Original article

A multicenter, randomized, parallel-group, clinical trial comparing the safety and efficacy of loteprednol etabonate 0.5%/tobramycin 0.3% with dexamethasone 0.1%/tobramycin 0.3% in the treatment of Chinese patients with blepharokeratoconjunctivitis

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Keywords:
Blepharokeratoconjunctivitis – Dexamethasone – Intraocular pressure – Loteprednol etabonate – Safety – Tobramycin

Abstract

Objective:
To compare the efficacy and safety of loteprednol etabonate 0.5%/tobramycin 0.3% (LE/T) and dexamethasone 0.1%/tobramycin 0.3% (DM/T) ophthalmic suspensions in a Chinese population with ocular inflammation associated with blepharokeratoconjunctivitis (BKC).

Research design and methods:
This study was a multicenter, randomized, investigator-masked, parallel-group clinical trial. Patients aged ≥18 years with a clinical diagnosis of BKC in at least one eye received LE/T or DM/T administered 4 times daily for 2 weeks. At baseline and on days 3, 8, and 15 (visits 2, 3, and 4), clinical assessments of ocular signs and symptoms, visual acuity (VA), biomicroscopy, and intraocular pressure (IOP) were performed in both eyes.

Main outcome measures:
The primary efficacy endpoint was the change from baseline (CFB) to visit 4 in the signs and symptoms composite score in designated study eyes using a non-inferiority metric to compare LE/T to DM/T. Safety evaluation included adverse events, biomicroscopy findings, and changes in VA and IOP.

Clinical trial registration:
NCT number, NCT01028027.

Results:
A total of 308 patients were included in the per protocol population (n = 156 LE/T, n = 152 DM/T). A significant CFB in composite signs and symptoms was seen with both treatments at each follow-up visit (p < 0.0001). The mean (SD) CFB at visit 4 was −11.63 (4.56) and −12.41 (4.71) in the LE/T and DM/T groups, respectively, and the upper bound of the 90% confidence interval for the difference was less than the prespecified non-inferiority margin. Comparable results were found for secondary efficacy outcomes. Patients treated with DM/T experienced a significantly greater increase in mean CFB in IOP compared to those treated with LE/T at all follow-up visits (p ≤ 0.0186) and nearly twice as many IOP elevations ≥5 mmHg (p = 0.0020).

Conclusion:
Treatment with LE/T was at least as effective as DM/T in Chinese patients with BKC and had a better safety profile with respect to change in IOP.

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Introduction

Blepharokeratoconjunctivitis (BKC) is defined as an eyelid margin disease with secondary conjunctival and corneal involvement. It is characterized by a spectrum of clinical manifestations, typically comprising inflamed eyelids, anterior lid margin telangiectasia, and accumulations of hard, fibrinous, and crusting scales around the base of the cilia. In chronic cases, mild-to-moderate papillary follicular hypertrophy of the palpebral conjunctiva is usually involved. In addition, inferior corneal involvement includes punctate epithelial erosions with marginal infiltrates; sterile marginal abscesses are also seen in acute exacerbations.

The treatment regimen for BKC usually involves lid hygiene in combination with topical antibiotics and topical corticosteroids. Although topical corticosteroids are often prescribed to treat ocular inflammation, most possess a safety risk profile that limits their utility. A common risk associated with corticosteroid therapy is an elevation of intraocular pressure (IOP). In addition, long-term use of topical corticosteroids may result in the development of cataracts. Therefore, an ideal ophthalmic corticosteroid should have potent anti-inflammatory activity, but without the propensity to increase IOP or cause cataracts.

Loteprednol etabonate (LE) is a C-20 ester corticosteroid that undergoes predictable transformation to inactive metabolites. The relatively rapid metabolism of LE to inactive metabolites improves its safety profile. In controlled trials, LE 0.5% had a reduced incidence of significant IOP increase compared with prednisolone acetate, even in known steroid responders. Further, LE was reported to be safe and effective in a wide range of inflammatory ocular conditions, including seasonal and perennial allergic conjunctivitis, postoperative inflammation, giant papillary conjunctivitis, and acute anterior uveitis, and may be beneficial in patients with keratoconjunctivitis sicca.

The combination of LE with tobramycin, a broad-spectrum aminoglycoside antibiotic with proven effectiveness, provides additional benefit of treating an underlying infection while controlling the host inflammatory response. Although loteprednol etabonate 0.5%/tobramycin 0.3% (LE/T) ophthalmic suspension was evaluated for the treatment of BKC in a previous study, fewer than 2% of subjects in that study were Asian. The purpose of this study was to compare the safety and efficacy of LE/T with dexamethasone 0.1%/tobramycin 0.3% (DM/T) ophthalmic suspension specifically in a Chinese population with ocular inflammation associated with BKC.

Patients and methods

This study was a 4-visit, 2-week, multicenter, randomized, investigator-masked, parallel-group clinical trial (Clintrials.gov identifier: NCT01028027). Patients from seven clinical centers in China were enrolled between October 2009 and February 2010. Written, informed consent was obtained from all participants before enrollment in the study. This study was approved by ethics committees at the Eye Nose and Throat Hospital of Fudan University and the First Affiliated Hospital of Medical School at Zhejiang University and was conducted in accordance with China State Food and Drug Administration’s and ICH good clinical practices and the Declaration of Helsinki.

Patients

Male or female patients were eligible to participate in the study if they were at least 18 years old on the date the informed consent form was signed, and were able to understand study procedures and provide voluntary informed consent. Patients had to have a clinical diagnosis of BKC in at least one eye (total ocular signs and symptoms score of at least 10, with at least one ocular sign and one ocular symptom each having a severity of grade 2 or higher). A willingness to discontinue contact lens use for the duration of the study and a pin-holed decimal visual acuity (VA) test result on an E chart equal to or better than 0.5 in both eyes were required. Additional inclusion criteria included the ability to comply with all treatment and follow-up/study procedures and self-administer drugs; a negative urine pregnancy test in female patients of childbearing potential; or no childbearing potential at screening.

Potential participants were excluded if they participated in any drug or device clinical investigation within 30 days prior to entry into the study and/or during the period of study participation; had a known hypersensitivity to the study drugs or their components (including benzalkonium chloride); or contraindications to tobramycin or topical corticosteroids. Other reasons for exclusion included treatment with any of the following systemic or topical ophthalmic medications: nonsteroidal anti-inflammatory drugs, analgesics, and antihistamines within 2 days before or during the study; tear substitutes within 2 hours before or during the study; antibiotics within 72 hours before or during the study; corticosteroids within 7 days before or during the study; mast cell stabilizers within 14 days before or during the study; or immunosuppressants (e.g., Restasis) within 30 days before or during the study. Patients also could be excluded if they had suspected preseptal cellulitis or any other diseases that the investigator determined could interfere with safety and efficacy evaluations of the study drug; suspected dacryocystitis; or ocular surgery (including laser surgery) in either eye within 3 months prior to the screening visit.
**Study procedures**

At the first visit, patients’ eligibility was determined by a clinical assessment of ocular signs and symptoms in both eyes and an eye examination that included pin-hole VA, biomicroscopy, and IOP assessments. Eligible patients were randomized in a 1:1 ratio by a computer-generated randomization list to receive either LE/T or DM/T, which were coded by the packaging site and patient-specific information. The randomization list was developed prior to enrollment by an independent statistician. Labels on commercial bottles of LE/T and DM/T were replaced with investigational labels and bottles were packaged in identical kit boxes in an attempt to mask subjects. However, due to differences in the appearance of the bottles, full masking of patients was not possible. Uniquely randomized and numbered subject kit boxes were provided to the investigator at each site and assigned to each subject at the first visit in ascending order. Patients were instructed to instill one drop of the study drug topically in the affected eye(s) four times a day at approximately 4-hour intervals beginning on day 1 and continuing for 14 days, and to record study medication instillation times in a study diary. To ensure investigators were masked to study treatment, site study coordinators dispensed the subject kit boxes to the study subjects and retrieved them from the subjects at the end of the study, and investigators were not present during any in-office instillations. The clinical assessments and examinations performed by the investigator at visit 1 were repeated at visit 2 (day 3 ± 1), visit 3 (day 8 ± 1), and visit 4 (day 15 ± 2). The overall study drug compliance rate was calculated by dividing the total number of doses recorded in the study diary across the entire treatment period by the number of expected doses. Patients who did not follow instructions to such a degree that, in the sponsor or investigator’s opinion, their noncompliance jeopardized their wellbeing were discontinued.

**Outcome measures**

**Efficacy**

Ocular signs and symptoms were recorded for both eyes at each study visit using a 0–4 grading scale assessed as 0 = none, 1 = minimal/trace, 2 = mild, 3 = moderate, and 4 = severe. Ocular symptoms included itchiness, light sensitivity, foreign body sensation, painful or sore eyes, blurred vision, and burning, and were reported in response to a query by the investigator. Ocular signs included blepharitis (lid hyperemia, lid scaling or crusting, and lid margin hypertrophy), conjunctivitis (conjunctival hyperemia, conjunctival discharge, and conjunctival chemosis), and keratitis (punctate epithelial keratopathy). Hence, the signs and symptoms composite score, the signs composite score, and the symptoms composite score could range from 0–52, 0–28, and 0–24, respectively. The blepharitis signs composite score and the conjunctivitis signs composite score could range from 0–12.

The primary efficacy endpoint for this study was the change from baseline (CFB) to day 15 (visit 4) in the ocular signs and symptoms composite score, defined as the sum of each individual sign or symptom score. This composite endpoint or similar composite endpoints have been used in previous studies. Secondary efficacy endpoints included the CFB to day 3 (visit 2) and to day 8 (visit 3) in the signs and symptoms composite score; the CFB to each visit in the signs and symptoms composite scores; the CFB to each visit in the signs composite scores for blepharitis, conjunctivitis, and keratitis; and the CFB to each visit in individual signs and symptoms.

**Safety**

Safety assessments included adverse events (AEs), VA, biomicroscopy findings, and IOP at each visit. Visual acuity was assessed using a pinhole (either unaided or with historical correction) and a standardized E chart. The anterior chamber was assessed under a slit lamp microscope for cells, flare, and synechiae and lenses for cataracts. For cells in the anterior chamber, the ratings were 0 = none; 1 = 1–5 cells; 2 = 6–15 cells; 3 = 16–30 cells; and 4 = more than 30 cells. For flare, the ratings were 0 = none; 1 = mild, Tyndall phenomenon (±); 2 = moderate, clear visible iris; 3 = severe, invisible iris; and 4 = profound, white and chylous aqueous humor. For synechiae, the ratings were 0 = absent and 1 = present. For lenses, the ratings were 0 = with lens and 1 = without lens. For a cataract, if with lens, the ratings were 0 = clear; 1 = mild, compact in density; 2 = moderately compact in density; 3 = compact in density; and 4 = very compact in density. The IOP was measured using a calibrated non-contact tonometer at all visits. Changes in IOP were evaluated as CFB in IOP measurements. Any IOP increase greater than 5 mmHg was also recorded as an AE. All AEs, whether voluntarily disclosed by the patient or observed by the investigator, were reported using the MedDRA classification, assessed for their relationship to the study drug, and rated as mild, moderate, or severe in intensity. Drug-related AEs were those with a relationship to study drug of possibly, probably, or definitely.

**Statistical analysis**

Approximately 172 patients (172 study eyes) were planned to be randomized to each treatment group to yield approximately 155 patients (155 study eyes) in each group who completed the study without major protocol deviations. This sample size was determined to yield 90% power to show non-inferiority of LE/T to DM/T with respect to the primary endpoint (CFB to visit 4 in signs and symptoms).
symptoms composite score) using a non-inferiority limit of 2.5 and the upper limit of a two-sided 90% confidence interval (one-sided, \( \alpha = 0.05 \) test). This sample size calculation was based on the variability observed in a pilot study (data unpublished) and a standard deviation in CFB of 7.5 and a 10% dropout/major protocol deviation rate observed in a previous study comparing LE/T to DM/T in BKC\(^{18}\).

In cases of diagnosed bilateral BKC, the eye with the most severe condition at baseline was chosen as the study eye. If the severity of the condition was equal in both eyes, the right eye was chosen as the study eye.

For the primary efficacy analysis, missing values at day 15 were only imputed for study eyes that were placed on rescue therapy, using the last observation prior to rescue therapy. Missing data were not imputed for secondary endpoints.

Comparisons of LE/T to DM/T with respect to signs and symptoms scores were carried out using a general linear model to calculate the least square means for each treatment group and the 90% CI on the difference in CFB scores between the two treatments. The linear model included terms for baseline score as a covariate and treatment and site as fixed effects. A preliminary test for interactions between treatment and site and between treatment and baseline scores for the primary analysis found these to be non-significant, and these terms were therefore removed from the final model. Finally, the CFB in signs and symptoms scores was analyzed within each treatment, evaluating whether the baseline and follow-up scores differ using paired t-tests.

The mean, median, standard deviation (SD), and minimum and maximum data values were used to summarize the quantitative demographic variables, which were then analyzed with either a two-sided t test or the Wilcoxon rank sum test, as appropriate. The counts and percentages were used to summarize qualitative variables, which were analyzed with either the Fisher exact test or a \( \chi^2 \) test, as appropriate. All CFB scores were calculated as follow-up minus baseline. Statistical tests of secondary endpoints were two-sided at the 0.05 significance level. All analyses were performed with SAS software (Version 9.1.3).

The safety population included all patients who received at least one dose of study product and for whom safety data were available; the modified intent to treat (mITT) population included all subjects who received at least one dose of study drug and for whom data from at least one follow-up visit was available; and the per protocol (PP) population included subjects in the mITT population without major protocol deviations. Major protocol deviations were categorized using masked data prior to locking the database. The PP population was used for the primary analysis in this non-inferiority setting and to evaluate pre-specified secondary efficacy endpoints. The mITT population was used for secondary efficacy analyses of the primary and all secondary efficacy parameters.

Results

Study population

Subject disposition is shown in Figure 1. A total of 357 patients were randomized to receive LE/T (\( n = 180 \)) or DM/T (\( n = 177 \)), and 354 patients were included in the mITT population (\( n = 178 \) for LE/T, \( n = 176 \) for DM/T). One patient randomized to LE/T received DM/T. A total of 328 patients completed the study (164 in each treatment group). Reasons for discontinuations included AEs (\( n = 4 \) for LE/T, \( n = 7 \) for DM/T), withdrawal of consent (\( n = 5 \) for LE/T, \( n = 3 \) for DM/T), loss to follow-up (\( n = 4 \) for LE/T, \( n = 1 \) for DM/T), non-compliance with study procedure (\( n = 2 \) for LE/T, \( n = 1 \) for DM/T), use of disallowed medication (\( n = 1 \) for LE/T), and failure to show improvement (\( n = 1 \) for DM/T). A further 20 patients were excluded from the PP population due to protocol violations, including non-compliance with study treatment (\( n = 5 \) for LE/T, \( n = 11 \) for DM/T), unauthorized concomitant therapy (\( n = 1 \) for DM/T), non-compliance with study visits (\( n = 1 \) for LE/T, \( n = 3 \) for DM/T), non-compliance with randomization treatment allocation (\( n = 1 \) for LE/T), non-compliance with selection criteria (\( n = 3 \) for LE/T, \( n = 8 \) for DM/T), and non-compliance with study assessment (\( n = 1 \) for LE/T). Three subjects randomized to LE/T had two deviations each and ten subjects randomized to DM/T had two or more deviations each. Thus, there were 308 patients in the PP population (\( n = 156 \) for LE/T, \( n = 152 \) for DM/T).

The two treatment groups were comparable with respect to demographic characteristics (Table 1). All patients were Chinese; in agreement with previous studies in BKC\(^{18}\), the majority of patients were female. The overall mean (SD) baseline signs and symptoms composite score for the mITT and PP population was 14.58 (4.69) and 14.75 (4.65), respectively, and was similar between treatments. Most patients had a decimal VA of 0.5–1.5 at baseline. A total of 100% and 99.4% of subjects in the LE/T and DM/T treatment groups, respectively, had no anterior chamber abnormalities at baseline, and all patients had baseline IOPs between 7 and 23 mmHg.

Compliance rates were similar between the LE/T and DM/T groups, with 86.4% of LE/T patients and 88.7% of DM/T patients in the 90–110% compliance category. The overall mean number of days of exposure to treatment was 14.6 in both treatment groups.

Outcomes

Efficacy

At baseline, the mean (SD) composite signs and symptoms scores were 14.44 (4.11) and 15.07 (5.13) for LE/T-treated and DM/T-treated patients in the PP population and 14.43 (4.25) and 14.73 (5.09), respectively, in the
mITT population. The mean CFB in the signs and symptoms composite score at each follow-up visit for the PP and mITT population are shown in Table 2. A significant CFB in the composite signs and symptoms score was seen in both treatment groups at all follow-ups ($p < 0.0001$). The mean (SD) CFB to visit 4 in the signs and symptoms composite scores for the PP population were $-11.63 (4.56)$ and $-12.41 (4.71)$ in the LE/T and DM/T groups, respectively. The two-sided 90% CI of the difference of $-0.31$ to $0.75$ demonstrated non-inferiority of LE/T to DM/T, as the upper CI is less than the predefined non-inferiority limit of 2.5. Results at visit 2 and visit 3 likewise showed non-inferiority of LE/T to DM/T, and results for the mITT population were consistent with the PP population. Further analysis showed no significant difference in treatment effects between treatment groups at any visit with the exception of visit 3 for the mITT population in favor of treatment with DM/T ($p = 0.0117$).

The mean (SD) baseline signs composite scores and the symptom composite scores for the PP population were 6.67 (2.66) and 7.78 (2.75) for LE/T and 7.08 (3.21) and 7.99 (3.00) for DM/T, respectively. The mean (SD) CFB to visit 4 in the signs and symptoms composite scores for the PP population were $-11.63 (4.56)$ and $-12.41 (4.71)$ in the LE/T and DM/T groups, respectively. The two-sided 90% CI of the difference of $-0.31$ to $0.75$ demonstrated non-inferiority of LE/T to DM/T, as the upper CI is less than the predefined non-inferiority limit of 2.5. Results at visit 2 and visit 3 likewise showed non-inferiority of LE/T to DM/T, and results for the mITT population were consistent with the PP population. Further analysis showed no significant difference in treatment effects between treatment groups at any visit with the exception of visit 3 for the mITT population in favor of treatment with DM/T ($p = 0.0117$).

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Results for the mITT population were in agreement with the PP population with the exception of visit 3 symptom composite scores in favor of treatment with DM/T ($p = 0.0111$).

The mean (SD) CFB in the blepharitis, conjunctivitis, and keratitis signs composite scores for the PP population is shown in Table 3. The mean (SD) baseline scores were 1.82 (2.01), 4.40 (1.75), and 0.44 (0.92), respectively, for the LE/T group, and 1.97 (2.27), 4.48 (1.69), and 0.63 (1.08), respectively, for the DM/T group. Significant improvements from baseline were seen at all visits for any visit ($p = 0.0038$ with DM/T having higher mean baseline scores), CFB to visits 2, 3, and 4 for light sensitivity ($p < 0.0443$), and CFB to visit 3 for burning ($p = 0.0331$). Results for the mITT population were generally consistent with the PP population (data not shown).

### Safety

There were no serious AEs or unusual/unexpected AEs in this study. In the LE/T group, a total of four non-ocular AEs occurred in four patients: one patient each had mild nausea (related to study drug), moderate spinal disorder (not related), mild headache (related), and mild alopecia (not related). In the DM/T group, a total of three non-ocular AEs occurred in three patients, all of which were not related to the study drug: mild nausea, mild nasopharyngitis, and mild dizziness were seen in one patient each.

The overall incidence of ocular AEs in the study eye was 13.0% (23 AEs in 23 patients) for the LE/T group and 23.2% (43 AEs in 41 patients) for the DM/T group. Ocular AEs in study eyes are summarized in Table 4. The most frequent ocular AEs in both treatment groups were increased IOP (9.0 vs. 20.3% in the LE/T and DM/T groups, respectively) and instillation-site stinging (1.7 vs. 2.8% in the LE/T and DM/T groups, respectively). All ocular AEs were considered related to treatment with

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### Table 2. Change from baseline in the signs and symptoms composite score*.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Per protocol population</th>
<th>Modified intent-to-treat population</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>90% CI†</td>
<td></td>
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<tr>
<td>LE/T</td>
<td>DM/T</td>
<td></td>
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<tr>
<td>Visit 2 (day 3 ± 1)</td>
<td></td>
<td></td>
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<tr>
<td>n</td>
<td>155</td>
<td>152</td>
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<tr>
<td>Mean (SD)</td>
<td>-5.66 (3.46)</td>
<td>-5.98 (3.68)</td>
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<td>&lt;0.0001</td>
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<tr>
<td>Visit 3 (day 8 ± 1)</td>
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<td></td>
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<tr>
<td>n</td>
<td>155</td>
<td>150</td>
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<tr>
<td>Mean (SD)</td>
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<td>-10.21 (4.23)</td>
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<td>p-value‡</td>
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<tr>
<td>Visit 4 (day 15 ± 2)</td>
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<tr>
<td>n</td>
<td>156</td>
<td>152</td>
</tr>
<tr>
<td>Mean (SD)</td>
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<tr>
<td>p-value‡</td>
<td>&lt;0.0001</td>
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*Range, 0–52.
†The primary analysis tested the non-inferiority of LE/T to DM/T using the upper limit of the 90% confidence interval for the difference between treatments for the change from baseline to visit 4 and a margin of 2.5. For this analysis only, missing data were imputed for study eyes that were placed on rescue therapy using the LOCF prior to rescue medication. At visit 4, there were no study eyes with missing data in the PP population; while in the mITT population, there were 14 and 11 study eyes in the LE/T and DM/T treatment group with missing data at this visit.
‡Paired t-test.
Table 3. Change from baseline in blepharitis, conjunctivitis, and keratitis signs composite scores (per protocol population).

<table>
<thead>
<tr>
<th>Visit 2 (day 3 ± 1)</th>
<th>Blepharitis signs composite score*</th>
<th>Conjunctivitis signs composite score*</th>
<th>Keratitis signs composite score†</th>
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<tr>
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<td>DM/T</td>
<td>90% CI</td>
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<td>Mean (SD)</td>
<td>155</td>
<td>152</td>
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<tr>
<td>LS mean</td>
<td>−0.50 (1.03)</td>
<td>−0.64 (1.07)</td>
<td>−1.92 (1.42)</td>
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<td>p-value‡</td>
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<td>&lt;0.0001</td>
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<td>150</td>
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<tr>
<td>LS mean</td>
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<td>−2.97 (1.71)</td>
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<td>LS mean</td>
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<td>−1.56 (1.87)</td>
<td>−2.44 (1.80)</td>
</tr>
<tr>
<td>p-value‡</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Range, 0–12.
†Range, 0–4.
‡Paired t-test.
LE/T, loteprednol etabonate 0.5%/tobramycin 0.3%; DM/T, dexamethasone 0.1%/tobramycin 0.3%

n, patients with non-missing data.
the exception of two events of increased IOP (mild) in each treatment group. All ocular AEs were mild-to-moderate in severity with the exception of one event of increased IOP in the DM/T treatment group which was considered severe.

At baseline, mean (SD) IOP was 14.20 (2.90) mmHg in the LE/T group and 14.22 (3.05) mmHg in the DM/T group. Study eyes treated with DM/T experienced a statistically significantly higher increase in mean CFB in IOP compared to study eyes treated with LE/T at each visit (p ≤ 0.0186) (Figure 2). Consistent with the AE data above, overall twice as many patients in the DM/T group experienced IOP increases of 5 mmHg or more above baseline compared to the LE/T group (p = 0.0020; Table 5). One eye in the DM/T group experienced an IOP ≥ 30 mmHg.

No patient had any anterior chamber cells or synechiae at any post-baseline visit, and one patient (DM/T treatment group) had mild flare at visits 2 and 3. No difference was seen in cataract ratings between baseline and follow-up visits in both groups.

VA improved from baseline in both groups. In the LE/T group there was a decrease in the number of patients decimal VA in the categories 0.5–0.6 and, to a lesser extent, 0.7–0.8, and an increase in the number of patients in the categories of 0.9–1.0, 1.1–1.2, and 1.3–1.5. Similar results were obtained in the DM/T group.

### Table 4. Ocular adverse events by decreasing incidence.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number of patients or study eye (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LE/T (n = 177)</td>
</tr>
<tr>
<td>Total number of AEs</td>
<td>23</td>
</tr>
<tr>
<td>Patients with ≥ 1 AE</td>
<td>23 (13.0)</td>
</tr>
<tr>
<td>Increased IOP*</td>
<td>16 (9.0)</td>
</tr>
<tr>
<td>Instillation site stinging</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Application site dryness</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Keratitis, bacterial</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Pain after application</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Superficial punctate keratitis</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

*p < 0.05 mmHg.

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

### Figure 2. Mean (SD) change from baseline in intraocular pressure at visits 2, 3, and 4 for LE/T and DM/T. Statistically significant increases in IOP with DM/T vs. LE/T: *p = 0.0186; †p = 0.0002; ‡p = 0.0039. LE/T, loteprednol etabonate 0.5%/tobramycin 0.3%; DM/T, dexamethasone 0.1%/tobramycin 0.3%.

### Table 5. Change from baseline in intraocular pressure by treatment group. Data are number (%) of patients. Safety population.

<table>
<thead>
<tr>
<th></th>
<th>Visit 2</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LE/T</td>
<td>DM/T</td>
<td>LE/T</td>
<td>DM/T</td>
<td>LE/T</td>
<td>DM/T</td>
</tr>
<tr>
<td>≥ 5 mmHg</td>
<td>3 (1.7)</td>
<td>15 (8.5)</td>
<td>9 (5.3)</td>
<td>25 (14.5)</td>
<td>22 (13.5)</td>
<td>31 (18.8)</td>
</tr>
<tr>
<td>p-value*</td>
<td>0.004</td>
<td>0.0004</td>
<td>0.3237</td>
<td>0.002</td>
<td>0.3011</td>
<td>0.0958</td>
</tr>
<tr>
<td>≥ 10 mmHg</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>3 (1.7)</td>
<td>6 (3.7)</td>
<td>10 (6.1)</td>
</tr>
<tr>
<td>p-value*</td>
<td>0.0002</td>
<td>0.3011</td>
<td>0.0958</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p-Cochran–Mantel–Haenszel test.

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

### Discussion

The results of this study indicate that LE/T was at least as effective as DM/T in improving the signs and symptoms of ocular inflammation associated with BKC in a Chinese population. Non-inferiority of LE/T to DM/T was demonstrated for the primary efficacy endpoint – the signs and symptoms composite score at day 15 – for both the PP population as well as mITT population, and no significant differences were seen between treatment groups for the majority of secondary parameters at most visits. Exceptions in favor of DM/T in a few individual signs and symptoms were likely not clinically relevant as they were inconsistent with findings for prior and subsequent study visits and the overall study results.

Our findings are in agreement with those reported previously on the comparative effectiveness of LE/T and DM/T in patients with BKC. The results of the investigator-masked study by White et al. comparing LE/T with DM/T in patients aged 18 years and older showed that LE/T was as effective as DM/T in reducing the signs and symptoms of ocular inflammation associated with BKC. The authors reported a small difference in favor of DM/T for the individual sign of conjunctival chemosis at visit 4 and the individual symptom of burning at visit 3, and in favor of LE/T for keratitis at visit 3. However, they

Table 5. Change from baseline in intraocular pressure by treatment group. Data are number (%) of patients. Safety population.
considered these findings as clinically insignificant, as do we. Although other authors reported a difference between LE/T and DM/T in favor of DM/T in clinical signs of ocular inflammation in one study, we think that fewer cases of chronic disease, a narrower range of disease severity, and different study designs (including different treatment regimens) could account for the inconsistency.

Of great importance to the safety of LE is the nature and extent of corticosteroid-induced elevation of IOP. Overall, the incidence and magnitude of elevations in IOP in the present study were greater in the DM/T treatment group than in the LE/T group. Current results corroborate those from several prior studies showing that LE produces little or no change in IOP, whereas dexamethasone carries a 7–8% risk of producing a significant rise in IOP. Hence, LE/T may be a safer alternative to DM/T in the treatment of ocular inflammation. Although the exact mechanism by which LE treatment elicits less IOP elevation than other steroids has not been conclusively demonstrated, as a C-20 ester corticosteroid, LE can be quickly hydrolyzed into inactive metabolites by esterases, thereby reducing active drug levels in the aqueous humor after exerting its activity and improving the drug’s safety profile. Conversely, all other available ocular steroids (such as prednisolone and dexamethasone) are C-20 keto steroids and are not subject to esterase metabolism. Consequently, they remain in the anterior chamber for longer periods, leading to elevated IOP. However, our results are different from those of White et al., which found only one patient with an IOP increase >10 mmHg in the DM/T group. No patients treated with LE/T in that study had an IOP increase >10 mmHg, whereas six patients treated with LE/T in the current study had an IOP increase ≥10 mmHg. The differences in IOP increases across studies may be attributable to multiple factors, including different IOP testing methods or different family histories of ocular hypertension. Chang et al. recently reported longer axial length as a risk factor for steroid-related IOP elevation suggesting that racial diversity could account for the difference. Finally, several studies, including the study by Chang et al., have demonstrated that younger age may be a significant risk factor for steroid-related IOP elevation. The age of patients in our study is at least 10 years younger than those in the White et al. study, which may also contribute to the differences between studies.

Treatment with LE/T was well-tolerated in the present study. Visual acuity improved in both groups as signs and symptoms improved, and the frequency and type of AEs due to the study medications were similar, with the exception of elevations in IOP. Our results were consistent with AEs reported in patients with ocular inflammation treated with LE/T.

A potential limitation of this study was the lack of a vehicle or non-treatment control. However, the long history of corticosteroid use for the treatment of inflammatory conditions such as BKC, together with the statistically significant reduction in the severity of inflammation observed in both groups in this study indicates that both LE/T and DM/T treatments were equally effective rather than equally ineffective. The single-masked design of this study could also be considered a potential limitation. Despite the replacement of commercial labels with investigational labels, due to physical differences in the appearance of the commercial bottles of LE/T and DM/T themselves, the patients may not have been masked to treatment. However, the investigators were not present when patients opened their masked kit boxes, nor were they present during any in-office study instillation and were therefore fully masked to treatment.

Conclusion

In conclusion, in a Chinese patient population, treatment with LE/T was at least as effective as DM/T for improving the signs and symptoms of BKC. LE/T may provide greater safety benefits than DM/T, as evidenced by significantly less elevation of IOP.

Transparency

Declaration of funding

This study was sponsored by Bausch & Lomb, Inc., Rochester, NY.

Declaration of financial/other relationships

The authors have disclosed that they have no relevant financial relationships, and have served as clinical investigators in this study. CMRO peer reviewers may have received honoraria for their review work. The peer reviewers on this manuscript have disclosed that they have no relevant financial relationships.

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References


