Evaluation of the Effects of 0.03% Tacrolimus on Schirmer Tear Test and Tear Film Break-Up Time in Patients of Chronic Dry Eye Disease

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ABSTRACT

Introduction: The aim of this study was to evaluate the effects of 0.03% tacrolimus on Schirmer tear test and tearfilm breakup time in patients with chronic dry eye disease.

Material and Methods: This was a single centred, open label, 3 months prospective study. Patients with unilateral or bilateral dry eye disease and an ocular surface disease index score >12, atleast one eye with schirmer score <5mm and TBUT <10 s were enrolled in the study. Tacrolimus 0.03% eye ointment was instilled twice daily for three months in the affected eye.The primary efficacy outcome was Schirmer score after 3 months. The secondary outcomes were TBUT, OSDI score and adverse events.

Results: A total of 30 patients with the mean age of 51.92 ± 8.86 were enrolled and 25 patients completed the study. After 3 months significant improvement was seen in schirmer tear test (P<0.001), 44% patients showed ≥ 5 mm improvement and 12% patients showed ≥ 10 mm improvement in Schirmer score. Mean tear film breakup time also showed significant improvement after 3 months (p <0.001).Patients also reported significant improvement in ocular discomfort and dry eye symptoms suggested by decrease in OSDI score (p < 0.001). No patients discontinued treatment because of mild burning or irritation or any other ocular adverse event.

Conclusion: Dry eye patients demonstrated improvement in both signs and symptoms of dry eye after 3 months of treatment with 0.03% tacrolimus ointment.

Keywords: Keratoconjunctivitis sicca, Cyclosporine A, Ocular Inflammation, Schirmer Score, OSDI, TBUT

INTRODUCTION

Due to a wide variety of presenting symptoms, Dry eye disease (DED) is often unrecognized and this causes great frustration to the patient and treating physician. While these symptoms often improve with appropriate treatment, usually in majority of the cases the disease may not be curable. Dry eye disease is defined as a "multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and subacute inflammation of the ocular surface".[1] Dry eye disease is also called keratoconjuctivitis sicca, keratitis sicca, sicca syndrome, xerophthalmia, dry eye syndrome, ocular surface disease, dysfunctional tear syndrome or merely dry eyes.[2] The dry eye disease in which eyes don't produce sufficient tears is called Sjogren's syndrome.[3]

The prevalence of dry eye disease increases with age, affecting especially those older than 50 yrs of age.[4,5] Dry eye disease is more common in women and can affect any race.[6,7] According to the OSDI data, the prevalence of DED ranges from 5-35% worldwide while in India it is 29.25%.[8] Based on multiple epidemiological studies, older age and female sex are widely recognized as the two most common risk factors for dry eye.[9,10] Peri- and postmenopausal females seem to be particularly at a higher risk. This perhaps suggests that dry eye is an involutional disorder.

There are great advances in the understanding of dry eye disease over the past 10- 15 years in the area of epidemiology, pathogenesis, clinical manifestation, and possibly in the therapeutic regimen. Identification of inflammation as a major factor in dry eye helped make a tremendous step forward in the description and treatment of this condition. The recommended treatments for mild dry eye disease are lifestyle changes and the use of artificial tears. However, patients with moderate to severe disease may require anti-inflammatory medications or surgery. Ocular lubricants are often used as a first-line agent for managing all dry eye cases. As it is widely recognized that inflammation has a significant role in the etiopathogenesis of dry eye, a number of anti- inflammatory treatments like, steroids, tetracycline, azithromycin, and calcineurin inhibitors e.g. cyclosporine and tacrolimus are currently in use for its management. Many more anti-inflammatory medications are in development or clinical trial phases. These agents inhibit the expression of inflammatory mediators on the ocular surface, thereby restoring the secretion of a healthy tear film and reducing signs and symptoms.

US FDA approved topical cyclosporine A (CsA) 0.05% emulsion in 2002 which is the only medication in this category with a specific indication for chronic dry eye. Various clinical studies demonstrating the use of CsA in cases unresponsive to artificial tears, concluded that topical cyclosporine has shown beneficial effects in all categories of dry eye disease. Long-term evaluation of cyclosporine has demonstrated that the drug may occasionally halt progression of chronic dry eye disease in some patients and may be associated with a

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cure of signs and symptoms in another subset of patients with chronic dry eye disease.[11] Tacrolimus is a calcineurin inhibitor which inhibits the production of IL-2. However, it's mechanism of action is similar to CsA, it has a significantly greater potency in vitro, it is about 100 times more potent than CsA.[12] After its successful use in vernal keratoconjunctivitis and graft-versus-host disease (GVHD)[13], tacrolimus has also been evaluated in the treatment of dry eye disease. Topical tacrolimus, 0.03% and 0.1% drops or ointment, may be a promising treatment for DED patients.[14-16]

Study aim was to evaluate the effects of 0.03% tacrolimus on Schirmer tear test and tearfilm breakup time in patients with chronic dry eye disease.

MATERIAL AND METHODS

The present study was randomized, prospective, interventional study carried out on patients who were diagnosed as case of dry eye disease, attending outpatient department at Regional Institute of Ophthalmology (M.D. Eye Hospital), Allahabad during the year 2016-2017, after taking permission from ethical committee of M.L.N. Medical College, Allahabad. Out of the patients who attended outpatient department, adult patients of either sex were screened on the basis of inclusion criteria and those fulfilling the criteria were included in the study.

Inclusion criteria

- Patients included men and women aged ≥ 18 years.
- Have symptoms of dry eye disease for ≥ 6 months in any or both the eyes supported by a previous clinical diagnosis.
- Must be able to understand and follow study related advice.
- Patients reporting no improvement in response to artificial tear therapy.
- OSDI score ≥ 12 at screening.

Following signs at screening and baseline visits in atleast one eye:

- Tear film break up time ≤ 10 s
- Schirmers tear test without anesthesia ≤ 5 mm in 5 minutes.

Exclusion Criteria

- Not willing to give consent.
- Active blepharitis, meibomian gland disease, lid margin inflammation or ocular allergy.
- Any structural abnormalities on external eye examination for ex: entropion, trichiasis, lid scarring etc.
- Any inflammation or active structural changes in the iris or anterior chamber.
- Single functioning eye.
- Glaucoma.
- Previous eye surgery or punctual occlusion 6 months before study entry.
- Any systemic or topical medication other than artificial tears.
- Any systemic or topical antibacterial or antiinflammatory drug treatment 30 days before study entry.
- Immunosuppressive systemic therapy 90 days before the study entry.
- Contact lens wearer.
- Presence of any corneal infection or any corneal disease (marginal ulcer,opacity,scar,bullous keratopaty, symblepharon or tumor)

The study consisted of 5 visits conducted during 2 sequential phases (i) screening/eligibility phase which included a screening visit, and (ii) treatment phase which included next 4 visits conducted at day 1, 1 month, 2 months, and 3 months. At screening, patients discontinued use of all pre study medications, and the eligibility visit was scheduled after a predetermined washout period according to patient's pre study medication. One eye from each patient was chosen as the study eye, and only the study eye was used in the efficacy analysis. If only 1 eye of a patient was treated, that eye was selected as the study eye. If both eyes were treated, the worse evaluable eye was selected as the study eye. The worse eye was defined as the eye with the lower Schirmer score across the eligibility visit, if the score in both the eyes were equal the right eye was selected for analysis.

At each study visit, an interval medical history was obtained and any side effects were assessed, an ophthalmic examination including slit lamp biomicroscopy of the anterior eye segment, Schirmer test, tear film breakup time (TBUT),was performed and the OSDI (Ocular surface disease index) questionnaire was completed. In each study visit, TBUT was evaluated first, followed by Schirmer tear test. TBUT was conducted at room temperature with fans switched off, and all readings were taken by a single observer. We performed this test by moistening a fluorescein sodium strip with sterile normal saline and applying it to the inferior fornix. After several blinks, patient was instructed not to blink further, and the tear film was examined using a broad beam of the slit lamp with a blue filter. The time lapse between the last blink and the appearance of the first randomly distributed dark discontinuity in the fluorescein stained tear film was taken as the TBUT, it was measured before conducting other tests. TBUT was performed three times and mean of the readings was noted. Tear production was measured with Schirmer paper strips. The paper is carefully placed on the junction of the middle third and the lateral margin of the lower eyelid towards the temporal angle. In our study we used Schirmer without anesthesia to measure the basal as well as reflex tear production. The length of the moistened portion of the strip was recorded as Schirmer Score to an accuracy of 0.5 mm.

All patients were required not to use any other topical ophthalmic medications, other than given medication during the study period. Commercially available standard pharmaceutical preparation of the same batch, available in our set up was used in our study. Patients were instructed to visit after 1 month, 2 months, and 3 months after starting treatment for the subsequent study visits, which was scheduled for each patient. The need for at least a 3-month trial period to fully gauge the effectiveness of this therapy was stressed to each patient. All patients were advised to contact us and return at any time should problems arise and

in 3 months for a follow-up examination after their initial evaluations. Patients were also advised that mild burning or irritation on application of tacrolimus is common and also to avoid sun exposure following instillation of tacrolimus.

Efficacy was evaluated primarily with an objective measure and secondarily with objective and subjective measures. There was one primary objective outcome which is Schirmer score at each study visit. Secondary objective outcome was TBUT at each follow- up visit and secondary subjective outcome was ocular surface disease index (OSDI) questionnaire for the grading of the symptoms score. The OSDI composite scores before initiation of treatment i.e baseline and post treatment after completion of treatment i.e, after 3 months was used in the analysis. The safety outcome was measured as the incidence of adverse reactions and the nature of adverse reactions, determined at various visits by means of physical signs and symptoms, external eye examination, slit-lamp microscopy, visual acuity, intraocular pressure, and funduscopy. All patients were also questioned regarding any ocular symptoms related to the study medications by phone calls as well as at all follow up visits.

STATISTICAL ANALYSIS

Data were expressed as means ± SD. In all analysis, $P < 0.05$ was taken to indicate statistical significance for each time interval of 1 month, 2 months, and 3 months. All data were summarized using frequency distributions and/or descriptive summary statistics (mean and standard deviation [SD]). The efficacy analysis population included all patients who completed the study. The safety analysis population included all patients who were enrolled in the study. All statistical analyses included data for the selected eye. Paired Student's *t* test was used to assess the statistical significance. Chi square test ($\chi 2$) was used to analyse the categorical variables. All tests were two tailed, with a significance level of 0.05. Minitab 18.0 software was used for statistical analysis.

RESULTS

A total of 30 patients were enrolled in the study out of which 25 patients completed the study. The study covered wide range of age (40-75 years). The mean standard derivation (SD) age was 51.92 ± 8.86 yrs, 11 were females and 14 were males.

Efficacy - Efficacy was evaluated primarily with Schirmer score and secondarily with TBUT and OSDI.

Schirmer Score - Schirmer tear test was done in all patients. Baseline mean ± SD Schirmer score was 3.02 ±1.19 (mm) and at 1 month, 2 months and 3 months were 5.06 ± 1.65 (mm), 6.64 ± 2.24 (mm), and 8.58 ± 2.98 (mm).

We also observed the responder rate in terms of number of patients who achieved atleast 5 mm and 10 mm improvement in Schirmer score after completion of treatment i.e, 3 months. 11 patients (44%) showed 5 mm improvement and 3 patients (12%) showed 10 mm improvement in Schirmer score at 3 months (table-1, figure-1).

Tear film breakup time (TBUT) - Secondary efficacy outcome was objectively measured in terms of changes in TBUT (seconds) at baseline, 1 month, 2 months and 3 months visit to evaluate quality of tear films. Baseline mean ± SD TBUT (secs) was 5.68 ± 2.03 (secs) and at 1 month, 2 months and 3 months were 7.50 ± 2.32 (secs),9.06 ±2.64 (secs) and 10.50 ± 3.16 (secs), respectively (figure-1).

Point of time	Mean Schirmer score (mm)	SD
Baseline	3.02	1.19
1 month	5.06	1.65
2 months	6.64	2.24
3 months	8.58	2.98

Table-1: Mean (SD) Schirmer Score (in mm) at baseline and follow-up visits

Point of time	Mean TBUT	SD	P value
Baseline	5.68	2.03	
1 month	7.50	2.32	0.001
2 months	9.06	2.64	0.001
3 months	10.50	3.16	0.001

Table-2: Mean (SD) TBUT (in secs) at baseline and follow-up visits

Point of time	Mean OSDI	SD	P value
Baseline	43.61	9.43	
3 months	36.20	11.62	0.001

Table-3: Mean OSDI (SD) before treatment and after 3 months

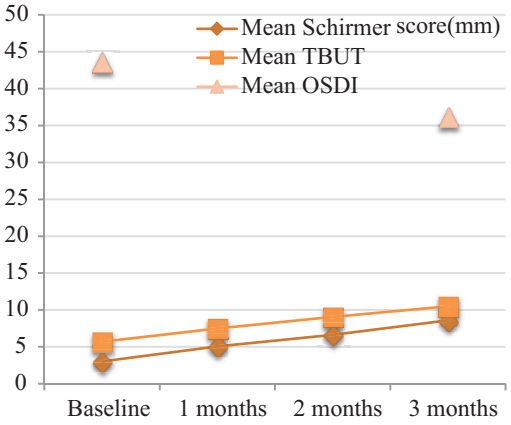

Figure-1: Improvement after treatment with tacrolimus.

OSDI Score

OSDI scores was also calculated before initiation of treatment (baseline) and after completion of treatment (3 months) for evaluating dry eye symptoms. Baseline mean ± SD OSDI score was 43.61±9.43 and at 3 months 36.20±11.62, reduction in OSDI score was statistically significant showing remarkable reduction in ocular and visual symptoms (table-2).

Safety - Incidences of non-serious adverse effects were also reported in our study. No ocular infection was reported during the treatment period. No serious adverse effects warranting the discontinuation of treatment was reported. The most common treatment related ocular adverse event

was ocular burning (11 patients) followed by ocular irritation (6 patients) followed by ocular pain (2 patients).

DISCUSSION

Although often disregarded as a minor problem, dry eye is a growing public health concern. Dry eye disease continues to be a challenging disease and its therapy depends on its severity. Based on the most recent concept, the armamentarium used to control dry eye disease comprises of a large range of therapeutic strategies.

The recommended treatment for mild dry eye disease are life style changes and the use of artificial tears. As it is widely recognized that inflammation has a significant role in the etiopathogenesis of dry eye, promoting ocular surface disruption and symptoms of irritation, a number of anti-inflammatory treatments are currently in use for its management. Anti-inflammatory medications are considered to be the first causative therapeutic approach in the treatment plethora of dry eye disease. Tacrolimus represents a very promising anti-inflammatory drug. Its mechanism of action is similar to cyclosporine A.

Several clinical trials have shown the beneficial effect of systemic and topical tacrolimus in the treatment of refractory ocular surface inflammation due to vernal keratoconjunctivitis[17], atopic keratoconjunctivitis[18], mooren ulcer[19], uveitis[20], ocular pemphigoid and corneal graft rejection[21,22]. These have laid the groundwork for studies using topical tacrolimus eye ointment for the treatment of ocular inflammation in severe dry eye. First of all Berdoulay et al in 2005 studied the effect of topical tacrolims 0.02% on tear production in dogs with keratoconjunctivitis sicca[23]. In three months trial of 8 dry eye patients, Moscovici et al reported improvement in all patients at the end of treatment in subjective symptoms, ocular surface staining and tear film stability in 2012.[14] Topical 0.03% tacrolimus eye drops improved tear stability and ocular surface status in cases of inflammatory SS-related dry eye as reported by Moscovici et al in prospective double blind randomized study in 2015.[24] Kharbanda et al used tacrolimus 0.03% eye ointment BD (twice a day) for three months in 15 patients and reported clinically and statistically significant improvement in subjective assessment of symptoms, staining, Schirmer score and tear film break up time.[25] This is consistent with our findings, during the first month of treatment Schirmer test and TBUT score were lower. The mean Schirmer score (in mm) increased significantly ($P < 0.001$) at all follow- up periods i.e, after 1 month,2 months and 3 months as compared to the baseline and also when compared to respective predecessor periods. Similarly, the secondary objective outcome of our study, mean TBUT (in secs) increased significantly ($P< 0.001$) at all follow- up periods. In this study, after 3 months of treatment patients´ response on OSDI score in both groups when compared to the pre-treatment OSDI score showed significant reduction in symptoms suggesting significant improvement in visual function. At the end of three months trial, we found significant improvement in all the subjective and objective outcomes in patients treated with tacrolimus eye ointment. As the enrollment criteria included only those patients who were unresponsive to artificial tears therapy,we can conclude that the active ingredient and not the vehicle was responsible for the improvement. Safety measures outcome at each visit included incidences and nature of adverse reactions. The study did not show any serious adverse events associated with topical tacrolimus therapy. Patients reported very good compliance with the treatment. No patient discontinued the use of tacrolimus because of ocular intolerability following instillation.

Our study demonstrates that in patients who have dry eye symptoms and are refractory to standard artificial tear therapy, 0.03% tacrolimus ointment is safe and effective. However, there are several limitations for our study. The first limitation is that the interpretation of our study findings are limited by its partially masked study design. The dry eye disease of the patients according to the cause and severity was not grouped, so we are unable to determine which patients may or may not respond to our study drug. Ocular surface staining, impression cytology, and hyperemia were not graded and evaluated. The final limitation is the power of the study and also the duration of study to ascertain long term effects and safety.

CONCLUSION

This study shows that 0.03% tacrolimus ointment improves symptoms and signs of dry eye disease in patients unresponsive to artificial tear supplementation. Tacrolimus ointment has been safe and effective in our study

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