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Treatment of chronic dry eye: focus on cyclosporine

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Abstract

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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 conjuctiva 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 doxycicline 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

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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 all 1997; McCarty et all 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

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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 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 Shirmer 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) Shirmer test I is performed without topical anesthesia, which evaluates better the ability of the ocular gland to respond to ocular surface stimulation; b) Shirmer test II (or Basic Secretion test) which is performed after topical anesthesia, evaluating better the basal tear secretion. Meibonian gland disease is diagnosed by biomicroscopic recognition of pathological signs such as ductal orifice metaplasia, reduced expressibility of meibonian 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 use 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

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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, conjuctival injection, conjunctival staining, corneal staining, corneal/tears signs, lid/meibonian glands, tear break-up time, and Shirmer 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%), Shirmer 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

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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 all 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 all 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

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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 metalloproteinasis), 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 loteprendol 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 (Plugfelder 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 administrated 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

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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

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Cyclosporine A is a fungal-derived peptide that inhibits T-cell activation and consequently inhibits the inflammatory cytokine production (selective inhibition of IL-I). 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 conjuctival 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 nephrotoxity 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 another 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

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