Value-Based Medicine, Comparative Effectiveness, and Cost-effectiveness Analysis of Topical Cyclosporine for the Treatment of Dry Eye Syndrome

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Objective: To assess the comparative effectiveness and cost-effectiveness (cost-utility) of a 0.05% emulsion of topical cyclosporine (Restasis; Allergan Inc, Irvine, California) for the treatment of moderate to severe dry eye syndrome that is unresponsive to conventional therapy.

Methods: Data from 2 multicenter, randomized, clinical trials and Food and Drug Administration files for topical cyclosporine, 0.05%, emulsion were used in Center for Value-Based Medicine analyses. Analyses included value-based medicine as a comparative effectiveness analysis and average cost-utility analysis using societal and third-party insurer cost perspectives.

Main Outcome Measures: Outcome measures of comparative effectiveness were quality-adjusted life-year (QALY) gain and percentage of improvement in quality of life, and for cost-effectiveness were cost-utility ratio (CUR) using dollars per QALY.

Results: Topical cyclosporine, 0.05%, confers a value gain (comparative effectiveness) of 0.0319 QALY per year compared with topical lubricant therapy, a 4.3% improvement in quality of life for the average patient with moderate to severe dry eye syndrome that is unresponsive to conventional lubricant therapy. The societal perspective incremental CUR for cyclosporine over vehicle therapy is $34,953 per QALY and the societal perspective average CUR is $11,199 per QALY. The third-party–insurer incremental CUR is $37,179 per QALY, while the third-party–insurer perspective average CUR is $34,343 per QALY.

Conclusions: Topical cyclosporine emulsion, 0.05%, confers considerable patient value and is a cost-effective therapy for moderate to severe dry eye syndrome that is unresponsive to conventional therapy.

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Approximately 14.6% of adults who are old enough to be eligible for Medicare in the Salisbury Study reported frequent dry eye symptoms, while in Taipei, Taiwan, the prevalence of dry eyes in an older population was found to be 33.7%. Among ophthalmic consultations in Germany, 25% of patients reported dry eye symptoms.

The morbidity associated with dry eyes (keratoconjunctivitis sicca) is considerable. Schiffman and colleagues assessed patients with dry eye syndrome with time-tradeoff utility analysis and found that the mean utility associated with mild dry eye disease was 0.81, similar to the quality of life associated with symptomatic human immunodeficiency virus infection. The utility associated with severe dry eye disease was 0.72, a quality-of-life diminution similar to that encountered with hemodialysis.

Patients with dry eye syndrome have more difficulty reading, carrying out professional work, using a computer, watching television, and driving compared with those without dry eyes. The burden of dry eye disease from both the prevalence and patient morbidity standpoints makes this a sizeable public health dilemma.

Multiple modalities have been used to treat dry eye disease, including topical tear and gel replacements, punctal plugs, canalicular ligation, and permanent punctal occlusion.

The underlying autoimmune pathophysiology of tear deficiency has been known for more than 2 decades. In some instances, treatments such as topical corticosteroid therapy in Sjogren syndrome and systemic immunosuppressants for autoimmune diseases like systemic lupus erythematosus, Sjogren syndrome, rheumatoid arthritis, and psoriatic arthritis have been shown to benefit dry eye syndrome.
In keeping with the autoimmune pathophysiology paradigm, a topical cyclosporine emulsion was developed for dry eye treatment. 

Cyclosporine, 0.05%, ophthalmic emulsion (Restasis; Allergan Inc, Irvine, California) is a topical immunomodulator with antiinflammatory properties. More specifically, it inhibits the activation of T cells, which release cytokines that damage lacrimal tissue.

To our knowledge, an in-depth cost-utility analysis has not been performed on the use of topical cyclosporine eye drops for the treatment of dry eye syndrome. It is the intention of the current study to objectively assess the (1) comparative effectiveness (conferred patient value), (2) average cost-effectiveness (compared with no treatment), and (3) incremental cost-effectiveness (compared with sham, or cyclosporine vehicle treatment) for the control patient’s (usual patient with dry eye disease) use of topical cyclosporine emulsion for the treatment of moderate to severe dry eye syndrome that is unresponsive to conventional therapies.

Value-based medicine is the practice of medicine based on the value conferred by health care interventions. Value is defined as the numerical improvement an intervention confers on a patient’s length of life and/or quality of life. The value conferred by ophthalmologic interventions typically occurs from improved quality of life rather than increased longevity.

<table>
<thead>
<tr>
<th>Level of Severity</th>
<th>Utility</th>
<th>SD</th>
<th>95% CI</th>
<th>OSDI</th>
<th>Similar Utilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>0.81</td>
<td>0.18</td>
<td>0.76-0.86</td>
<td>12-14</td>
<td>Severe migraines³</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.78</td>
<td>0.19</td>
<td>0.72-0.84</td>
<td>19-21</td>
<td>Ankylosing spondylitis⁴</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>0.75</td>
<td>0.21</td>
<td>0.71-0.79</td>
<td>32-35</td>
<td>Moderate to severe dyspnea⁴</td>
</tr>
<tr>
<td>Severe</td>
<td>0.72</td>
<td>0.23</td>
<td>0.65-0.77</td>
<td>46-48</td>
<td>Hemodialysis⁵</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OSDI, ocular surface disease index (the higher the index, the more severe the dry eye symptoms).

Inclusion Criteria
1. Schirmer test without anesthesia of 5 mm or less per 5 minutes in at least 1 eye (if Schirmer without anesthesia was 0 mm per 5 minutes, then Schirmer with nasal stimulation had to be more than 3 mm per 5 minutes in the same eye).
2. Corneal and interpalpebral conjunctival staining.
3. An Ocular Surface Disease Index with no more than 3 responses of “not applicable.”
4. An abnormal Subjective Facial Expression Score. The symptoms and signs had to be present despite the use of tear drops, gels, ointments, sympathomimetic agents, parasympathomimetic agents, and/or punctal occlusion.
5. The symptoms and signs had to be present despite the use of tear drops, gels, ointments, sympathomimetic agents, parasympathomimetic agents, and/or punctal occlusion.

Exclusion Criteria
1. Pregnancy.
2. Hypersensitivity to cyclosporine ophthalmic emulsion.
3. End-stage lacrimal gland disease (Schirmer less than 3 mm per 5 minutes with nasal stimulation).
4. Pterygium.
5. Use of temporary punctal plugs during the study.
6. Punctal occlusion within 3 months of entrance into the study.

Demographics
1. Women, 82%; Men, 18%.
2. Mean age, 58.7 years.
3. Ethnicity: White, 86%; African American, 3%; Asian, 3%; Hispanic, 8%.
4. Of the 877 patients enrolled in the 2 large trials, Sjogren syndrome was present in 270 (30.8%).

Data for adults using cyclosporine, 0.05%, ophthalmic emulsion were obtained from two 6-month, large, multicenter, randomized trials for moderate to severe dry eye disease; from 2 identical, multicenter, 6-month trials for the New Drug Application submitted by Allergan, Inc, to the Food & Drug Administration (FDA) and from additional studies. The clinical features of the combined patient cohort are illustrated in the Figure.

Patients were randomized to the use of (1) 0.05% cyclosporine ophthalmic emulsion, twice per day, (2) 0.1% cyclosporine ophthalmic emulsion twice per day, or (3) the vehicle of cyclosporine ophthalmic emulsion twice per day. Data for the 0.1% cyclosporine emulsion are not presented because this concentration was not approved by the FDA. Participants were permitted to use preservative-free artificial tears (Refresh Lubricant Eye Drops; Allergan Inc) as frequently as needed as an adjunct treatment in all study cohorts.

Total value gain is measured in quality-adjusted life-years (QALYs) and calculated by multiplying the years of utility gain by years of benefit duration. This total value gain, or comparative effectiveness, can be compared with that of any health care intervention, no matter how disparate.
Physician costs are based on the average 2007 Medicare Fee Schedule and are correlated with Current Procedural Terminology codes. Pharmaceutical costs are calculated using the 2007 average wholesale price.

Restasis (cyclosporine, National Drug Code 00023-9163-32) comes in a 32–daily use package with an average wholesale price of $112.43. Its daily cost is $3.30 and its yearly cost is $1276.43

For the use of 0.05% cyclosporine or the vehicle emulsion compared with no treatment, it is assumed that 5 physician visits (1 consultation and 4 follow-up visits) occur during the year. This yearly physician cost is $173 for a consultation + ($96 × 4 follow-up visits) = $558. The costs of the adverse events are presumed to be encompassed within the 4 follow-up visits. The total 1-year direct medical cost of using cyclosporine is therefore $1276 + $558 =$1834. It is not known whether cyclosporine treatment precludes the necessity of therapies such as punctal plugs or tarsorrhaphy, so these costs are not incorporated into the analysis, thereby allowing for a more conservative cost-utility ratio.

Vehicle Costs

The total direct medical costs for use of the vehicle are $90 for Refresh artificial tears plus $558 in physician costs, for a total cost of $648. The incremental cost of cyclosporine over the vehicle is $1834−$648 = $1186.

Net Present Value Analysis

Costs and QALY gain are accrued at the same rate annually, thus obviating the need for discounting with a net present value analysis.

Societal Cost Perspective

The societal cost perspective includes direct nonmedical costs such as transportation, baby-sitting, and caregiver costs. These costs are believed to be negligible for dry eye syndrome and are therefore not included in the current analysis.23

Indirect Costs

Concerning the indirect cost of diminished productivity, Kozma and colleagues found that the average person with dry eyes experiences 184 days of reduced productivity during the year. This diminished productivity, according to Kozma and colleagues, resulted in an estimated annual cost of $3362 per worker in the year 2000 (US dollars). Adjusted for inflation to 2007, this cost is $6466. When this cost is ameliorated by cyclosporine therapy, there is a net gain of $4632 ($1834−$6466) annually if every person who uses cyclosporine is rehabilitated to the point that they can work effectively. Nonetheless, this scenario is overly optimistic.

Increased Worker Productivity

The FDA data show that 6.0% of patients with moderate to severe dry eye syndrome that is unresponsive to standard therapy improve clinically to the point that the condition is almost cleared (90% global improvement), and 9.9% have a marked response (75% global improvement), for a total of 15.9% of patients who are likely to be able to work at normal productivity while using topical cyclosporine drops. Assuming this 15.9% and half of the additional
17.2% of patients with a moderate response (50% global improvement) are also able to work effectively with topical cyclosporine therapy, a total of 24.5% [15.9% + (17.2%/2)] of patients with dry eye syndrome using the 0.05% cyclosporine emulsion are consequently able to work at normal productivity. The concomitant re- eye syndrome using the 0.05% cyclosporine emulsion are conse-

Cost-Utility Analysis

Cost-utility analysis, also referred to as cost-effectiveness analysis, integrates the value of a medical intervention with its associated costs using the dollars per QALY (dollars expended per quality-adjusted life-year) or cost-utility ratio (CUR). An average CUR compares an intervention with no treatment while an incremental CUR compares one intervention with another. The incremental CUR is the most clinically relevant because preceding treatments are generally in place prior to the introduction of a new intervention (topical cyclosporine), as is the case for lubricants that are similar to the vehicle.

Criteria for the cost-effectiveness of health care interventions in the United States are based on "soft" standards in the peer-reviewed literature. It has been suggested in the United States that interventions with a CUR of less than $50 000 per QALY are cost-effective, while those with a CUR of less than $100 000 per QALY are cost-effective, and those with a CUR of less than $100 000 per QALY or more are not cost-effective.

**RESULTS**

**VALUE GAIN (COMPARATIVE EFFECTIVENESS)**

The total annual value conferred by cyclosporine topical emulsion for moderate to severe dry eye syndrome, including the disutility of 0.0016 QALY to account for adverse events, is 0.053 − 0.0016 = 0.0534 QALY. This correlates with a conferred value gain (comparative effec-

**Table 3. Adverse Events Associated With the Use of Topical Cyclosporine, 0.05%, Emulsion**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Incidence of AE, % (min/d[^d])</th>
<th>Days, %</th>
<th>Disutility of AE</th>
<th>QALY Loss From AE[^b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning eye</td>
<td>14.7 (10)</td>
<td>0.7</td>
<td>0.11</td>
<td>0.00011</td>
</tr>
<tr>
<td>Stinging eye</td>
<td>3.4 (10)</td>
<td>0.7</td>
<td>0.11</td>
<td>0.00003</td>
</tr>
<tr>
<td>Discharge from eye</td>
<td>3.1 (10)</td>
<td>0.7</td>
<td>0.04</td>
<td>0.00001</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>3.1 (60)</td>
<td>4.2</td>
<td>0.13</td>
<td>0.00017</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>2.9 (1440)</td>
<td>100.0</td>
<td>0.04</td>
<td>0.00116</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>1.70 (60)</td>
<td>4.2</td>
<td>0.18</td>
<td>0.00013</td>
</tr>
<tr>
<td>Eye pain</td>
<td>1 (10)</td>
<td>0.7</td>
<td>0.11</td>
<td>0.00001</td>
</tr>
<tr>
<td>Overall, No. (%)</td>
<td>85 (29)</td>
<td></td>
<td></td>
<td>0.0016[^c]</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Description</th>
<th>CPT Code[^4]</th>
<th>Cost, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office consultation</td>
<td>99244</td>
<td>173</td>
</tr>
<tr>
<td>Ophthalmic examination with treatment</td>
<td>92014</td>
<td>96</td>
</tr>
<tr>
<td>Cyclosporine, 1-y supply (NDC 00023-9163-32)</td>
<td>NA</td>
<td>1276</td>
</tr>
<tr>
<td>Refresh, preservative-free, 1-y supply (NDC 00023-0506-50)</td>
<td>NA</td>
<td>90</td>
</tr>
<tr>
<td>Incremental societal cost perspective, productivity saving for cyclosporine compared with its vehicle</td>
<td>NA</td>
<td>71</td>
</tr>
</tbody>
</table>

**Table 3. Adverse Events Associated With the Use of Topical Cyclosporine, 0.05%, Emulsion**

Abbreviations: AE, adverse event; QALY, quality-adjusted life-year.

[^d]: Minutes per day that the AE is encountered.
[^b]: The QALY loss per year is calculated as incidence of AE × percentage of day × disutility of AE.
[^c]: Utility (QALY) loss incurred by cyclosporine, 0.05%, emulsion.
The current study demonstrates that topical cyclosporine emulsion confers a 7.1% improvement in value (quality of life) referent to no treatment and a 4.3% incremental value gain referent to use of the cyclosporine vehicle. These value gains are considerably more than the 1% to 2% gain conferred by α-adrenergic blockers for the treatment of prostate hyperplasia and also compare favorably with the 4.0% gain conferred by the commonly prescribed hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) for the treatment of hyperlipidemias (Table 5).

**VALUE (COMPARATIVE EFFECTIVENESS)**

Overall, topical cyclosporine confers a value similar to that conferred by treatment with oral agents for systemic arterial hypertension. Despite the fact that the conferred value for topical cyclosporine occurs wholly as an improvement in quality of life while that of systemic antihypertensives occurs because of improvements in both quality of life and length of life, value-based medicine cost-utility analysis can still readily assess the comparative effectiveness of 2 such dissimilar interventions using the same outcomes of percentage of improvement in value and QALYs gained.

**COSTS**

A societal cost perspective is the most inclusive and ideally the best for health care cost-utility analyses, but unfortunately, which costs to include and the cost bases are not currently agreed on. Costs owing to the loss of employment productivity, however, can be identified and assessed as different between patients treated with cyclosporine and those who did not receive treatment.

Generally, the societal perspective yields a more favorable CUR than the third-party insurer perspective, such as the case herein. Despite differences, both the third-party insurer and societal cost perspectives in the current analysis resulted in cost-effective treatment strategies for topical cyclosporine emulsion therapy.

**COST-UTILITY**

The use of topical cyclosporine for the treatment of moderate to severe dry eye syndrome is cost-effective because it is well under the conventional US standard of $50 000 per QALY that most would likely agree is cost-effective. It has been noted, however, that many thousands of input and outcome combinations can be used in cost-utility analysis, with more than 4000 possible utility variants alone. While a comparison of diverse CURs is presented in Table 6, the observer can have greater confidence in the precise comparability of value-based medicine cost-utility analyses because they are standardized with patient time trade-off utilities, Medicare costs, and both third-party insurer and societal cost perspectives.

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**Table 5. Comparative Effectiveness of Interventions Across Health Care**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Indication</th>
<th>Value Gain, %&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Adrenergic blockers&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Prostate hyperplasia</td>
<td>1.2</td>
</tr>
<tr>
<td>Statins&lt;sup&gt;49&lt;/sup&gt; (HMG-CoA reductase inhibitors)</td>
<td>Hyperlipidemias</td>
<td>4.0</td>
</tr>
<tr>
<td>Laser photoablation&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Subfoveal choroidal neovascularization</td>
<td>4.4</td>
</tr>
<tr>
<td>Pegaptanib, intravitreal&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Subfoveal choroidal neovascularization</td>
<td>6.9</td>
</tr>
<tr>
<td>β-Adrenergic blockers&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Systemic arterial hypertension</td>
<td>7.1</td>
</tr>
<tr>
<td>Topical cyclosporine current study</td>
<td>Moderate to severe dry eye syndrome</td>
<td>12.8</td>
</tr>
<tr>
<td>Cataract surgery, second eye&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Cataract, second eye, 20/80 visual acuity</td>
<td>15.8</td>
</tr>
<tr>
<td>Ranibizumab, intravitreal&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Occult, subfoveal choroidal neovascularization</td>
<td>20.8</td>
</tr>
<tr>
<td>Cataract surgery, first eye&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Cataract, 20/80 visual acuity</td>
<td>20.8</td>
</tr>
</tbody>
</table>

Abbreviation: HMG-CoA, hydroxymethyl glutaryl coenzyme A.

<sup>a</sup>Value-based medicine cost-utility analyses.

**SOCIETAL COST PERSPECTIVE, AVERAGE COST-UTILITY**

The total direct medical cost associated with the use of cyclosporine emulsion is $1834. Integrating the $1236 gain from 24.5% of treated workers returning to full usual productivity, however, results in a net cost of $598 ($1834 - $1236). The societal cost perspective average CUR of cyclosporine emulsion for the treatment of moderate to severe dry eyes is therefore $598/0.0534 = $11 199 per QALY.

**THIRD-PARTY INSURER COST PERSPECTIVE, AVERAGE COST-UTILITY**

The total direct medical cost associated with the use of cyclosporine emulsion is $1834 compared with no treatment. The third-party insurer perspective average CUR of cyclosporine emulsion for the treatment of moderate to severe dry eyes is therefore $1834/0.0534 = $34 343 per QALY.

**SENSITIVITY ANALYSIS**

Sensitivity analyses were performed using the societal cost perspective, average CUR, and incremental CUR. These are shown in eTable 2.

The incremental cost-utilities range from $24 953 when the cost of cyclosporine is decreased by 25% to $46 604 when the value gain is decreased by 25%. The average cost-utilities range from $57 370 when 33.1% of treated patients are able to work at normal productivity to $34 343 when no treated patients are able to work at normal productivity. Because all CURs are less than the conventional US upper limits for cost-effectiveness, the analysis is considered to be robust.

**CYCLOSPORINE PRICING**

Pricing models for topical cyclosporine for the treatment of refractory moderate to severe dry eye disease are shown in eTable 3. Included are models using US, UK, and World Health Organization criteria.
Despite the use of societal or third-party insurer costs, the cost-utility for cyclosporine remains less than $50 000 per QALY for all of the sensitivity analyses, indicating that the overall analysis is robust. Using the conventional US upper limit of cost-effectiveness of $100 000 per QALY, the price of the drug could be increased by 175% before exceeding this limit. Using the average CUR, the cost of topical ocular cyclosporine could be increased up to 372% and still remain cost-effective. The Commission on Macroeconomics and Health of the World Health Organization suggests that an entity similar to the QALY, quality-adjusted life-year, is cost-effective. The possibility of a higher-risk population analysis herein is different from that in a clinic setting is also a potential weakness. This anomaly, however, is accounted for in the sensitivity analyses.

In summary, 0.05% ophthalmic cyclosporine emulsion provides a 4.3% improvement in quality of life over conventional lubricant therapy for the treatment of moderate to severe dry eye disease. The use of topical cyclosporine is a cost-effective treatment strategy for a common disease that, when unresponsive to conventional lubricant therapy, causes a marked diminution in quality of life.

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Author Contributions: Dr M. M. Brown and Ms H. C. Brown had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosures: Drs. M. M. and G. C. Brown report being shareholders in the Center for Value-Based Medicine. Allergan, Inc, is a client of the Center for Value-Based Medicine and supported the current study with a grant. Ms H. C. Brown reported no financial disclosures.

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Role of the Sponsor: Neither Allergan, Inc, the Center for Value-Based Medicine, nor the Eye Research Institute had any say in the design of the study, execution of the study, the interpretation of data, or writing of the manuscript.


Table 6. Comparison of Cost-Utility Ratios of Topical Cyclosporine Therapy for Dry Eye With Other Interventions Across Health Care6

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Cost-Utility Ratio, $/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract surgery, first eye56</td>
<td>2472</td>
</tr>
<tr>
<td>Cataract surgery, second eye57</td>
<td>3240</td>
</tr>
<tr>
<td>Cyclosporine for moderate to severe dry eye syndrome58</td>
<td>11 199</td>
</tr>
<tr>
<td>Computer tomography for equivocal neurologic symptoms59</td>
<td>24 790</td>
</tr>
<tr>
<td>Cyclosporine for moderate to severe dry eye syndrome58</td>
<td>34 953</td>
</tr>
<tr>
<td>Chemoprophylaxis after occupational HIV exposure</td>
<td>48 559</td>
</tr>
<tr>
<td>Intravitreal ranibizumab for occult or minimally classic subfoveal choroidal neovascularization60</td>
<td>50 691</td>
</tr>
<tr>
<td>Treating mildly symptomatic Herpes zoster55 in a 70-y-old patient</td>
<td>59 122</td>
</tr>
<tr>
<td>Intravitreal pegaptanib for the treatment of subfoveal choroidal neovascularization61</td>
<td>66 978</td>
</tr>
<tr>
<td>Treating mildly symptomatic Herpes zoster55 in a 40-y-old patient</td>
<td>129 574</td>
</tr>
<tr>
<td>Magnetic resonance imaging for equivocal neurologic symptoms53</td>
<td>135 815</td>
</tr>
<tr>
<td>Use of interferon-β 1B for the treatment of progressive relapsing multiple sclerosis62</td>
<td>222 068</td>
</tr>
<tr>
<td>Three-day chemoprophylaxis for patients with a prosthetic joint prior to dental treatment63</td>
<td>1 640 600</td>
</tr>
</tbody>
</table>

POTENTIAL WEAKNESSES

As with any analysis, there are inherent weaknesses in the current study. The absence of randomized clinical trial data beyond 6 months is a drawback because the beneficial effect of cyclosporine could deteriorate with time. Nevertheless, it seems just as likely that the therapeutic effect in a trial population could improve with time if tear-producing cells continue to function more effectively.57 The possibility that a higher-risk population analyzed herein is different from that in a clinic setting is also a potential weakness. This anomaly, however, is accounted for in the sensitivity analyses.

Despite possible weaknesses, value-based medicine cost-utility analyses produce hard data with excellent reliability.22,23 These analyses build on level 1 evidence while integrating the drug benefits, adverse events, and quality-of-life aspects often overlooked in trials.23 As compared with evidence-based data alone, value-based analyses more accurately predict which therapies have the best comparative effectiveness and cost-effectiveness.23


