Cost-utility analysis of maintenance treatment with tacrolimus ointment in adults and children with moderate and severe atopic dermatitis

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ISPOR 15th Annual International Meeting, 15-19 May 2010

BACKGROUND

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disease. The main symptom is itch, which may be intense, causing excessive scratching resulting in damaged skin with erosions, bleeding, and a susceptibility to infection. AD is reported to reduce quality of life through sleep deprivation (due to itch, and resultant scratching), and can have a detrimental impact on social activities and personal relationships.[1]

In addition to the substantial personal burden, a systematic review conducted in 2008 evaluated direct and indirect costs of AD in the US, reporting a financial burden between $364 million and $3.8 billion per year.[2]

Topical corticosteroids are currently the mainstay of treatment for AD, although the long-term use of steroids is limited due to poor tolerability such as skin atrophy and tachyphylaxis.[3] Other treatment options include oral therapies (such as sedative antihistamines to help the patient sleep, oral steroids such as prednisolone and immune suppression with ciclosporin or azathioprine), topical calcinuerin inhibitors (TCIs) and phototherapy. Treatment is usually administered in reaction to a disease exacerbation (DE), also known as a flare. The aim of treatment is to control DEs and maintain longer periods of remission.[4]

Tacrolimus ointment for moderate and severe AD in adults and children (≥ 2 years)[5,6]

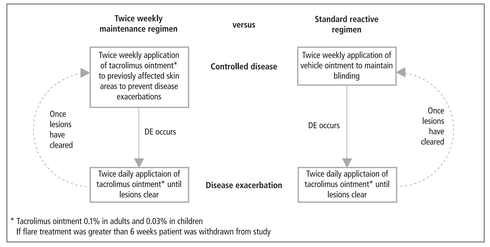
Tacrolimus ointment (a TCI) was initially indicated for the treatment of moderate and severe AD, administered in response to DEs (referred to here as a reactive regimen), in adults and children in whom conventional therapy, such as topical steroids, is not effective or is poorly tolerated.

Recently, tacrolimus ointment was approved in Europe for twice-weekly application to previously affected skin in patients with moderate or severe atopic dermatitis (≥ 4 DEs / year). The approval of this 'maintenance regimen' was based on data from two Phase III RCTs (the 'CONTROL' trials) that evaluated the efficacy and safety of tacrolimus ointment 0.1% and 0.03% in adults and children, respectively.[5,6] After an initial open-label reactive treatment period with twice-daily tacrolimus ointment patients were randomised to receive twice-weekly tacrolimus ointment or vehicle; DEs were treated with open-label tacrolimus ointment twice-daily for 1–6 weeks until resolution (Figure 1).

The CONTROL studies demonstrated that compared with the reactive regimen, twice-weekly application of tacrolimus ointment:

- Reduced the number of DEs
- Increased the time between DEs
- Improved signs and symptoms
- Improved quality of life

Figure 1: The two treatment regimens



* Tacrolimus ointment 0.1% in adults and 0.03% in children
If flare treatment was greater than 6 weeks patient was withdrawn from study

Study objective

The aim of this *post hoc* cost-utility analysis was to evaluate the cost-effectiveness of the maintenance versus reactive regimen with tacrolimus ointment for moderate and severe AD, from the perspective of a third party payer (UK National Health Service).

METHODS

Model overview and data sources

A decision analytic model was constructed in Microsoft Excel using data from the CONTROL trials.[5,6] The analysis was performed from a UK perspective, where the suggested threshold for cost-effectiveness is £30,000/QALY.[7]

- The time horizon was 12 months
- Clinical data were taken from the CONTROL trials: the cost of tacrolimus ointment was applied to days in DE for maintenance and reactive regimens, and to disease-controlled days for the maintenance regimen (total days less those spent in DE)
- Utility data were derived from a published source:[8] for moderate, severe, and controlled AD, scores in adults were 0.99, 0.875 and 0.675, respectively, and scores in children were 0.98, 0.69 and 0.59, respectively
- Tacrolimus ointment costs were calculated as cost per gram (g), using costs taken from MIMS October 2009
- DE treatment days among patients who discontinued treatment before 12 months were estimated using data from a published source:[9] for moderate and severe AD, the average number of DEs/year were 8.3 and 11.1, respectively, and the average number of days in DE were 13.6 and 17.3, respectively
- Days of treatment and ointment use are shown in Tables 1 and 2
- Patients who discontinued treatment with tacrolimus ointment continued to incur other treatment costs for the remainder of the 12-month period modelled
- Estimates of resource use (see Table 3) among patients who discontinued treatment before 12 months were based on expert clinical opinion, with the following assumptions:
  - all patients require one dermatology outpatient visit
  - potent topical steroids are prescribed in primary care
  - phototherapy is undertaken by a dermatologist in a secondary care outpatient visit, and the cost does not vary with DE severity
  - the cost of an inpatient stay does not vary with DE severity

Model assumptions

- Emollient use was the same for the maintenance and reactive regimens
- Patients who discontinued treatment with tacrolimus ointment experience DEs based on the rate and duration reported by Zuberbier et al,[9] adjusted to the time spent in the discontinuation state during the 12-month period modelled
- Utility scores for moderate and severe AD were applied to the DE period only. A DE in patients with moderate or severe AD at baseline was assumed to have a utility score equal to that of patients with moderate or severe AD, respectively
- Adverse events were assumed to be equivalent for the maintenance and reactive regimens, and were not included in the model

Sensitivity analyses

One-way and probabilistic sensitivity analyses were conducted:

- In the one-way (univariate) sensitivity analysis, model parameters were individually varied between their minimum and maximum value and the incremental cost-effectiveness ratio (ICER) recorded. Minimum and maximum values were based on the 95% confidence interval for all parameters, apart from the utility values as confidence intervals were unavailable and could not be estimated. Utility values were varied randomly between a value of 0.5 and 1
- The probabilistic sensitivity analysis (multivariate) was based on Monte Carlo simulation techniques

Table 1: Days of treatment during the 12-month study period [5,6,9]

	Moderate AD		Severe AD	
	Adults	Children	Adults	Children
Days in DE				
Maintenance regimen	40.7	35.3	34.4	50.10
Standard regimen	64.0	68.7	94.8	69.20
Discontinuation rate (any reason)				
Maintenance regimen	33.3%	24.4%	37.1%	37.8%
Standard regimen	50.0%	38.5%	58.1%	47.2%
Time to discontinuation (days) †				
Maintenance regimen	120.3	201.1	129.5	152.5
Standard regimen	98.6	146.8	84.1	180.8
Days in DE post discontinuation †				
Maintenance regimen	25.2	12.4	46.0	42.3
Standard regimen	41.2	26.0	85.9	45.7

† Calculation based on the time to discontinuation and the discontinuation rate. Data from clinical trials have been reproduced in this table as they represent inputs into the decision-analytic model
AD, atopic dermatitis; DE, disease exacerbation

Table 2: Mean tacrolimus ointment usage per day [5,6]

	Moderate AD		Severe AD	
	Adults	Children	Adults	Children
DE treatment (g/day)				
Maintenance regimen	4.1	2.9	3.6	3.0
Standard regimen	5.0	2.4	6.3	5.4
Maintenance treatment (g/day) †				
Maintenance regimen (g / twice-weekly application equivalent)	1.1 (3.85)	0.81 (2.84)	1.4 (4.9)	1.0 (3.5)
Standard regimen	NA	NA	NA	NA

† Maintenance dose is presented in g/day however patients received this dose in twice-weekly applications
Abbreviations: AD, atopic dermatitis; DE, disease exacerbation; NA, not applicable

Table 3: Treatment options post tacrolimus ointment discontinuation: distribution (based on expert clinical opinion) and costs

	Moderate AD		Severe AD	
	Adults	Children	Adults	Children
Treatment distribution				
Phototherapy	40.57%	31.96%	36.65%	34.62%
Inpatient stay	7.95%	6.81%	14.81%	12.90%
Oral therapies	31.42%	24.55%	45.45%	31.51%
Topical steroids	20.06%	36.68%	3.09%	20.97%
Treatment costs				
Total oral therapy cost † per DE	£31.82	£15.50	£40.48	£19.72
Total topical steroid cost per DE	£2.80	£1.60	£3.11	£2.61
Phototherapy per DE §	£1,216			
Dermatology outpatient visit	£76 ¶			
GP surgery consultation ††	£27			
Cost per inpatient stay	£1,157 ¶			

† Average weighted cost of 3 typically used oral therapies; ciclosporin, prednisolone and azathioprine. Unit costs were taken from MIMS October 2009
†† GP surgery consultation without qualification costs (excluding direct care staff costs)
§ Calculated as 2 treatments per week over 8 weeks, that is, 16 dermatology outpatient visits
¶ NHS reference costs 2008/09
Abbreviations: AD, atopic dermatitis; DE, disease exacerbation

RESULTS

Base-case analysis

In the base-case analysis for both adults and children with moderate and severe AD, the maintenance regimen over 12 months with tacrolimus ointment was dominant over the reactive regimen (Table 4):

- Moderate AD: in adults, the maintenance regimen cost £623.38 less than the reactive regimen and gained an additional 0.01 QALYs; in children, the maintenance regimen cost £364.69 less and gained an extra 0.04 QALYs
- Severe AD: in adults, the maintenance regimen cost £1,559.60 less than the standard regimen and gained an additional 0.09 QALYs; in children, the maintenance regimen cost £102.35 less and gained 0.02 QALYs in children

Table 4: Base case results for adults and children with moderate and severe AD

	Moderate AD				Severe AD			
	Adults		Children		Adults		Children	
	Maintenance	Standard	Maintenance	Standard	Maintenance	Standard	Maintenance	Standard
Tacrolimus ointment costs	£298.58	£221.07	£207.77	£100.26	£315.32	£409.50	£244.44	£230.23
Cost of discontinuations	£1,133.33	£1,834.22	£457.69	£929.88	£1,723.87	£3,189.29	£1,438.87	£1,555.43
Total cost	**£1,431.91**	**£2,055.30**	**£665.45**	**£1,030.14**	**£2,039.19**	**£3,598.79**	**£1,683.31**	**£1,785.66**
Difference in costs	-£623.38		-£364.69		−£1,559.60		−£102.35	
Days of DE	65.90	105.20	47.67	94.68	80.36	180.66	92.35	114.95
QALY	0.97	0.96	0.94	0.90	0.92	0.83	0.88	0.86
Difference in QALYs ‡	0.01		0.04		0.09		0.02	
ICER §	Dominant		Dominant		Dominant		Dominant	

‡ A 0.01 QALY gain equates to c.3.7 additional days of perfect health per annum (0.01 x 365); a 0.09 QALY gain equates to 32.9 additional days of perfect health per annum (0.09 x 365)
§ ICER: incremental cost effectiveness ratio = incremental cost / incremental QALY gained. If the ICER is dominant the intervention under evaluation (tacrolimus ointment maintenance regimen) is both more effective and less costly than the comparator (tacrolimus ointment standard regimen)
Abbreviations: AD, atopic dermatitis; DE, disease exacerbation

Sensitivity analyses

One-way

The tacrolimus ointment maintenance regimen remained more effective and less costly than the reactive regimen in almost every scenario tested in univariate sensitivity analysis:

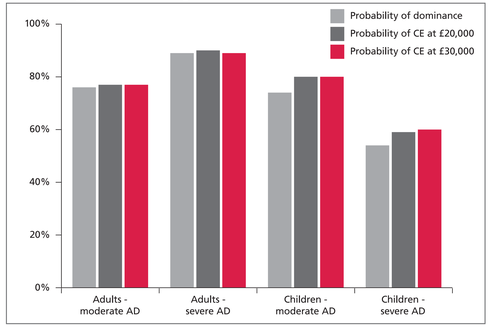
- The maintenance regimen remained dominant (with an ICER <£0) relative to the reactive regimen when the majority of parameters were varied between their upper and lower confidence interval
- Variables resulting in an ICER which exceeded £30,000 were: Days of DE for the reactive regimen in adults with moderate AD; and time to discontinuation for the maintenance regimen in children with severe AD

Probabilistic

The probability of the tacrolimus ointment maintenance regimen being dominant over the reactive regimen (figure 2):

- 76% for adults with moderate AD
- 89% for adults with severe AD
- 75% for children with moderate AD
- 54% for children with severe AD

Figure 2: Probability of cost-effectiveness (CE) with tacrolimus ointment for moderate and severe AD: maintenance regimen versus reactive regimen



DISCUSSION

The twice-weekly maintenance regimen versus the conventional reactive treatment regimen with tacrolimus ointment for moderate and severe AD was associated with fewer days in DE and was cost-saving. Indeed, the maintenance regimen now offers a treatment option that provides longer periods of remission and offers an economic benefit compared with a conventional reactive treatment regimen with tacrolimus ointment.

CONCLUSION

This analysis demonstrates that tacrolimus ointment applied twice-weekly as a maintenance treatment regimen is dominant over a conventional reactive treatment regimen with tacrolimus ointment in adults and children with moderate and severe AD, providing incremental health benefits at a lower cost.

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This research was funded by Astellas Pharma Europe Ltd