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**ORIGINAL ARTICLE**

**Loteprednol Etabonate 0.5%/Tobramycin 0.3% Compared with Dexamethasone 0.1%/Tobramycin 0.3% for the Treatment of Blepharitis**

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**ABSTRACT**

**Purpose:** To compare the efficacy of loteprednol etabonate 0.5%/tobramycin 0.3% (LE/T) and dexamethasone 0.1%/tobramycin 0.3% (DM/T) ophthalmic suspensions in reducing select signs of blepharitis.

**Methods:** Data were pooled from two studies (one from the USA; one from China) of adults (n = 627) with blepharokeratoconjunctivitis treated with LE/T or DM/T four times daily for 2 weeks (safety population). Efficacy analyses included 495 eyes (247 LE/T, 248 DM/T) with any baseline sign of blepharitis.

**Results:** At Day 15, the least squares mean change from baseline in composite blepharitis severity was similar between LE/T (–2.86) and DM/T (–2.99) (90% CI for mean treatment difference: –0.35, 0.11). Intraocular pressure (IOP) increases ≥10 mmHg over baseline were reported for 1 US patient (DM/T group) and 19 Chinese patients (6 LE/T; 13 DM/T).

**Conclusions:** LE/T was similarly effective in reducing the signs of blepharitis compared with DM/T, but demonstrated a better safety profile with respect to changes in IOP.

**Keywords:** Blepharitis, dexamethasone, loteprednol etabonate, tobramycin

Blepharitis is a common, chronic inflammatory condition affecting the eyelid margin that can affect all age and ethnic groups.¹² Typical signs and symptoms include eyelid redness, itching, and burning, and crusting of the eyelid margins.² In a survey conducted in 2008 of US ophthalmologists and optometrists, respondents indicated that 37–47% of their adult patients had findings suggestive of blepharitis.³ The pathology of the condition is not yet completely understood, but low-grade bacterial infection (primarily *Staphylococcus*), Demodex mites, environmental factors, and certain systemic disease, have all been implicated as potential contributors.¹⁴ Blepharitis can be difficult to treat, usually with little chance of a complete cure.¹² The chronic discomfort caused by blepharitis and its impact on appearance may be a source of physical and psychological distress for patients, including anxiety and depression.⁵⁶

While there are no products approved by the US Food and Drug Administration (FDA) specifically for the treatment of blepharitis, current therapeutic approaches aim to control and minimize symptoms and signs of inflammation.⁴ The most recent guidelines of the American Academy of Ophthalmology (AAO) identify various treatments that may be helpful alone or in combination, including warm compresses, eyelid cleansing/ massage, topical and/or systemic antibiotics, and topical anti-inflammatory agents, such as corticosteroids and cyclosporine.¹ Topical antibiotic-corticosteroid combination products are useful for decreasing the bacterial load as well as managing inflammation.¹

Loteprednol etabonate (LE) is an ophthalmic corticosteroid that differs from others in this class by the replacement of the carbon 20 ketone group with an ester.⁷ The LE molecule was specifically designed using ‘retrometabolic’ engineering with the goal of...
lowering the potential for known corticosteroid adverse events. While it binds with high affinity to the glucocorticoid receptor, any unbound LE is rapidly metabolized to an inactive form, minimizing the potential for unwanted effects such as elevated intraocular pressure (IOP) and cataract formation.\textsuperscript{7} Tobramycin is a broad spectrum aminoglycoside antibiotic with activity against staphylococcal organisms (including penicillin-resistant) and a wide variety of other pathogens.\textsuperscript{8} The combination of LE 0.5% with tobramycin 0.3% (LE/T, Zylet\textsuperscript{®}, Bausch & Lomb) formulated as an ophthalmic suspension was approved in the USA in 2004 for the treatment of steroid-responsive inflammatory ocular conditions warranting steroid use and associated with superficial ocular bacterial infection or a risk of ocular bacterial infection.\textsuperscript{9}

In two multicenter, randomized, investigator-masked, parallel-group studies, one in a US population, the other in a Chinese population, LE/T was demonstrated to be non-inferior to dexamethasone 0.1%/tobramycin 0.3% (DM/T) in decreasing the composite signs and symptoms of ocular inflammation in patients with blepharokeratoconjunctivitis (BKC) and was associated with less IOP elevation compared with DM/T.\textsuperscript{10,11} In the current study, data from these two similar studies were pooled, providing a large, international study population. Given that blepharitis can present as a sole diagnosis, this analysis was designed to specifically analyze the blepharitis outcomes in the pooled dataset and evaluate the comparative efficacy of LE/T and DM/T ophthalmic suspensions for this indication.

\section*{MATERIALS AND METHODS}

\subsection*{Study Design}

Data were pooled from two multicenter, randomized, investigator-masked, parallel-group clinical trials with similar designs, one conducted at 17 sites in the USA\textsuperscript{10} and the other at seven sites in China.\textsuperscript{11} Patients were enrolled from January 2007 through June 2007 for the US study (NCT00447577) and from October 2009 through February 2010 for the China study (NCT01028027). Written, informed consent was obtained for all patients prior to study enrollment. The study protocols were approved by the institutional review board (USA) or ethics committee (China) for each participating site and all research was conducted in accordance with the principles of Good Clinical Practice\textsuperscript{12} and the Declaration of Helsinki.\textsuperscript{13}

Each study enrolled adult patients (\(\geq\)18 years of age) with a diagnosis of BKC in at least one eye. Full inclusion and exclusion criteria have been previously described.\textsuperscript{10,11} Investigators determined the baseline severity of ocular signs of all three disease components: blepharitis (lid hyperemia, lid scaling or crusting, lid margin hypertrophy); conjunctivitis (conjunctival hyperemia, conjunctival discharge, conjunctival chemosis); and keratitis (corneal punctate epithelial keratopathy), using a 5-point rating scale of 0 (none); 1 (minimal/trace); 2 (mild); 3 (moderate); or 4 (severe). In order to be eligible for the current efficacy analysis, patients were required to have a baseline blepharitis composite severity \(\geq 1\) in at least one eye (maximum possible composite severity = 12). One eye per patient was included as the study eye. In cases with bilateral blepharitis, the eye with the highest baseline blepharitis severity was the study eye; if severity was equal in both eyes, the right eye was designated as the study eye. All patients from the original study populations were included in the safety analyses, regardless of baseline blepharitis severity.

\subsection*{Study Procedures}

Patients were randomized in a 1:1 ratio to investigator-masked treatment with LE/T or DM/T ophthalmic suspension four times daily for 2 weeks. Commercial packaging labels for both treatments were replaced with study labels, and site study coordinators, not investigators, handled all drug dispensing and retrieval activities. Further details on masking and randomization have been published.\textsuperscript{10,11} Study assessments and examinations were performed on Visit 1 (Day 1; baseline); Visit 2 (Day 3 \(\pm\) 1); Visit 3 (Day 7 \(\pm\) 1 [USA]; Day 8 \(\pm\) 1 [China]); and Visit 4 (Day 15 \(\pm\) 1 [USA]; Day 15 \(\pm\) 2 [China]). For simplicity, the latter three endpoints will be referred to hereafter as Day 3, Day 7, and Day 15, but should be interpreted as including the 1–2 day variations within each study.

\subsection*{Outcome Measures}

Efficacy endpoints for this pooled analysis included the change from baseline (CFB) in composite blepharitis severity and CFB in severity of individual blepharitis signs at each visit. Each of these endpoints was evaluated for all study eyes in the ITT population and for study eyes having the most severe signs at baseline (composite blepharitis severity \(\geq 6\)). As with source studies, Day 15 was considered the primary efficacy evaluation time point.

Safety endpoints were assessed at each visit and included adverse events (AEs), visual acuity (VA), biomicroscopy findings, and IOP. Visual acuity was evaluated using a pinhole, either unaided or with historical correction, and a Snellen Chart. Intraocular pressure was measured for each patient at each visit using applanation tonometry (USA) or non-contact tonometry (China). In addition to IOP measures taken at each visit according to the study protocols, investigators could report IOP elevations as an AE at their discretion. In the China study, it was recommended that IOP elevations >5 mmHg also be
reported as AEs. Because of marked differences in IOP responses noted in the US and Chinese patients, IOP findings were not pooled, but analyzed and reported separately for the respective populations.

**Statistical Methods**

Efficacy analyses were performed using the intent-to-treat (ITT) population, which included the study eye of all patients who had a baseline blepharitis severity ≥1 at baseline, received at least one dose of study drug, and had available blepharitis severity data from at least one follow-up visit. Treatment comparisons were based on the least squares (LS) mean using a linear regression model for the CFB in blepharitis severity (whether composite or individual) controlling for baseline severity and treatment. A 90% confidence interval (CI) was constructed for the mean difference between the two treatment groups.

The proportion of study eyes demonstrating a ≥1-grade reduction in blepharitis sign (individual and composite) severity and the proportion of study eyes in which blepharitis signs were fully resolved at Day 15 were compared between treatments using a two-tailed Fisher’s exact test.

All IOP changes from baseline were calculated as post-baseline IOP minus baseline IOP. Differences between treatments for CFB in mean IOP were analyzed using a general linear model adjusting for treatment, site, and baseline. A Cochran–Mantel–Haenszel test was used to evaluate differences between treatments in CFB in IOP categorized by degree of elevation (≥5 mmHg or ≥10 mmHg).

Statistical analyses of pooled outcomes were performed using Statistix 10.0 (Analytical Software, Tallahassee, FL). IOP changes were analyzed previously using SAS software, version 9.1 or higher (SAS Institute Inc., Cary, NC).

**RESULTS**

**Study Populations**

The total pooled study population included 627 (273 US; 354 China) patients with BKC who received at least one dose of study medication. Of these, 495 patients (247 LE/T; 248 DM/T) had a baseline severity ≥1 for at least one blepharitis sign and were included in the ITT efficacy population. Baseline demographics and characteristics of the ITT population were similar between the two treatment groups (Table 1). Demographic characteristics of the safety populations (313 LE/T; 314 DM/T), comprised of all patients in the pooled study population who received at least one dose of study medication, were also similar at baseline as reported for the source studies (data not shown). Of the patients in the ITT efficacy population, 124 patients (59 LE/T; 65 DM/T) had a baseline severity ≥6 for composite blepharitis.

**Efficacy Outcomes**

The LS mean CFB in composite blepharitis severity at Day 15 was similar between the LE/T (–2.86) and DM/T (–2.99) treatment groups with a 90% CI for the mean treatment difference of (–0.35, 0.11) (Table 2). LS mean CFB in composite blepharitis severity was slightly greater for the DM/T group at Day 3 and at Day 7. In the subset of patients with baseline blepharitis severity ≥6, the LS mean CFB in composite blepharitis severity was slightly greater in the DM/T group at Day 15 (LE/T –4.71 vs DM/T –5.13; 90% CI –0.80, –0.05), but was similar between LE/T and DM/T groups at the earlier visits.

By Day 15, following 2 weeks of treatment, a majority of study eyes demonstrated ≥1-grade reduction (improvement) from baseline in the severity of individual blepharitis signs as well as composite blepharitis signs (Table 3), with no differences between treatment groups (P ≥0.546). Mean severity of each individual
blepharitis sign showed a gradual and similar decrease at each study visit in both treatment groups (Figure 1). Complete resolution of blepharitis signs (i.e., grade 0 for all signs) was noted in similar proportions of eyes in each study group at Day 15 (Figure 2), for both all eyes (LE/T 48.1% vs DM/T 42.9%; \( p = 0.265 \)) and the subset of eyes with the highest blepharitis severity at baseline (LE/T 23.7% vs DM/T 21.3%; \( p = 0.828 \)).

**Safety Outcomes**

A total of eight patients in the LE/T group and seven in the DM/T group reported a non-ocular treatment emergent AE (TEAE). These included headache (\( n = 4 \), LE/T, \( n = 1 \) DM/T); nausea (\( n = 1 \) for LE/T, \( n = 2 \) for DM/T); alopecia (\( n = 1 \) for LE/T); anxiety (\( n = 1 \) for DM/T); dizziness (\( n = 1 \) for DM/T); epicondylitis (\( n = 1 \) for LE/T); hypertension (\( n = 1 \) for DM/T); nasopharyngitis (\( n = 1 \) for DM/T); and spinal disorder (\( n = 1 \) for
All non-ocular TEAEs were mild to moderate in severity, with the exception of one event of headache in a LE/T patient and the event of hypertension in a DM/T patient, considered severe. The latter event was classified as a serious AE but considered unrelated to treatment and associated with concurrent illness; the patient was provided medical therapy and the AE resolved.

Treatment emergent ocular AEs were reported for 27 patients in the LE/T group and 50 in the DM/T group (Table 4). The most common ocular TEAEs were increased IOP, reported for 5.4% of LE/T patients and 13.7% of DM/T patients; and instillation site stinging, reported in 1.0% of LE/T and 1.6% of DM/T patients. All other ocular AEs were reported in <1% of patients. All ocular TEAEs were mild to moderate in severity, with the exception of one event of increased IOP in a DM/T patient (China study), which was considered severe. Adverse events in treated non-study eyes were similar to those observed in study eyes.

Six patients in the LE/T group discontinued treatment early because of a TEAE (n = 1 each of headache, allergic conjunctivitis, increased IOP, lumbar spinal disease, eye pain upon medication instillation, and bacterial keratitis). The event of allergic conjunctivitis was thought to be possibly related to a benzalkonium chloride sensitivity. Seven patients in the DM/T group discontinued early due to TEAEs; all had increased IOP.

In the US study, VA was consistently similar between the two treatment groups and across visits within each treatment group, and all patients had 20/40 or better VA at all visits. In the Chinese study, both treatment groups showed improvements from baseline in VA.

Biomicroscopy findings were unremarkable. Anterior chamber abnormalities were within normal limits for both treatment groups at post-baseline study visits, with the exception of one Chinese patient in the DM/T group who had mild flare at Visits 2 and 3. In both treatment groups, no differences in cataract severity were seen between baseline and follow-up visits.

Intraocular Pressure
Mean (SD) changes in IOP for the LE/T and DM/T at each study visit are shown in Figure 3. Subjects treated with DM/T experienced a statistically significant increase in IOP compared with subjects treated with LET/T as early as Day 3 in the Chinese population (p = 0.0190), and at Day 7 and Day 15 in both the US and Chinese populations (p≤0.034).

Table 5 presents the proportion of patients in each study who were observed to have IOP increases of ≥5 mmHg or ≥10 mmHg from baseline at each visit and overall. In both studies, the percentages of patients with such magnitudes of IOP increase overall were approximately two-fold higher in the DM/T groups compared with the LE/T groups. In the China study, the proportion of patients with increases ≥5 mmHg above baseline was statistically significantly higher on Day 3, 8, and overall (p≤0.0020). In the US study, only one patient (DM/T) developed an IOP increase of ≥10 mmHg from baseline, while there were six (LE/T) and 13 (DM/T) patients in the China study who exhibited this degree of IOP elevation.

<table>
<thead>
<tr>
<th>Patients</th>
<th>LE/T (n = 315)</th>
<th>DM/T (n = 315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of AEs</td>
<td>27</td>
<td>52</td>
</tr>
<tr>
<td>Patients with ≥1 AE</td>
<td>27 8.6</td>
<td>50 15.9</td>
</tr>
<tr>
<td>Increased IOP*</td>
<td>17 5.4</td>
<td>43 13.7</td>
</tr>
<tr>
<td>Instillation site stinging</td>
<td>3 1.0</td>
<td>5 1.6</td>
</tr>
<tr>
<td>Eye pain</td>
<td>2 0.6</td>
<td>0</td>
</tr>
<tr>
<td>Allergic conjunctivitis</td>
<td>1 0.3</td>
<td>0</td>
</tr>
<tr>
<td>Application site dryness</td>
<td>1 0.3</td>
<td>0</td>
</tr>
<tr>
<td>Eye irritation</td>
<td>1 0.3</td>
<td>0</td>
</tr>
<tr>
<td>Keratitis, bacterial</td>
<td>1 0.3</td>
<td>0</td>
</tr>
<tr>
<td>Superficial punctate keratitis</td>
<td>1 0.3</td>
<td>2 0.6</td>
</tr>
<tr>
<td>Decreased lacrimation</td>
<td>0</td>
<td>1 0.3</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>0</td>
<td>1 0.3</td>
</tr>
</tbody>
</table>

LE/T, loteprednol etabonate 0.5%/tobramycin 0.3%; DM/T, dexamethasone 0.1%/tobramycin 0.3%.

*In the China study, investigators agreed to report IOP measures >5 mmHg above baseline as AEs.

FIGURE 2. Percentages of patients (eyes) whose blepharitis signs were resolved (i.e., grade 0) at Day 15. LE/T, loteprednol etabonate 0.5%/tobramycin 0.3%; DM/T, dexamethasone 0.1%/tobramycin 0.3%.

TABLE 4. Treatment emergent ocular adverse events (study eye).
DISCUSSION

These findings, based on a large, multinational, pooled dataset, are the first to specifically compare the efficacy of LE/T compared with DM/T for the treatment of select signs of blepharitis. The trials which served as the source studies for this pooled analysis included patients with a broader diagnosis of BKC.

By limiting this analysis to those subjects with signs of blepharitis at baseline, we were able to evaluate the potential benefits of LE/T compared with DM/T on the blepharitis component uniquely. Both LE/T and DM/T treatment resulted in measurable, progressive, and similar reductions in blepharitis severity over the course of the 2-week treatment period. By Day 15, blepharitis signs were assessed as fully resolved (i.e., grade 0) in almost half of the patients in both treatment groups, and the majority of patients had a ≥1-grade reduction in severity of individual and composite blepharitis signs, whether considering all patients or those with the greatest blepharitis severity at baseline. While few statistical advantages were found with DM/T for the reduction in mean composite blepharitis severity at some visits, these differences were small (difference <1 grade) and likely clinically insignificant. Adverse events were infrequent, generally mild or moderate, and except for IOP elevation, similar between treatments.

Aside from the original studies pooled for the current analysis, few studies have evaluated antibiotic-steroid combinations for the treatment of BKC or blepharitis. Rhee and Mah evaluated the efficacy of LE/T and DM/T, each dosed BID for only 3–5 days, in reducing signs and symptoms in 40 patients with BKC. In that short timeframe, reduced blepharitis severity was observed in patients using DM/T compared with LE/T. There were no clinical AEs reported in either treatment group, and IOP measurements were reportedly similar for each group before and after treatment.

Another antibiotic-steroid combination, moxifloxacin plus dexamethasone, was shown to produce clinical improvement in patients with bacterial blepharitis. The risk of elevated IOP is a concern with ocular steroid administration, especially when used for extended periods of time. In the two source studies upon which the current analysis was based, marked differences were observed in the magnitude of IOP change in the US and Chinese populations, and for this reason, IOP findings were not pooled. In both treatment groups, the mean IOP changes in the Chinese population were notably higher than those observed in the US population. In addition, greater proportions of Chinese patients demonstrated IOP increases of ≥5 or a ≥10 mmHg from baseline. In the US population using LE/T, mean IOP changed very little over time, with slight mean decreases noted at
days 7 and 15, while mean IOP demonstrated further elevation at each successive visit in the DM/T group.

To our knowledge, racial or ethnic differences in ocular steroid-induced IOP elevation have not yet been described, and therefore reasons for the observed apparent variation in IOP response are not clear. Risk factors for steroid-induced IOP elevation suggested by previous studies include a history of primary open angle glaucoma (POAG)\textsuperscript{16-18} and axial myopia.\textsuperscript{19,20} These risk factors have been reported to be more prevalent among Asian versus non-Asian populations.\textsuperscript{21-23} Conversely, among patients with existing glaucoma, no differences in axial length were observed between Chinese and Caucasian patients.\textsuperscript{24} Further research into this phenomenon is warranted to confirm if there is a higher predisposition to steroid-induced IOP elevation in patients of Asian ethnicity. It is also worth noting that the average age of the China study population was about 14 years younger than that of the US study population, and younger age has also been associated with steroid-induced IOP elevations.\textsuperscript{20,25} Furthermore, different techniques were used to measure IOP in the US (applanation tonometry) and China (non-contact tonometry) studies. Non-contact tonometry has been shown to overestimate IOP relative to applanation tonometry in some studies,\textsuperscript{26,27} while others have reported similar results between the two methods.\textsuperscript{28,29} A number of studies have noted better intra- and interoperative reproducibility of IOP measurements with Goldmann applanation tonometry and dynamic contour tonometry (DCT) compared with non-contact methods.\textsuperscript{30-32} The influence of central corneal thickness and corneal curvature on IOP readings has also been reported to differ among individual measurement techniques.\textsuperscript{30,33,34}

Regardless, each patient in the individual source studies in our analysis was evaluated using a consistent tonometry method and therefore within-study differences in the magnitude of steroid-induced IOP changes from baseline are valid.

The lower risk of IOP elevation seen with LE/T compared with DM/T observed in both the US and Chinese populations of our study is a well-documented phenomenon, and an expected outcome given the unique retrometabolic design of LE and its rapid hydrolysis into inactive metabolites following administration.\textsuperscript{35,36} Previous studies have confirmed the relatively lower risk of IOP elevation with LE compared with other ocular steroids, including studies in known steroid responders.\textsuperscript{37-45}

Limitations of this analysis included the lack of either a non-active control, or a control of a different drug category and the 2-week follow-up period. The study treatments both contained the same antibacterial (tobramycin), and a highly effective corticosteroid (loteprednol etabonate or dexamethasone). While the study design allowed for a robust comparison of the two treatments, it cannot be known whether the improvement in blepharitis signs was attributed to the steroid, the antibacterial, or to the combination, although we assume that improvement was likely due to the combination of both, given that concurrent bacterial infection and inflammation are likely at play in many cases of blepharitis.\textsuperscript{1,4} Furthermore, because patients in the source studies were initially selected for study based upon a broader diagnosis of BKC, not blepharitis, specifically, non-drug measures encouraged for the management of blepharitis, such as lid hygiene and warm compresses,\textsuperscript{1} were not included. Finally, given the chronic nature of blepharitis, the 2-week follow-up period may not have been sufficient to evaluate the full efficacy of LE/T and DM/T for this indication. Based on the pattern of improvements noted over time with both LE/T and DM/T, it would be expected that ongoing improvement would continue to occur/is likely possible beyond the 15-day study interval that was assessed. Conversely, progressive increases in IOP were also observed over the 15-day period, particularly with DM/T use and in Chinese patients. The IOP risk of continued treatment in at-risk populations is a concern and warrants clinical vigilance.

In conclusion, this large pooled dataset demonstrates the efficacy of LE/T in reducing the severity of blepharitis, including full resolution of signs in nearly half of patients after only 15 days of treatment. While LE/T and DM/T demonstrated a similar degree of efficacy in this regard, LE/T appears to have a clear safety advantage with regard to IOP response.

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