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 (Table 1) 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 standpoint 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.\textsuperscript{17-21}

Cyclosporine, 0.05%, ophthalmic emulsion (Restasis; Allergan Inc, Irvine, California) is a topical immunomodulator with antiinflammatory properties.\textsuperscript{22} 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.

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|}
\hline
Level of Severity & Utility & SD & 95\% CI\textsuperscript{a} & OSDI & Similar Utilities \\
\hline
Mild & 0.81 & 0.18 & 0.76-0.86 & 12-14 & Severe migraines\textsuperscript{5} \\
Moderate & 0.78 & 0.19 & 0.72-0.84 & 19-21 & Ankylosing spondylitis\textsuperscript{6} \\
Moderate to severe & 0.75 & 0.21 & 0.71-0.79 & 32-35 & Moderate to severe dyspnea\textsuperscript{6} \\
Severe & 0.72 & 0.23 & 0.65-0.77 & 46-48 & Hemodialysis\textsuperscript{7} \\
\hline
\end{tabular}
\caption{Table 1. Ocular Time Trade-off Utilities Associated With the Severity of Dry Eye Disease\textsuperscript{4}}
\end{table}

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

\textsuperscript{a}Calculated for the current article with data from Schiffman et al.\textsuperscript{4}

\section{METHODS}

Value-based medicine\textsuperscript{23,24} is the practice of medicine based on the value conferred by health care interventions. Value is defined as the numerical improvement an intervention confers in 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.

\section{UTILITY ANALYSIS}

The time trade-off visual acuity and adverse event utilities used in this manuscript were obtained with the unconditional approval of the Wills Eye Hospital institutional review board. These patient utilities are reliable and validated across age, level of education, ethnicity, sex, income level, and presence or absence of comorbidities.\textsuperscript{25-30} The previously reported\textsuperscript{7} patient dry eye utilities used in the current analysis are also reliable, validated, time trade-off utilities. Ophthalmic disease utilities generally correlate most highly with vision in the better-seeing eye.\textsuperscript{25,24,26-30} Although dry eye syndrome utilities (Table 1) depend on vision and multiple other factors incorporated in the Composite Score of Symptom Severity.\textsuperscript{4}

\section{TOTAL VALUE GAIN (COMPARATIVE EFFECTIVENESS)}

Total value gain is measured in quality-adjusted life-years (QALYs)\textsuperscript{23,24} 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.\textsuperscript{23,24}

\section{CYCLOSPORINE THERAPY STUDIES}

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;\textsuperscript{31} from 2 identical, multicenter, 6-month trials for the New Drug Application submitted by Allergan, Inc, to the Food & Drug Administration (FDA);\textsuperscript{32} and from additional studies.\textsuperscript{4,20,22} 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.\textsuperscript{31} 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.

\section{COMPOSITE SCORE OF SYMPTOM SEVERITY}

Data submitted by Allergan, Inc, to the FDA,\textsuperscript{33} correlated with data from Schiffman et al,\textsuperscript{4} integrate time trade-off utilities with the Ocular Surface Disease Index\textsuperscript{39,40} and the Composite Score of Symptom Severity.\textsuperscript{4} Thus, the average person with un-
Normal vision bilaterally without symptoms (utility, 0.9724). The utilities are treated as listed in and thus do not theoretically affect the scale. Adverse event disutility (utility, 0.978) are associated with higher utilities (as calculated with decision analysis) than the upper anchor of 0.97, suggesting that the adverse events are not incorporated into the analysis, thereby allowing for a more conservative cost-utility ratio.

**ADVERSE EVENTS (DISUTILITIES)**

The adverse events associated with cyclosporine topical therapy include the ocular symptoms and signs listed in Table 3. With the exception of burning in 14.7% of eyes treated with cyclosporine vs 4.7% with the vehicle and blurred vision in 1.7% of the cyclosporine group vs 4.1% of those in the vehicle group, the incidences of adverse events are similar.

**QALY GAIN INCLUDING ADVERSE EVENTS**

Table 3 also lists the daily time assumed to be associated with each of the adverse events as well as the disutility encountered with each event and the QALY loss attributable to each event. When the disutility incurred from adverse events (−0.0016 QALY) is integrated with the benefit conferred by the use of 0.05% topical ocular cyclosporine emulsion, the total 1-year QALY gain is 0.055−0.0016=0.0534 QALY. The corresponding QALY gain from use of the vehicle, including its inherent adverse events (−0.0010 QALY), is 0.0215 QALY. The incremental annual QALY gain of cyclosporine over the vehicle is therefore 0.0534−0.0215=0.0319 QALY (Table 2).

### Table 2. Utility Gain Conferred by the Use of Topical Ocular Cyclosporine, 0.05%, Emulsion for Moderate to Severe Dry Eye Syndrome

<table>
<thead>
<tr>
<th>Health State</th>
<th>Composite Score</th>
<th>Utility (1-y QALY accrual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms, 20/20 OU permanently</td>
<td>0</td>
<td>1.09&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dry eye syndrome with no symptoms</td>
<td>0</td>
<td>0.97</td>
</tr>
<tr>
<td>Utility for use of cyclosporine, 0.05%</td>
<td>NA</td>
<td>0.971</td>
</tr>
<tr>
<td>Utility for use of cyclosporine vehicle</td>
<td>NA</td>
<td>0.978</td>
</tr>
<tr>
<td>No treatment, moderate to severe dry eye</td>
<td>12</td>
<td>0.805&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cyclosporine, 0.05%, emulsion therapy for moderate to severe dry eye</td>
<td>16</td>
<td>0.75&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Utility associated with death</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Average utility gain, cyclosporine over no treatment</td>
<td>NA</td>
<td>0.055</td>
</tr>
<tr>
<td>Cyclosporine AE QALY loss</td>
<td>NA</td>
<td>−0.0016</td>
</tr>
<tr>
<td>Cyclosporine vehicle AE QALY loss</td>
<td>NA</td>
<td>−0.0010</td>
</tr>
<tr>
<td>Average utility gain, cyclosporine over no treatment (disutility from AE included)</td>
<td>NA</td>
<td>0.0534&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Average utility gain, cyclosporine vehicle (disutility from AE included)</td>
<td>NA</td>
<td>0.0215&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Incremental utility gain, cyclosporine over vehicle (AE included)</td>
<td>NA</td>
<td>0.0319&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event(s); NA, not applicable; QALY, quality-adjusted life-year.

<sup>a</sup>Because the calculation is referent to a 1-year period, the difference in utility between treatment and no treatment is equivalent to the annual QALY accrual.

Table 2. Utility Gain Conferred by the Use of Topical Ocular Cyclosporine, 0.05%, Emulsion for Moderate to Severe Dry Eye Syndrome

Adverse event disutility in utility of 0.055. The utility anchors in this scoring system are considered to be moderate to severe dry eye (utility, 0.75) to a symptom severity composite score of 12 and subtracted from the overall cyclosporine value gain.

### COSTS

**Third-Party Insurer Cost Perspective**

The third-party insurer cost perspective is illustrated in Table 4. Physician costs are based on the average 2007 Medicare Fee Schedule<sup>44−46</sup> and are correlated with Current Procedural Terminology codes.<sup>47</sup> 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.<sup>48</sup> Its daily cost is $3.30 and its yearly cost is $1276.

For the use of 0.05% cyclosporine or the vehicle emulsion compared with no treatment, it is assumed that 3 physician visits (1 consultation and 4 follow-up visits) occur during the year. Because the calculation is referent to a 1-year period, the difference in utility between treatment and no treatment is equivalent to the annual QALY accrual.

**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.<sup>23</sup>

**Indirect Costs**

Concerning the indirect cost of diminished productivity, Kozma and colleagues<sup>44</sup> 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,<sup>48</sup> 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<sup>13</sup> 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% [13.9% + (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 result for the vehicle is 4.1% + 9.3% + (19/2)= 23.1%.

The control patient for the use of topical cyclosporine is aged 58 years, so 78% of topical cyclosporine users should theoretically be used. This results in an annual productivity gain of 24.5% × $6466 × 78% = $1236 for the average topical cyclosporine patient. The increased productivity cost is negative, off-setting direct costs and resulting in a total direct medical cost of $1834−$1236 = $598. The increased productivity with the vehicle is 23.1% × $6466 × 78% = $1165, and the incremental productivity gain of cyclosporine over the vehicle is $1236 − $1165 = $71.

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 tend to be cost-effective, while those with a CUR of less than $100 000 per QALY are cost-effective, and those with a CUR of $100 000 per QALY or more are not cost-effective.

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 effectiveness, or improvement in quality of life) of 7.1% for the average patient. The cyclosporine vehicle alone confers 0.0215 QALY, a 2.9% quality-of-life gain, leaving an incremental 4.2% improvement in quality of life, or a 0.0319-QALY gain (0.0534−0.0215), for cyclosporine.

COST-UTILITY

The cost-utility is analyzed from both the societal and the third-party insurer cost perspectives. A summary of cost-utility data are shown in eTable 1 (http://www.archophthalmol.com).

SOCIETAL COST PERSPECTIVE, INCREMENTAL COST-UTILITY OVER VEHICLE

The incremental cost utility of cyclosporine compared with its vehicle is ($1834−$558−$71−$90)/0.319 = $34 953 per QALY.

THIRD-PARTY INSURER COST PERSPECTIVE, INCREMENTAL COST-UTILITY OVER VEHICLE

The third-party insurer incremental cost-utility of cyclosporine referent to its vehicle is ($1834−$558−$71−$90)/0.319 = $34 953 per QALY.
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.
Table 6. Comparison of Cost-Utility Ratios of Topical Cyclosporine Therapy for Dry Eye With Other Interventions Across Health Care

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

Abbreviations: HIV, human immunodeficiency virus; QALY, quality-adjusted life-year.
a Adjusted to 2007 US dollars.
b $/QALY indicates the number of dollars expended per QALY gained.c Value-based medicine cost-utility analysis.d Current study, societal cost perspective, average cost-utility.

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 for the societal incremental CUR, 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 intervention costing less than less than 3 times the Gross Domestic Product per capita for each disability-adjusted life-year (an entity similar to the QALY) is cost-effective.66 For the United States, this equates to approximately $20 000 for cost-effectiveness. In this instance, the price of cyclosporine emulsion could be raised 228% using the societal incremental CUR model and 445% using the societal average CUR model before the upper limit of cost-effectiveness is reached.

POTENTIAL WEAKNESSES

As with any analysis, there are inherent weaknesses in the current study. The absence of randomized controlled 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

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.

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REFERENCES
