Intracanalicular Dexamethasone Combined with Topical Cyclosporine for the Treatment of Dry Eye Disease

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INTRODUCTION

Dry eye disease (DED) is a chronic, multifactorial disease process of the tear film and ocular surface associated with pain, discomfort and blurry vision with the potential to have a considerable impact on quality of life.[1–3] The multifactorial and complex nature of DED was highlighted in the recently revised definition by the Tear Film and Ocular Surface Society's Dry Eye Workshop II in 2017[1] in which DED was defined as a "multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, accompanied by ocular symptoms in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles." As inflammation of the ocular surface is thought to be a core mechanism of DED, topical anti-inflammatory agents play a pivotal role in the management of DED.[4]

The importance of addressing and minimizing ocular surface inflammation in the treatment of DED is well established.[4,5] Multiple topical treatment options are available including topical corticosteroids and topical immunomodulators such as cyclosporine 0.05% and lifitegrast.[6–8] Topical corticosteroids are effective at reducing and controlling ocular surface inflammation but long-term use carries the risk of cataract formation, increased intraocular pressure (IOP) and glaucoma. Cyclosporine and lifitegrast are both staples of the dry eye treatment armamentarium for long-term, local control of ocular surface inflammation.[9] Cyclosporine 0.05%, which has been in use for nearly 20 years, has a well-established safety profile and has been shown to be efficacious in reducing ocular surface inflammation and increasing tear production. [10]

Although topical steroids have a limited role for chronic use in DED, they have been demonstrated to be of value in the short-term for refractory DED and for managing acute flares of DED.[11] Studies have also demonstrated the value of topical steroids as an induction agent prior to initiating topical cyclosporine therapy. Cyclosporine 0.05%, while an effective topical immunomodulator agent, is associated with side effects upon instillation such as burning, stinging and conjunctival hyperemia. These side effects can discourage use of the topical agent and to promote improved adherence, prior work has described the short-term, adjuvant use of topical corticosteroids when starting cyclosporine 0.05% to mitigate the burning, stinging and other associated side effects. Furthermore, this combined approach has been shown to produce a faster response to therapy with a quicker improvement in signs and symptoms of dry eye.[12,13]

Topical medication regimens, when used appropriately, can effectively manage ocular surface inflammation. However, drop adherence, complex medication regimens and difficulties with instillation are well-recognized challenges associated with topical therapies.[14,15] In recent years,

notable innovation has occurred across ophthalmology as it relates to drug delivery to circumvent the known barriers associated with topical therapies.[16,17] Recently, the dexamethasone ophthalmic insert (Dextenza 0.4 mg; Ocular Therapeutix) was introduced and was approved on-label for postoperative ocular inflammation and pain.[18] The insert is a drug-eluting, intracanalicular plug that that aims to provide a sustained and tapered release of steroid to the ocular surface over 30 days. In addition to studies reporting favorable results in patients after cataract surgery, a recent study by Ibach et al[19] evaluated the insert in patients following PRK and reported that patients preferred the insert compared to topical steroids.

This present study aims to evaluate the use of adjunctive dexamethasone (in the form of the insert) in patients started on cyclosporine 0.05% (Restasis) for the treatment of dry eye disease. To the best of our knowledge, no prior studies have evaluated the use of the insert to manage ocular surface inflammation in DED.

Methods

This was a prospective, open-label, interventional study performed at a single site (Cleveland, OH). This study was conducted in compliance with the Declaration of Helsinki and was reviewed and approved by the Salus ~~Institutional Board~~IRB on August 12, 2020. All participants provided written informed consent.

Patients

60 eyes of 30 patients age ≥18 with clinically diagnosed aqueous-deficient dry eye disease and determined to be a candidate (based on clinical judgment) for treatment with a topical immunomodulator were enrolled in the study.

Patients were excluded if they had been on topical immunomodulation therapy in the 3 months prior to screening, were actively being treated with topical, oral or intravenous immunosuppressive agents, had a hypersensitivity to dexamethasone, had active infectious systemic or ocular disease or had altered nasolacrimal flow of either acquired or congenital origin. Pregnant patients were also excluded.

Following screening and informed consent, patients were randomized into 3 groups; a study group and 2 control groups. Each group included 10 patients. The study group was started on cyclosporine 0.05% and was implanted with an intracanalicular, 0.4 mg dexamethasone insert in both eyes. The first control group was started on cyclosporine 0.05% in conjunction with topical loteprednol 0.5% twice daily. The 2nd control group was started on cyclosporine 0.05% as monotherapy.

The study period lasted 12 weeks including one screening/prescription visit and follow-up visits which occurred at weeks 1, 2, 4, 8 and 12 following initiation of therapy. At weeks 1, 2, 4, 8 and 12 the primary and secondary endpoints were assessed.

Main Outcome Measures

The primary outcome measure was the mean change in corneal surface staining (guided by use of fluorescein and lissamine green) at weeks 1, 2, 4, 8 and 12 based on the NEI grading scale. Corneal fluorescein staining was graded from 0 to 3 (none to heavy) in five regions of the cornea and summed for a total score.

All secondary outcome measures followed the same timeline with comparison at weeks 1, 2,4, 8 and 12 in comparison to baseline. Secondary outcome measures included the mean change in tear break-up time (TBUT), the mean change in conjunctival staining (graded 0-3 in 6 regions), the mean change in tear osmolarity as measured by TearLab, the mean change in DEQ-5, the mean change in meibomian gland scores as measured by quality of meibum expression, the mean change in best-corrected distance visual acuity (BCDVA) as measured by ETDRS chart and the mean change in Schirmer's score as measured by a Schirmer's test strip.

Meibomian gland scoring involved grading the quality of expression (0-3) from 15 glands along the lower eyelid including temporal, central and nasal. For scoring, 3 was representative of clear, liquid secretions and 0 was no secretions. The DEQ-5 Dry Eye Questionnaire was used to evaluate symptoms and characterize severity of discomfort, dryness and tearing. Possible scores ranged from 0 to 22 with higher scores representing worse symptoms.

On the screening visit and the initiation of therapy including implantation of the dexamethasone insert in the study group, a physician ease of insertion questionnaire was also completed by the physician implanting the device. All device-related complications were recorded. All subject-reported adverse events were recorded at each study visit.

Study Device

The sustained-release depot is a single-use insert containing 0.4 mg of active dexamethasone designed for implantation through the punctum in the canaliculus. The device was approved by the FDA for the treatment of ocular inflammation and pain in association with ocular surgery. The insert's composition is polyethylene glycol (PEG) and employs hydrogel technology to deliver dexamethasone. The insert is also conjugated with fluorescein allowing for visualization of the insert after it is inserted into the canaliculus. With contact of fluid (hydration), the insert swells to securely conform to the canalicular location, allowing direct delivery of the

preservative-free dexamethasone on to the ocular surface over the course of 30 days. Over time, with continuous hydrolysis, the insert gradually softens and degrades and is eventually cleared through the nasolacrimal drainage system without the need for removal.

Statistical Analysis

All statistical analysis was performed using Prism 9 software (GraphPad Software, Inc.). Repeated measures analysis of variance was performed to compare the values at each time point in each group. Post hoc analyses were also performed with Bonferroni correction to directly compare the mean values at each time point in comparison to baseline. A *P* value less than 0.05 was considered statistically significant.

RESULTS

Patient Demographics

Sixty eyes of 30 subjects were successfully enrolled into the study including 20 eyes of 10 subjects in the dexamethasone/cyclosporine group, 22 eyes of 11 subjects in the loteprednol/cyclosporine group and 18 eyes of 9 subjects in the cyclosporine monotherapy group. All 3 groups were summarized by baseline characteristics, which are shown in Table 2.

None of the three groups, including the study and two control groups met the primary endpoint. In the dextenza group, the mean baseline corneal staining score was 0.5 ± 1.0 with 70% (n=14) without evidence of corneal staining at baseline. The mean score at weeks 4, 8 and 12 was 0.6 ± 1.0 (P = 0.99), 0.5 ± 1.1 (P = 0.99) and 0.7 ± 1.4 (P = 0.97), respectively. In the loteprednol group, the mean baseline corneal staining score was 0.8 ± 1.5 with 64% (n=14) without corneal staining at baseline. At weeks 4, 8 and 12, the mean score was 0.9 ± 0.9 (P = 0.99), 0.0 ± 0.0 (P = 0.06) and 0.6 ± 1.0 (P = 0.78), respectively. In the cyclosporine monotherapy group, the mean baseline corneal staining score was 0.5 ± 0.5 with 50% (n=9) of eyes absent of any corneal staining at baseline. There was no significant change in corneal staining at any time point with a mean score of 1.1 ± 1.4 (P = 0.26), 0.3 ± 0.6 (P = 0.63) and 0.5 ± 0.7 (P = 0.99) at weeks 4, 8 and 12, respectively. These results, in addition to comparisons of other outcome measures, are summarized in Table 3.

There was no significant change in conjunctival staining, Schirmer scores, TBUT, tear osmolarity or meibomian gland scores at any of the follow-up time points in comparison to baseline in all three groups. These results are summarized and also demonstrated in Table 3.

Across all visits, the mean IOP remained stable in all three groups. In the cyclosporine monotherapy group, there were no instances of IOP elevation >10 mmHg above baseline. Similarly, in the dextenza and loteprednol groups, there were no instances of IOP elevation >10

mmHg above baseline at any time point. There were no canalicular-related complications or adverse events related to implantation of the dexamethasone insert. No patients required removal of the insert.

To evaluate symptoms, a subjective questionnaire, DEQ-5, was administered at each time point. At baseline, the mean DEQ score was 14.1 ± 4.0, 14.4 ± 2.4 and 14.4 ± 3.7 in the dextenza, loteprednol and cyclosporine monotherapy groups, respectively. In the dextenza group, the mean DEQ score improved to 10.6 ± 4.6 (P = 0.22), 11.3 ± 4.5 (P = 0.19) and 10.3 ± 6.3 (P = 0.20) and weeks 4, 8 and 12, respectively but the change was not statistically significant. In the loteprednol group, there was a significant improvement in the DEQ score with a mean score of 11.0 ± 2.4 (P <0.01), 9.1 ± 4.0 (P <0.01), and 10.2 ± 3.8 (P <0.01), at weeks 4, 8 and 12, respectively. Similarly, there was an improvement in the DEQ score in the cyclosporine monotherapy from baseline at weeks 8 (10.6 ± 2.6, P <0.01) and 12 (9.4 ± 3.1, P<0.01), but the change at 4 weeks (12.2 ± 2.2, P = 0.39) was not statistically significant.

DISCUSSION

This prospective, randomized, open-label clinical study evaluated the use of an intracanalicular 0.4 mg dexamethasone insert in combination with topical cyclosporine 0.05% for the treatment of dry eye. Although the efficacy of this combination remains unclear based on the results of this pilot study, the results of this study support the safety of this approach without any adverse events, no IOP spikes above baseline and no device-related complications.

Topical cyclosporine 0.05% has been shown to provide an improvement in tear production and dry eye-related symptoms but many patients in clinical trials leading to its approval reported a delay in symptomatic relief.[7,10] As a delay in relief can contribute to reduced compliance, providers may initiate adjuvant use of topical steroids in combination with topical cyclosporine 0.05% and studies evaluating this combined regimen reported findings of quicker symptomatic relief and more rapid improvement of objective parameters such as Schirmer testing and corneal staining.[12,13] No groups in this study met the primary endpoint, however, patients in the loteprednol group reported a significant improvement in symptoms as measured by the DEQ-5 questionnaire, consistent with prior studies evaluating the combined use of corticosteroids and topical cyclosporine 0.05%. The dextenza group also noted an improvement in symptoms, but the change was not statistically significant. An improvement in symptoms with a combination of cyclosporine 0.05% and corticosteroids corroborates what has previously been reported.[12,13]

Several prior studies[18,20–22] have highlighted the safety and efficacy of the dexamethasone insert evaluated in this present study with regards to postoperative pain and inflammation following cataract surgery. However, multiple recent studies[19,23,24] have described use of the insert beyond the postoperative setting including a recent report describing the combined use of thermal pulsation therapy with the dexamethasone insert for the treatment of meibomian gland dysfunction.[24] To our knowledge, this is the first study evaluating the adjuvant use of the dexamethasone insert in combination with cyclosporine 0.05%. Although this present study did not yield any significant results, we anticipate future studies will involve the dexamethasone insert evaluating its utility in the treatment of dry eye.

Prior studies have demonstrated the favorable use of topical corticosteroids as an induction agent in combination with topical cyclosporine to augment the anti-inflammatory properties offered by cyclosporine. Although both the topical steroid and intracanalicular dexamethasone groups in this present study offered similar results, there are considerations unique to corticosteroids as it relates to sustained drug delivery. The sustained-release insert described herein offers theoretical benefits to bypass the challenges and potential side effects of topical corticosteroids.[25,26] Topical agents, which are instilled intermittently, inevitably lead to variability in drug concentration owing to the poor bioavailability of the agent. The insert's intracanalicular location, with close proximity to the ocular surface, purports to offer a superior bioavailability profile with improved consistency of drug concentration in contrast to topical administration. The tapered delivery of drug from the insert over the course of 30 days minimizes the risk for rebound inflammation, which can occur with abrupt discontinuation of topical steroids. In addition, the preservative-free composition of the insert overcomes concerns related to preservatives and ocular surface toxicity, an established issue related to long-term use of topical drops.[27]

This study has a number of limitations. The sample size was small in each group. The primary endpoint, which was improvement in corneal staining, was not met by any of the three groups. However, it is important to note that corneal staining was not a component of the inclusion criteria and thus future studies with refined inclusion criteria would be beneficial to evaluate the value of dexamethasone combined with cyclosporine 0.05% in improving corneal staining. Further, it's possible that an increase in sample size and an adequately powered study could lead to meaningful changes in other parameters such as TBUT and Schirmer scores, both of which have been demonstrated to improve following use of cyclosporine 0.05% in prior studies.[12,28]

CONCLUSION

The challenges of topical medication use are widespread and well recognized across ophthalmology. The safety profile reported in this study, albeit a small sample size, indicates the dexamethasone intracanalicular insert is a safe alternative option to topical steroids to augment the anti-inflammatory properties of topical cyclosporine 0.05%. Further study is necessary but use of the dexamethasone insert may provide a means to optimize medication delivery without compromising safety or efficacy in the treatment of dry eye disease.

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Table 1 – Baseline Demographics			
Parameter	**Dextenza + Cyclosporine N = 10**	**Loteprednol + Cyclosporine N = 11**	**Cyclosporine monotherapy N = 9**
Age			
Mean ± SD (years)	56.6 ± 18.3	61.4 ± 11.6	61.1 ± 11.9
Race, n (%)			
White African American Asian	8 (80%) 2 (20%) 0	11 (100%) 0 0	6 (67%) 1 (11%) 2 (22%)
Gender			
Male / Female	4 M / 6 F	2 M / 9 F	1 M / 8 F
IOP			
Mean ± SD (mmHg)	6.6 ± 2.2	5.4 ± 1.5	5.7 ± 3.3

Table 1. Demographic and clinical characteristics. IOP = intraocular pressure; SD = standard deviation.

Table 2 - Results			
Parameter	**Dextenza + Cyclosporine**	**Loteprednol + Cyclosporine**	**Cyclosporine monotherapy**
Corneal staining			
• **Baseline**	0.6 ± 1.0	0.8 ± 1.5	0.5 ± 0.5
• **1 month**	0.6 ± 1.0	0.9 ± 0.9	1.1 ± 1.4
• **2 month**	0.5 ± 1.1	0.0 ± 0.0	0.3 ± 0.6
• **3 month**	0.7 ± 1.4	0.6 ± 1.0	0.5 ± 0.7
Conjunctival staining			
• **Baseline**	0.5 ± 1.8	1.5 ± 1.8	0.4 ± 0.6
• **1 month**	0.3 ± 0.6	0.9 ± 1.4	0.5 ± 0.7
• **2 month**	0.4 ± 0.8	0.8 ± 1.8	0.3 ± 0.6
• **3 month**	0.8 ± 1.7	1.0 ± 1.6	0.7 ± 1.4
Schirmer scores (mm/5 min)			
• **Baseline**	14.9 ± 10.3	10.3 ± 7.2	11.6 ± 10.5
• **1 month**	15.4 ± 10.1	12.9 ± 9.1	10.1 ± 8.5
• **2 month**	15.8 ± 9.4	12.4 ± 8.4	10.8 ± 6.4
• **3 month**	12.3 ± 7.1	10.1 ± 6.0	9.6 ± 5.5
Tear breakup time (seconds)			
• Baseline	6.6 ± 2.2	5.4 ± 1.5	5.7 ± 3.3
• 1 month	8.0 ± 3.6	6.1 ± 2.8	7.4 ± 3.7
• 2 month	7.7 ± 3.1	6.2 ± 2.2	7.1 ± 3.4
• 3 month	7.7 ± 2.5	6.1 ± 2.4	7.3 ± 3.6
Tear osmolarity			
• **Baseline**	295.5 ± 17.4	311.3 ± 19.8	306.9 ± 28.4
• **1 month**	304.4 ± 30.1	307.7 ± 17.3	307.9 ± 24.2
• **2 month**	303.9 ± 22.1	300.1 ± 19.2	295.3 ± 20.7
• **3 month**	299.5 ± 16.2	304.4 ± 28.7	304.6 ± 19.6
Meibomian gland scores			
• **Baseline**	8.7 ± 2.4	7.1 ± 2.1	9.2 ± 2.6
• **1 month**	7.6 ± 1.8	6.7 ± 2.5	7.2 ± 1.4
• **2 month**	8.3 ± 2.0	6.3 ± 2.6	8.2 ± 2.2
• **3 month**	8.7 ± 2.0	6.0 ± 2.3	7.3 ± 1.4

Table 2. Results of clinical parameters are summarized with the mean and standard deviation demonstrated at weeks 4, 8 and 12 in comparison to baseline.