

Treatment of chronic dry eye: focus on cyclosporine

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Abstract: To review the current treatment of chronic dry eye syndrome, focusing on cyclosporine A (CsA), a systematic literature search was performed using PubMed databases in two steps. The first step was oriented to articles published for dry eye. The second step was focused on the use of CsA in dry eye. A manual literature search was also undertaken based on citations in the published articles. The knowledge on the pathogenesis of dry eye syndrome has changed dramatically during the last few years. Inflammation and the interruption of the inflammatory cascade seem to be the main focus of the ophthalmologic community in the treatment of dry eye, giving the anti-inflammatory therapy a new critical role. The infiltration of T-cells in the conjunctiva tissue and the presence of cytokines and proteasis in the tear fluid were the main reason introducing the use of immunomodulator agents such as corticosteroids, cyclosporine, and doxycycline in order to treat dry eye syndrome. CsA emulsion is approved by the FDA for the treatment of dry eye, while clinical trials of this agent have demonstrated efficacy and safety of CsA. CsA seems to be a promising treatment against dry eye disease. New agents focused on the inflammatory pathogenesis of this syndrome in combination with CsA may be the future in the quest of treating dry eye. More studies are needed to determine the efficacy, safety, timing, and relative cost/effect of CsA.

Keywords: dry eye, cyclosporine A, inflammation, immunomodulator agents

Introduction

Epidemiology

Dry eye is a frequent disease. Among dry eye patients over the age of 65 in the US, 25% reported using artificial tears on a frequent basis and 73% visited an eye care professional during the previous year for this condition (Shein et al 1997).

It is estimated that approximately 7.1 million people over the age of 40 in the US experience symptoms of ocular irritation due to dry eye syndrome (Pflugfelder 2004), while more than 6% of the population over the age of 40 and more than 15% of the population over the age of 65 suffer from dry eye (Bjerrum 1997; Schein et al 1997; McCarty et al 1998).

The estimated global sales of artificial tears exceeded US\$540 million annually in 2002 (Harmon and Murphy 2003), whereas the total annual healthcare cost of 1,000 dry eye syndrome sufferers managed by ophthalmologists ranged from US\$0.27 million (95% CI: \$0.20; US\$0.38 million) in France to US\$1.10 million (95% CI: US\$0.70; US\$1.50 million) in the UK. A large proportion of dry eye patients is either self-treated or managed by their general practitioner (Clegg et al 2006).

Diagnosis of dry eye

Clinically there is a plethora of irritation symptoms associated with dry eye such as ocular burning, stinging, scratchiness, soreness, photophobia, blurred vision and foreign body sensation. Tear film stability can be assessed with the fluorescein tear

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break-up time test, measuring the interval in seconds between a complete blink and the first appearing dry spot or discontinuity in the precorneal film. Aqueous tear production is measured more commonly with Shimer test, calculating the length in millimeters that a folded filter paper strip placed in the lower lid wets during a 5-minute test period. There are two ways to perform this test: a) Shimer test I is performed without topical anesthesia, which evaluates better the ability of the ocular gland to respond to ocular surface stimulation; b) Shimer test II (or Basic Secretion test) which is performed after topical anesthesia, evaluating better the basal tear secretion. Meibomian gland disease is diagnosed by biomicroscopic recognition of pathological signs such as ductal orifice metaplasia, reduced expressibility of meibomian gland secretions, increased viscosity of the expressed secretion and dropout of glandular acini. Conjunctival goblet cell density and epithelial morphology can be directly evaluated by cytology. The most practical clinical method for assessing the severity of dry eye is the ocular surface dye staining. Fluorescein, rose Bengal and lissamine green are used as diagnostic dyes for evaluating the staining. Fluorescein staining occurs when the epithelial barrier is disrupted, due to the loss of the epithelial cells, is well tolerated by patients and evaluates better corneal staining. Rose Bengal and lissamine green stain the conjunctiva more brightly than the cornea. Rose Bengal stains devitalized epithelial cells or cells without protective mucus layer, but cause transient irritation after installation. Lissamine green dyes degenerated or dead cells and produces less irritation than rose Bengal (Plufelder 2006).

However, many times symptoms and signs are not always specific and are often underestimated by the patient or under diagnosed by ophthalmologist (Schein et al 1997; Afonso et al 1999; Lin et al 2003).

Definitions and classifications of dry eye

In 1995 the National Eye Institute workshops, defined dry eye as "a disorder of the tear film due to tear deficiency or excessive evaporation that causes damage to the interpalpebral ocular surface and is associated with symptoms of discomfort" (Lemp 1995). In the Definition and Classification Subcommittee of the international Dry Eye Workshop in 2007, a new contemporary definition of dry eye disease was reported, supported within a comprehensive classification framework. In accordance with the committee, dry eye was defined as a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort,

visual disturbance, and tears film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. The committee recommended a three part classification system. The first part was etiopathogenic, illustrating the multiple causes of dry eye. In this group dry eye was divided in two principal categories: aqueous deficient (Sjogren or non-Sjogren related) and evaporative (intrinsic or extrinsic causes); the second was mechanistic, showing the way each cause may act through a common pathway (tear hyperosmolarity and tear film instability); the third part was based on the severity of the disease (four groups correlated to visual symptoms, conjunctival injection, conjunctival staining, corneal staining, corneal/tears signs, lid/meibomian glands, tear break-up time, and Shimer test), providing a rational basis for therapy (DEW 2007).

In 2006 in a Delphi panel approach to treatment recommendations by 17 international specialists on dry eye syndrome, a new term was proposed for dry eye disease: dysfunctional tear syndrome (DTS). In our study the most commonly used diagnostic test reported by more than half of the panelists for evaluating probable dry eye were fluorescein staining (100%), tear break up time (94%), Shimer test (71%), and rose Bengal staining (65%). Panelists agreed on three particular relevant symptoms and historical elements to be considered: ocular discomfort (itch, scratch, burn, foreign body sensation, and/or photophobia), tear substitute requirements, and visual disturbance. There was a consensus that most cases of DTS have an inflammatory basis that either triggers or maintains the inflammation. However, there was an agreement on the difficulty in clearly identifying inflammation in most patients and consequently the panel agreed to subclassify the disease as either DTS with clinically apparent inflammation or DTS without clinically evident inflammation (Behrens et al 2006).

Pathogenesis

The ocular surface and the lacrimal gland are considered, studied, and treated as an integrated functional unit interconnected by neural sensory/autonomic reflex arcs. Sensory afferent nerves, which enervate the ocular surface, traffic along the ophthalmic branch of the trigeminal nerve to the Pont area of the central nervous system. After received inputs from cortical areas (emotional central nervous centers), efferent nerves, consisting of parasympathetic fibers traveling in the facial nerve and of sympathetic fibers from the paraspinal sympathetic

chain, lead to the main and the accessory lacrimal gland (Pflugfelder et al 2000).

Over recent years, inflammation has been shown to be the key in the pathogenesis of this syndrome, as it seems to be the cause and the consequence of dry eye. Regardless of the triggering factor, a vicious cycle of inflammation may be developed on the ocular surface in patients with dry eye. A glandular dysfunction creating tear deficiency or instability could irritate the surface of the eye and promote inflammation, which increases further the tear deficiency (Jones et al 1998). The results are antigen presentation and cytokine secretion by the epithelial cells of the lacrimal gland which promote the activation of the T-cells lymphocytes. Finally, the T-cells secrete pro-inflammatory cytokines, increasing further the level of inflammation (Meggs 1993; Mircheff et al 1998; Gao et al 1998). Consequently, the tears will contain cytokines. The ocular surface reacts, promoting inflammatory response which consists of inflammatory cell infiltration, epithelial activation, increased concentrations of cytokines and other inflammatory factors, and increased activity of matrix-degrading enzymes (Baudouin et al 1997; Tishler et al 1998; Afonso et al 1999; Pflugfelder 1999; Pflugfelder 2000; Sobrin et al 2000). This knowledge concerning the inflammation pathogenic mechanism in dry eye syndrome alters also the therapeutic approach against this syndrome which is now based on anti-inflammatory agents.

Therapy

The therapy of dry eye depends on its severity. Based on the most recent concept, the armamentarium used to control dry eye comprises a large range of therapeutic strategies.

Modification of the environmental conditions that increase tear evaporation (eg, low humidity), avoiding the use of systemic medications with anticholinergic side effects (eg, antihistamines), occlusion of the lacrimal canaliculi (punctal occlusion), stimulation of tears production (oral secretagogues pilocarpine), and minimization of corneal exposure (tarsorrhaphy, gas permeable contact lenses). Although these treatment options are very useful, all of them are considered to be symptomatic therapeutic approaches and not pathogenic.

Artificial tears

Artificial tears provide temporal improvement in eye irritation and blurred vision symptoms, visual contrast sensitivity, tear break up time, and ocular surface dye staining. (Gifford et al 2006; Ousler et al 2007). Artificial tears contain polymers

such as cellulose esters, polyvinyl alcohol, and povidone, which determine their viscosity, shear properties, retention time, and adhesion to the ocular surface. Gels have longer retention times than artificial tear solutions (Bron et al 1998; Wilson et al 1998).

Anti-inflammatory therapy

Anti-inflammatory therapy is considered to be the first "causative therapeutic approach" in the treatment of dry eye, since its objective is to interrupt the inflammatory cascade. Topical corticosteroids, tetracyclines, and cyclosporine A (CsA) are the drugs used in the anti-inflammatory therapy of dry eye.

Corticosteroids

Topical corticosteroids can be used in order to decrease ocular surface inflammation inhibiting MMPs (matrix metalloproteinases), inflammatory cytokines and adhesion molecule production. They demonstrate satisfactory results as pulse therapy. In a retrospective study which included Sjogren syndrome patients with keratoconjunctivitis sicca (KCS), the administration of 1% solution of methylprednisolone (3 times a day for 2 weeks) relieved symptoms in all patients (Marsh and Pflugfelder 1999). Corticosteroids should not be administered for long-term use owing to the side effects they can provoke (steroid response increasing of IOP, cataractogenesis). Corticosteroids with minimal potential to raise IOP (fluorometholone and loteprednol etabonate) could be considered a safer approach. A randomized, double-masked, placebo-controlled study of loteprednol etabonate and its vehicle was conducted on 64 patients with delayed tear clearance and KCS. After 2 and 4 weeks of treatment, there was no change in IOP in the corticosteroid-treated group. Patients with the most severe inflammatory signs at entry showed a significantly greater decrease in central corneal fluorescein staining scores while a significant decrease in inferior bulbar conjunctival hyperemia was demonstrated after 2 weeks (Pflugfelder et al 2004).

Tetracyclines

Tetracyclines have also a variety of anti-inflammatory properties such as inhibition of MMPs and interleukine-I (IL-I) production (Amin et al 1996; Shlopov et al 1999). Orally administered they decrease ocular surface symptoms in patients with ocular rosacea (Frucht-Pery et al 1993; Akpek et al 1997) and in patients with recurrent corneal epithelial erosions (Hope-Ross et al 1994).

The best tolerated tetracycline is doxycycline, which is effective in doses of 20–50 mg orally twice a day for a treatment up to 4 weeks (Plugfelder 2004).

Cyclosporine A

Today CsA seems to represent a very promising treatment against dry eye syndrome since it is the first agent focused on the pathogenesis of this disease. It can be used for long term without presentation of the adverse effects characterizing the other anti-inflammatory agents.

Methodology

A systematic literature review was performed using PubMed databases in two steps. The first step was oriented to articles published for dry eye. The second step was focused on the use of CsA in dry eye. The search strategy was not limited by year of publication. A manual literature search was also undertaken based on citations in the published articles.

Results

Cyclosporine A is a fungal-derived peptide that inhibits T-cell activation and consequently inhibits the inflammatory cytokine production (selective inhibition of IL-1). In addition, CsA inhibits apoptosis by blocking the opening of the mitochondrial permeability transition pore (MPTP) (Matsuda and Koyasu 2000) and by increasing the density of conjunctival goblet cells (Kunert et al 2002).

In the US, CsA is commercially distributed as Restasis®. This ophthalmic emulsion (0.05% cyclosporine [Allergan, Inc. Irvine, CA, USA]) is preservative free packaged in unit-dose vials. Restasis has been a prescription drug in the US since April 2003 when it was approved by the FDA for patients whose tear production is presumed to be suppressed due to ocular inflammation associated with KCS.

CsA was used for years routinely as an oral immunosuppressor for organ transplantation. Its action is non toxic and reversible after the treatment. In ophthalmology prior to dry eye treatment, CsA was used also for the treatment of severe posterior segment inflammations, when administered systemically (iv) or orally (Masuda et al 1989). Systemically CsA was also used for the treatment of peripheral ulcerative keratitis associated with Wegener's granulomatosis, in severe Graves's ophthalmopathy, and for the prevention of the recurrence of graft rejection after keratoplasty (Prummel et al 1989; Nussenblatt et al 1991; Georganas et al 1996; Reinhard et al 1997).

All these indications were the result of CsA's pharmacokinetics, since extraocular and intraocular tissues can be reached by this agent through the systemic

pathway after oral administration. In fact, after oral daily administration of 5 mg/kg daily, the concentration of CsA was measured to be 25–75 µg/mL in human tears (BenEzra et al 1990); systemic administration may be accompanied by severe side effects such as nephrotoxicity and hypertension (Mihatsch et al 1998). As a result topical ocular delivery was proposed as a good alternative. Despite its poor intraocular penetration, topical CsA has been successfully used in dry eye syndrome. Another pharmacokinetic limitation was that CsA could not be prepared in a formulation based on aqueous ophthalmic vehicles because of both its hydrophobicity and its low aqueous solubility. Therefore, the agent was dissolved in vegetable oils (Lallemand et al 2003).

The potential of CsA for treating dry eye syndrome and its clinical expression KCS was initially tested in 1989 in dogs affected with spontaneous canine KCS. Tear production was increased. CsA caused marked regression of chronic corneal neovascularization and granulation even in eyes in which lacrimation failed to improve. Additional benefits of topical cyclosporine were: reduced mucopurulent conjunctivitis, rapid healing of non-healing corneal ulcers, and reduced dependence on frequent topical treatments of KCS (Kaswan et al 1989). The experimental results were verified by other similar studies in dogs (Morgan and Abrams 1991; Olivero et al 1991; Izci et al 2002). Furthermore, experiments in a mutant mouse model used for primary Sjogren's syndrome has demonstrated the anti-inflammatory effect of both topical and orally administrated CsA on the lacrimal gland (Tsubota et al 1998), whereas other experiments in mice suggested that CsA accelerates tear secretion by releasing neurotransmitters from sensory nerve endings, which interact with the parasympathetic nerves (Yoshida et al 1999). Similar conclusions were also demonstrated in studies with rabbits (Toshida et al 1998).

The use of CsA delivered as ointment or oil suspension was then studied for treatment of humans KCS. Topical CsA 2% in olive oil was investigated for its possible immunoregulatory role on the dry eye state in patients with secondary Sjogren's syndrome. Thirty eyes of 15 patients were randomized to undergo treatment with topical cyclosporine in olive oil, while an other group of 15 patients (30 eyes) received a placebo (which was the sterile olive oil used as a vehicle for the cyclosporine). There was a significant increase in the break-up time and a significant decrease in rose Bengal staining score between the cyclosporine and control groups at the end of the 2-month study period (Gunduz and Ozdemir 1994). Laibovitz et al

(1993) conducted a study in which patients with KCS underwent 6 weeks of treatment with either cyclosporine 1% ophthalmic ointment or placebo, followed by 6 weeks of the alternative treatment. Cyclosporine ointment was associated with initial mild to moderate redness, itching, and burning that returned to baseline levels within 1–2 weeks. Rose Bengal results and results of 4 subjective (patient diary) efficacy parameters favored cyclosporine: foreign body sensation, overall symptoms, hours of symptom control per day, and overall effectiveness. No systemic adverse events or laboratory abnormalities occurred. Subsequently, CsA for treating KCS in patients with dry eye was evaluated in large multi-center randomized double-masked FDA clinical trials. An FDA phase 2, randomized, multicenter, double masked, parallel-group, dose-response clinical trial compared 4 different dose of CsA (CsA ophthalmic emulsion 0.05%, 0.1%, 0.2%, 0.4%) administered twice daily into both eyes of 129 patients and 33 patients treated with a vehicle for 12 weeks, followed by a 4-week post-treatment observation period. In a subset of 90 patients with moderate to severe KCS, CsA was found to decrease rose Bengal staining, superficial punctate keratitis, and symptoms of ocular discomfort. Although there was no clear dose-response relationship, CsA 0.1% seemed to produce the most consistent improvements in subjective and objective end points, whereas CsA 0.05% demonstrated the most consistent improvement in patients' symptoms. All treatments were well tolerated by patients (Stevenson et al 2000).

In the FDA phase 3 study group, 2 independent multicenter, randomized, double-masked, parallel group, 6-month, vehicle control clinical trials compared the efficacy and safety of CsA in 877 patients with defined moderate to severe dry eye disease. The patients were treated twice daily with either CsA 0.05% or 0.1%, or vehicle (292 to 293 patients in each group). The results of these two trials were combined for analysis. There was no dose-response effect. A treatment effect was observed after first month of treatment and increased over the 6-month follow-up period. Patients treated with CsA (0.05% or 0.1%) showed significantly greater improvements than vehicle in 2 objective signs (corneal fluorescein staining and categorized Shirmmer values). CsA 0.05% treatment also demonstrated significantly greater improvements in three subjective measures of dry eye (blurred vision, need for concomitant artificial tears, and physician's evaluation of global response to treatment). After 6 months of treatment there was a statistically significant improvement from baseline within both groups in Shirmmer tear test obtained with anesthesia, whereas in those obtained without anesthesia there was a statistically

significant improvement from baselines within all treatment groups but no statistically significant differences among the groups. The most common treatment-related adverse effect was burning eye sensation (15% for CsA 0.05% group and 17% for CsA 0.1% group). Patients receiving the vehicle had a lower frequency of burning eye sensation (7%). Other common adverse events (reported by >3% of patients) were stinging eye, eye discharge, foreign body sensation, conjunctival hyperemia, visual disturbance, and eye pain (Sall et al 2000).

A multicentered, non-randomized, open label extension study of the two previous phase 3 clinical trials, evaluated the safety and efficacy of CsA 0.1% ophthalmic emulsion over 1–3 years in moderate to severe dry eye disease patients. In 412 patients previously dosed for 6–12 months with CsA 0.05% or 0.1%, CsA 0.1% was instilled twice daily for up to 3 consecutive 12-month periods. For the duration of almost all the 20-month treatment, improvements in objective and subjective measures of dry eye were modest. The changes in corneal staining and Shirmmer scores were not statistically significant. Treatment-related adverse effects were found in 22% of patients. The most common were burning eye, stinging eye, and conjunctival hyperemia, but only 2 patients reported these symptoms as severe. In a survey of patients receiving CsA during a 12-month treatment period, most patients reported that during the first clinical trial preceding this study, their symptoms began to resolve after the first 3 months. Although 85% of respondents continued to use artificial tears, their frequency decreased from 7.6 times per day to 3.8 times per day. 95.2% of respondents said that they would continue taking CsA after the study and 98% would recommend it to other patients. A 2 line loss of visual acuity was found in 13% of patients, whereas only 5% showed a gain of 2 lines (Barber et al 2005).

The use of CsA for the treatment of dry eye was also tested in a variety of situations correlated with this syndrome. It is well known that LASIK, despite its positive attributes in keratorefractive surgery, can induce dry eye syndrome in some patients (Aras et al 2000; Battat et al 2001; Toda et al 2001; Nassaralla et al 2003). Dry eye in patients that underwent LASIK seems to be a result of multifactorial processes such as decreased corneal sensation or alteration ocular surface and lacrimal gland function (Heigle and Plugfelder 1996; Linna et al 2000; Stern et al 2000). As a result, dry eye is considered to be almost a contraindication for LASIK surgery. A prospective clinical trial evaluated the safety and efficacy of CsA 0.05% versus artificial tears in dry eye patients, from 1 month before to 3 months after

having LASIK. There were no statistically significant differences between baselines or between the two groups in response to ocular surface disease index questionnaire or best spectacle-corrected visual acuity. Treatment with CsA provided greater refractive predictability than artificial tears 3 and 6 months after surgery (Salib et al 2006).

Rao and Rao (2006) assessed the efficacy of cyclosporine in patients with dry eye associated with graft versus host disease after stem cells transplantation. After completing a 3-month run-in period of using only artificial tears to control dry eye symptoms in both eyes, patients who failed to achieve adequate relief were instructed to instill topical cyclosporine twice a day. Dry eye signs improved significantly with cyclosporine treatment.

Based on its anti-inflammatory action, topical CsA could also be used in a variety of other ocular surface disease such as vernal keratoconjunctivitis (Pucci et al 2002), atopic keratoconjunctivitis (Akpek et al 2004), lichenoid conjunctivitis (Rubin et al 1991), conjunctival lichen planus (Levell et al 1992), and superior limbic keratoconjunctivitis (Perry et al 2003).

The concomitant use of cyclosporine with artificial tears has also been analyzed. Sal et al (2006) evaluated the efficacy of marked artificial tears in relieving the signs and symptoms of dry eye when used as a supportive therapy to a cyclosporine-based ophthalmic emulsion in a 6-month randomized investigator masked parallel study of 61 patients. The patients were divided in 3 groups; in the first two cyclosporine was combined with a preservative-free carboxymethylcellulose 0.5% agent (Refresh Plus[®], Allergan, Irvine, CA, USA) and with a hydroxypropyl-guar gellable lubricant eye drop (Systane[®], Alcon laboratories, Inc., Fort Worth, TX, USA), whereas in the third group only Systane was used. Results indicated that the choice of concomitant therapy had significant effects on outcome measures. The combination of Restasis-Systane was statistically significantly better in reducing the signs and symptoms of dry eye than the combination of Restasis-Refresh. In addition, Systane used alone was statistically significantly better than Restasis-Refresh for 3 ocular symptom frequency scales (burning, dryness, and scratchiness) and 6 Likert acceptability questions. Finally, Restasis-Systane, compared with Systane alone, was not statistically different for any of the signs and symptoms measured except for the frequency of ocular blurring (Sal et al 2006).

Discussion

Although traditional symptomatic treatment still remains the method of choice, a more reasonable approach in the

treatment of this syndrome would seem to be consider the inflammatory mechanism of dry eye. The trend nowadays in patients with slight to mild episodic dry eye seems to be symptomatic therapy (eg, artificial tears, punctual occlusion), while in patients who already use artificial tears and who continue to have detectable ocular surface disease associated with inflammatory signs, anti-inflammatory agents seem to be the treatment of choice.

The use of CsA as anti-inflammatory treatment for dry eye has advantages over corticosteroids because until now a) it has not demonstrated serious adverse effects; b) its action is reversible after the treatment; and c) it has a very low rate of systemic absorption. These pharmacokinetic characteristics are critical, since the possibility for long-term therapy in these patients is absolutely necessary for a chronic disease such as dry eye. In fact, the benefits of CsA begin after 1 month of treatment and a therapy of at least 3 months seems to be indispensable.

Also other conditions associated with dry eye could benefit from CsA. For example, refractive surgery of the cornea, most particularly LASIK, is almost contraindicated now in patients with dry eye. CsA treatment before and after surgery could help these patients obtain a surgical correction of their refractive error without the risk of dry eye. Graft versus Host disease cells after stem transplantation could also benefit from CsA. Similar results were found in other pathologies with an inflammatory base, such as vernal kerato-conjunctivitis, atopic kerato-conjunctivitis, lichenoid conjunctivitis, and superior limbic kerato-conjunctivitis.

Plugfelder (2004) reviewed anti inflammatory therapy for chronic dry eye. He stated that dry eye is associated with ocular surface inflammation that may further compromise tear secretion and cause ocular surface disease and irritation symptoms. Ocular surface inflammation should be assumed in patients with an unstable tear film and ocular surface epithelial disease that is detected by staining with diagnostic dyes. Of course, there is no diagnostic test available to gauge easily the level of inflammation on the ocular surface. As a result, no firm recommendations can be made about the optimal timing for initiating anti-inflammatory therapy in patients with dry eye. He concluded that it is reasonable to consider anti-inflammatory therapy for patients using artificial tears who continue to have clinically detectable ocular surface disease, particularly if inflammatory signs (for example, conjunctival redness) and irritation symptoms are present.

The Delphi panel in 2006 proposed treatment recommendation for dry eye on the basis of level of severity. They recommended

that topical administration of CsA must be given only when the disease is in severity level two, characterized by moderate to severe symptoms, tear film signs, mild cornea punctuate staining, conjunctival staining, and visual signs.

However, a new treatment must take consider the relationship between cost and effect. Miljanovic et al (2007) measured the impact of dry eye syndrome on vision-related quality of life. They asked 190 participants with clinically diagnosed dry eye or severe symptoms and 399 without dry eye to complete a questionnaire, asking how much their everyday activities were limited by symptoms of dry eye and to what degree problems with their eyes limited their reading, driving, working at the computer, professional activities, and watching television. They concluded that dry eye syndrome is associated with a measurable adverse impact on several common and important tasks of daily living, further implicating this condition as an important public health problem deserving increased attention and resources. Clegg et al (2006) estimated the annual cost associated with the management of dry eye patients by ophthalmologists in France, Germany, Italy, Spain, Sweden, and the UK from the perspective of the health-care systems in the respective countries. They concluded that dry eye syndrome did not appear to impose a direct burden on the health care expenditure of the country investigated (Clegg et al 2006). However, among these countries CsA was used only in Germany for severe cases associated with Sjogren's syndrome. CsA costs much more than other medicines and the economic impact of this medicine must be seriously considered in relation to its effect on dry eye, given that it not only substitutes for but also complements the existing treatments for dry eye.

It is likely that future clinical and epidemiological studies will provide more definitive recommendations about the timing, efficacy, safety, and relative costs/benefits of anti-inflammatory therapy with CsA for dry eye.

Disclosures

The authors have no financial or proprietary interest in any materials or methods described herein.

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