

# Clinical utility of cyclosporine (CsA) ophthalmic emulsion 0.05% for symptomatic relief in people with chronic dry eye: a review of the literature

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**Abstract:** To review the literature on the efficacy of cyclosporine (CsA) ophthalmic emulsion 0.05% on symptomatic relief in chronic dry eye disease. There is consistent evidence of objective improvements in chronic dry eye disease (Schirmer score, corneal and interpalpebral dye staining, and tear breakup time) with CsA, but variable results with symptomatic improvement, possibly due to patient tolerance of CsA, similar comforting effect with artificial tears and CsA vehicle, and the inherent subjective nature of symptom monitoring and analysis. This review explores the literature on CsA with special attention to symptomatic relief.

**Keywords:** dry eye, cyclosporine, symptoms

## Introduction

In 2003, cyclosporine (CsA) ophthalmic emulsion 0.05% was the first Food and Drug Administration (FDA)-approved prescription medication (Restasis<sup>®</sup>, Allergan, Irvine, CA, USA) for dry eye disease (DED), as well as the first to modify disease<sup>1</sup> rather than to act as a palliative measure as lubricants do. It achieved the indication for increasing tear production in patients with diminished tear production due to ocular inflammation associated with keratoconjunctivitis sicca.<sup>2</sup> Given the recent FDA approval of lifitegrast ophthalmic solution 5% (Xiidra<sup>®</sup>, Shire, Lexington, MA, USA), revisiting the literature on CsA is timely. Although the mechanisms of action are different, both CsA and lifitegrast address the underlying inflammatory process in DED.<sup>1,3</sup>

## Epidemiology

DED is a widespread and challenging disorder to manage, largely due to its multifactorial causes, chronic nature, need for patient compliance, and limited diagnostic and treatment options. It is the most common form of chronic ocular surface disease;<sup>4</sup> 5%–34% of the global population is affected.<sup>5</sup> Forty-three percent of asymptomatic patients have shown signs of dry eye,<sup>6</sup> indicating a need for earlier diagnosis and intervention to prevent advanced disease. The signs and symptoms of DED often do not correlate,<sup>7</sup> and there is no gold standard for its diagnosis. Recently, Vehof et al<sup>8</sup> performed the largest clinical study of DED to date, which identified predictors of discordance between symptoms and signs of DED. Significant predictors of greater symptoms than signs included the presence of a chronic pain syndrome, atopic disease, depression, and osteoarthritis; predictors of lesser symptoms than signs included increased age, primary Sjögren's disease, and graft-versus-host disease (GVHD).

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A subset of patients with incongruous signs and symptoms may have neuropathic ocular pain,<sup>9</sup> the result of somatosensory dysfunction and central sensitization, which consists of pain without ongoing peripheral pathology.<sup>10</sup>

DED is a significant public health issue. More than 20 million Americans have DED.<sup>11</sup> As the aging population rises, so does DED, with more than 15% of those over 65 suffering from it.<sup>12</sup> The Beaver Dam Eye Study found prevalence rates of 8% in those younger than 60 years of age, 19% in those older than 80 years of age, and higher numbers among women than men.<sup>13</sup> Patients with severe dry eye had health-related quality-of-life scores in the range of conditions such as class III/IV angina.<sup>14</sup>

Patients with dry eye experience symptoms of ocular discomfort, dryness, and episodic visual disturbances.<sup>15–17</sup> The disease is not only uncomfortable but interferes with the ability to work and carry out daily functions.<sup>14,18,19</sup> Although it is not usually a blinding disease, these patients spend a substantial amount of money per year to ease the distress associated with it. Estimated global sales of artificial tears exceeded US\$540 million annually in 2002.<sup>20</sup> Galor et al<sup>21</sup> analyzed spending data of patients with dry eye and found that in 2005, the mean prescription medication expenditure per patient per year was \$299 in the USA. According to the US Medical Expenditure Panel Survey, glaucoma patients spent a mean of \$556 per year on glaucoma prescription medications in 2006,<sup>22</sup> and spine patients spent a mean of \$397 per year on prescription medications in 2006.<sup>23</sup>

## Inflammation in dry eye

Dry eye is a complex disorder of the tears and ocular surface that leads to symptoms of discomfort, visual disturbance, tear film instability, and potential damage to the ocular surface. Increased osmolarity of the tear film and inflammation of the ocular surface are integral to the disease.<sup>11</sup>

Inflammation of the ocular surface and lacrimal gland can occur as both the instigator and product of DED. The understanding of inflammation as a key factor in DED supports the use of topical corticosteroids and topical CsA. This was a therapeutic turning point; the underlying mechanism of pathology was targeted rather than mollifying symptoms with the conventional strategy of lubrication.

## Management of dry eye

An arsenal of treatment options exists for DED.<sup>24</sup> They include the following:

1. Lubricants, including artificial tears, gels, ointments, inserts.

2. Anti-inflammatory agents, such as topical CsA, corticosteroids, lifitegrast, essential fatty acids, and oral tetracyclines.
3. Environmental and behavioral modifications, such as the use of humidifier, purposeful blinking, and computer screen adjustment.
4. Cessation of systemic medications linked to DED, such as antihistamines and other anticholinergic agents.
5. Others including punctal occlusion, oral secretagogues, pulse corticosteroids, autologous serum, mucolytic therapy, moisture chamber spectacles, management of eyelids, contact lens (CL) therapy, and acupuncture.<sup>25</sup>

While topical corticosteroids are effective in breaking the cycle of inflammation, their known side effects, such as ocular hypertension, cataract, decreased wound healing, and predisposition to infection limit chronic use.<sup>26</sup> Alternatively, topical CsA has a favorable risk–benefit profile for chronic use. Blood levels of CsA are barely detectable at a maximum level of 0.16 ng/mL,<sup>27</sup> and the most common side effect of CsA is ocular burning.<sup>28</sup> Other side effects of CsA include blurred vision, ocular itching, conjunctival hyperemia, discharge, foreign body sensation, and stinging.<sup>29</sup>

CsA is a lipophilic, neutral cyclic undecapeptide consisting of 11 amino acids.<sup>30</sup> It acts as an immunosuppressant by inhibiting T-cell-mediated inflammation and cytokines in the conjunctiva,<sup>1,31</sup> stimulates natural tear production,<sup>32</sup> and increases goblet cell density.<sup>33</sup> Topical CsA enhances ocular surface health.

## Methods

A PubMed search was performed using the keywords “cyclosporine dry eye,” “cyclosporine ophthalmic and dry eye,” and “topical cyclosporine and thyroid eye disease.” All searches were limited to papers published in or translated into the English language, ranging from 1986 to March 2017. The papers reviewed were limited to human studies that focused on symptomatic relief of chronic dry eye with CsA emulsion 0.05% treatment. There were no restrictions on the study design.

## Results

### CsA for moderate-to-severe dry eye

When considering objective signs such as Schirmer scores and ocular staining, CsA 0.05% quite reliably outperformed vehicle and artificial tears in several randomized controlled trials.<sup>27,32,34–38</sup> However, despite many groups<sup>27,29,32,34,36,39–43</sup> reporting beneficial effects of CsA on symptomatic relief in DED, it is challenging to compare and produce consistent

conclusions given the various study designs. Nevertheless, in general, CsA was found to improve at least one symptom, usually ocular dryness, with variability among studies regarding ocular surface disease index<sup>44</sup> (OSDI) and particular symptom alleviation (Table 1).

As part of The Cyclosporin A Phase II Study Group, Stevenson et al<sup>27</sup> led a randomized, multicenter, double-masked controlled trial of 162 patients with either Sjögren's syndrome (SS) or non-SS dry eye. Hundred twenty-nine patients received CsA (varying concentrations of 0.05%, 0.1%, 0.2%, and 0.4%), and 33 patients received vehicle. CsA 0.05% produced the most consistent improvement in patient symptoms such as ocular dryness and sandy/gritty feeling. However, OSDI scores differed in that at treatment week 12, only the 0.1% and 0.2% groups had significant improvement, and at 4 weeks posttreatment, only the 0.2% group had sustained significant improvement; there was no change or worsening in the vehicle group.

The subsequent Cyclosporin A Phase III Study Group<sup>32</sup> performed two identical multicenter, randomized, double-masked, parallel-group clinical trials focusing on the efficacy of CsA 0.05% and 0.1% to vehicle in 671 patients with moderate-to-severe DED with or without SS. Blurred vision was the most prominent subjective change in the CsA 0.05% group compared to vehicle at all follow-up visits, which ended at 6 months. This is consistent with the Phase II Study Group finding that the 0.05% group had the most reliable subjective improvement, although it was in ocular dryness and sandy/gritty feeling. In addition, the 0.05% group required less rescue artificial tear drops. With OSDI, again, there was no significant difference among the groups.

Rao<sup>37</sup> performed a single-center, investigator-masked, prospective randomized trial comparing CsA 0.05% (36 patients) to vehicle (Refresh Endura<sup>®</sup>, Allergan; 22 patients) for 12 months in moderate-to-severe DED. OSDI scores were significantly better in the CsA group at months 8 and 12 when compared to the vehicle group. Likewise, Chen et al<sup>34</sup> studied 233 Chinese patients with moderate-to-severe DED in a multicenter, randomized, double-masked 8-week trial comparing CsA 0.05% to vehicle. They found CsA superiority in symptomatic relief, as measured by ocular dryness and foreign body sensation.

In a large patient survey study<sup>45</sup> of 5,884 patients, recruited by 4,504 ophthalmologists, optometrists, and primary care physicians throughout the USA, CsA 0.05% was found to significantly improve symptom severity by 30% and activity impairment by 31%–36%. The greatest impact on symptom reduction and activity impairment occurred

after 30 days, with continued reduction up to the 60-day follow-up. This survey noted a very rapid response in symptomatic relief; 41% experienced symptomatic relief within 1–3 weeks. This is in contrast to other studies that required 6 months to achieve statistical significance for improvement in symptoms.<sup>27,32</sup> Although this study had limitations with regard to lack of study protocol, lack of objective clinical testing, and dependence on patient self-reported subjective information, the large volume of patients evaluated in a nonclinical trial setting nonetheless added observational information, corroborating clinical trial results.

An important rationale for determined encouragement of CsA therapy is its ability to reduce disease progression,<sup>37</sup> and progressive improvements in corneal staining with treatment maintained over 24 months.<sup>46</sup> Wilson and Perry<sup>47</sup> showed that CsA could prevent progression of DED in some patients. Although it was a small retrospective case series, they presented 8 patients (3.9% of patients with dry eye from one practice, and 1.5% from another practice) with chronic DED who were essentially cured (free of symptoms and signs of disease) for at least 1 year after completion of CsA treatment. Perry et al<sup>29</sup> prospectively evaluated 158 patients who were unresponsive to artificial tears, and monitored OSDI for symptomatic improvement. They found that 74.1% of mild DED, 72.4% of moderate DED, and 66.7% of severe DED improved with CsA bid. The new information gleaned from this study was that the biggest improvement in OSDI occurred in those with mild disease, suggesting that early treatment of DED may produce the best results, including decelerating disease progression.<sup>37</sup>

## CsA and topical steroids

Barriers to patient tolerance and acceptance of CsA therapy are ocular burning (10.9%), ocular stinging (3.9%), and conjunctival hyperemia (3.4%).<sup>28</sup> These symptoms impact patient tolerance and adherence to medication, leading to dropout and a lost opportunity for dry eye relief. The Physician's evaluation of Restasis satisfaction in second trial (PERSIST) of topical cyclosporine ophthalmic emulsion 0.05% for dry eye study<sup>48</sup> was a multicenter, retrospective chart review that evaluated clinical outcomes of 35 patients with dry eye who received a second trial of CsA following a prior treatment failure, defined as discontinuation of CsA within 12 weeks. The second trial success was linked to patient education directly by physician provided in 97.1% of cases, and simultaneous topical corticosteroids in 28.6% of cases. Upon study conclusion, physicians reported on a questionnaire that 80% of patients benefited from a second trial of

Table 1 Key papers: CsA for symptomatic relief in chronic dry eye

| Study                           | Title   | No. of patients | Population  | Treatment   | Conclusion  |
|---------------------------------|---|-----------------|---|---|---|
| Stevenson et al <sup>27</sup>   | Efficacy and safety of cyclosporine A ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: a dose-ranging, randomized trial. The Cyclosporin A Phase II Study Group                    | 162             | Moderate-to-severe dry eye with or without Sjögren's syndrome | CsA 0.05%, 0.1%, 0.2%, and 0.4% versus vehicle      | CsA 0.05% produced the most consistent improvement in patient symptoms, but only the 0.2% group had sustained significant improvement in OSDI   |
| Sall et al <sup>32</sup>        | Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase III Study Group   | 671             | Moderate-to-severe dry eye with or without Sjögren's syndrome | CsA 0.05% and 0.1% versus vehicle                   | CsA 0.05% produced the most reliable subjective improvement and required less rescue AT   |
| Stonecipher et al <sup>45</sup> | The impact of topical cyclosporine A emulsion 0.05% on the outcomes of patients with keratoconjunctivitis sicca   | 5,884           | Dry eye diagnosed by the healthcare provider                  | CsA 0.05%   | CsA significantly improved symptom severity by 30% and activity impairment by 31% to 36%; 41% had rapid symptomatic relief response (within 1–3 weeks) Eight patients studied were cured for at least 1 year after CsA; CsA may prevent progression of dry eye in some patients |
| Wilson and Perry <sup>47</sup>  | Long-term resolution of chronic dry eye symptoms and signs after topical cyclosporine treatment   | 8               | Chronic dry eye   | CsA 0.05%   | Greatest improvement in OSDI occurred in mild disease   |
| Perry et al <sup>29</sup>       | Evaluation of topical cyclosporine for the treatment of dry eye disease   | 158             | Mild, moderate, and severe dry eye                            | CsA 0.05%   | OSDI scores were significantly better in the CsA group  |
| Rao <sup>37</sup>               | Topical cyclosporine 0.05% for the prevention of dry eye disease progression  | 58              | Moderate-to-severe dry eye                                    | CsA 0.05% versus vehicle                            | CsA superiority in symptomatic relief   |
| Chen et al <sup>34</sup>        | A comparison of cyclosporine 0.05% ophthalmic emulsion versus vehicle in Chinese patients with moderate to severe dry eye disease: an eight-week, multicenter, randomized, double-blind, parallel-group trial | 233             | Moderate-to-severe dry eye                                    | CsA 0.05% versus vehicle                            |   |
| Rao <sup>46</sup>               | Reversibility of dry eye deceleration after topical cyclosporine 0.05% withdrawal   | 48              | Moderate-to-severe dry eye                                    | CsA 0.05% versus AT                                 | Earlier CsA treatment resulted in significantly better OSDI; maintenance CsA therapy reduced disease progression  |
| Prabhasawat et al <sup>50</sup> | A randomized double-masked study of 0.05% cyclosporine ophthalmic emulsion in the treatment of meibomian gland dysfunction  | 70              | Meibomian gland dysfunction dry eye                           | CsA 0.05% versus AT                                 | No difference in OSDI   |
| Mah et al <sup>48</sup>         | PERSIST: Physician's evaluation of Restasis® satisfaction in second trial of topical cyclosporine ophthalmic emulsion 0.05% for dry eye: a retrospective review   | 35              | Chronic dry eye   | CsA 0.05%   | The second trial success was linked to patient education directly by the physician (97.1%), and simultaneous topical corticosteroid use (28.6%)   |
| Sheppard et al <sup>49</sup>    | Effect of loteprednol etabonate 0.5% on initiation of dry eye treatment with topical cyclosporine 0.05%   | 112             | Mild-to-moderate dry eye                                      | Loteprednol etabonate 0.5% or AT prior to CsA 0.05% | Loteprednol etabonate group showed superior results in OSDI improvement   |

**Abbreviations:** AT, artificial tears; CsA, cyclosporine; OSDI, ocular surface disease index.

CsA, measured as improved patient symptoms in 57.1% and a reduction in corneal staining in 22.9%. The role of topical corticosteroids and CsA was studied by Sheppard et al<sup>49</sup> in a multicenter, randomized, double-masked parallel group, prospective study to compare pretreatment with loteprednol etabonate 0.5% (LE) to that with artificial tears prior to chronic CsA treatment. Hundred and twelve patients with mild-to-moderate DED were included. The LE group showed superior results in OSDI improvement. They found that LE induction improved patient tolerance and acceptance of chronic CsA therapy by addressing the CsA side effect of instillation burning.

### CsA in the Asian population

Dry eye is particularly prevalent in the Asian population. Byun et al<sup>39</sup> performed a large prospective, multicenter, open-label surveillance study of 362 Korean patients with moderate-to-severe DED. After 3 months of CsA treatment, symptom scores and use of supplemental artificial tears were significantly reduced. Another smaller Korean study found less definitive results. Park et al<sup>42</sup> compared CsA 0.05% emulsion to sodium hyaluronate 0.1%, 0.15%, or 0.3% in the treatment of 176 patients with non-SS, SS, and evaporative dry eye. They found that CsA had better, but not statistically significant, OSDI scores compared with the sodium hyaluronate groups. Similarly, outside of the Korean population, Prabhawat et al<sup>50</sup> randomized 70 Thai patients in a prospective, double-masked, parallel-group clinical trial comparing CsA 0.05% bid with preservative-free artificial tears in patients with meibomian gland dysfunction for 3 months and found no difference between the two groups with respect to OSDI. In a small study of 38 female SS patients, Hyon et al<sup>51</sup> demonstrated that CsA 0.05%, prednisolone acetate 1%, and autologous serum, in combination or when sequentially used, improved subjective symptoms, visual acuity, and fluorescein staining, but had a limited effect on Schirmer scores, tear breakup time, and rose bengal staining. Another example of mismatched subjective and objective findings occurred in a Turkish study<sup>52</sup> that included 40 patients with SS and non-SS dry eye. They found OSDI score improvement in all the severities of dry eye, but only the mild-to-moderate stages had significant response in Schirmer score and tear breakup time.

### CsA dosages

The majority of studies look at CsA emulsion, but Baiza-Duran et al<sup>53</sup> compared two different concentrations (0.05% and 0.1%) of CsA in aqueous solution to vehicle in

moderate-to-severe DED. This was a multicenter, randomized, double-masked, vehicle-controlled trial of 183 Mexican patients which found CsA 0.1% in aqueous solution to be superior to the other treatment arms in the reduction of certain symptoms such as ocular dryness, red eye, photophobia, and ocular fatigue, but not for tearing or foreign body sensation. Again, discordantly, there was no difference in tear breakup time, corneal staining, and Schirmer scores when comparing CsA and vehicle.<sup>54</sup>

Some patients who fail traditional on-label CsA 0.05% bid therapy may require more frequent application. Dastjerdi et al<sup>55</sup> performed a retrospective review of 22 patients with severe DED who after an inadequate response to a 4-month course of traditional bid CsA dosing were treated with off-label use of 3–4 times a day CsA. They found a significant response to this higher frequency dosing, as measured by symptom improvement and corneal staining. Although Phase II and III clinical trials established safety of higher concentrations of CsA, they did not demonstrate a definite dose–response relationship; therefore, the FDA approval was set at bid dosing. This study reported safety and an enhanced response in 68.2% of the 22 patients with ocular GVHD or SS. The group hypothesized that bid dosing was inadequate for this subset of severe DED patients because of: an incomplete drug effect due to insufficient dosing; end-stage lacrimal gland disease or conjunctival scarring; and other individual risk factors and immunologic mechanisms not yet known.

Alternatively, some patients may tolerate a reduction of CsA 0.05% to qd frequency after 12 months of bid frequency. Su et al<sup>56</sup> randomized 50 patients to qd dosing and 50 patients to bid dosing; all of the patients had previously completed 12 months at bid dosing. At 6 months, there was no significant difference between the groups with regard to any outcome measure other than OSDI: surprisingly, the once-daily group had superior results compared to the bid group.

### CsA versus punctal occlusion versus combination

Roberts et al<sup>40</sup> randomized 30 patients into one of three treatment groups for 6 months: CsA 0.05% bid; lower lid punctal plugs; or plugs and CsA combination. They found that all the three methods treated dry eye, but the combination group produced the greatest reduction (5.5–6 to 1.6 times/d) in patient self-medication with artificial tears, a surrogate marker for relief from dryness and burning. Furthermore, continued reduction in lubricant use was noted during the course of the study in the combination group. This diminished

need for supplemental artificial tears was also observed by Sall et al.<sup>32</sup> In contrast, Perry et al<sup>29</sup> did not find any difference in CsA response with punctal plugs.

## CsA versus topical vitamin A

Kim et al<sup>36</sup> studied 150 Korean patients with DED and divided them into groups receiving CsA 0.05% emulsion bid, retinyl palmitate 0.05% qid, or only preservative-free artificial tears qid. They found that both CsA and vitamin A led to significant improvement in blurred vision when compared to the lubricant only group.

## CsA in other autoimmune diseases, such as thyroid eye disease- and Stevens–Johnson syndrome-related chronic DED

There have been small studies on CsA in dry eye related to other systemic diseases. A Thai study<sup>57</sup> examined 17 patients with Stevens–Johnson syndrome for 6 months and found significant alleviation of symptoms including foreign body sensation, photophobia, eye pain, and dry sensation, which were graded by the visual analog scale. A Turkish study of 12 consecutive thyroid orbitopathy patients with dry eye showed a significant improvement in OSDI with 2 months of twice-daily CsA treatment.<sup>58</sup>

## CsA in trachomatous DED

Guzey et al<sup>38</sup> examined 64 patients with severe trachomatous DED and divided them into CsA 0.05% emulsion bid with nonpreserved artificial tears 5 times daily, and vehicle emulsion bid with nonpreserved artificial tears 5 times daily. They found that the CsA group had significantly improved OSDI.

## CsA in hematopoietic stem cell transplantation patients

There are a handful of studies on the use of CsA in hematopoietic stem cell transplantation (HSCT) patients. The earliest study of CsA's potential benefit in DED related to GVHD was reported by Kiang et al<sup>59</sup> in 1998. They reviewed five case reports where topical CsA 1% was applied from twice daily to 8 times a day with varying results. This was followed by Lelli et al<sup>60</sup> who performed a retrospective chart review of 16 patients treated with CsA (varying concentrations/dosing) to validate safety. Rao and Rao<sup>61</sup> undertook a 3-month prospective study of 8 patients who failed lubricant therapy, and found that CsA 0.05% bid for 3 months significantly improved Schirmer scores and tear breakup time. Subjective complaints of tearing, burning, and blurring were

also alleviated, but did not achieve statistical significance. Wang et al<sup>62</sup> examined 13 patients with chronic GVHD in a prospective comparative study with seven patients in the CsA 0.05% emulsion qid group and six patients as a control group. There was a significant improvement in the visual analog scale symptom scores in the CsA group.

A further rationale for early treatment with CsA was supported by Malta et al.<sup>63</sup> They studied 105 patients in a retrospective, comparative, interventional case series where 81 patients received CsA 1 month prior to bone marrow transplant (BMT) and 24 patients did not receive CsA until at least 6 months after BMT (control group). Dry eye symptoms by OSDI were significantly more severe in the control group, even at the 2-year follow-up. They concluded that pre-BMT treatment with CsA reduces the lacrimal gland inflammation responsible for DED in BMT patients.

Boynton et al<sup>64</sup> studied 75 patients prior to initiation of HSCT, comparing CsA 0.05% bid to LE 0.5% bid in the prevention and progression of GVHD-related DED. This was a single-center, randomized, control group, prospective study with unclear masking that concluded LE to be safe and as effective as CsA in the prophylaxis and treatment of GVHD-related DED. Both groups of patients started either LE or CsA 1 month prior to HSCT. Unfortunately, despite the prophylactic therapy, the majority of patients in each group progressed to dry eye, and a minority in each group experienced improved OSDI and corneal staining by 12 months post-HSCT.

## CsA in children with radiation-associated DED

Hoehn et al<sup>65</sup> did a retrospective review of 11 children who had radiation-associated DED that failed conventional therapy for at least 6 months. Symptomatic relief from CsA 0.05% emulsion bid was measured by intensity of photophobia; only three of the 11 children had any improvement. Although this study was limited, CsA 0.05% had little benefit on photophobia and corneal staining.

## CsA in CL wearers

CL intolerance is often caused by dry eye, as lens wear can be associated with tear film alterations.<sup>66</sup> Despite reducing wear time, using rewetting drops and lubricants, and managing meibomian gland dysfunction, some patients are unable to tolerate the lenses and discontinue their use. Hom<sup>67</sup> randomized 17 CL wearers in an investigator-masked study comparing twice-daily CsA 0.05% to rewetting drops for 5 weeks in patients with self-reported CL-related dryness. In the CsA group,

he noted a statistically significant increase in CL wear time and reduced amount of supplemental rewetting drops; OSDI scores improved, but there was not a statistically significant difference between the two groups. Conversely, Willen et al<sup>68</sup> studied 44 patients in a double-masked, randomized trial and found no significant difference between CsA and rewetting drop groups in objective or symptomatic parameters. The inability to show statistically significant improvement with CsA may be linked to the small sample sizes of these CL studies. Another consideration is that CsA may not be as effective in this subset of patients with dry eye.

### CsA in laser vision correction patients

Laser in situ keratomileusis (LASIK) is associated with DED by exacerbating the symptoms in preexisting dry eye or by triggering it in previously asymptomatic patients. It is one of the most common complaints leading to patient dissatisfaction with the procedure.<sup>69</sup> Severing corneal nerves in the creation of the LASIK flap interrupts the neural feedback loop to the lacrimal glands with resultant diminished tear production.<sup>70</sup> In a small study of 21 patients with dry eye, Salib et al<sup>71</sup> found that those patients treated with twice-daily CsA 0.05% 1 month prior to surgery had superior refractive predictability at 3 and 6 months after LASIK compared to those treated with artificial tears. However, OSDI scores were not statistically different between the groups. In a consecutive case series, Torricelli et al<sup>72</sup> showed success with CsA 0.05% bid treating postoperative dry eye following LASIK and photorefractive keratectomy. After 12 months or more of CsA treatment, 5/82 (6.1%) eyes continued to have signs or symptoms of dry eye. Lee et al<sup>73</sup> performed a retrospective, nonrandomized comparative analysis in 40 patients who underwent myopic laser epithelial keratomileusis and were treated with CsA 0.05% plus the conventional regimen of moxifloxacin 0.5%, fluorometholone 0.1%, and preservative-free sodium hyaluronate 0.1% qid; and 20 patients who received the conventional regimen alone. The CsA group had less ocular discomfort by 4 weeks postoperatively, especially those with preoperative dry eye. Likewise, Ursea et al<sup>74</sup> found faster recovery of vision in patients treated with CsA 0.05%, even at 1 week postoperatively. Conversely, in a study of 124 refractive patients, Hessert et al<sup>75</sup> found no difference in symptoms or visual recovery with or without CsA 0.05% bid for 3 months postoperatively.

### Conclusion

The evidence for objective parameter response to CsA 0.05% bid in DED is strong, but subjective results are less

consistent. The lack of correlation in signs and symptoms is an inherent challenge of the disease.<sup>7</sup> In addition, there is now a growing body of literature studying neuropathic ocular pain, an entity where mismatch in signs and symptoms is common, overlap with DED exists, and response to topical therapy is less effective.<sup>10</sup> The current practice of symptom evaluation, slit-lamp examination, and metrics such as osmolarity may fail to delineate neuropathic ocular pain.<sup>76</sup>

Subjective questionnaires that document symptoms and their impact on vision-related functioning, such as the OSDI, are widely used, but have limitations. Consisting of 12 questions, the OSDI evaluates for ocular symptoms of DED, limitations while performing vision-related activities, and environmental triggers. The answers are divided into five categories, ranging from “none of the time” to “all of the time.” The scores range from 0 to 100 points, with 100 being the most severe DED.<sup>44</sup> Although the OSDI has been shown to be a valid and reliable tool in DED evaluation, the limited number of symptoms, activities, and triggers queried is a weakness. For instance, “sensitive to light,” “gritty,” “painful or sore,” and “blurred or poor vision” are the only symptoms evaluated. Furthermore, the OSDI provides one total score to classify disease severity, but individual questions actually address different root causes of DED. For example, the questions regarding pain triggered by wind and light may indicate a neuropathic etiology of DED.<sup>10,77</sup>

Future directions for investigation may include different formulations such as the 0.1% CsA cationic emulsion<sup>78</sup> Ikervis<sup>®</sup> (Santen SAS, Evry, France), recently launched in Europe, which is once-daily dosing; and novel delivery systems of CsA such as episcleral implant,<sup>79</sup> ophthalmic insert,<sup>30</sup> CL,<sup>80</sup> and punctal plug.<sup>81</sup> With the recent addition of lifitegrast, new studies will likely compare it with CsA and possibly evaluate it as a combination therapy. Further studies on potential synergism between LE and CsA may be warranted.<sup>49</sup> Developing newer questionnaires and enhancing analysis of current questionnaires may more accurately reflect the heterogeneity of DED, and improve our knowledge of this complex disorder. Despite the variability and limitations of study design and study end points, in general, CsA ophthalmic emulsion 0.05% bid appears to have utility in symptomatic relief in people with chronic dry eye.

### Disclosure

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