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. Schifflman 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 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.17-21

Cyclosporine, 0.05%, ophthalmic emulsion (Restasis; Allergan Inc, Irvine, California) is a topical immunomodulator with antiinflammatory properties.22 More specifically, it inhibits the activation of T cells, which release cytokines that damage lacrinal 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 (conferring 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 medicine23,24 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.

UTILITARIAN 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.25-30 The previously reported 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.25,26,28-30 although dry eye syndrome utilities (Table 1) depend on vision and multiple other factors incorporated in the Composite Score of Symptom Severity.4

TOTAL VALUE GAIN (COMPARATIVE EFFECTIVENESS)

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

Table 1. Ocular Time Trade-off Utilities Associated With the Severity of Dry Eye Disease

<table>
<thead>
<tr>
<th>Level of Severity</th>
<th>Utility</th>
<th>SD</th>
<th>95% CI</th>
<th>ODSI</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 migraines5</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 spondylitis6</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 dyspnea6</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>Hemodialysis7</td>
</tr>
</tbody>
</table>

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

a Calculated for the current article with data from Schiffman et al.4

Figure. Clinical features of the dry eye cohort under study. Inclusion criteria are the features by which moderate to severe dry eye disease was characterized.

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;26 from 2 identical, multicenter, 6-month trials for the New Drug Application submitted by Allergan, Inc, to the Food & Drug Administration (FDA);33 and from additional studies.19,20,22 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.26 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.

COMPOSITE SCORE OF SYMPTOM SEVERITY

Data submitted by Allergan, Inc, to the FDA,33 correlated with data from Schiffman et al,34 integrate time trade-off utilities with the Ocular Surface Disease Index30,32 and the Composite Score of Symptom Severity.33 Thus, the average person with un-
physician costs are based on the average 2007 Medicare Fee Schedule41-43 and are correlated with Current Procedural Terminology codes.43 Pharmaceutical costs are calculated using the 2007 average wholesale price.43

Restasis (cyclosporine, National Drug Code 00023-9163-32) comes in a 32–daily use package with an average wholesale price of $112.41 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. 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.25

### Indirect Costs

Concerning the indirect cost of diminished productivity, Kozma and colleagues46 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,46 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 data33 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

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### 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</td>
</tr>
<tr>
<td>Dry eye syndrome with 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>16</td>
<td>0.75</td>
</tr>
<tr>
<td>Cyclosporine, 0.05%, emulsion therapy</td>
<td>12</td>
<td>0.805</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</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.
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 result for the vehicle is 4.1%

The control patient for the use of topical cyclosporine is aged 58 years, so 78% of topical cyclosporine users should theoretically be used.45 This results in an annual productivity gain of 24.5%/H11003 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.45 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,46 integrates the value of a medical intervention with its associated costs47 using the dollars per QALY (dollars expended per quality-adjusted life-year) or cost-utility ratio (CUR).17,18 An average CUR compares an intervention with no treatment while an incremental CUR compares one intervention with another.13 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.17-21,23 Criteria for the cost-effectiveness of health care interventions in the United States are based on “soft” standards in the peer-reviewed literature.16 It has been suggested in the United States that interventions with a CUR of less than $50 000 per QALY are very 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.23-24,34,35

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 0.055 − 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 − 90/0.319 = $37 179 per QALY.
ment of refractory moderate to severe dry eye disease are
Pricing models for topical cyclosporine for the treat-
ment. The third-party insurer perspective average CUR of
cyclosporine emulsion is $1834 compared with no treat-
ment. The societal cost perspective average CUR
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
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 per-
centage of improvement in value and QALYs gained.23

VALUE (COMPARATIVE EFFECTIVENESS)

Overall, topical cyclosporine confers a value similar to that
conferred by treatment with oral agents for systemic arte-
rial 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 per-
centage of improvement in value and QALYs gained.23

COSTS

A societal cost perspective is the most inclusive and ide-
ally the best for health care cost-utility analyses, but un-
fortunately, which costs to include and the cost bases are
not currently agreed on.23 Costs owing to the loss of em-
ployment productivity, however, can be identified and
assessed as different between patients treated with cy-
closporine and those who did not receive treatment.44

Generally, the societal perspective yields a more fa-
orable CUR than the third-party insurer perspective,23
such as the case herein. Despite differences, both the third-
party insurer and societal cost perspectives in the cur-
rent analysis resulted in cost-effective treatment strate-
gies for topical cyclosporine emulsion therapy.

COST-UTILITY

The use of topical cyclosporine for the treatment of mod-
erate 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.23

It has been noted, however, that many thousands of in-
put and outcome combinations can be used in cost-
utility analysis, with more than 4000 possible utility vari-
ants alone.23 While a comparison of diverse CURs is
presented in Table 6, the observer can have greater con-
fidence in the precise comparability of value-based medi-
cine cost-utility analyses because they are standardized with
patient time trade-off utilities, Medicare costs, and both
third-party insurer and societal cost perspectives.23,24
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\textsuperscript{23} with 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 three times the Gross Domestic Product per capita for each disability-adjusted life-year (an entity similar to the QALY) is cost-effective.\textsuperscript{16} For the United States, this equates to approximately $120,000 for cost-effectiveness. In this instance, the price of cyclosporine emulsion could be raised 228% using the societal averageCUR model and 445% using the average societal incremental CUR model before the upper limit of cost-effectiveness of $100,000 per QALY\textsuperscript{23} is reached.

**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 as likely to improve effectiveness as it does to deteriorate, and therefore a trial that could improve effectiveness could function more effectively.\textsuperscript{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.\textsuperscript{23,24} These analyses build on level 1 evidence while integrating the drug benefits, adverse events, and quality-of-life aspects often overlooked in trials.\textsuperscript{25} As compared with evidence-based data alone, value-based analyses more accurately predict which therapies have the best comparative effectiveness and cost-effectiveness.\textsuperscript{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.

**Table 6. Comparison of Cost-Utility Ratios of Topical Cyclosporine Therapy for Dry Eye With Other Interventions Across Health Care\textsuperscript{a}**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Cost-Utility Ratio, $/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract surgery, first eye\textsuperscript{ac b}</td>
<td>2472</td>
</tr>
<tr>
<td>Cataract surgery, second eye\textsuperscript{ac}</td>
<td>3240</td>
</tr>
<tr>
<td>Cyclosporine for moderate to severe dry eye syndrome\textsuperscript{cd}</td>
<td>11 199</td>
</tr>
<tr>
<td>Computer tomography for equivocal neurologic symptoms\textsuperscript{53}</td>
<td>24 790</td>
</tr>
<tr>
<td>Cyclosporine for moderate to severe dry eye syndrome\textsuperscript{cd}</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 neovascularization\textsuperscript{56}</td>
<td>50 691</td>
</tr>
<tr>
<td>Treating mildly symptomatic Herpes zoster\textsuperscript{55} in a 70-y-old patient</td>
<td>59 122</td>
</tr>
<tr>
<td>Intravitreal pegaptanib for the treatment of subfoveal choroidal neovascularization\textsuperscript{52 c}</td>
<td>66 978</td>
</tr>
<tr>
<td>Treating mildly symptomatic Herpes zoster\textsuperscript{55} in a 40-y-old patient</td>
<td>129 574</td>
</tr>
<tr>
<td>Magnetic resonance imaging for equivocal neurologic symptoms\textsuperscript{53}</td>
<td>135 815</td>
</tr>
<tr>
<td>Use of interferon-(\beta) 1B for the treatment of progressive relapsing multiple sclerosis\textsuperscript{56}</td>
<td>222 068</td>
</tr>
<tr>
<td>Three-day chemoprophylaxis for patients with a prosthetic joint prior to dental treatment\textsuperscript{55}</td>
<td>1 640 600</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; QALY, quality-adjusted life-year.

\textsuperscript{a}Adjusted to 2007 US dollars.

\textsuperscript{b}$/QALY indicates the number of dollars expended per QALY gained.

\textsuperscript{c}Value-based medicine cost-utility analysis.

\textsuperscript{d}Current study, societal cost perspective, average cost-utility.