Comparisons of efficacy and cost-effectiveness of topical immunomodulators in the management of atopic dermatitis

Abramovits W, Boguniewicz M, Prendergast M M, Tokar M, Tong K B

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of topical immunomodulators as monotherapy for the treatment of patients with moderate atopic dermatitis (AD). The topical immunomodulators compared were tacrolimus ointment and pimecrolimus cream.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with moderate AD not responsive to, or not well controlled with topical corticosteroids. "Not well-controlled AD" was characterised by a lower than 75% improvement from baseline disease, based on physician global assessment.

Setting
The setting was primary care. The economic study was conducted in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 2001 and 2002. The resource use data related to 2002. The prices used related to 2002.

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of completed studies. Some estimates of effectiveness were based on opinion.

Modelling
A Markov model was used to determine the costs, outcomes and cost-effectiveness ratios for each treatment. The model consisted of three states:

- primary treatment with tacrolimus or pimecrolimus;
- secondary treatment for not well-controlled patients, consisting of oral cephalexin and mid-potency topical steroids; and
- disease-controlled, prescription-free treatment, in which the patients showed more than a 75% improvement from baseline disease.
The duration of the model was 52 weeks. Each cycle lasted 4 weeks, with the exception of the primary treatment state. This was assumed to last either 2 or 4 weeks, depending on the (likely) success of the treatment.

**Outcomes assessed in the review**
The outcome assessed in the review included success rates for tacrolimus (expressed as a greater than 75% improvement from baseline disease). Moreover, since there were no published data on the success rates for pimecrolimus, the authors calculated the relative efficacy of tacrolimus and pimecrolimus on the basis of published studies comparing the efficacy of each agent with that of a vehicle-control, using the Eczema Area and Severity Index (EASI) scores. This was necessary since there were no studies directly comparing the efficacy of the two immunomodulators.

**Study designs and other criteria for inclusion in the review**
It appears that most of the effectiveness evidence came from pivotal phase III studies.

**Sources searched to identify primary studies**
Not stated.

**Criteria used to ensure the validity of primary studies**
Not stated.

**Methods used to judge relevance and validity, and for extracting data**
Not stated.

**Number of primary studies included**
Four primary studies were included in the review.

**Methods of combining primary studies**
The results of the primary studies were combined using a narrative method. The authors combined the results of studies examining the efficacy of tacrolimus and pimecrolimus compared with vehicle-controls, in order to estimate the relative efficacy of the two agents.

**Investigation of differences between primary studies**
The authors adopted the efficacy rates (EASI scores) for the two alternative therapies from studies with similar study design (randomised, double-blind, vehicle-controlled, clinical trials), patient populations (paediatric patients), study period, efficacy end points and sample size. However, they reported that there were differences in the disease severity at baseline and the duration of treatment. No further analysis of the studies was performed.

**Results of the review**
The efficacy of tacrolimus (75% improvement) was found to be 36% at week 2 and 52% at week 4.

EASI changes referred to the relative efficacy of each agent with respect to a vehicle-control.

At week 2, the change in EASI score for pimecrolimus was 65% of that for tacrolimus (-4.4 versus -6.8). At week 4, this percentage was 61% (-5.5 versus -9.0).

Using these relative EASI scores, the efficacy for pimecrolimus was calculated to be 23% at week 2 and 32% at week
Methods used to derive estimates of effectiveness
A panel of physicians made estimates of effectiveness and key assumptions.

Estimates of effectiveness and key assumptions
The efficacy rates for secondary therapy were 0% after 4 weeks of treatment.

The relapse rates following treatment success (disease control) were 50% after 4 weeks.

A key assumption was that the overall outcomes from published clinical trials represented the outcomes for moderate disease patients, in spite of the fact that the trials had recruited patients with varying severity of disease.

Additional assumptions involved resource use and changes in patient management.

Measure of benefits used in the economic analysis
The summary benefit measure used in the analysis was the disease-controlled days (DCD) on treatment. The DCDs represented days in which patients did not require primary prescription topical therapy. They were derived using modelling and no discounting was applied.

Direct costs
The direct costs measured were consistent with the study perspective stated, which was that of a third-party payer. The costs consisted of primary drug costs, secondary treatment costs and physician costs. The costs of over-the-counter medication and non-medical costs, such as transportation expenses, were excluded. The quantities were not analysed separately from the unit costs. Resource use for every state of the model was based on expert opinion. The total resource use was derived using modelling. The medical resources costs and drug prices were based on published average wholesale prices (AWP) as at September 2002. All of the prices referred to 2002. Discounting was not carried out, which was appropriate since the model estimated the total costs of therapy for 52 weeks.

Statistical analysis of costs
No statistical analysis of the costs was performed. The costs were treated deterministically.

Indirect Costs
The indirect costs were not included in the analysis.

Currency
US dollars ($).

Sensitivity analysis
A sensitivity analysis was carried out to assess the impact of key variables on the results. The variables examined were the relative efficacy between tacrolimus and pimecrolimus (the effect of alternative calculations was explored), the transition probabilities used in the model, and the costs of the two agents. The type of analysis used was not specified. Presumably, one-way analyses were conducted. In addition, a threshold analysis on the relative efficacy between pimecrolimus and tacrolimus was carried out. The ranges selected were not justified, and the ranges of the variables examined were not reported.
Estimated benefits used in the economic analysis
During the 52-week period, patients receiving tacrolimus experienced 190 DCDs while those receiving pimecrolimus experienced 137 DCDs. Possible side effects of treatment were not considered in the analysis.

Cost results
During the 52-week period, the total costs of therapy were $1,393 for tacrolimus and $1,550 for pimecrolimus.

The costs of potential side effects were not incorporated when calculating the total costs.

Synthesis of costs and benefits
The costs and benefits were combined separately for each alternative therapy, so that an average cost-effectiveness ratio was estimated for each agent. The average cost-effectiveness ratio was $7.34 per DCD for tacrolimus, and $11.34 per DCD for pimecrolimus. These ratios, in practice, compared the cost-effectiveness between each agent and "no method". No further incremental analysis was performed to show the cost-effectiveness of one method compared with the other. However, this was not necessary, as the results indicated that tacrolimus was the dominant therapy (more effective and less costly than pimecrolimus).

The sensitivity analysis showed that the model was sensitive to the relative efficacy of the two agents. Thus, if the efficacy of pimecrolimus rose to 90% of the efficacy of tacrolimus, then pimecrolimus would be equal to tacrolimus in terms of cost-effectiveness. The cost-effectiveness ratios reported were also sensitive to the drug costs. Changes in the other variables examined had no effect on the results of the analysis.

Authors' conclusions
Tacrolimus was more cost-effective than pimecrolimus for the treatment of moderate atopic dermatitis (AD).

CRD COMMENTARY - Selection of comparators
The choice of the comparators was not explicitly justified. However, both treatments had been approved for marketing in the USA for the treatment of AD only one year before the study was published. The target population differed between the two agents, but patients with moderate AD were a target group for both. Hence, the two therapies appear to have represented alternative choices for a sub-group of patients with AD. This justified the comparison in terms of the cost-effectiveness. You should decide whether the treatments represent valid comparators in your own setting.

Validity of estimate of measure of effectiveness
It was not stated that a systematic review of the literature had been undertaken. The effectiveness data were combined to estimate possible values for missing data. More specifically, the relative efficacy of the two alternatives was estimated by combining the results of studies that compared each agent with a vehicle-control. The authors investigated similarities and differences between the primary studies, but the way they combined the data may have introduced bias into the analysis. However, since there were no primary studies directly comparing the two interventions, this synthesis of the data was probably justified. Moreover, alternative methodologies were used to estimate the relative efficacy of the two agents, and the results were tested in a sensitivity analysis. A panel of physicians agreed on key assumptions and some transition probabilities. No details on the process by which the physicians were selected, or the procedures used to derive such estimates, were reported.

Validity of estimate of measure of benefit
The estimation of benefits was modelled. The Markov model used was appropriate for the study question, as it incorporated all possible states relating to the treatment of moderate AD. However, the benefit measure appears to have been specific to the disease considered in the study. This makes comparisons with the benefits of other health care interventions difficult.
Validity of estimate of costs
The study perspective was stated to be that of a third-party payer. Given that perspective, all the relevant categories of costs appear to have been included in the analysis. The costs and the quantities were not reported separately, which would make it difficult to replicate the study in other settings. The costs were treated deterministically and only a sensitivity analysis of the drug costs was conducted. The ranges used and the results were not reported. Discounting was not carried out, which was appropriate, as the model had a time horizon of 52 weeks. The price year was reported, thus permitting reflation exercises.

Other issues
The authors compared their results with those of other studies, but to a limited extent only, as they stated that there were no published studies directly comparing the two agents. The issue of the generalisability of the results to other settings was not addressed. The results of the analysis were adequately reported. However, they were presented as cost-effectiveness ratios for each comparator separately, and no incremental analysis was performed. Nonetheless, because one option was dominant (less costly, more effective), an incremental analysis was not necessary, although the dominance of one treatment over the other was not explicitly stated.

The study conclusions referred generally to a population of patients with moderate disease. However, the authors acknowledged that the effectiveness estimates were derived mainly from studies that enrolled paediatric patients, and the outcomes in adults might be different. This fact may limit the generalisability of the results to paediatric patients only. Another limitation of the study was that, although its target population was patients with moderate AD, effectiveness estimates were adopted from studies that enrolled patients with various levels of disease severity. Despite its limitations, the study appears to have been the first attempt to directly compare two new agents for the treatment of patients with moderate AD.

Implications of the study
The authors suggested that their study provides a framework for the evaluation of the cost-effectiveness of the two treatments, as there were no other studies that directly compared the two interventions.

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Bibliographic details

Other publications of related interest

Indexing Status
Subject indexing assigned by CRD

MeSH
Adjuvants, Immunologic /pharmacology /therapeutic use /economics /administration & dosage; Adolescent; Adrenal Cortex Hormones /administration & dosage /therapeutic use; Adult; Child; Clinical Trials as Topic; Costs and Cost Analysis; Dermatitis, Atopic /drug therapy /prevention & control; Drug Costs; Eczema; Humans; Placebos; Sensitivity and Specificity; Tacrolimus /pharmacology /therapeutic use /economics /administration & dosage

AccessionNumber
NHS Economic Evaluation Database (NHS EED)