



REVIEW

# Review of Loteprednol Etabonate 0.5%/Tobramycin 0.3% in the Treatment of Blepharokeratoconjunctivitis

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## ABSTRACT

Use of a combination corticosteroid and antibiotic in a single formulation is common in the treatment of ocular inflammatory conditions for which corticosteroid therapy is indicated and there exists a risk of superficial bacterial infection. Loteprednol etabonate (LE) is a corticosteroid engineered to maintain potent anti-inflammatory activity while minimizing the risk of undesirable class effects of corticosteroids, such as elevated intraocular pressure and cataract. Tobramycin is a broad-spectrum aminoglycoside antibiotic that is considered generally safe and well tolerated. An ophthalmic suspension combining LE 0.5% and tobramycin 0.3% (LE/T) is approved in the US and several other countries. Use of a combination therapy increases convenience, which may promote patient adherence. A systematic literature review was conducted to examine the efficacy and safety of LE/T for ocular inflammatory conditions within the scope of its labeled indications. Results of published studies indicate that LE/T is effective in the treatment

of blepharokeratoconjunctivitis in adults, with similar efficacy as dexamethasone 0.1%/tobramycin 0.3%, but is associated with a lower risk of clinically significant increases in intraocular pressure as demonstrated in both efficacy and safety studies and studies with healthy volunteers. Furthermore, studies in children with blepharitis or blepharoconjunctivitis indicate LE/T was well tolerated in this population, although efficacy vs vehicle was not demonstrated, potentially due to improvements in all groups overall and/or limited sample size. Separately, tobramycin demonstrated potent in vitro activity against most bacterial species associated with blepharitis. In conclusion, published data demonstrate the utility of LE/T for the treatment of the various clinical manifestations of blepharokeratoconjunctivitis in adults.

**Keywords:** Combination drug; Intraocular pressure; Ocular inflammation; Loteprednol etabonate; Tobramycin; Topical ophthalmic

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### Key Summary Points

The use of a combination corticosteroid and antibiotic is common in ocular inflammatory conditions with a risk of superficial bacterial infection providing patient convenience and potentially improving adherence

A review of the literature indicates loteprednol etabonate 0.5% and tobramycin 0.3% (LE/T) ophthalmic suspension is effective for the treatment of blepharokeratoconjunctivitis in adults with efficacy comparable to that of dexamethasone 0.1%/tobramycin 0.3%, but with a lower propensity to impact intraocular pressure. While the combination appears well tolerated in children with blepharitis or blepharoconjunctivitis, large studies with no confounders are required to demonstrate efficacy compared to vehicle

In vitro, tobramycin demonstrated potent activity against bacterial species implicated in blepharitis

Together, published data demonstrate the utility of LE/T suspension for the treatment of the blepharokeratoconjunctivitis in adults

## INTRODUCTION

There are many ocular inflammatory conditions for which corticosteroid therapy is indicated and there exists a risk of superficial bacterial infection [1], such as ocular surface infections and certain inflammatory diseases, superficial ocular diseases, and some forms of conjunctivitis [1–5]. Corticosteroid/antibiotic combination products are often used to treat these types of conditions [1]. Use of such products is expected to facilitate adherence, be more convenient for the patient [6, 7], and assure that

appropriate dosages of both drugs will be delivered simultaneously. Zylet [1], an ophthalmic suspension combining loteprednol etabonate 0.5% (LE) and tobramycin 0.3% (LE/T) (Zylet®; Bausch + Lomb; Bridgewater NJ), was initially approved by the United States (US) Food and Drug Administration in 2004 [8] and is now also approved for use outside the US in several countries including Argentina, Mexico, Brazil, Israel, Morocco, Lebanon, the Philippines, Singapore, China, Thailand, Turkey, and Saudi Arabia. This formulation is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and either a superficial bacterial ocular infection or a risk of bacterial ocular infection is present. Recommended dosing for LE/tobramycin (LE/T) is 1–2 drops every 4–6 h, although dosing may be increased to every 1–2 h during the first 24 to 48 h of treatment, if indicated.

Loteprednol etabonate is a carbon-20 ester corticosteroid that was retrometabolically designed via modification of the prednisolone molecule with the goal of maintaining potent anti-inflammatory activity while minimizing the risk of undesirable class effects of corticosteroids [9, 10]. Early development studies showed LE to be highly lipophilic with a binding affinity 4.3 times greater than that of dexamethasone for the glucocorticoid receptor [9]. However, LE is rapidly de-esterified to its inactive carboxylic acid metabolite after exerting its pharmacological activity, thus providing the molecule with a high therapeutic index [9, 10]. Studies have demonstrated a low risk of clinically significant intraocular pressure (IOP) elevations with short- and long-term use of LE [11]. LE is also likely less cataractogenic than ketone corticosteroids, because it lacks the ketone at carbon-20 that has been implicated in one of the known pathways of cataract formation [12]. The efficacy of LE as a single agent in reducing inflammation across a range of clinical ocular inflammatory conditions is the focus of a previous review [10].

Tobramycin is an aminoglycoside antibiotic that provides coverage against a broad spectrum of common ocular pathogens [13, 14] and is considered generally safe and well tolerated [15]. This antibiotic has been used to treat infection in a wide range of ocular conditions

**Table 1** Study design and key results from clinical trials of LE/T

Study	Design (country)	Treatments and duration	Efficacy findings	Safety findings	Other
Blepharokeratoconjunctivitis—adults					
White et al. [24]	Multicenter, randomized, investigator-masked trial (US)	2 weeks of treatment with: LE/T QID ( <i>n</i> = 138) DM/T QID ( <i>n</i> = 138)	Mean (SD) change from baseline in composite signs and symptoms at day 15 (LE/T vs DM/T): − 15.2 (7.3) vs − 15.6 (7.7); <i>P</i> = NS Investigator global assessment of cured (Grade 0; LE/T vs DM/T) at day 3 (2.2% vs 0.7%), day 7 (20.1% vs 16.5%), and day 15 (43.6% vs 40.9%); <i>P</i> = NS for all time points	Mean (SD) IOP change (LE/T vs DM/T) from baseline to day 7 (− 0.1 [2.2] mm Hg vs 0.6 [2.3] mm Hg, <i>P</i> = 0.04), day 15 (− 0.1 [2.4] mm Hg vs 1.0 [3.0] mm Hg, <i>P</i> = 0.01), and overall (1.6 mm Hg vs 2.3 mm Hg, <i>P</i> = 0.02) ↑IOP (≥ 10 mm Hg): LE/T, <i>n</i> = 0; DM/T, <i>n</i> = 1 (0.7%)	≥ 1 ocular AE (LE/T vs DM/T): 2.9% vs 6.5% LE/T: allergic conjunctivitis, eye irritation, eye pain, ↑IOP (1 subject each) DM/T: ↓ lacrimation, foreign body sensation (1 subject each); punctate keratitis (2 subjects); ↑IOP (5 subjects) No serious ocular AEs ≥ 1 nonocular AE (LE/T vs DM/T): 2.9% vs 2.9% Discontinuation due to AEs: LE/T: 1 subject (headache) DM/T: 1 subject (allergic conjunctivitis) No clinically meaningful changes in VA or biomicroscopy findings
Chen et al. [25]	Multicenter, randomized, investigator-masked trial (China)	2 weeks of treatment with: LE/T QID ( <i>n</i> = 180) DM/T QID ( <i>n</i> = 177)	Significant ( <i>P</i> < 0.01) improvement from baseline to day 15 in composite signs and symptoms in both treatment groups Mean (SD) change from baseline in composite signs and symptoms at day 15 (LE/T vs DM/T): − 11.6 (4.6) vs − 12.4 (4.7); <i>P</i> = NS	Mean IOP change (LE/T vs DM/T) from baseline to day 3 (0.61 mm Hg vs 0.6 1.15 mm Hg, <i>P</i> = 0.02), day 7 (0.61 mm Hg vs 1.73 mm Hg, <i>P</i> < 0.01), and day 15 (1.33 mm Hg vs 2.43 mm Hg, <i>P</i> < 0.01) ↑IOP (≥ 10 mm Hg): LE/T, <i>n</i> = 6 (3.4%); DM/T, <i>n</i> = 13 (7.3%); <i>P</i> = NS One eye in the DM/T group had IOP ≥ 30 mm Hg	≥ 1 ocular AE (LE/T vs DM/T): 13.0% vs 23.2% LE/T: dryness, bacterial keratitis, pain after application, superficial punctate keratitis (1 subject each), instillation site stinging (3 subjects), ↑IOP > 5 mm Hg (16 subjects) DM/T: instillation site stinging (5 subjects), ↑IOP (36 subjects) ≥ 1 nonocular AE (LE/T vs DM/T): 2.2% vs 1.7% No serious AEs Discontinuation due to AEs: LE/T: 4 subjects (headache) DM/T: 7 subjects No differences between groups in VA or biomicroscopy findings

Table 1 continued

Study	Design (country)	Treatments and duration	Efficacy findings	Safety findings		
				IOP	Other	Other
Rhee and Mah [21]	Single-center, randomized, double-masked trial (US)	3–5 days of treatment with: LE/T BID ( <i>n</i> = 20) DM/T BID ( <i>n</i> = 20)	Severity scores (lower is better) after 3–5 days of treatment (LE/T vs DM/T): Blepharitis: 1.35 vs 0.9 ( <i>P</i> = 0.02) Discharge: 0.6 vs 0.2 ( <i>P</i> = 0.03) Conjunctivitis: 0.6 vs 0.15 ( <i>P</i> = 0.01) Total ocular surface: 3.4 vs 1.8 ( <i>P</i> = 0.01) No significant difference between groups in corneal punctate epithelial keratopathy scores	No differences between groups in IOP findings (mean IOP similar before and after treatment in both groups) No ↑IOP ( $\geq 10$ mm Hg)	No AEs reported No clinically meaningful changes in VA	
Blepharitis—pediatric						
Comstock et al. [26]	Multicenter, randomized, double-masked trial (US)	Warm compresses BID plus: LE/T QID week 1, BID week 2 ( <i>n</i> = 72) Vehicle QID week 1, BID week 2 ( <i>n</i> = 36)	Efficacy findings ambiguous due to improvements in all treatment groups and use of warm compresses throughout the study	No significant differences between groups on day 1, day 8, or day 15 of treatment No ↑IOP ( $\geq 10$ mm Hg)	$\geq 1$ ocular AE (LE/T vs vehicle): 4.2% vs 5.6% LE/T: Meibomian gland dysfunction, corneal staining (1 subject each), conjunctivitis (2 subjects) Vehicle: Meibomian gland dysfunction, erythema of eyelid, eyelid edema (1 subject each) No significant differences between treatments in proportions of subjects with any specific ocular AE No serious ocular AEs $\geq 1$ nonocular AE (LE/T vs vehicle): 8.3% vs 5.6% Discontinuation due to AEs: 1 subject in LE/T group (rash)	No clinically meaningful changes in VA in either treatment group or between treatment groups

**Table 1** continued

Study	Design (country)	Treatments and duration	Efficacy findings	Safety findings	
				IOP	Other
Blepharocconjunctivitis—pediatric					
Comstock et al. [26]	Multicenter, randomized, double-masked trial (US)	2 weeks of treatment with: LE/T QID ( <i>n</i> = 34) LE 0.5% QID ( <i>n</i> = 35) Tobramycin 0.3% QID ( <i>n</i> = 34) Vehicle QID ( <i>n</i> = 34)	Efficacy findings ambiguous due to improvements in all treatment groups	IOP not evaluated	<p>≥ 1 ocular AE (LE/T vs LE vs tobramycin vs vehicle): 2.9% vs 11.4% vs 0.0% vs 0.0%</p> <p>LE/T: eye pain (1 subject)</p> <p>LE: eye pain, conjunctivitis, eye discharge, eye inflammation (1 subject each)</p> <p>No serious ocular AEs</p> <p>≥ 1 nonocular AE (LE/T vs LE vs tobramycin vs vehicle): 5.9% vs 17.1% vs 17.6% vs 15.2%</p> <p>Discontinuation due to AEs: 1 subject in the tobramycin group (respiratory distress)</p> <p>No clinically meaningful changes in VA in either treatment group or between treatment groups</p>

Table 1 continued

Study	Design (country)	Treatments and duration	Efficacy findings	Safety findings	
				IOP	Other
Healthy volunteers					
Holland et al. [23]	Multicenter, randomized, double-masked trial (US)	4 weeks of: LE/T QID ( <i>n</i> = 156) DM/T QID ( <i>n</i> = 150)	Efficacy not evaluated	Significant ↑IOP observed at all visits from day 3 to day 29 with DM/T ( <i>P</i> < 0.01); no significant ↑IOP with LE/T at any visit ↑IOP significantly greater with DM/T vs LE/T at every study visit ↑IOP (≥ 10 mm Hg): LE/T, <i>n</i> = 3 (2.0%); DM/T, <i>n</i> = 11 (7.5%); <i>P</i> = 0.03	≥ 1 ocular AE (LE/T vs DM/T): 14.7% vs 12.0% LE/T: lacrimation increased, foreign body sensation in eyes, allergic conjunctivitis, corneal erosion (3 subjects each) DM/T: lacrimation increased (1 subject), iridocyclitis, iritis (3 subjects each) ↑IOP reported as an AE for 3 (1.9%) subjects in LE/T group vs 13 (8.7%) in DM/T group ( <i>P</i> < 0.01) Sinus headache occurred in 5 subjects in DM/T group (3.3%) vs none in LE/T group ( <i>P</i> = 0.03) Reductions in VA of ≥ 2 lines from baseline observed in 14 (4.6%) eyes in LE/T group vs 23 (7.8%) in DM/T group; significant difference at day 3 only (0.6% vs 3.4%, <i>P</i> = 0.02) No clinically significant changes in biomicroscopy or undilated direct ophthalmoscopy results

*AE* adverse event, *BID* twice daily, *DM/T* dexamethasone 0.1%/tobramycin 0.3%, *IOP* intraocular pressure, *LE* loteprednol etabonate 0.5%/tobramycin 0.3%, *NS* not significant, *QID* 4 times daily, *SD* standard deviation, *VA* visual acuity

**Table 2** In vitro potency of tobramycin against bacterial species commonly implicated in blepharitis [29]

	Range ( $\mu\text{g/ml}$ )	MIC <sub>50</sub> ( $\mu\text{g/ml}$ )	MIC <sub>90</sub> ( $\mu\text{g/ml}$ )
<i>Acinetobacter</i> spp. ( $n = 30$ )	0.06 $\geq$ 64	0.5	1
<i>Bacillus</i> spp. ( $n = 30$ )	0.03–4	0.25	2
<i>Corynebacterium</i> and <i>Brevibacterium</i> spp. ( $n = 34$ )	$\leq$ 0.008–4	0.06	2
<i>Cutibacterium</i> ( <i>Propionibacterium</i> ) spp. ( $n = 30$ )	16 $\geq$ 64	32	32
<i>Enterococcus</i> spp. ( $n = 30$ )	2 $\geq$ 64	16	> 64
<i>Klebsiella</i> spp. ( $n = 30$ )	0.06–32	0.5	4
<i>Micrococcus</i> and <i>Kocuria</i> spp. ( $n = 30$ )	1–8	2	4
<i>Moraxella</i> spp. ( $n = 30$ )	0.06–0.25	0.25	0.25
<i>Neisseria</i> spp. ( $n = 30$ )	$\leq$ 0.008–32	1	8
<i>Rothia</i> spp. ( $n = 33$ )	$\leq$ 0.008–32	4	16
<i>Staphylococcus</i> spp. ( $n = 150$ )	0.015 $\geq$ 64	0.25	8
MSSA ( $n = 30$ )	0.25 $\geq$ 64	0.25	0.5
MRSA ( $n = 30$ )	0.25 $\geq$ 64	0.5	> 64
MSSE ( $n = 30$ )	0.06 $\geq$ 64	0.12	0.25
MRSE ( $n = 30$ )	0.06–64	0.12	16
CoNS spp ( $n = 30$ )	0.015–16	0.06	4
<i>Streptococcus</i> spp. ( $n = 30$ )	1 $\geq$ 64	8	32

CoNS coagulase-negative staphylococci, MRSA methicillin-resistant *Staphylococcus aureus*, MRSE methicillin-resistant *Staphylococcus epidermidis*, MSSA methicillin-sensitive *Staphylococcus aureus*, MSSA methicillin-sensitive *Staphylococcus aureus*

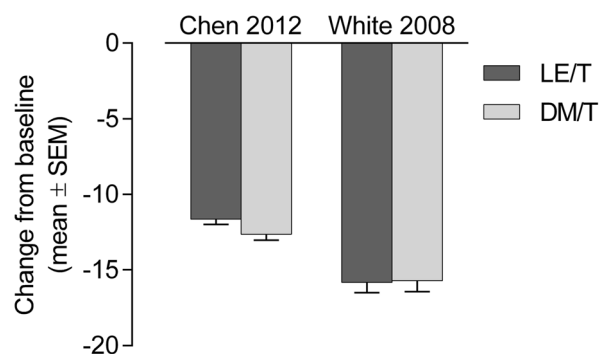
[13]. For instance, tobramycin has demonstrated high rates of bacterial eradication in patients with bacterial conjunctivitis (94.3–98.5%) [16–19] and blepharoconjunctivitis (bacterial eradication or reduction of potentially pathogenic bacteria in 88.9% of eyes) [20].

This article systematically reviews the published literature on the efficacy and safety of LE/T in the treatment of ocular inflammatory conditions consistent with its labeled indications.

## METHODS

This article reviews previously conducted studies published in the literature and does not contain any new studies performed by any of the authors.

A literature search was conducted using PubMed and Embase with no time limitation using the following search terms: “loteprednol” plus “tobramycin.” All results were reviewed, and relevant articles were obtained. Bibliographies of identified references and review articles were also searched for additional references of interest. Additionally, abstracts from the following congresses were searched from 2010 to 2021 using the same terms: the Association for Research in Vision and Ophthalmology annual meeting, the American Academy of Ophthalmology annual meeting, and the American Academy of Optometry annual meeting. All articles and abstracts selected for inclusion reported on the use of LE/T for any



**Fig. 1** Mean (SEM) change from baseline in the blepharokeratoconjunctivitis signs and symptoms composite score in two randomized controlled multicenter studies [24, 25]. In both studies, ocular signs included blepharitis (lid hyperemia, lid scaling or crusting, and lid margin hypertrophy), conjunctivitis (conjunctival hyperemia, conjunctival discharge, and conjunctival chemosis), and keratitis (corneal punctate epithelial keratopathy). Ocular symptoms included itchiness, foreign body sensation, blurred vision, light sensitivity, painful or sore eyes, and burning. Each sign and symptom was measured on a 5-point scale from 0 (none) to 4 (severe). In both studies the signs and symptoms composite score could range from 0 to 52. *LE/T* loteprednol etabonate 0.5%/tobramycin 0.3%, *DM/T* dexamethasone 0.1%/tobramycin 0.3%

labeled ophthalmologic conditions or assessment in healthy volunteers.

## RESULTS

The literature search identified ten relevant journal articles, six of which featured clinical trials [21–26], while three featured pooled analyses or meta-analyses of study data [11, 27, 28]. An additional conference abstract was identified featuring a study not found in full manuscript form [29]. Table 1 summarizes the study design and key results from clinical trials of *LE/T*. Table 2 describes the *in vitro* potency of tobramycin against bacterial species commonly implicated in blepharitis derived from a recent study of *LE/T* [29].

### Blepharokeratoconjunctivitis (BKC) in Adults

White et al. [24] conducted a multicenter, randomized, investigator-masked study in the US

comparing *LE/T* ( $n = 138$ ) with dexamethasone 0.1%/tobramycin 0.3% (*DM/T*;  $n = 138$ ) in adults aged 18 and older with BKC. Subjects were instructed to administer the study drug 4 times daily (QID) at approximately 4-h intervals over 14 days. Ocular signs of blepharitis (lid hyperemia, lid scaling or crusting, and lid margin hypertrophy), conjunctivitis (conjunctival hyperemia, conjunctival discharge, and conjunctival chemosis), keratitis (corneal punctate epithelial keratopathy), and symptoms (itchiness, foreign body sensation, blurred vision, light sensitivity, painful and sore eyes, and burning) were assessed or queried by the investigator at baseline and each visit thereafter and scored on a scale from 0 (none) to 4 (severe); the signs and symptoms composite score (sum of all scores) ranged from 0 to 52. Additionally, investigators completed a global assessment by rating overall global changes relative to the previous visit on a scale from 0 (cured) to 3 (worsened). The mean (standard deviation [SD]) signs and symptoms composite score improved from baseline to day 15 in patients treated with *LE/T* ( $-15.2 [7.3]$ ) or *DM/T* ( $-15.6 [7.7]$ ), corresponding to a 78% reduction from baseline in this score for both treatments (Fig. 1); *LE/T* met the criteria of noninferiority to *DM/T* with the upper bound of the 90% confidence interval for the difference in change from baseline within the prespecified noninferiority margin of 2.3. Both treatments showed similar changes from baseline to day 3 and day 7, with noninferiority of *LE/T* to *DM/T* also demonstrated at these time points. Additionally, there were no statistically significant differences between *LE/T* and *DM/T* in the percentage of study eyes considered cured based on investigator global assessment at day 3 (2.2% and 0.7%, respectively), day 7 (20.1% and 16.5%, respectively), or day 15 (43.6% and 40.9%, respectively).

Rates of nonocular adverse events (AEs) and ocular AEs were low in both treatment groups, although five patients in the *DM/T* group (3.6%) versus only one in the *LE/T* group (0.7%) experienced an AE of increased IOP. Treatment with *DM/T* was associated with a small but significantly greater mean (SD) change from baseline in IOP (in mm Hg) compared with *LE/T* at day 7 (0.6 [2.3] vs  $-0.1 [2.2]$ ,  $P = 0.034$ ) and day



15 (1.0 [3.0] vs  $-0.1$  [2.4],  $P = 0.009$ ). Over the course of the study, twice as many subjects in the DM/T group (14.4%) versus the LE/T group (7.1%) had an increase in IOP of 5–9 mm Hg, and 1 subject in the DM/T group had an IOP elevation of at least 10 mm Hg. Visual acuity (VA) and biomicroscopy findings were unchanged over the course of the study in both treatment groups.

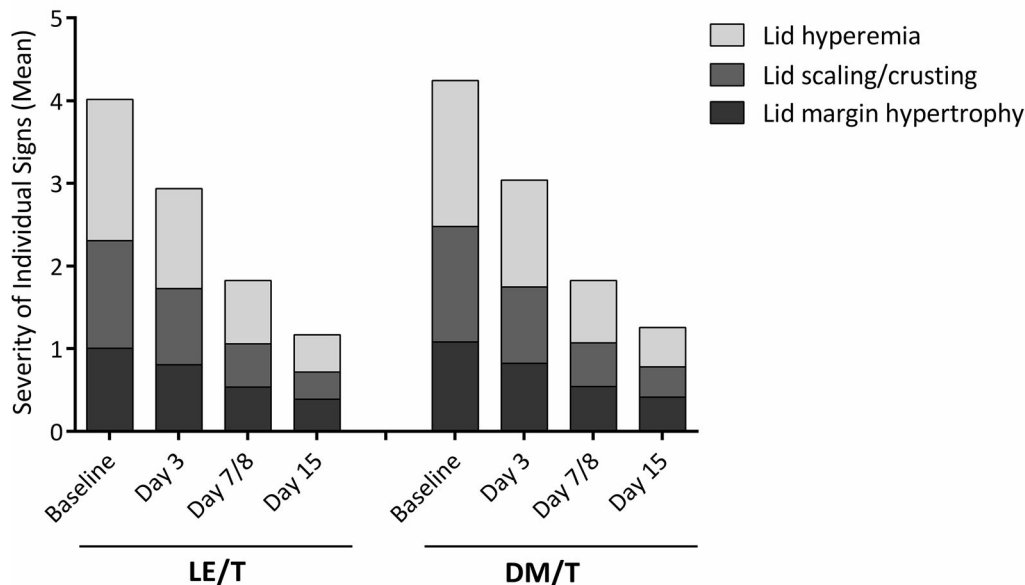
A similarly designed study compared LE/T ( $n = 180$ ) with DM/T ( $n = 177$ ) in Chinese adults with BKC [25]. Treatment with LE/T resulted in a statistically significant change from baseline to day 15 in the signs and symptoms composite score ( $P < 0.001$ ), the primary efficacy endpoint (Fig. 1). As observed in US adults, LE/T and DM/T provided similar reductions from baseline in this score at day 15 ( $-11.6$  [4.6] and  $-12.4$  [4.7], respectively), and LE/T again met the criteria for noninferiority to DM/T with the upper bound of the 90% confidence interval for the difference less than the prespecified margin of 2.5. Results at day 3 and day 7 likewise showed noninferiority of LE/T to DM/T. Ocular AEs occurred in 13.0% of subjects in the LE/T group and 23.2% in the DM/T group, with the most frequent AE in both groups being increased IOP (9.0% versus 20.3%, respectively). Consistent with findings from the US study, the mean change from baseline in IOP (in mm Hg) was significantly greater in the DM/T group compared with the LE/T group at day 3 (1.15 versus 0.61,  $P = 0.019$ ), day 7 (1.73 versus 0.61,  $P = 0.001$ ), and day 15 (2.43 versus 1.33,  $P = 0.004$ ). Overall, twice as many patients in the DM/T group experienced an IOP elevation of  $\geq 5$  mm Hg compared with the LE/T group (26.0% vs 13.0%;  $P = 0.002$ ). An increase in IOP  $\geq 10$  mm Hg was experienced by 6 patients (3.4%) in the LE/T group and 13 (7.3%) in the DM/T group ( $P = 0.096$ ), and 1 subject in the DM/T group had an IOP  $\geq 30$  mm Hg. There were no meaningful findings in biomicroscopy with either treatment, while VA improved to a similar degree from baseline in both treatment groups.

In a pooled analysis of data from these two trials focusing on blepharitis outcomes, LE/T reduced composite blepharitis severity (sum of ratings of lid hyperemia, lid scaling or crusting,

and lid margin hypertrophy, each scored on a scale from 0 [none] to 4 [severe]; maximum composite score, 12) from baseline to day 15 and achieved full resolution of blepharitis signs in approximately half of patients after 15 days [27]. Figure 2 shows the mean severity of individual signs and symptoms of blepharitis as well as composite blepharitis severity at each visit. While both treatments demonstrated similar efficacy, LE/T appeared to have an advantage with respect to minimal changes in IOP: increased IOP as an AE was reported for 17/315 subjects (5.4%) in the LE/T group compared with 43/315 subjects (13.7%) in the DM/T group. Overall, 6/315 subjects (1.9%) receiving LE/T and 13/315 (4.1%) DM/T-treated subjects experienced a  $\geq 10$  mm Hg increase in IOP.

Zhao and colleagues (2021) performed a meta-analysis of published randomized controlled trials of topical steroid and antibiotics for adults with BKC [28]. Of the 43 studies considered, only the 2 summarized above [24, 25] met the authors' inclusion criteria. No significant differences were observed between LE/T and DM/T with respect to mean change from baseline to day 15 in ocular signs and symptoms composite score (95% CI  $-0.33$  to 1.50; mean difference, 0.58;  $P = 0.21$ ), blepharitis composite score (95% CI  $-0.16$  to 0.48; mean difference, 0.16;  $P = 0.32$ ), conjunctivitis composite score (95% CI  $-0.55$  to 1.76; mean difference, 0.61;  $P = 0.30$ ), or keratitis composite score (95% CI, 0.00–0.28; mean difference, 0.14;  $P = 0.05$ ). Compared with DM/T, LE/T was associated with a lower risk of AEs (8.6% of patients in LE/T group vs 16.5% in DM/T group; risk ratio [RR; 95% CI], 0.52 [0.34, 0.80];  $P = 0.003$ ) and a lower risk of elevated IOP by  $\leq 10$  mm Hg (RR, 0.47 [0.32, 0.70];  $P = 0.0002$ ). Six patients in the LE/T group and 14 in the DM/T group had elevated IOP  $> 10$  mm Hg (RR, 0.45 [0.18, 1.11];  $P = 0.08$ ). As expected, results of this meta-analysis were consistent with those of the pooled analysis of these two studies described above [27].

A single-center, randomized, double-masked study compared LE/T and DM/T in 40 patients with at least moderate BKC (total score  $> 6$  out of possible 12 in blepharitis, conjunctivitis,



**Fig. 2** Mean individual blepharitis sign severity at each study visit. Entirety of stacked bar depicts composite severity [27]. Severity of each sign rated on a 5-point scale of 0 (none) to 4 (severe). *LE/T* loteprednol etabonate 0.5%/tobramycin 0.3%, *DM/T* dexamethasone 0.1%/tobramycin 0.3%. Reproduced from Comstock TL & DeCory HH, Loteprednol etabonate 0.5%/tobramycin 0.3% compared with dexamethasone

0.1%/tobramycin 0.3% for the treatment of blepharitis, *Ocul Immunol Inflamm* 2017;25(2):267–274, under the Creative Commons Attribution-NonCommercial-NoDerivatives License which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited and is not altered, transformed, or built upon in any way

ocular discharge, and punctate epithelial keratitis; each graded on a scale from 0 to 3) using twice daily (BID) dosing over 3–5 days of treatment [21]. Results of this study should be interpreted with caution considering the small number of subjects, the reduced dosing frequency relative to the approved regimen for *LE/T*, and the short duration of treatment. There were no significant differences between treatment groups in mean pretreatment scores. In contrast to findings from the previous multicenter studies, patients in the *DM/T* group had significantly lower BKC severity than the *LE/T* group after 3–5 days of treatment based on blepharitis scores (0.9 versus 1.4,  $P = 0.017$ ), discharge scores (0.2 versus 0.6,  $P = 0.025$ ), conjunctivitis scores (0.2 versus 0.6,  $P = 0.013$ ), and total ocular surface scores (1.8 versus 3.4,  $P = 0.002$ ). A reduction in corneal punctate epithelial keratopathy was observed in both treatment groups, but the difference between treatments was not statistically significant. No

AEs were reported in any patients during the study, and there were no significant changes in IOP in either treatment group.

### Blepharitis and Blepharoconjunctivitis in Pediatric Populations

Comstock et al. [26] reported safety findings from two multicenter, randomized, double-masked studies that evaluated the safety and tolerability of *LE/T* in children 0–6 years of age. In the first study, 108 subjects with blepharitis were treated with warm compresses BID for 2 weeks in addition to *LE/T* ( $n = 72$ ) or vehicle ( $n = 36$ ); both *LE/T* and vehicle were administered QID for the first week and BID for the second week. The second study randomized 137 subjects with blepharoconjunctivitis to 14 days of treatment with *LE/T* ( $n = 34$ ), *LE* ( $n = 35$ ), tobramycin ( $n = 34$ ), or vehicle ( $n = 34$ ) administered QID.

In both studies, ocular AEs were infrequent, and none were serious. Additionally, there were no significant differences between LE/T and comparator groups in the frequency of any specific ocular AE. 1 subject receiving LE/T in the first study discontinued treatment because of an AE (moderately severe rash judged possibly related to study drug) compared with no subjects in the vehicle group. In the second study, no subjects in the LE/T, LE, or vehicle group discontinued treatment because of an AE, whereas 1 subject in the tobramycin group discontinued because of an AE of respiratory distress, which was considered unrelated to the study drug. No clinically meaningful changes in VA occurred in either study. IOP was evaluated in the first (blepharitis) study only, and no statistically significant differences in mean IOP were found between LE/T and vehicle on day 1, day 8, or day 15 of treatment; no subject in either treatment group had an IOP increase of  $\geq 10$  mm Hg. The authors concluded that LE/T treatment was safe and well tolerated in pediatric populations 0 to 6 years of age with blepharitis or blepharoconjunctivitis.

Efficacy findings indicated that treatment with LE/T resulted in similar outcomes as vehicle under the conditions evaluated in these two studies. In the blepharitis study, the majority of patients in either the LE/T or vehicle group showed improvements in signs of blepharitis likely due to the concurrent use of warm compresses. In the blepharoconjunctivitis study, there were no significant differences between treatment groups in mean change from baseline in severity score (sum of eight individual signs) at any of the assessed time points. However, the following individual ocular signs showed significant improvements in the LE/T group vs the comparator groups: at day 3, lid erythema vs vehicle or tobramycin and bulbar conjunctival injection vs tobramycin; at day 7, lid erythema vs vehicle; and at day 15, meibomian plugging vs LE, ( $P \leq 0.0493$ ). The small study populations employed in these studies likely contributed to the lack of clear differentiation between the treatment groups.

### Safety and Tolerability in Healthy Volunteers

Holland et al. [23] investigated the effects of LE/T ( $n = 156$ ) or DM/T ( $n = 150$ ), instilled in both eyes QID for 28 days, on IOP and other safety parameters in healthy volunteers in a Phase 4, multicenter, randomized, double-masked study. Ocular AEs were reported in 14.7% of subjects in the LE/T group and 12.0% of those in the DM/T group; other than increased IOP (LE/T, 1.9%; DM/T, 8.7%;  $P = 0.009$ ), ocular AEs were similar between treatment groups. Statistically significant elevations in IOP over the course of treatment occurred in the DM/T group but not the LE/T group. At all postbaseline study visits, significantly greater mean changes in IOP were observed in the DM/T group versus the LE/T group (day 3 [0.78 vs 0.08 mm Hg], day 8 [1.09 vs 0.08 mm Hg], day 15 [1.48 vs 0.15 mm Hg], day 22 [1.71 vs  $-0.01$  mm Hg], and day 29 [1.45 vs 0.35 mm Hg];  $P \leq 0.002$ ). Furthermore, a significantly lower proportion of subjects in the LE/T group experienced an IOP increase  $\geq 10$  mm Hg compared with the DM/T group (3 subjects [2.0%] versus 11 subjects [7.5%];  $P = 0.028$ ). Only transient minimal changes in VA were observed, and there were no clinically significant changes in biomicroscopy or undilated direct ophthalmoscopy results in either treatment group.

The ocular comfort and tolerability of LE/T and DM/T in the Phase 4 safety study were reported separately by Bartlett [22] in a companion article. Baseline assessments were completed 5 min after instillation of artificial tears (AT) on day 1, prior to administration of any study drug. For each treatment, mean differences between baseline and the final week of diary assessments were determined for each of seven comfort/tolerability parameters (pain, stinging/burning, irritation, itchiness, foreign-body sensation, dryness, and light sensitivity), with each parameter rated on a scale from 0 (extremely uncomfortable) to 100 (extremely comfortable). The tolerability of LE/T was non-inferior to that of DM/T, based on the 97.5% lower confidence bounds for differences between treatments being within  $-10$  for all seven parameters. Within-treatment analyses of

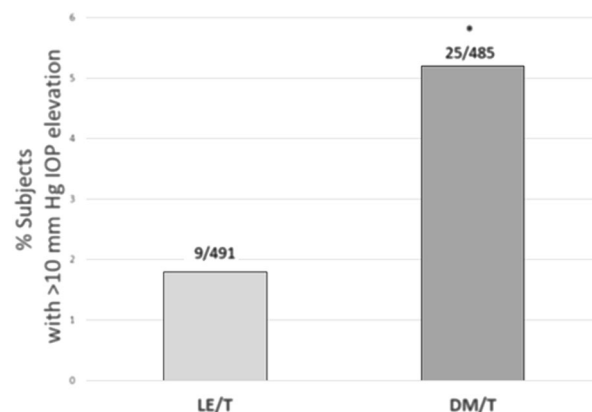
changes from baseline to the final week of diary assessments favored LE/T over AT for pain and favored DM/T over AT for light sensitivity (both  $P < 0.01$ ). Small but statistically significant advantages in comfort/tolerability were observed for LE/T over DM/T at individual study visits. Combined with IOP results, these findings suggest safety and tolerability advantages of LE/T over DM/T.

### Effect on IOP: A Pooled Analysis

Sheppard et al. [11] conducted a pooled analysis of the incidence of IOP elevations with various formulations of LE reported in randomized comparative trials in adults that included, among other comparisons, subjects treated with LE/T ( $n = 491$ ) versus DM/T ( $n = 485$ ). In that analysis, subjects treated with LE/T had a low (1.8%) risk of clinically significant IOP elevation ( $\geq 10$  mm Hg) that was almost three times less than that of subjects receiving DM/T (5.2%; Fig. 3).

### Antimicrobial Efficacy

While the antibacterial activity of tobramycin has previously been reported to be the same whether used alone or in combination with prednisolone acetate or prednisolone phosphate in an animal model of keratitis induced by *Pseudomonas aeruginosa* [30], there are no studies to date specifically evaluating the anti-infective efficacy of tobramycin in combination with LE other than an in vitro study submitted as part of the LE 0.5%/T 0.3% (Zylet<sup>®</sup>) NDA filing package demonstrating equivalent antibacterial activity between tobramycin alone and LE/T against the 20 bacterial pathogens listed in the package insert of tobramycin ophthalmic solution (Staphylococci, including *Staphylococcus aureus* and *S. epidermidis* [coagulase-positive and coagulase-negative], including penicillin-resistant strains; Streptococci, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae*, *P. aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Proteus mirabilis*, *Morganella morganii*, most



**Fig. 3** Cumulative rates of clinically significant IOP elevation ( $> 10$  mm Hg) in head-to-head studies [11]. DM/T dexamethasone 0.1%/tobramycin 0.3% suspension, IOP intraocular pressure, LE/T loteprednol etabonate 0.5%/tobramycin 0.3% suspension. \* $P < 0.01$  Adapted from Sheppard JD, Comstock TL, & Cavet ME, Impact of the topical ophthalmic corticosteroid loteprednol etabonate on intraocular pressure, *Adv Ther* 2016;33(4):532–552, under the Creative Commons Attribution 4.0 International License, (<https://creativecommons.org/licenses/by/4.0>), which permits use, duplication, adaptation, distribution, and reproduction in any medium or format

*Proteus vulgaris* strains, *Haemophilus influenzae* and *H. aegyptius*, *Moraxella lacunata*, *Acinetobacter calcoaceticus*, and some *Neisseria* species).

Deom et al. [29] recently evaluated the in vitro antibacterial activity of tobramycin against bacterial species most commonly implicated in blepharitis in their assessment of LE/T for the infectious aspect of this condition. Tobramycin was tested against 487 unique isolates from 14 genera (67 species) cultured from known infections and was found to have low minimum inhibitory concentrations (MICs) against most isolates, including staphylococci and most methicillin-resistance strains thereof. The MIC range, MIC<sub>50</sub> (MICs for 50% of isolates), and MIC<sub>90</sub> (MIC for 90% of isolates) for tobramycin are shown in Table 2. The MIC<sub>50</sub>/MIC<sub>90</sub> against the subset of methicillin-sensitive and methicillin-resistant staphylococci were, respectively, 0.25/0.5 and 0.5/ $> 64$  for *S. aureus* and 0.12/0.25 and 0.12/16 for *S. epidermidis*. These MICs are well below expected tear concentrations of tobramycin following instillation

of a topical drop containing 0.3% tobramycin and led the authors to conclude that combination LE 0.5%/tobramycin 0.3% is a suitable treatment option for blepharitis, including that caused by staphylococcal infection.

## DISCUSSION

Ocular corticosteroids are one of the most potent and effective classes of medication for treatment of ocular inflammation induced by conditions such as conjunctivitis, keratitis, anterior uveitis, and surgical trauma [31, 32]. These agents prevent functional changes and deterioration of vision by suppressing inflammatory mediators and thereby blocking inflammation at many levels [33]. Topical ophthalmic antibiotics are used to protect against potential infection after surgery as well as to treat existing infections by eradicating susceptible organisms [1]. Treatment with a combination corticosteroid and antibiotic is indicated for several ocular inflammatory conditions that may have a risk of superficial bacterial infection. LE/T was introduced in 2004 and remains the only combination ophthalmic formulation of a C-20 ester corticosteroid and an antibiotic. The retrometabolic drug design of LE has resulted in a potent ocular corticosteroid with an excellent safety profile, including a low risk of increased IOP [9–11]. Tobramycin is a broad-spectrum antibiotic [13, 14] that is safe and well tolerated [15]. As described in this review, LE/T has been evaluated extensively in patients with BKC, a chronic inflammatory disorder that encompasses a broad range of clinical manifestations from chronic inflammation of the eyelid margin, to conjunctival congestion and/or follicles, punctate epithelial erosions, corneal infiltrates, and corneal ulcers, to neovascularization and scarring, all of which are associated with bacterial infection/proliferation [24–26]. Given the documented utility of LE/T for this broad inflammatory disorder, it follows that LE/T may be an appropriate treatment for other ocular surface inflammatory conditions that carry a risk of infection, such as contact lens-induced red eye (CLARE) and nonspecific conjunctivitis [2, 34].

Two large randomized studies demonstrated comparable anti-inflammatory effects of LE/T and DM/T instilled QID in adults with BKC [24, 25]. In addition, a pooled analysis of blepharitis data from these two studies showed similar efficacy of LE/T and DM/T, both given QID, for reducing signs of blepharitis [27], while a recent meta-analysis of all data from these two studies confirmed no differences in improvements in BKC signs and symptoms composite score or in individual blepharitis, keratitis, and conjunctivitis scores between treatments, but fewer IOP elevations with LE/T [28]. Findings from a small single-center study did not replicate the outcomes of these multicenter trials but utilized a reduced dosing regimen inconsistent with the FDA approved dosing recommendations [21].

Studies in healthy adults [22, 23], adults with various ocular conditions [24, 25], and children with blepharitis or blepharoconjunctivitis [26] support the good tolerability and safety of LE/T and suggest that LE/T may be associated with a lower risk of clinically significant increases in IOP compared with DM/T (Fig. 3) [11]. In agreement, in a recent systematic review of randomized controlled trials, dexamethasone 0.05% to 0.1% and LE 0.2% to 0.5% were associated with IOP elevations  $\geq 10$  mm Hg in 2.3% and 0.9% of patients, respectively, when a medium course of corticosteroids ( $\leq 112$  applications) was used and in 7.3% and 2.7% of patients, respectively, when patients received extended treatment ( $> 112$  applications) [35]. Similarly, animal studies directly comparing LE with dexamethasone have shown smaller increases in IOP and lower risk of elevated IOP with LE compared to dexamethasone [36, 37]. As well, these data are consistent with multiple studies which reported a low propensity of various LE formulations to cause increases in IOP [10, 11, 38].

Interestingly, while both multicenter, randomized, investigator-masked studies conducted in the US and in China reported lower rates of IOP elevations with LE/T than with DM/T in patients with BKC, rates of clinically significant IOP elevations were relatively higher in the Chinese study population [24, 25]. This finding is consistent with literature suggesting that Asian

populations/those with longer axial length may be more susceptible to IOP spikes [39, 40]. Differences in IOP changes between the two studies may also be attributable to differences in study population ages, as younger age has been identified as a potential risk factor for steroid-induced IOP elevation [39, 41, 42], and patients in the study conducted in China were at least 10 years younger than those in the US study.

None of the clinical studies evaluating LE/T reported cataract formation as an adverse effect. Although the short duration of these studies would reduce the risk of steroid-induced cataract development, it is noted that LE (or LE/T) is less likely to induce cataract formation because it lacks a ketone moiety at carbon-20 of the steroid molecule required to form Schiff base intermediates with lens proteins, one of the known pathways in cataractogenesis [12]. Accordingly, there have been very few reports of cataracts/cataract formation with other LE formulations or LE/T based on a review of the Bausch + Lomb adverse event database through September 2020 conducted by Cavet et al. [43] or reported in the FDA Adverse Event Reporting System (FAERS) Public Dashboard since these drugs were approved for marketing in the US [44].

Finally, an increasing number of studies in recent years have demonstrated associations between ocular surface inflammatory conditions/diseases and alterations in normal ocular flora and how such alterations may also lead to infection with opportunistic bacteria. For instance, the ocular microbiota of contact lens wearers has a greater amount of *Methylobacterium* spp., *Acinetobacter* spp., and *Pseudomonas* spp. and is less abundant in *Haemophilus* spp., coagulase-negative staphylococci, *Streptococcus* spp., and *Corynebacterium* spp. compared with healthy eyes [45], underscoring contact lens wear as a risk factor for keratitis due to *Pseudomonas*. A study comparing the ocular surface microbiome in vernal keratoconjunctivitis (VKC) patients with that from healthy subjects showed similar microbial diversity in both groups; however, the bacterial load was higher in VKC patients [46]. Lee et al. [47] observed an increase in the amount of *S. aureus*, *Corynebacterium* spp., and certain environmental spp. and

a decrease in *Propionibacterium* spp. in eyes of patients with blepharitis compared to eyes of healthy controls, while Groden et al. [48] reported that while *Propionibacterium*, *Corynebacterium*, *Staphylococcus*, and *Acinetobacter* species were most commonly isolated from lids of both blepharitis and non-blepharitis patients, commensal skin bacteria (*S. epidermidis* and *Propionibacterium* spp.) were found in greater quantities in blepharitis patients. Results from the antibacterial potency study conducted by Deom et al. [29] to assess the potential efficacy of LE/T for blepharitis suggest tobramycin may be ideally suited for this ocular surface inflammatory condition given its broad-spectrum pathogen coverage as well as its in vitro activity against those species potentially at higher than normal bacterial counts in blepharitis. Thus, inclusion of tobramycin in the LE/T formulation is expected not only to address certain opportunistic infecting bacterial pathogens but also to help the eye reestablish its normal, healthy proportions of microbiota. The retained in vitro potency of tobramycin against methicillin-resistant staphylococcal isolates may be beneficial in patients with ocular surface inflammatory conditions at risk of infection with drug-resistant staphylococci such as elderly patients [49].

## CONCLUSION

The results of this systematic literature review demonstrate the utility of LE/T in the treatment of the various clinical manifestations of BKC, a broad inflammatory disorder with an associated risk of bacterial infection. Compared with DM/T, LE/T demonstrates similar efficacy across a range of signs and symptoms within this disorder with a lower propensity for elevated IOP. The in vitro antimicrobial data for tobramycin together with previous published clinical studies support the use of combination LE/T in the treatment of blepharitis, including in staphylococcal blepharitis. Given the in vitro antimicrobial efficacy of tobramycin and the demonstrated utility of LE/T in BKC, use of LE/T in other ocular inflammatory conditions with a risk of

bacterial infection, such as CLARE or non-specific conjunctivitis, is warranted.

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