Management of Dry Eye Disease by Ophthalmic Emulsion of Cyclosporine A

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Purpose: To evaluate the efficacy, safety and tolerability of topical Cyclosporine A in the treatment of moderate to severe dry eye disease.

Patients and Methods: Sixty four patients of dry eye disease were enrolled in this study and divided into two groups A & B. Cyclosporine A, ophthalmic emulsion in two concentrations 0.05% and 0.1% was used for treatment of the two groups respectively twice daily for about 3 months. Schirmer's test, rose bengal staining, superficial punctate keratitis, IOP, visual acuity and ocular surface disease index "OSDI" were recorded before and after treatment. Follow up period was continued for about 3 months after stoppage of the 3 months treatment, also for detecting any other adverse effects.

Results: Nearly all the tests, symptoms and signs of this disease were improved with the use of Cyclosporine A. The most significant improvement was in rose bengal staining, superficial punctate keratitis and the sandy or gritty feeling. There was also decrease in the "OSDI" score indicating decrease in the effect of dry eye symptoms on the patients daily lives. There was no significant difference in dose - response relationship between the two groups, and no significant adverse effect was detected.

Conclusion: Cyclosporine A in both concentrations was safe and well tolerated. It improved the ocular symptoms and signs of dry eye disease and so decreased the effect of this disease on the visually related functions.

Dry eye, formally known as keratoconjunctivitis sicca, is a persistent dryness of cornea and conjunctiva due to decreased function of the tear glands or increased evaporation of tears.

Most dry – eye symptoms result from an abnormal, nonlubricative ocular surface that increases shear forces under the eyelids and diminishes the ability of the ocular surface to respond to environmental challenges. This ocular – surface dysfunction may result from immunocompromise due to systemic autoimmune disease or may occur locally from a decrease in systemic androgen support to the lacrimal gland as seen in aging, most frequently in the menopausal female. HYPOTHESIS: components of ocular surface (cornea, conjunctiva, accessory lacrimal glands, and meibomian glands), the main lacrimal gland, and interconnecting innervation act as a functional unit. When one portion is comprised, normal lacrimal support of the ocular surface is impaired. Resulting immune-based inflammation can lead to lacrimal gland and neural dysfunction.

Symptoms of dry eye range from mild irritation and foreign body sensation to severe discomfort with sensitivity to light. Depending on the duration and severity of disease, damage to ocular surface may also be present, with increase the risk of ocular infections.

The cause of dry eye is usually unknown but some known causes include: congenital disorders (puppies), infections (canine distemper virus), drug – induced (sulfa antibiotics), aging (as we get older, glands in the eyelid produce less oil), diseases including diabetes, Sjogren’s and Parkinson’s, and hormonal changes, especially after menopause. Hot dry or windy conditions, contact lenses and some types of eye surgery, including LASIK can aggravate dry eye.

There are several objectives in treating dry eye. These include: tear replacement, lubrication, reduce bacterial overgrowth, reduce inflammation and stimulate natural tear production. Since the aqueous tear fraction is absent or reduced, tear replacement is
very important but artificial tears alone do not lubricate as well as natural tears (5).

It is a fact that immune – based inflammation plays a role in the pathophysiology of dry eye related to Sjogren’s syndrome as well as in non-Sjogren’s keratoconjunctivities sicca (KCS). The inflammatory process involve the lacrimal gland and ocular surface also (3).

So, having the opportunity to treat with a drug that can interrupt the inflammatory process may reduce disease severity.

Topical treatment with the immunomodulatory agent cyclosporine A has been shown to reduce cell-mediated inflammatory responses associated with inflammatory ocular surface diseases resulting in improvement of signs and symptoms of dry eye disease (15,20).

The aim of this research is to evaluate the efficacy, safety and the tolerability of topical cyclosporine A ophthalmic emulsion in the treatment of moderate to severe dry eye disease.

Patients and Methods

64 patients suffered from dry eye syndrome were included in this study between January and October 2003, aging from 23 to 54 years with mean age of 42 ± 12. 40 patients were male while 24 were females, they were diagnosed as patients with moderate to severe dry eye disease depending on having Schirmer tear test (without anesthesia) ≤ 7mm/5 minutes and or superficial punctuate keratitis diagnosed by corneal punctuate fluorescein staining with score ≥1 (scale o (non).1 (mild punctuate keratitis), 2 (moderate) and score 3 (severe punctuate keratitis)), in addition to the traditional symptoms of dry eye disease including itching, burning, blurred vision, foreign body sensation, dryness, photophobia, and soreness or pain.

The exclusion criteria included pregnant and lactating women, patients with ocular infection, non dry eye ocular inflammation and recent ocular surgery within one year and also those patients with hepatic disorder, renal impairment and significant illness.

We divided patients into two groups A and B each of them was 32 patients. Group A was treated by cyclosporine A ophthalmic emulsion with concentration of 0.05%, while group B was treated by concentration of 0.1%. We advised patients in both groups to instill this ophthalmic emulsion twice daily at 8 am and pm, one or two drops in each instillation. We instructed them to use artificial tear eye drops from 4 to 6 times daily in addition to this emulsion. The course of treatment was continued for 12 weeks.

Preparation of the emulsion:

As cyclosporine eye drop is not available, we prepare it in the form of ophthalmic emulsion by using cyclosporine A solution (each ml contain 100 mg cyclosporine), we added it to corn oil to prepare two concentrations 0.05% and 0.1% and used it as ophthalmic emulsion.

All the patients were examined and investigated at the start of the treatment and every 4 weeks throughout the period of 12 weeks treatment.

In each visit the following was done

- Schirmer’s tear test without anesthesia.
- Rose Bengal staining (graded on a scale from 0 = non to 3 = severe).
- Superficial punctuate keratitis (also graded on a scale from 0 = non to 3 = severe).
- Visual acuity on the Snellen’s chart.
- Intraocular pressure measured by applanation tonometry.

- Symptoms of ocular discomfort (graded by the patient diaries on a scale from 0 = no discomfort to 4 = discomfort that interferes with normal daily activity).

In addition we tried to evaluate the patient response to the treatment by using the ocular surface disease index (OSDI) which is a global assessment parameter consisting of 12 questions designed to assess the symptoms of ocular irritation consistent with dry eye disease and their impact on vision-related functioning. The questions covered three areas: ocular symptoms, environmental triggers and vision-related function.

The answer of each question was graded on a scale from 0 to 4 (where 0 = “never” and 4 = “all the time”). Patient responses to all answers were then combined for a composite OSDI score ranging from 0 to 100.

After the completion of the 12 weeks of treatment, the patients were still examined every 4 weeks for another 12 weeks follow up. In each visit again; Schirmer test. Rose Bengal staining superficial punctate keratitis, visual acuity, intraocular pressure and ocular symptoms of discomfort were evaluated.

Results

64 patients with dry eye who continued the course of 12 weeks treatment and the follow up period were enrolled in this study. Some patients rather than those...
Mean scores for conjunctival rose bengal staining at baseline ranged from 1.2 to 2.0 for both temporal and nasal regions in both treatment groups. In temporal conjunctival rose bengal staining scores, there was significant improvement in group B at all treatment and posttreatment visits ($P \leq 0.016$) this improvement is significantly greater than group A ($P \leq 0.024$). figure (1) rose bengal staining scores were observed in both groups at treatment week 4 and posttreatment week 4 ($P \leq 0.031$). There were no significant among - group differences in the change from baseline in nasal conjunctival rose bengal staining.

At baseline, mean scores for superficial punctate keratitis ranged from 1.6 to 1.9 in the two groups.
Significant improvements were seen in both groups at all time points during the 12-week treatment phase (P ≤ 0.012) and 12 week post-treatment period (P ≤ 0.018). Cyclosporine A 0.1% produced greater improvement from baseline throughout the treatment and post-treatment periods (range -0.9 to -1.4 units). No statistically significant among-group differences in superficial punctate keratitis values were observed. (Figure 2)

Symptoms of ocular discomfort were evaluated from scheduled visit queries. At baseline, the mean score for sandy or gritty feeling ranged from 1.7 to 2.2 (mild to moderate). There was a significant improvement from baseline in sandy or gritty feeling in both groups at several visits (P ≤ 0.039). (Figure 3) Significant improvements from baseline in nasal conjunctival

At baseline the mean score for ocular dryness ranged from 2.1 to 2.5 (moderate to severe). Significant improvements from baseline in ocular dryness were seen at two or more time points in both groups (P ≤ 0.036).

As regard itching, there was also significant improvements from baseline at one or more time points in both groups (P ≤ 0.031), but there were no statistically significant differences among the groups at any time point. There were no significant within-group or between-group differences in photophobia, pain, or burning and stinging at any time point.

No clinically significant changes in visual acuity or intraocular pressure from baseline were recorded in both groups.

Baseline OSDI scores ranged from 30 to 46 (on a scale from 0 to 100, where 0 indicates no disability and 100 indicates complete disability). At both treatment week 12 and post-treatment week 12 there was at least a trend toward improvement in the OSDI score in group A.

Discussion

The mechanisms contributing to dry eye disease are still being non explained. Dry eye regardless of whether it is associated with systemic autoimmune disorder, is a lymphocytemediated inflammatory process.

This process affects the lacrimal gland acini and ducts, leading to abnormalities in the tear film and ultimately disrupting the homeostasis of the ocular surface. To date, much of the evidence for this hypothesis has come from the observation of lymphocytic infiltrates, proinflammatory cytokines, and autoantibodies in the lacrimal glands of patients with dry eye disease associated with immune-mediated systemic disease (Sjogren’s syndrome).  

In addition, some inflammatory makers, HLA-DR, CD40, and CD40 ligand, were strongly expressed in both Sjogren’s and non - Sjogren’s eyes. Some studies demonstrated that inflammatory processes was associated with abnormal lacrimal gland histologic findings, suggesting that inflammation in dry eye may contribute to the