Safety and Efficacy of Topical Azithromycin Ophthalmic Solution 1.0% in the Treatment of Contact Lens–Related Dry Eye

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Purpose: The purpose of this pilot study was to evaluate the safety and efficacy of azithromycin ophthalmic solution 1% in patients with contact lens–related dry eye (CLDE).

Methods: This was a 4-week, single-center, open-label clinical trial in patients diagnosed with CLDE using the Contact Lens Dry Eye Questionnaire (CLDEQ). Fifty patients were enrolled in this study. The patients were randomized to 1 of 2 treatment groups: azithromycin ophthalmic solution administered bid on days 1 and 2 and on days 3 to 29±1 or Visine for Contacts rewetting drops administered qid on days 1 to 29±1. The patient diaries were used daily to collect data on comfortable and total contact lens wear time and ocular dryness throughout the treatment period. Tear osmolarity, fluorescein corneal staining, and visual acuity were also assessed during clinic visits.

Results: Fifty patients were enrolled, and 44 completed the study. One patient discontinued in the azithromycin group, and five patients discontinued in the rewetting drops group because of adverse events. A statistically significant increase in mean comfortable contact lens wear time from baseline was observed for the subjects treated with azithromycin ophthalmic solution as compared with the subjects treated with rewetting drops at week 4 (P=0.004; primary endpoint), in addition to weeks 2 and 3. The improvement in the mean comfortable wear time for the patients in the azithromycin treatment group exceeded 2 hrs throughout the treatment period (weeks 1–4). No significant differences were observed between the groups for total wear time, low contrast visual acuity, or tear osmolarity. Subject-rated ocular dryness (PM time assessments) was significantly improved from baseline in the subjects treated with azithromycin ophthalmic solution as compared with those treated with rewetting drops at weeks 2 and 3 endpoints (P=0.015 for each week). Additionally, a statistical difference was observed in favor of the azithromycin treatment group at week 2 for the subjects reclassifying as nondry eye as determined by the CLDEQ (P=0.05).

Conclusions: Treatment with topical azithromycin ophthalmic solution was well tolerated and resulted in a significant improvement in comfortable contact lens wear time in the patients with CLDE.

Key Words: Contact lens—Dry eye—Clinical trial—Azithromycin—Pharmaceutical.

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Contact lens wear is commonly associated with symptoms of ocular irritation including symptoms such as dryness, discomfort, soreness, tiredness, and irritation, among other symptoms.[1–4] Reports have shown that between 25% and 50% of contact lens wearers have these symptoms, albeit differing frequencies and severities.[1–4] Further, these symptoms have been shown to increase in their intensity or severity over the course of a day's wear of lenses, with an average increase of approximately 25% as demonstrated in at least 1 study.[1,4]

A consequence of these symptoms is that they commonly lead to reductions in daily wearing times, dissatisfaction with contact lenses, or ultimately, permanent discontinuation of contact lens wear. Prior work from our laboratory showed that approximately 25% of individuals have tried contact lenses and subsequently discontinued contact lens wear, with practitioners estimating approximately a 16% patient discontinuation rate from contact lens wear each year.[3,5] The overwhelming reason for this discontinuation is because of symptoms of ocular irritation (and specifically, dryness), rather than because of other issues such as preference for another modality or vision problems with contact lenses.[3]

Although strides have been made in understanding the cause of dry eye in contact lens wearers, there is still room for further insight. Traditionally, contact lens–related dry eye (CLDE) is classified as an ''evaporative'' form of dry eye disease.[6] Interestingly, there have actually been few, if any, studies that have shown an increase in evaporation in contact lens wearers with dry eye. Although CLDE is probably evaporative in nature, it needs further evidence in support. Studies have shown that patients using certain contact lens polymers (Food and Drug Administration [FDA] groups II and IV) are more likely to experience CLDE, in addition to having a reduced lipid layer thickness, rapid tear film thinning as measured by interferometry, and increased osmolarity.[7,8] As has been shown in

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other studies, an increase in osmolarity is associated with an increase in inflammatory mediators, such as cytokines, on the ocular surface.[9,10] One study showed that contact lens wearers also have increased meibomian gland atrophy when using meibography techniques when compared with nonlens wearers.[11] These findings—reduced lipid layer thickness, increased tear film thinning, and increased meibomian gland dropout—lead to the suggestion that lens wearers may be more prone to meibomian gland disease (a form of posterior blepharitis), although further confirmation of this through larger scale epidemiologic studies is warranted.[12]

It also is clear that the understanding of the causes and pathologic conditions of blepharitis remains incomplete. Therefore, it is not surprising that although it is a common ocular disorder, no FDA-approved treatment for blepharitis or CLDE has been established to date. Azithromycin ophthalmic solution 1% (AzaSite, Merck, Whitehouse Station, NJ) is a topical macrolide broad-spectrum antibiotic approved by the US FDA for the treatment of bacterial conjunctivitis caused by susceptible isolates of CDC coryneform group G, *Hemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus mitis* group, and *Streptococcus pneumonia*.[13] Research has demonstrated that in addition to their antimicrobial activity, macrolides inhibit cytokine production in vitro, in a mouse model and in bronchoalveolar fluid of subjects with chronic inflammatory airway diseases.[14–16] Azithromycin ophthalmic solution 1% is a broad-spectrum topical antibiotic with antiinflammatory properties. In animal models, ophthalmic azithromycin penetrates the conjunctiva and cornea within minutes of instillation and reaches a peak concentration in the eyelids after 7 days of treatment.[17] In 1, small-scale pilot study, subjects with posterior blepharitis were treated with a 30-day regimen of azithromycinophthalmic solution, and the signs and symptoms of posterior blepharitis improved.[18] Azithromycin ophthalmic solution has also been found to improve the phase transition temperature of lipids secreted by subjects with meibomian gland disease.[19]

Although there is a significant interest in reducing the problem of contact lens–related dry eye, there has been little relative progress because of a lack of evidence for efficacious treatments. In this regard, new materials, designs, care solutions, and even things such as punctal plugs, have shown to have little effect on reducing this problem.[20,21] There has also been a paucity of research that has evaluated the impact of a pharmaceutical in the treatment of contact lens–related dry eye, probably given the limited therapeutic options available in this regard.[22,23] Because of the mechanism of action of azithromycin, and the potential factors associated with CLDE (e.g., inflammation,[15,16,22,23] blepharitis[19,24]), it is hypothesized that this compound could serve as an efficacious therapy for CLDE. Thus, this pilot study was designed to evaluate the safety and efficacy of azithromycin ophthalmic solution in patients with CLDE.

METHODS

This was a single-center, open-label, randomized clinical trial of the effects of azithromycin ophthalmic solution versus rewetting drops in subjects diagnosed with CLDE. All study visits were conducted in a clinical setting, and all the procedures were conducted by certified investigators and technicians. The study protocol, protocol amendments, informed consent form, investigator qualifications and sites, and recruiting materials were reviewed and approved by the Western Institutional Review Board. The study was conducted in accordance with current Good Clinical Practice guidelines and the Declaration of Helsinki and was registered at ClinicalTrials.gov under the registry number NCT01105624.

The subjects were recruited through a recruitment database and advertisements and were included if they were at least 18 years of age and provided written informed consent. Additionally, to be included in the study, the subjects were required to have a positive diagnosis of CLDE based on their responses to the described Contact Lens Dry Eye Questionnaire (CLDEQ) and a score of ≥ 2, (i.e., moderate severity on a 0–4 scale, where 0=no ocular dryness and 4=very severe ocular dryness) on a self-reported assessment of ocular dryness at the screening Visit.[25] All the subjects were required to have a self-reported use of daily wear soft contact lens that had been properly fitted for at least 30 days before screening and report that they were able to wear their contacts lenses for at least 8 hrs per day. There were no inclusion or exclusion criteria related to the contributing cause associated with their CLDE, other than the subjects needing to be symptomatic as per the above. The subjects were excluded if they demonstrated evidence of an ongoing ocular infection, disease, or ocular abnormality that would require the use of additional topical ophthalmic medications. The subjects were also excluded if they underwent cauterization of the puncta or had punctal plugs inserted or removed within 90 days of the screening Visit. Additionally, the subjects were excluded if they used rigid or extended wear contact lenses or had changed the brand of their contact lenses within 30 days of the screening visit.

VISIT 1 (DAY 1)

All the subjects were required to provide written informed consent before any study procedures. Demographic data, ocular and nonocular medical history, and concomitant medications were recorded, and women of childbearing potential were required to submit a negative urine pregnancy test. Habitual high contrast visual acuity (HCVA) and low contrast visual acuity (LCVA) were obtained with contact lenses, and each subject then completed the CLDEQ. The subjects were scheduled for visit 1 to be approximately in the middle of a wear cycle (1 or 2 weeks for 2 or 4 week replacement lenses, respectively) and to bring a new pair of their lenses to the clinic. The subjects were asked to estimate and record the average number of hours of comfortable contact lens wear time and the average total number of hours of contact lens wear time per day over the past week. The subjects were asked to rate their level of ocular dryness on a 0 to 4 scale. Tear osmolarity was then assessed for each eye using the TearLab Osmolarity System. The subjects were then instructed to remove their contact lenses, and slitlamp biomicroscopy and external eye examinations were performed. Fluorescein corneal staining was then performed on each eye (5 μL of 2% fluorescein applied to the ocular surface) and graded according to National Eye Institute/Industry Workshop Guidelinescriteria.[26]

Eligible subjects were then randomized to receive either azithromycin ophthalmic solution 1% (AzaSite) or rewetting drops (Visine for Contacts) in the 1:1 ratio, and they were not masked as to the treatment assignment. The subjects randomized to azithromcyin 1% were instructed to administer 1 drop to each eye bid for the first 2 days and then 1 drop QD for days 3 to 29 (± 1) applied to the ocular surface in the morning before contact lens

application. The subjects randomized to rewetting drops were instructed to administer 1 to 2 drops qid throughout the 29-day treatment period, spaced by approximately 4 hrs on each dosing. The first dose of study medication was self-administered at the clinic once dosing instructions were provided. The subjects were instructed to apply a new pair of contact lenses to their eyes 10 min after the instillation of study medication. The subjects were queried for adverse events (AEs) and scheduled to return for visit 2 in approximately 2 weeks.

Diary cards were provided to each subject along with instructions for their completion. The subjects were instructed to begin using the diary cards the day after visit 1. The subjects were instructed to record the morning (AM) ocular dryness assessment before instilling study medication (and lens application) and record evening (PM) dryness levels before lens removal each day. Further, the subjects were required to record the time that their contact lenses were inserted, the time lenses became uncomfortable, and the time lenses were removed.

VISIT 2 (DAY 14±2)

Concomitant medication usage was recorded, an AE query performed, and study medication and diary cards were collected. The subjects underwent habitual HCVA and LCVA assessment, completed the CLDEQ, and had tear osmolarity readings measured before removing their contact lenses. Biomicroscopy, external eye examination, and fluorescein corneal staining were subsequently performed. The subjects then reapplied the lenses worn to that visit, and additional study medication and diary cards were provided. The subjects were scheduled to return for visit 3 in approximately 2 weeks.

VISIT 3 (DAY 29±1)

All the assessments and procedures were performed as at visit 2. Once the assessments were complete, any unused study medication and diary cards were collected. The subjects were made to exit from the study and instructed to discard their current pair of lenses after their next removal and resume normal contact lens wear routine with a new set of lenses.

STATISTICAL ANALYSES

The primary efficacy endpoint for this study was the CFB in the duration of subject-reported comfortable contact lens daily wear time (hours per day) at the week 4 endpoint for the intent-to-treat (ITT) population (all randomized subjects). The week 4 endpoint was defined as the average of the CFB values for comfortable contact lens daily wear time from days 23 to 29, inclusive. Assuming the common SD of the duration of comfortable contact lens daily wear time at the week 4 endpoint for each group was 2 or 2.5 hrs, 25 subjects per group would provide 93% and 79% power, respectively, to detect a 2-sided difference of 2 hrs between groups at alpha=0.05.

Descriptive statistics were provided with statistical testing performed using an analysis of covariance (ANCOVA) model with treatment and baseline as main effects. Secondary efficacy endpoints from the data captured from the diaries included the following: CFB in comfortable contact lens wear time at week 1 (days 2–8), week 2 (days 9–15), week 3 (days 16–22), CFB in total contact lens wear time (week 1–4 time intervals as defined for comfortable contact lens wear), and CFB in subject-reported levels of ocular dryness both at the AM assessment and PM assessment. Secondary efficacy endpoints from data captured at the clinic included the following: no diagnosis of CLDE as assessed by the subjects' responses to the CLDEQ, CFB in tear osmolarity during the treatment period and CFB in the habitual LCVA. Except as noted below, for each of these endpoints, descriptive statistics were provided with statistical testing performed using an ANCOVA model with treatment and baseline as main effects to evaluate treatment efficacy. For no diagnosis of CLDE, the proportion of the subjects who did not have CLDE based on the CLDEQ for each treatment group was compared using Fisher exact test at visits 2 and 3. Change from baseline for tear osmolarity and habitual LCVA was summarized by eye and overall by treatment group and visit. A mixed-effects ANCOVA model with CFB as an outcome was performed to assess treatment differences. The model included treatment and baseline as covariates and a random intercept for study subjects to account for the correlation among eyes.

Adverse events were recorded at each visit and were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 13.0) and categorized by system organ class using preferred terms. Slitlamp biomicroscopy, HCVA, and fluorescein corneal staining findings were summarized only for safety outcomes but not analyzed for hypothesis testing per the approved study protocol.

RESULTS

Fifty subjects were enrolled in the study and were included in the safety and ITT population (25 in each treatment group). Six subjects discontinued prematurely from the study because of AEs, one in the azithromycin treatment group and 5 in the rewetting drops group. The demographics (age, sex, and race) for all the subjects enrolled in the study are listed in Table 1.

Efficacy

The mean daily duration of comfortable contact lens wear time was longer for the subjects treated with azithromycin 1% ophthalmic solution than rewetting drops at each of the weekly endpoints (weeks 1–4) after initiating treatment (Fig. 1A). Significant differences were observed between treatment groups for the CFB in the duration of comfortable contact lens time at not only the primary endpoint, week 4 endpoint (P=0.004) but also at weeks 1–3 (P=0.006, P=0.001, $P<0.001$, respectively) endpoints (Fig. 1B). No statistically significant differences were observed

TABLE 1. *Subject Demographics by Treatment Group*

	Azithromycin 1%	Rewetting Drops	Total
	n=25	n=25	n=50
Mean age (y) ± SD	32.0±12.9	33.0±9.8	32.5±11.4
Age range (min, max)	18, 67	18, 51	18, 67
Female, n (%)	19 (76)	20 (80)	39 (78)
Male, n (%)	6 (24)	5 (20)	11 (22)
White, n (%)	19 (76)	23 (92)	42 (84)

Demographic information (age, sex, and race) is summarized for subjects according to dosing assignment (azithromycin 1% or rewetting drops) and for the treatment groups combined.

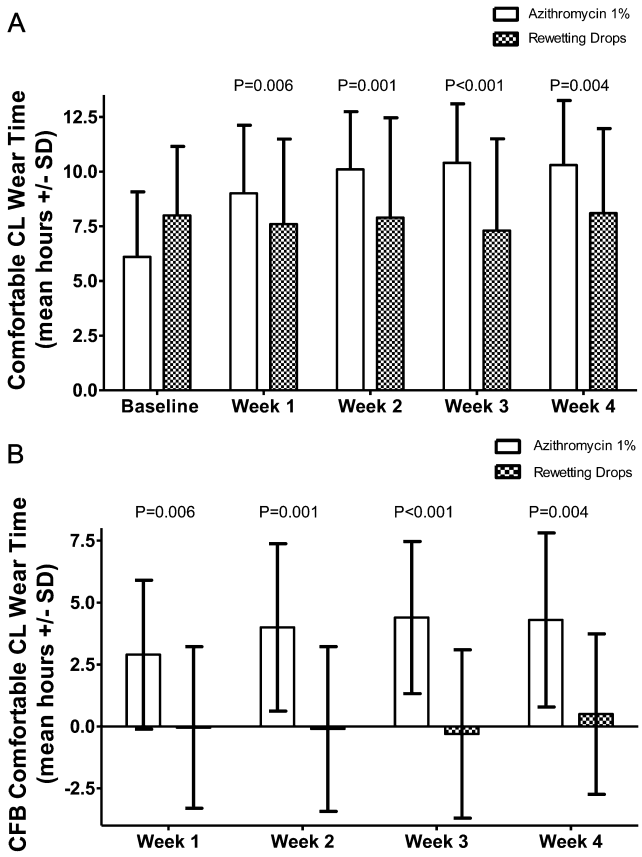

FIG. 1. Comfortable contact lens wear time. Comfortable contact lens wear time (mean±SD) reported by the subjects at the baseline assessment and over each week of treatment out to 4 weeks are depicted. Mean wear time by treatment group, either azithromycin 1% ophthalmic solution or rewetting drops, are shown in (A), and mean wear times calculated as a change from baseline (CFB) for each treatment group are shown in (B). Statistical testing was performed using an analysis of covariance (ANCOVA) model with treatment and baseline as main effects to evaluate treatment efficacy.

with regard to the mean daily total contact lens wear time (Table 2), although this was not expected given the ceiling effect associated with overall wearing time.

Subject-rated levels of ocular dryness were reduced in both groups after the initiation of treatment. Mean ocular dryness scores of the subjects treated with azithromycin 1% ophthalmic solution were lower than those treated with rewetting drops at both the AM (Fig. 2A) and PM assessments (Fig. 2B). Statistically significant differences in the CFB levels of ocular dryness between treatment groups were only observed at the PM assessment; at weeks 2 and 3, a statistically significant reduction in ocular dryness (PM assessment) was observed for the subjects treated with azithromycin 1% ophthalmic solution as compared with the CFB for the subjects treated with rewetting drops (P=0.015for both endpoints).

A statistical difference was observed in favor of the azithromycin 1% ophthalmic solution treatment group at visit 2 (week 2) for a nondry eye classification (subjects reclassifying at visit 2 as nondry eye) as determined by the CLDEQ (P=0.05). Five out of 25 subjects in the azithromycin 1% ophthalmic solution treatment group received a nondry eye classification at visit 2, as compared with 0 out of 25 subjects in the rewetting drops group. Statistical significance was not achieved at visit 3 (week 4) between treatment groups, although 6 out of 24 subjects in the azithromycin 1% ophthalmic solution group received a nondry eye classification based on the CLDEQ as compared with 1 out of 19 subjects in the rewetting drops group. The reduction in sample size (because of early discontinuation of 6 subjects because of AEs) was likely the cause for the lost power to show statistical significance for this trend.

No statistically significant differences were observed between treatment groups with regard to tear osmolarity. Mean tear osmolarity at baseline (all eyes) was 302.1 and 301.8 mOsm/L (normal range) for the azithromycin 1% ophthalmic solution and rewetting drops groups, respectively. At visits 2 and 3, mean tear osmolarity was 302.2 and 297.7 for the azithromycin 1% ophthalmic solution group and 300.6 and 304.3 for the rewetting drops group, respectively.

TABLE 2. *Total Contact Lens Wear Time Observed by Treatment Group*

	Mean Time (hrs)±SD	
	Azithromycin 1%	Rewetting Drops
Baseline	12.5±2.7 (n=25)	12.7±2.7 (n=25)
Week 1 endpoint	13.3±1.6 (n=25)	14.1±2.0 (n=25)
Week 2 endpoint	13.3±1.6 (n=25)	13.9±2.2 (n=25)
Week 3 endpoint	13.3±1.7 (n=24)	13.8±1.9 (n=20)
Week 4 endpoint	13.5±1.6 (n=24)	13.5±2.6 (n=20)

Mean total contact lens wear times (hours±SD) reported by the subjects is listed by week (baseline through week 4 of treatment) for each treatment group. There were no significant differences in total wear time between treatment groups.

Safety

There were no clinically significant changes from baseline observed in high contrast, habitual visual acuity measurements or corneal staining throughout the study. Ten subjects experienced 24 AEs in the azithromycin treatment group, 19 of which were ocular in nature (and all of which were mild or moderate in severity). Twelve subjects reported 17 AEs in the rewetting drops treatment group, 14 of which were ocular (and all of which were mild in severity). One subject was withdrawn from the study because of an AE in the azithromycin group, whereas five subjects were withdrawn from the rewetting drops group because of AEs. There were no deaths or serious AEs encountered throughout the study (Table 3).

DISCUSSION

To our knowledge, this is the first reported clinical trial examining the effect of azithromycin 1% ophthalmic solution as a treatment for dry eye associated with contact lenses. Azithromycin 1% ophthalmic solution was hypothesized to be efficacious in the treatment of CLDE because of results observed in preclinical studies involving inflammation and clinical studies in the subjects with anterior and/or posterior blepharitis.[18,19,24,27] Based on meeting the primary efficacy endpoint of the CFB in comfortable contact lens wear time, the results from this pilot study indicate that topical azithromycin 1% ophthalmic solution may be efficacious in treating subjects with CLDE. Increases in comfortable wear time greater

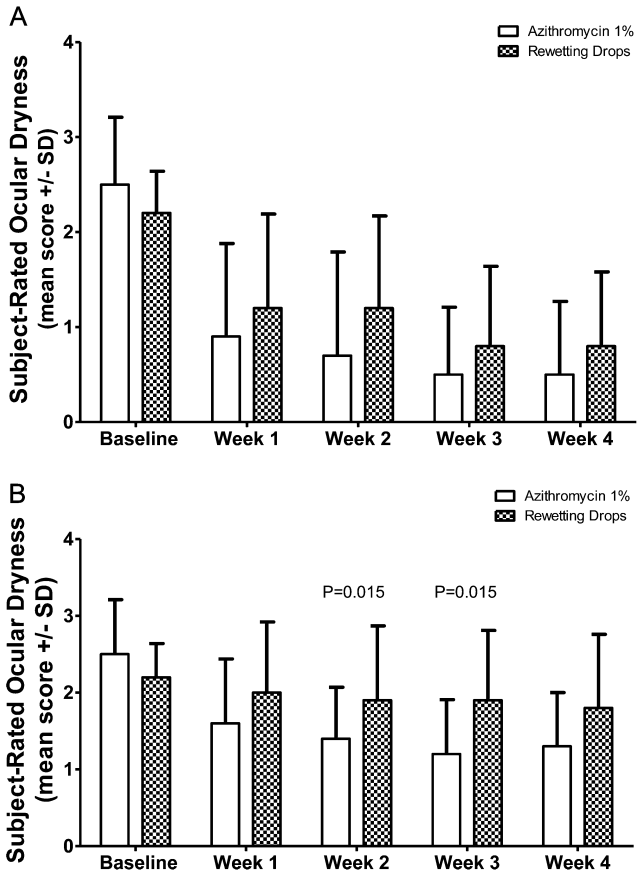

FIG. 2. Subject-rated assessment of ocular dryness. Scores for the perception of ocular dryness as reported by subjects (mean score±SD) at the baseline assessment and over each week of treatment out to 4 weeks are depicted. Baseline score was the ocular dryness score reported by subjects at visit 1. Mean morning (AM) ocular dryness scores by treatment group, either azithromycin 1% ophthalmic solution or rewetting drops, are shown in (A), and mean evening (PM) ocular dryness scores for each treatment group are shown in B). Statistical testing was performed using an ANCOVA model with treatment and baseline as main effects to evaluate treatment efficacy.

than 2 hrs were observed within the first week of treatment and continued throughout the treatment period, whereas comfortable wear time in the rewetting drops group was relatively consistent with baseline across the study. One might anticipate in an open-label design to see an improvement in outcomes after the first visit, with a fairly quick return to baseline; this was not the case here, although future studies should consider treatment masking. Further, because the subjects could have been using rewetting drops before the study, which were obviously not efficacious in controlling their symptoms per their eligibility for the study, they may have been randomized to what was a prior nonefficacious treatment if they were enrolled in the rewetting drop arm.

Despite randomization of the subjects, a disparity in baseline comfortable lens wear times between subject groups was noted. To take into account the imbalance of comfortable wear times at baseline, an adjusted mean difference and confidence interval were calculated for the statistical analysis between treatment groups. The increase in comfortable lens wear time was both clinically and

TABLE 3. *Number of Emergent AEs Occurring on or After the First Dose of Study Drug*

	Azithromycin 1%	Rewetting Drops
Number of AEs	24	17
Eye disorders	10 (40%)	7 (28%)
Conjunctival hyperemia	8 (32%)	4 (16%)
Conjunctival edema	1 (4%)	2 (8%)
Punctate keratitis	2 (8%)	0 (0%)
Eye irritation	1 (4%)	0 (0%)
Eye pain	1 (4%)	0 (0%)
Foreign body sensation in eyes	1 (4%)	0 (0%)
Meibomian gland dysfunction	0 (0%)	1 (4%)
Immune system disorders	0 (0%)	6 (24%)
Hypersensitivity	0 (0%)	6 (24%)
Respiratory, thoracic, and mediastinal disorders	2 (8%)	1 (4%)
Nasal congestion	1 (4%)	0 (0%)
Rhinorrhea	0 (0%)	1 (4%)
Sinus congestion	1 (4%)	0 (0%)
Infections and infestations	1 (4%)	1 (4%)
Nasopharyngitis	1 (4%)	1 (4%)
Investigations	2 (8%)	0 (0%)
Corneal staining	2 (8%)	0 (0%)
Musculoskeletal and connective tissue disorders	0 (0%)	1 (4%)
Arthritis	0 (0%)	1 (4%)
Reproductive system and breast disorders	1 (4%)	0 (0%)
Dysmenorrhea	1 (4%)	0 (0%)

Note that a subject could have more than one AE. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 13.0) and categorized by system organ class using preferred terms.

AE, adverse event.

statistically significant because the mean CFB was at least 2.5 hrs. The increase in comfortable wear time after 1 week may be important for patients who experience contact lens–related dry eye, particularly when they have attempted other treatments that may have failed. Increases in comfortable wear time were maintained throughout the treatment period with azithromycin 1% ophthalmic solution, potentially indicating a sustained therapeutic effect or effect of the vehicle. Total wear time after 4 weeks of treatment trended slightly higher for both groups (although neither was statistically significant), but mean times ranged from 12 to 14 hrs throughout the treatment period, which probably relates to the ceiling effect generally associated with this variable.

The subjects in both treatment groups tended to report improvement in the sensation of ocular dryness, particularly at the AM assessment. Initial dosing of both the drug and control may have had a role in this. In general, the AM feelings of dryness were more relieved than the PM feelings of dryness. Although there was a slight trend for a reduction in dryness in the rewetting drops group throughout the treatment period, the subjects treated with azithromycin 1% ophthalmic solution experienced a larger reduction in PM ocular dryness. The CFB between the 2 treatment groups was significant at weeks 2 and 3. These results are in agreement with reports from patients that ocular dryness and discomfort tends to worsen as the day progresses in the subjects with CLDE.[1,4] The relative inability of rewetting drops to alleviate ocular dryness, particularly beyond the short term, may play a role in the differing results with regard to increases in comfortable lens wear time. Likewise, based on a diagnosis of CLDE through responses on the CLDEQ, this study also indicated a trend in favor of subjects not

being classified with CLDE in the group of the subjects treated with azithromycin 1% ophthalmic solution, with statistical significance achieved at week 2 of treatment. A study with a larger sample size and more power may provide further insight into this endpoint.

The cause of dry eye in contact lenses wearers is likely multifactorial, and many factors might be considered in its management such as contact lens specific factors (e.g., contact lens material, replacement schedules, and contact lens care solutions), tear film factors (e.g., composition, stability), medical and demographic variables. In a prior large-scale study specific to contact lens factors, it was shown that patients wearing contact lens materials from FDA groups 2 and 4 tend to be more prone to having CLDE than patients wearing FDA group 1 lenses (including low water content, nonionic traditional, and silicone hydrogel–based materials).[7,21] It has also been reported that changing contact lens material in symptomatic patients can increase comfortable wear time, at least in one silicone hydrogel material used in the referenced study.[28] Other than that, few other contact lens–related factors were shown to be associated with CLDE.[7,21]

Beyond contact lens refitting into a different contact lens material, commercial formulations of lubricating and rewetting drops, or artificial tears, are the current standard of care for contact lens wearers who experience ocular dryness and discomfort.[5] Several clinical studies have been performed to assess the efficacy of artificial tears in treating these subjects.[29–32] Although study designs and patient inclusion criteria vary widely across studies, the subjects often report increased comfort with artificial tears, but few studies indicate a subject-reported increase in comfortable lens wear time.[30] It is also generally accepted that the benefits of artificial tears or rewetting drops are only short lived, lasting usually no more than 30 min.

Other agents also need to be considered in the treatment of contact lens dry eye. In a randomized, controlled, masked clinical trial, punctal plugging was shown to have little effect on contact lens dry eye.[20] Topical cyclosporine has also been studied in subjects who report dryness or discomfort related to wearing contact lenses. Two studies comparing cyclosporine to rewetting drops have been published, one indicating no statistical difference from rewetting drops over a 3-month period[23] and the other which indicated subjects demonstrated significantly reduced symptoms and increased comfortable lens wear time after a 5-week treatment.[22]

These inconsistencies in factors associated with contact lens dry eye have made it challenging for practitioners in the management of the condition, despite our insights regarding the mechanism including an alteration in the meibomian glands and/or lipid layer, with subsequent rapid thinning of the tear film that results in increased osmolarity.[7] This osmolarity increase may activate a host of inflammatory mediators that lead to increased symptoms of ocular irritation. In prior work, our laboratory showed that contact lens wearers with dry eye demonstrated a significantly higher tear film osmolarity than did those without dry eye (normals) using a nanoliterosmometer.[7] However, in this study, the mean tear osmolarity at baseline for both treatment groups (~302 mOsm/L), in conjunction with no significant changes in tear film osmolarity associated with either treatment, indicate that the subjects in this study may not be outside the normal tear osmolarity range or that these treatments have no effects on osmolarity. It should be noted that the technologies used in the two studies mentioned differ and may not be directly comparable. Regardless, either a larger sample size or selection of the subjects that have a more hyperosmotic tear film at baseline may allow for a determination of any treatment effect in follow-up studies specifically because it relates to the impact of a pharmaceutical agent on tear film osmolarity. Likewise, although azithromycin 1% ophthalmic solution has antiinflammatory properties as discussed, it could be that the vehicle (Durasite) provides a lubricant effect leading to the improved comfort, although one might have expected the control to also be associated with an improvement in comfort in this regard as well.

Ocular surface inflammation in dry eye has been documented by altered levels of cytokines, proteins, and microbial byproducts. Relative to nonwearers, the tear film of even normal contact lens wearers has aproinflammatory state as suggested by reports of increased interleukin-6,[33,34] eotaxin,[35] and histamine.[36] Conjunctival inflammation in contact lens wearers includes increased levels of human leukocyte antigen complex-DR, CD23, and intracellular adhesion molecule-l.[37,38] Sleeping in contact lenses is known to increase corneal levels of interleukin-1 beta, interleukin-6, and granulocyte-macrophage colony–stimulating factor.[39] Beyond these, altered expression of certain tear protein families with inflammatory implications (e.g., secretoglobulins 2A2and 1D1) have been documented in soft contact lens wearers.[40] Microbial colonization of lens and lens cases resulting from handling has been found asymptomatic contact lens wearers and is considered a key factor in contact lens–related inflammation.[41] It is this ocular surface inflammation related to contact lens wear that is hypothesized to be mitigated by topical azithromycin 1% ophthalmic solution. Animal and in vitro studies have shown that azithromycin can suppress corneal matrix metalloproteinases, modulate polymorphonuclearleukocytes, and of nuclear transcription factor nuclear factor kappa B.[15,16]

Inflammatory conditions of the ocular surface such as blepharitis can be frequently overlooked and may often play a role in the symptoms of CLDE. As new treatments become available, it is important to fully assess the ocular surface (including the lids and meibomian glands) of patients coming in for routine care or complaining of dryness. Recognition and early treatment of CLDE may significantly impact a patient's quality of life and reduce the dropout rate of contact lens wear. An increase in 4 hrs of comfortable contact lens wear could significantly improve a patient's quality of life. Although the study presented here would benefit from a larger sample size and double-masking, the results are encouraging and should prompt further study to elucidate the mechanism by which the significant increase in comfortable lens wear time is achieved with azithromycin 1% ophthalmic solution treatment and whether or not there are other potential risks associated with the continued use of azithromycin 1% ophthalmic solution (e.g., drug resistant infection). For instance, there have been recent reports of the repeated use of several antibiotics, including azithromycin, relative to antibiotic resistance of various microorganisms (e.g., *Staphylococcus epidermidis A*).[42] Future work must consider such important issues relative to the use of agents that act in multifunctional ways.

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