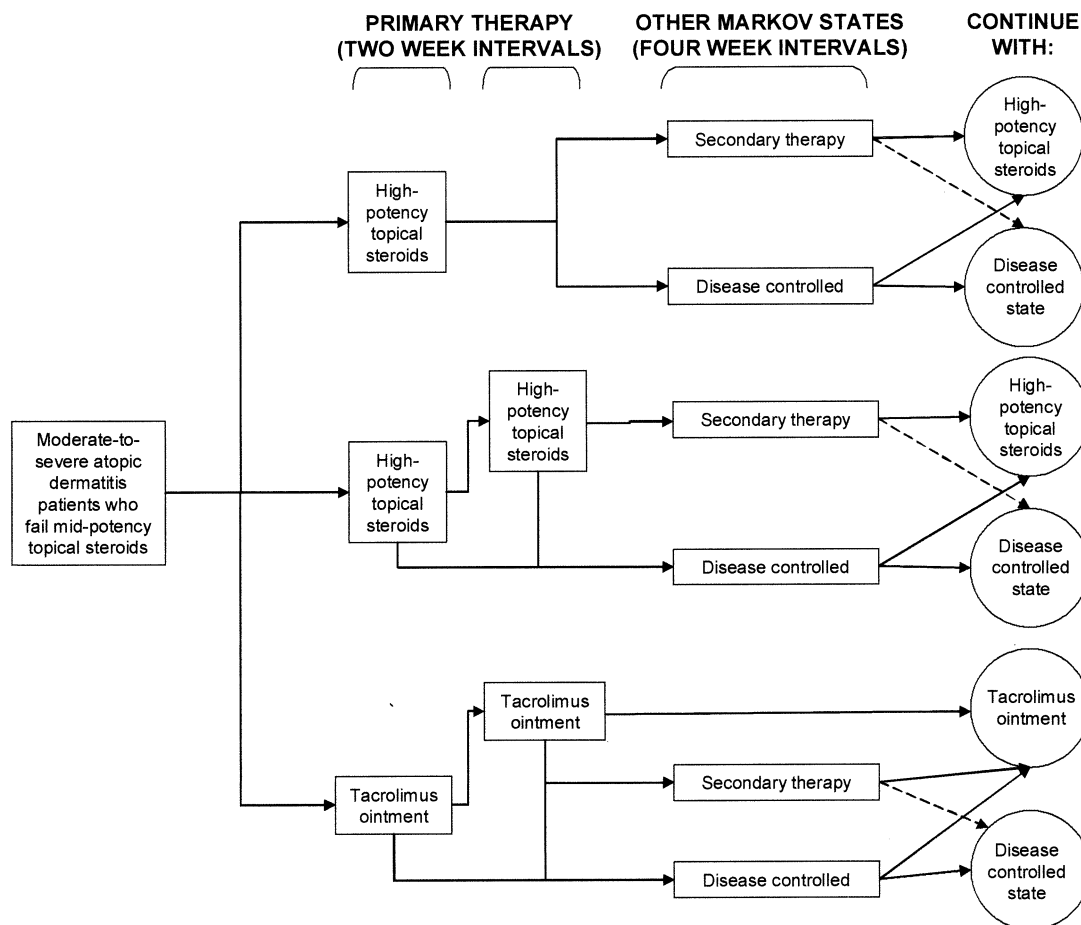


Fig 1. Markov model and comparative treatment regimens for cost-effectiveness analysis. Model examined random assignment of 1 of 3 primary therapy protocols for patients with moderate to severe atopic dermatitis who had failed treatment with mid-potency topical steroids. For high-potency topical corticosteroid (HPTC), 2 different scenarios were modeled: 1 limiting treatment to 2-week intervals and 1 allowing 4 consecutive weeks. Patients on tacrolimus ointment could be treated continuously, indefinitely. On any of 3 primary treatments, patients could achieve success at end of 2 weeks and transition into disease-controlled state. Only patients assigned to 4-week HPTC or to tacrolimus ointment therapy could transition into second 2-week primary treatment period if needed. At end of 4 continuous weeks of treatment, patients receiving HPTC therapy who did not achieve disease-controlled state were converted to secondary treatment for 4 weeks; patients receiving tacrolimus ointment could continue primary therapy (in 2-week intervals) until disease-controlled or transitioned to secondary treatment. See Table II for transition probabilities. Patients in disease-controlled, treatment-free state continued in remission, or relapsed back to primary treatment (evaluated every 4 weeks). In base case, secondary treatment did not lead to treatment success, so patients returned to primary treatment; however, allowing secondary treatment to lead to treatment success (*dashed lines*) was studied in sensitivity analysis (Fig 2).

overall cost-effectiveness was analyzed through a sensitivity analysis.

Model variables

Resource use and changes in management were on the basis of the opinion of the physician panel. Sensitivity analyses were performed for each variable to assess the impact of that variable

on cost-effectiveness ratios and the overall model (Table II).

Data from tacrolimus ointment clinical trials indicated that 80% of patients, if given the choice, would continue therapy indefinitely;²⁶ therefore, this patient preference, along with the published efficacy rates, were incorporated into the model in determining whether a patient would continue tacrolimus or

Table II. Summary of model variables and base case values

Variable	Base case value	Sources
Transition probabilities		
Probability of successful treatment		
HPTCs at 2 wk	52%	Literature, physician panel
HPTCs at 4 wk	64%	Literature, physician panel
Tacrolimus at 2 wk	36%	Tacrolimus clinical trial data
Tacrolimus at 4 wk	52%	Tacrolimus clinical trial data
Secondary treatment at 4 wk	0%	Assumption
Relapse rate after disease improvement for topical HPTCs	50%	Assumption
Relapse rate after disease improvement for tacrolimus	50%	Assumption
Continue on tacrolimus after 4 wk	80%	Tacrolimus clinical trial data
Primary treatment dosing assumptions		
Dosing per week	17.5 g wk	Tacrolimus clinical trial data
Physician visits	1 visit with every change in Markov state (see text for exceptions)	Assumption
Cost assumptions		
HPTCs	\$44.80/ 2 wk (\$1.28/ g)	Mean AWP of HPTCs
Tacrolimus	\$65.80/ 2 wk (\$1.88/ g)	Tacrolimus AWP
Secondary treatment	\$128.10/ 2 wk	Assumption based on 2-wk cost of concomitant midpotency topical steroids and oral antibiotics
Physician-related	\$59.00 per visit	Median fee schedule for CPT code 99213

CPT, Current Procedural Terminology.

move to one of the other clinical states (Table II). In clinical practice, patients could have continued to use lesser amounts of tacrolimus or HPTCs to prevent relapse. This model did not account for such prophylaxis regimens. Instead, patients were assigned to: continue therapy; convert to secondary therapy; or enter a disease-controlled, prescription-free state.

Transition probabilities represented the likelihood of patients maintaining their current state or moving from one state to another. Probabilities were assigned using information from phase III clinical trials of tacrolimus ointment, the medical literature, and consultation with the physician panel.

Topical corticosteroids. Efficacy data were derived from a meta-analysis of the medical literature on class I/II HPTCs used to treat AD and other dermatitis conditions (Table III). A search on MEDLINE was conducted, which identified all articles of class I/II HPTCs for the treatment of AD, using both generic and brand names as search terms. Articles were excluded if they: (1) did not use a physician global assessment of disease; (2) did not have a minimum of 2-week outcome data; or (3) only examined pediatric patients. Two articles that did not include efficacy at the 75% threshold were included on the basis of interpolations of reported data. Efficacy data were estimated by calculating the weighted average efficacy across all eligible studies.

On the basis of the meta-analysis, the base case value for successful treatment at the end of 2 weeks of treatment was 61% across class I/II HPTCs.²⁷⁻³⁴

The physician panel estimated the initial efficacy of HPTCs to result in 75% of patients achieving the disease-controlled state after 4 weeks of treatment, an estimate in line with the limited information on 2-, 3-, and 4-week efficacy reported in the literature.

However, the physician panel did not believe HPTCs maintained this degree of efficacy throughout the course of the 52-week study period. The progressive decrease in response after use of corticosteroids during extended periods (sometimes mislabeled as tachyphylaxis) was incorporated into the model by decreasing HPTC efficacy to account for repeated use.³⁵ The physician panel estimated the 4-week efficacy of HPTCs in achieving the disease-controlled state to be 75% at the initiation of the study, declining to 50% efficacy at the end of the study (a 33% decline in efficacy during 52 weeks). Incorporating this effect would require adding substantial complexity to the computerized model. Instead, to simulate a decline in efficacy during the year, the overall efficacy of HPTCs both at 2- and 4-week intervals was reduced by 15% (a more con-

Table III. Selected literature with data on topical corticosteroid efficacy*

Reference	Active ingredient	Class	No. of patients in study	Patients with >75% improvement
Bickers ²⁷	Amcinonide	II	16	75%
Bickers ²⁷	Halcinonide	II	13	77%
Delescluse and van der Endt ^{28†}	Betamethasone	I	44	61%
Guenther et al ²⁹	Halcinonide	II	12	67%
Johansson and Stiger ³⁰	Diflorasone	I	36	42%
Lawless and Stubbs ^{31†}	Diflorasone	I	161	49%
Lupton et al ³²	Halcinonide	II	214	64%
Maloney et al ³³	Clobetasol	I	41	54%
Marchesi et al ³⁴	Mometasone	II	30	90%
Marchesi et al ³⁴	Betamethasone	I	30	97%
Total patients			597	61%

*References met criteria listed in "Methods" section.

†Percent of patients achieving 75% improvement was interpolated from reported data.

servative approach than reducing efficacy by 16.6% using a purely mathematic approach). Therefore, the model applied efficacy rates for HPTCs of 52% and 64% after 2 and 4 weeks of treatment, respectively.

Tacrolimus ointment. Efficacy data for tacrolimus ointment were obtained from pivotal clinical trials.^{16,17,36} Because data at week 4 were not collected, the week-4 efficacy rate was interpolated from week-2 and week-6 efficacy rates. The efficacy rate for patients using tacrolimus ointment was estimated at 36% in week 2 and 52% in week 4.

Secondary treatment. According to the physician panel, patients who failed HPTCs or tacrolimus ointment could be prescribed a variety of secondary therapies. Patients often were treated with mid-potency topical corticosteroids to minimize exacerbations and flares, and oral antibiotics to minimize infections. However, a number of management options could be used, including psoralen-UVA, systemic steroids, and systemic immunosuppressives.

This model used the common regimen of mid-potency topical corticosteroids and oral antibiotics to estimate secondary costs in the base case. The base case value for the cost of 2 weeks of secondary treatment was set at \$128.10 (cephalexin [Keftab], \$96.88; mid-potency topical corticosteroids, \$31.22 [average of branded and generic formulations of triamcinolone acetonide, fluticasone propionate, hydrocortisone valerate, and mometasone furoate {cream formulation only to meet mid-potency requirement}]).

Because secondary treatment options and costs varied greatly, the impact of second-line costs was examined by a sensitivity analysis. Furthermore, because of the variability across secondary treatments, the base case model assumed that secondary treat-

ments did not achieve the disease-controlled state. This assumption regarding secondary treatment efficacy rates was also examined through sensitivity analysis.

Relapse rate after treatment success

Few data existed on relapse rates after successful treatment. In one study, 50% of patients with AD who were well controlled after topical treatment relapsed in about 30 days when left untreated.³⁷ For this analysis, the relapse rate after the disease-controlled, prescription-free state was set at 50% after 4 weeks, with half of all patients continuing to be controlled whereas the other half were retreated with the primary therapy. Variations in relapse rate were subjected to a sensitivity analysis.

Primary treatment dosing assumptions

Long-term studies with tacrolimus ointment indicated that patients were typically treated at a mean daily dose of 2.5 g per day.³⁶ In the base case, the model assumed that both tacrolimus ointment and HPTC groups used the same number of grams per day (equivalent to 17.5 g per week).

Other cost assumptions

Costs for primary topical therapies were on the basis of a published average wholesale price (AWP).³⁸ The HPTC group was composed of only class I/II corticosteroids, including both generic and branded formulations (Table D). A total of 10 topical corticosteroids (on the basis of their active ingredients) were included in this category; the model tested the average AWP for each active ingredient individually (range: \$0.63 to \$1.82 per gram), along with the average AWP across the entire class of steroids (\$1.28 per gram). The cost per gram of tacrolimus ointment was on the basis of the cost of

Table IV. Results of cost-effectiveness analysis in base case

	HPTCs in 2-week cycles	HPTCs in 4-week cycles	Tacrolimus ointment
Total costs*	\$1682	\$1317	\$1323
Primary drug costs	\$304	\$366	\$727
Secondary treatment costs	\$787	\$509	\$162
Physician costs	\$591	\$443	\$434
Total efficacy (in DCD)	185	194	190
Average cost-effectiveness in \$/DCD†	\$9.08	\$6.80	\$6.97

*Total costs may not sum because of rounding; primary drug costs are based on the average cost of all formulations; secondary treatment costs are for midpotency topical corticosteroids and oral antibiotics; see text for further details.

†Incremental cost-effectiveness ratios are not meaningful in the base case because none of the therapies provides additional DCDs at additional cost; each regimen that provides additional DCDs does so at a lesser cost.

the 2 marketed sizes of the 2 different concentrations (\$1.88 per gram).

Physician visits were applied each time a patient transitioned between one Markov state and another, except that no physician visit was obtained when patients entered the disease-controlled, prescription-free state. Patients who used tacrolimus ointment had a physician visit every 4 weeks unless the previous rule applied. Physician-related costs were determined from median physician charges for *Current Procedural Terminology* code 99213 for an established patient office visit for all physician visits; managed care organizations typically reimburse providers close to the 50th percentile of charges.³⁹

Authorship and responsibilities

All authors contributed to the design of the study and interpretation of the results. K. B. T. provided the computerization of the Markov model and the output of results. The sponsor reviewed and approved the final version of the manuscript.

RESULTS

Base case model results

Total costs, duration of time per disease state, total DCDs, and average and incremental cost-effectiveness ratios were calculated using the model under base case assumptions (Table IV).

Total annual costs

Total health care costs (including physician visits and prescription medications) for treatment of moderate to severe AD were highest for patients in the 2-week HPTC group (\$1682), but similar between patients in the 4-week HPTC group and those treated with tacrolimus ointment (Table IV). With 4-week HPTC therapy, the total cost during 52 weeks ranged from \$1133 (using betamethasone) to \$1470 (using augmented betamethasone). At an average cost of HPTCs, the total estimated cost was

\$1317; with tacrolimus ointment, total costs were \$1323.

Primary drug costs were higher for patients treated with tacrolimus ointment (\$727 vs \$366 for patients in the 4-week HPTC group) for 2 reasons: (1) higher cost per gram; and (2) longer duration of continued treatment. In contrast, secondary treatment costs were lower in patients undergoing tacrolimus ointment treatment (\$162 vs \$509) because patients treated with HPTCs more often required secondary treatment because they did not continue on primary therapy. As would be predicted, patients using 2-week HPTCs had even higher secondary treatment costs.

Duration of time within Markov states

The duration of time spent in primary treatment was considerably higher in the tacrolimus ointment treatment group (42% of the year) versus either 4- or 2-week HPTC groups (31% and 26%, respectively). However, the patients undergoing HPTC treatment spent significantly more time in the secondary treatment state (15% and 23%) compared with the tacrolimus group (5%). Time spent in the disease-controlled, prescription-free state was nearly equal between the 2 treatment groups (54% for 4-week HPTCs; 51% for 2-week HPTCs; 53% for tacrolimus ointment). The total number of DCDs were 194 with 4-week HPTCs, 190 with tacrolimus ointment, and 185 with 2-week HPTCs.

Cost-effectiveness ratios

The average cost-effectiveness ratio was most costly for 2-week HPTCs at \$9.08/DCD. The cost-effectiveness ratio for 4-week HPTC therapy using the average AWP was \$6.80, and ranged from \$5.85/DCD to \$7.59/DCD depending on the specific agent. Overall costs per DCD for tacrolimus ointment were within the range of the cost-effectiveness for 4-week HPTC therapy (\$6.97/DCD), and tacrolimus oint-

ment was more cost-effective compared with 4 of the 10 individual HPTC agents (halcinonide, halobetasol, diflorasone, and betamethasone augmented formulation; data not shown).

Incremental cost-effectiveness ratios are not meaningful in the base case because none of the therapies provides additional DCDs at additional cost; each regimen that provides additional DCDs does so at a lesser cost. Because the simulated patients had failed medium-potency topical corticosteroids, it would not be clinically reasonable to calculate the cost-effectiveness of no therapy (ie, nonprescription treatment) as a comparator for incremental cost-effectiveness ratios.

Sensitivity analyses

The different cost-effectiveness of the 2 HPTC regimens indicates that cost-effectiveness ratios were sensitive to the duration of continuous therapy allowed with HPTCs. Comparing 4-week HPTCs and tacrolimus, the model was sensitive to the relapse rate of patients being treated with tacrolimus ointment, and the costs and efficacy rate of secondary treatment. Adjusting for DCDs that occurred during the primary treatment periods was slightly favorable to tacrolimus ointment cost-effectiveness (data not shown).

Probability of relapsing from the disease-controlled state. In the base case model, 50% of patients who achieved disease control with either primary therapy remained in remission at the end of 4 weeks. A sensitivity analysis varying the probability of remaining disease-controlled from 0% to 100% simultaneously across treatment groups revealed nearly no impact on the incremental cost-effectiveness of the treatments. However, according to the physician panel, the anticipated relapse rates of the treatment groups were unlikely to be equivalent. The panel believed the probability of relapsing from the disease-controlled state was higher if the patient had most recently been treated with corticosteroids rather than tacrolimus ointment. A sensitivity analysis varying the probability that tacrolimus ointment had a longer-lasting effect (while keeping that of HPTCs constant) demonstrated that higher rates of continuation in the disease-controlled state after tacrolimus ointment treatment yielded correspondingly better cost-effectiveness ratios (data not shown).

Cost and efficacy of secondary treatment.

The base case cost of 2 weeks of secondary treatment was set at \$128.10. Because of the wide range of possible secondary treatments, the base case efficacy rate for secondary treatments was set at 0% (ie, the secondary treatment did not yield any addi-

tional DCDs). For the comparison of 4-week HPTC and tacrolimus therapies, a 2-way sensitivity analysis was conducted varying the cost of secondary treatment from \$0 to \$300 per 2 weeks while varying the efficacy rate of secondary treatment from 0% to 100%. The analysis revealed that a combination of high costs and low efficacy of secondary treatment yielded poorer cost-effectiveness ratios for HPTCs compared with tacrolimus ointment (Fig 2). This was expected because patients using HPTCs spent more time using secondary therapy than did patients receiving tacrolimus ointment.

DISCUSSION

AD has a profound financial impact on patients, families, and society as a whole.³⁻⁶ Most health care systems currently place great importance not only on the efficacy of an intervention, but also its cost. Cost-effectiveness analyses are becoming increasingly important to allow patients, physicians, and payers to evaluate trade-offs between clinical efficacy and financial impacts.

Our study finds that tacrolimus ointment is more cost-effective if class I/II HPTC use is restricted to 2-week intervals. Tacrolimus ointment reduces time and costs associated with secondary therapy, physician costs, and total costs, thereby offsetting the higher costs of the tacrolimus itself. Total efficacy as measured by DCDs also is higher.

If HPTC therapy is prolonged to 4-week treatment intervals, tacrolimus ointment is similar in cost-effectiveness. The cost-effectiveness ratios of 4-week HPTCs range from \$5.85/DCD to \$7.59/DCD, and tacrolimus ointment yields a cost-effectiveness ratio of \$6.97/DCD. The average cost-effectiveness ratio for tacrolimus ointment is slightly higher than that on the basis of the average AWP of the entire group of HPTCs (\$6.80); however, tacrolimus ointment has better cost-effectiveness ratios than 4 of the 10 agents in the class shown in Table I.

We find that under base case assumptions, total DCDs are similar among patients assigned to HPTCs or to tacrolimus ointment. From the third-party perspective, total costs for patients treated with tacrolimus ointment are lower than for patients undergoing 2-week HPTC treatment, and similar to patients undergoing 4-week HPTC treatment. Although tacrolimus ointment generally is more expensive than most HPTCs on a per-gram basis, patients who are treated with tacrolimus ointment are able to maintain primary therapy and avoid costly secondary treatments.

The annual mean expenditure per patient determined by this model is consistent with data found in our retrospective patient database study. In the da-

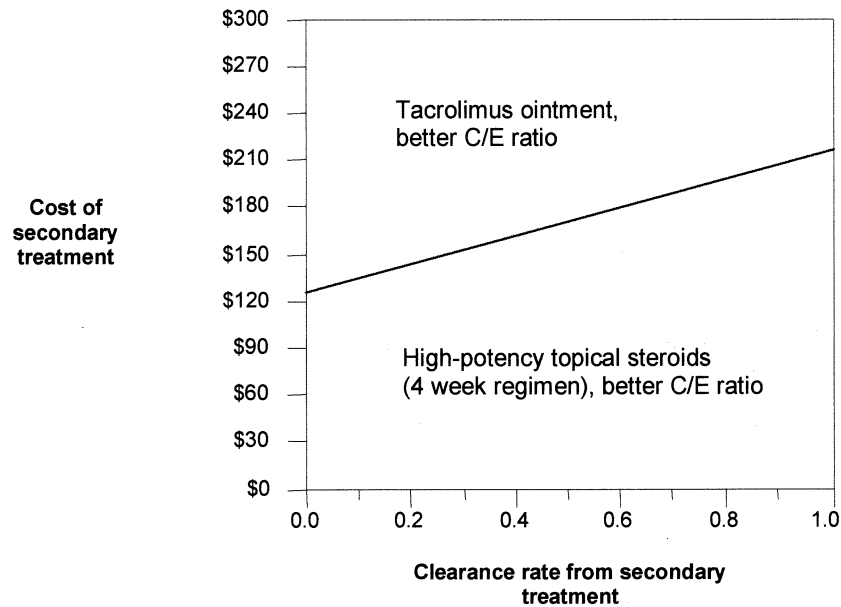


Fig 2. Two-way sensitivity analysis of change in cost and efficacy rate of secondary treatment on cost-effectiveness (*C/E*) of primary treatments; comparison between 4-week high-potency topical corticosteroid (HPTC) and continuous tacrolimus ointment therapy. Base case value for cost of 2 weeks of secondary treatment was \$128.10 and efficacy of secondary treatment in achieving disease-controlled state was set at 0. Two-way sensitivity analysis was conducted varying cost of secondary treatment from \$0 to \$300 and efficacy rate from 0% to 100%. When cost of and clearance rate from secondary treatment intersects at point above line, tacrolimus ointment has better *C/E* ratio; conversely, for points below line, 4-week HPTCs has better *C/E* ratio.

tabase study, which included patients with AD of differing disease severities, annual mean expenditure in 1997 and 1998 were estimated at \$580 per patient in the private-insurance population and \$1250 per patient in a Medicaid population.⁵ In this article, the model examines only patients with moderate to severe AD and finds that their annual mean expenditures ranged from \$1317 to \$1682 for the topical corticosteroid treatment group and \$1323 for the tacrolimus ointment treatment group. As expected, the adult patients in our model, with greater severity of disease, have higher annual costs of treatment than do patients of all ages and severities in a large database.⁵ Our model is limited to adult patients because pediatric patients typically are not treated with HPTCs.

Topical corticosteroids in the past have been considered the mainstay of treatment for AD. Unfortunately, quantifying the effectiveness of topical corticosteroid therapy is challenging. There are no standards in study design or definitions of end points. Furthermore, because duration of therapy is restricted because of concerns of side effects, observation periods can vary significantly, often being as short as 1 or 2 weeks.

In contrast to the rigorous studies of tacrolimus

ointment that report patient safety, efficacy, and quality of life during several months,^{14-17,26} the lack of quality data on HPTCs made it challenging to conduct a comparative cost-effectiveness analysis. Head-to-head clinical efficacy data were unavailable, and a number of assumptions had to be made. To overcome the lack of consistently defined end points, we quantified treatment efficacy by using DCDs.

To ensure the rigor of our model and results, several sensitivity analyses were performed. For example, many treatments can be used as second-line therapies for patients with moderate to severe AD. In the base case, secondary treatment cost was set as a common regimen of a mid-potency topical corticosteroid and an oral antibiotic. This cost assumption is conservative, as there are a number of expensive secondary treatments used in treating patients with AD (eg, phototherapy). As a result of the wide range of second-line therapies, efficacy rates for secondary treatment were set to 0 under base case assumptions. In a sensitivity analysis, a combination of low costs and high efficacy for secondary treatment caused topical corticosteroid treatment to be more cost-effective. Conversely, expensive secondary therapies resulted in better cost-effectiveness for

tacrolimus therapy because patients who received tacrolimus used less secondary treatment.

We also used conservative assumptions for other variables. Under base case assumptions, relapse rates for HPTCs and tacrolimus ointment were set equally at 50%. However, the physician panel believed relapse after tacrolimus treatment to be lower than relapse associated with topical corticosteroid use. Incorporating the panel's opinion would have benefitted the outcome of tacrolimus ointment. Furthermore, the base case model did not account for the possibility of DCDs during primary therapy. Incorporating intratreatment DCDs was slightly favorable to tacrolimus ointment cost-effectiveness because patients receiving tacrolimus remain in primary treatment for longer durations throughout the study period.

Costs not examined in this study included direct, nonmedical costs and indirect costs. Also, the model did not incorporate costs of side effects nor did it address long-term side effects. These costs were not included in the analysis because of the time period of the analysis (52 weeks), and the complexity of estimating the frequency, severity, and costs associated with these events. In general, these omissions were conservative, biased in favor of HPTCs for which concerns of side effects are greater.

The cost-effectiveness of tacrolimus ointment varies with practice patterns. Tacrolimus ointment is more cost-effective in situations in which: (1) treatment with HPTCs is limited to shorter durations; (2) higher-cost HPTCs are used as an alternative to tacrolimus; (3) secondary treatments are of higher cost or lesser efficacy; and (4) there are lower relapse rates after tacrolimus ointment therapy compared with HPTCs. Physicians may examine their own regimens and use our sensitivity analyses to estimate the cost-effectiveness of tacrolimus in their practices.

REFERENCES

1. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema. *Lancet* 1998;351:1225-32.
2. Laughter D, Istvan JA, Tofte SJ, Hanifin J. The prevalence of atopic dermatitis in Oregon schoolchildren. *J Am Acad Dermatol* 2000;43:649-55.
3. Lapidus C, Schwarz D, Honig P. Atopic dermatitis in children: who cares? Who pays? *J Am Acad Dermatol* 1993;28:699-703.
4. Herd R, Tidman M, Prescott R, Hunter J. The cost of atopic eczema. *Br J Dermatol* 1996;135:20-3.
5. Ellis CN, Drake LA, Prendergast MM, Abramovits W, Boguniewicz M, Daniel CR, et al. Cost of atopic dermatitis and eczema in the United States. *J Am Acad Dermatol* 2002;46:361-70.
6. Kemp A. Atopic eczema: its social and financial costs. *J Paediatr Child Health* 1999;35:229-31.
7. Tofte SJ, Hanifin JM. Current management and therapy of atopic dermatitis. *J Am Acad Dermatol* 2001;44:S13-6.
8. Pierard GE, Pierard-Franchimont C, Mosbah TB, Estrada JA. Adverse effects of topical corticosteroids. *Acta Derm Venereol* 1989;69:26-30.
9. Gilbertson EO, Spellman MC, Piacquadio DJ, Mulford MI. Super potent topical corticosteroid use associated with adrenal suppression: clinical considerations. *J Am Acad Dermatol* 1998;38:318-21.
10. Drake LA, Dinehart SM, Farmer ER, Goltz RW, Graham GF, Hordinsky MK, et al. Academy guidelines: guidelines of care for the use of topical glucocorticosteroids. *J Am Acad Dermatol* 1996;35:615-9.
11. Physicians' Desk Reference. Montvale (NJ): Medical Economics; 2000.
12. Yoshiike T, Aikawa Y, Sindhvananda J, Ogawa H. A proposed guideline for psoralen photochemotherapy (PUVA) with atopic dermatitis: successful therapeutic effect on severe and intractable cases. *J Dermatol Sci* 1993;5:50-3.
13. Naeyaert JM, Lachapelle JM, Degreef H, de la Brassinne M, Heenen M, Lambert J. Cyclosporine in atopic dermatitis: review of the literature and outline of a Belgian consensus. *Dermatology* 1999;198:145-52.
14. Alaiti S, Kang S, Fiedler VC, Ellis CN, Spurlin DV, Fader D, et al. Tacrolimus (FK506) ointment for atopic dermatitis: a phase I study in adults and children. *J Am Acad Dermatol* 1998;38:69-76.
15. Kang S, Lucky AW, Pariser D, Lawrence I, Hanifin JM. Long-term safety and efficacy of tacrolimus ointment for the treatment of atopic dermatitis in children. *J Am Acad Dermatol* 2001;44(Suppl):S58-64.
16. Hanifin JM, Ling MR, Langley R, Breneman D, Rafal E, and the Tacrolimus Ointment Study Group. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part I, efficacy. *J Am Acad Dermatol* 2001;44(Suppl):S28-38.
17. Paller A, Eichenfield LF, Leung DYM, Stewart D, Appell M, and the Tacrolimus Ointment Study Group. A 12-week study of tacrolimus ointment for the treatment of atopic dermatitis in pediatric patients. *J Am Acad Dermatol* 2001;44(Suppl):S47-57.
18. Ellis CN, Reiter KL, Wheeler JRC, Fendrick AM. Economic analysis in dermatology. *J Am Acad Dermatol* 2002;46:271-83.
19. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the panel on cost-effectiveness in health and medicine. *JAMA* 1996;276:1253-8.
20. Jolicoeur LM, Jones-Grizzle AJ, Boyer JG. Guidelines for performing a pharmacoeconomic analysis. *Am J Hosp Pharm* 1992;49:1741-7.
21. Pettiti D. Meta-analysis, decision analysis, and cost-effectiveness analysis. 2nd ed. New York: Oxford University Press; 2000.
22. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making* 1993;13:322-8.
23. De Rie MA, de Hoop D, Jonsson L, Bakkers EJM, Sorenson M. Pharmacoeconomic evaluation of calcipotriol (Daivaonex/Dovonex) and UVB phototherapy in the treatment of psoriasis. *Dermatology* 2001;202:38-43.
24. Ellis CN, Reiter KL, Bandekar RR, Fendrick AM. Cost-effectiveness comparison of therapy for psoriasis with a methotrexate-based regimen versus a rotation regimen of modified cyclosporine and methotrexate. *J Am Acad Dermatol* 2002;46:242-50.
25. Marchetti A, LaPensee K, An P. A pharmacoeconomic analysis of topical therapies for patients with mild-to-moderate stable plaque psoriasis: a US study. *Clin Ther* 1998;20:851-69.
26. Drake L, Prendergast M, Maher R, Breneman D, Korman N, Sato Y, et al. The impact of tacrolimus ointment on health-related quality of life of adult and pediatric patients with atopic dermatitis. *J Am Acad Dermatol* 2001;44(Suppl):S65-72.
27. Bickers DR. A comparative study of amcinonide and halcinonide in the treatment of eczematous dermatitis. *Cutis* 1984;34:190-4.
28. Delescluse J, van der Endt J. A comparison of the safety, tolera-

- bility, and efficacy of fluticasone propionate ointment, 0.005%, and betamethasone-17,21-dipropionate ointment, 0.05%, in the treatment of eczema. *Cutis* 1996;57:32-8.
29. Guenther L, Solomon AR, Voorhees JJ. A controlled comparison of amcinonide cream 0.1% and halcinonide cream 0.1% in the treatment of eczematous dermatitis. *Cutis* 1981;28:461-2,464,467.
 30. Johansson EA, Stiger TR. Comparative efficacy of once a day diflorasone diacetate and twice a day betamethasone valerate ointment applications in eczematous dermatitis. *Curr Med Res Opin* 1984;9:259-64.
 31. Lawless J, Stubbs S. Comparative efficacy of once-a-day diflorasone diacetate and t.i.d. hydrocortisone in treating eczematous dermatitis. *Curr Ther Res* 1978;23:159-65.
 32. Lupton ES, Abbrecht MM, Brandon ML. Short-term topical corticosteroid therapy (halcinonide ointment) in the management of atopic dermatitis. *Cutis* 1982;30:671-5.
 33. Maloney JM, Morman MR, Stewart DM, Tharp MD, Brown JJ, Rajagopalan R. Clobetasol propionate emollient 0.05% in the treatment of atopic dermatitis. *Int J Dermatol* 1998;37:142-4.
 34. Marchesi E, Rozzoni M, Pini P, Cainelli T. Comparative study of mometasone furoate and betamethasone dipropionate in the treatment of atopic dermatitis. *G Ital Dermatol Venereol* 1994;129:9-12.
 35. Du Vivier A, Stoughton RB. Acute tolerance to effects of topical glucocorticosteroids. *Br J Dermatol* 1976;94:25-32.
 36. Tacrolimus Clinical Study Report. Data on file, Fujisawa Healthcare Inc, Deerfield, IL.
 37. Van Der Meer JB, Glazenburg EJ, Mulder PG, Eggink HF, Coenraads PJ. The management of moderate-to-severe atopic dermatitis in adults with topical fluticasone propionate. *Br J Dermatol* 1999;140:1114-21.
 38. Red Book. Montvale (NJ): Medical Economics; 2001.
 39. National Physician Fee Schedule Relative Value File. Chicago, IL: American Medical Association; 2000.

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