A 6-Week, Prospective, Randomized, Single-Masked Study of Lifitegrast Ophthalmic Solution 5% Versus Thermal Pulsation Procedure for Treatment of Inflammatory Meibomian Gland Dysfunction

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Purpose: Meibomian gland dysfunction (MGD) is present in most cases of dry eye disease. MGD involves both inflammatory and obstructive etiologies. We compared efficacy and safety of treatment to reduce inflammation (lifitegrast) versus obstruction [thermal pulsation procedure (TPP)] in patients with inflammatory MGD over 42 days.

Methods: This was a single-center, 6-week, prospective, randomized, single-masked study of adults with inflammatory MGD, defined as having all of the following: burning, stinging, dryness; thickened secretions or occlusion of glands; eyelid redness; and elevated matrix metalloproteinase-9. Patients received lifitegrast ophthalmic solution 5% twice daily for 42 days or one TPP treatment at day 0. Seven symptoms and 8 objective measures of dry eye disease were assessed.

Results: Overall, 40 of 50 randomized patients (80%) were women with mean (SD) age 65.8 (8.9) years. Lifitegrast-treated (n = 25) versus TPP-treated (n = 25) patients had greater improvement from baseline to day 42 in eye dryness [mean (SD) change from baseline: −1.05 (0.79), lifitegrast; −0.48 (0.96), TPP; P = 0.0340], corneal staining [−0.55 (0.80), lifitegrast; 0.12 (1.09), TPP; P = 0.0230], and eyelid redness [−0.77 (0.43), lifitegrast; −0.38 (0.58), TPP; P = 0.0115]; trend favored lifitegrast for best corrected visual acuity and gland patency. Unexpectedly, TPP treatment did not improve lipid layer thickness or gland patency compared with lifitegrast. No adverse events were reported.

Conclusions: Although MGD is often considered a disease of gland obstruction, these findings demonstrate antiinflammatory treatment with lifitegrast significantly improved patient symptoms and signs compared with treatment for obstruction (TPP). Lifitegrast should be included in treatment for inflammatory MGD.

Key Words: lifitegrast, LipiFlow, meibomian gland dysfunction, dry eye disease

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It has been estimated that 50% to 75% of patients complaining of dry eyes have meibomian gland dysfunction (MGD).[1] The symptoms of MGD (evaporative dry eye) may be difficult to differentiate from those of dry eye syndrome (aqueous deficient dry eye), although patients with MGD tend to report more burning and stinging than grittiness, sandiness, or foreign body sensation in the eyes. Traditional treatment options for MGD include warm lid compresses using cloths or heat pads of various materials, systemic tetracyclines or azithromycin, and episodic treatment with topical antibiotics or antibiotic/steroid combinations.

Many patients develop active inflammation of the eyelid margin, which may be due to bacterial superinfection, accumulation of bacterial byproducts, or alterations in the quality of the meibomian gland secretion caused by bacteria. Many, but not all, patients with MGD have elevated tear matrix metalloproteinase-9 (MMP-9) levels, indicative of an active inflammatory process.[2,3] The pathogenesis of MGD remains uncertain but is believed to be consistent with obstruction of the meibomian gland ductules and orifices with consequent inflammation and reduction of ocular surface lipids.[1] More recent studies have cast doubt on this hypothesis and suggest that aging-related changes within meibomian glands together with an inflammatory process result in hyposecretion of lipid from nonobstructed glands, with obstruction occurring much later in the pathogenesis of symptomatic MGD. MGD and inflammation frequently coexist in patients with dry eye.[4–7]

This study is designed to explore whether treatment designed to relieve orifice and ductule obstruction [thermal pulsation procedure (TPP)] is superior to treatment intended to reduce the inflammatory process in ocular tissues (lifitegrast). TPP applies heat to inner eyelid surfaces and simultaneously applies pulsating pressure to the outer eyelids; the procedure is designed to evacuate the contents of the meibomian glands.[8] In numerous studies, TPP has been shown to improve gland function in MGD and to improve symptoms of dry eye disease (DED).[8–14] Lifitegrast ophthalmic solution 5% is approved for treatment of signs and

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symptoms of DED.[15] Lifitegrast interrupts an immune response that causes ocular surface inflammation.[2,16–18] In clinical trials, lifitegrast reduced signs and symptoms of DED compared with placebo[19–22] and was found to be safe and well tolerated.[23,24]

The objective of this study was to assess the safety and efficacy of twice daily application of lifitegrast ophthalmic solution 5% over 42 days versus a single TPP treatment in patients with inflammatory MGD.

MATERIALS AND METHODS

This was a single-center, 6-week, prospective, randomized, single-masked (investigator) study conducted between September 2017 and August 2018. The study was conducted in the United States under the approval of the Schulman Investigational Review Board (Columbia, MD). The study adhered to the principles of the Declaration of Helsinki. Patients provided written informed consent.

Patients

Participants were adult patients aged ≥18 years with clinical diagnosis of inflammatory MGD, defined as having all of the following: burning, stinging, or dryness of ≥1 (0–3 scale); thickened secretions or occlusion of at least 5 of 8 assessed glands of the central lower eyelid; clinically evident redness of eyelid margin of ≥1 (0–3 scale); and elevated (positive) MMP-9 as assessed with the InflammaDry (Quidel, San Diego, CA) assay. Although many patients diagnosed with DED report similar symptoms, it was felt that the above definition identified a particular subset with inflammatory MGD. Patients had to be willing to comply with protocol instructions, to read and sign an informed consent, and to not have used any topical ocular medication in the past 24 hours.

Exclusion criteria were history of adverse reaction to lifitegrast, active ocular infection or ocular inflammatory disease, use of topical cyclosporine or corticosteroid eye drops within the past 30 days, anterior membrane dystrophy or history of clinically significant recurrent erosion syndrome, history of severe/serious ocular pathology or other medical condition that could result in inability to safely complete the study, participation in any other investigational study within the past 30 days, current pregnancy or nursing, or requirement/possible requirement for intraocular surgery during the course of the study.

Study Design and Treatment

Patients were randomized using a computer-generated randomization schedule to receive lifitegrast ophthalmic solution 5% (Xiidra; Shire, Lexington, MA) twice daily for 42 days or one treatment at day 0 with TPP (LipiFlow; Johnson & Johnson Vision/TearScience, Morrisville, NC).

At visit 1 (day 0), patients randomized to lifitegrast were instructed in application of lifitegrast and to use one drop per eye twice daily for the duration of the study. For patients randomized to TPP, TPP treatment was performed following standard clinical practice on day 0.

All patients continued their preinvestigation regimen of twice daily warm compress/lid compression treatments at home. No changes in medications were permitted during the 42-day study period. Concomitant use of corticosteroids or cyclosporine was not permitted.

Outcome Measures

Study measures were recorded at visit 1 (day 0), visit 2 (day 21 ± 3 days), and visit 3 (day 42 ± 3 days). All assessments were made by a single, masked investigator (J.T.).

Ocular symptoms were reported by patients for each eye. Eye discomfort, a coprimary efficacy endpoint, was reported using a visual analog scale from 0 to 100 mm. Symptoms were reported on a scale of 0 to 3 (0, none/absent; 1, mild; 2, moderate; and 3, severe) and included burning, stinging, foreign body sensation, dryness, pain/soreness, and photophobia.

Tear lipid layer thickness, a coprimary efficacy endpoint, was measured using the LipiView (Johnson & Johnson Vision/TearScience) device, which uses noise canceling technology to measure the submicron thickness of the lipid layer. Additional objective assessments included best corrected visual acuity (BCVA; Snellen Visual Acuity for best corrected distance) and MMP-9 measured using InflammaDry (0–4 scale for intensity of color change at 10 minutes with reference to standardized photographs; 0, none; 1, trace; 2, mild; 3, positive; and 4, strong positive). MMP-9 was also analyzed based on the positive (any color change) or negative (no color change) result. BCVA was converted to logarithm of the minimum angle of resolution (LogMAR) scores by taking the negative log of the Snellen fraction [−log (20/XX)]. Slit-lamp examination for ocular signs was performed in the following sequence: meibomian gland patency (0–8 scale; patency of 8 glands in central lower lid was assessed), MGD score (0–3 scale; meibomian gland secretion was scored according to thickness), bulbar conjunctival injection (conjunctival redness; 0–3 scale; 0, absent; 1, mild; 2, moderate; and 3, severe), corneal fluorescein staining (superficial punctate keratitis; 0–3 scale; 0, absent; 1, mild, <10 areas of uptake; 2, moderate, <30 areas; and 3, severe, >30 areas), and eyelid redness (0–3 scale; 0, absent; 1, mild; 2, moderate; and 3, severe).

Adverse events were monitored throughout the study and were to be evaluated according to severity, seriousness, causality (relationship to use of any medication or procedure), treatment required, and outcome.

Statistical Methods

Sample size was not based on formal statistical calculations or clinical assumptions. However, a sample size of 50 analyzable patients was expected to be sufficient to adequately assess the objective of the study.

Demographic characteristics were summarized using descriptive statistics.

Efficacy variables were change from baseline (CFB) to day 21 and CFB to day 42 in each measure. Efficacy variables were planned to be analyzed for the worse eye (left or right)

and determined by the mean eye dryness score for each treatment group.

Between-group comparisons for continuous variables were tested using *t* tests. When the test for equality of variances yielded an F-value with $P < 0.1$, the Satterthwaite method was used. Otherwise, results from pooled variance *t* tests were reported. χ^2 test was used for the between-group comparison of MMP-9 analyzed as positive or negative.

The protocol identified 2 coprimary efficacy outcomes, CFB to day 42 in the eye discomfort score and lipid layer thickness. Statistical testing of the coprimary outcomes applied a Bonferroni correction for multiplicity whereby testing will use a 0.025 level of significance (2-sided comparison). *P*-values presented for other endpoints serve as descriptive statistics only.

RESULTS

Patient Disposition and Characteristics

A total of 59 patients were screened. Of these, 50 met the criteria for inclusion and were randomized to treatment (n = 25 to lifitegrast and n = 25 to TPP). Three patients in the lifitegrast group withdrew before day 42 because of the lack of efficacy.

Overall, 10 patients (20%) were men (lifitegrast, 4; TPP, 6) and 40 were women (80%) (lifitegrast, 21; TPP, 19). The overall mean (SD) age was 65.8 years (8.9) [median 66 (range, 45–83) years]; the mean (SD) age was 64.2 years (8.3) in the lifitegrast group [median 66 (range, 45–79)] and 67.4 years (9.4) in the TPP group [median 70 (range, 50–83)].

Mean eye dryness at baseline was 2.36 for both left and right eyes in the lifitegrast group and 1.88 for both left and right eyes in the TPP group. Because mean dryness scores were the same in the left and right eyes in each treatment group, baseline burning and stinging scores were used to determine worse eye. At baseline, mean burning was 1.36 in the right eye and 1.40 in the left eye in the lifitegrast group and 1.20 in the right eye and 1.28 in the left eye in the TPP group. Mean stinging was 1.24 in the right eye and 1.28 in the left eye in the lifitegrast group and 1.04 in the right eye and 1.08 in the left eye in the TPP group. Because both burning and stinging were worse in the left eye compared with the right eye in both treatment groups, all analyses were conducted for the left eye.

Findings for Ocular Symptoms

Both treatments improved self-reported eye symptoms compared with baseline (Table 1). There was no significant difference between treatment groups in CFB to day 21 for any symptom.

There was no significant difference between groups in CFB to day 42 in eye discomfort, a coprimary outcome measure. Lifitegrast-treated patients experienced greater improvement from baseline to day 42 in eye dryness compared with TPP-treated patients [mean (SD) difference in CFB to day 42, 0.57 (0.88), pooled t = 2.19; $P = 0.0340$].

TABLE 1. Change in Self-Reported Eye Symptoms From Baseline to Day 42 in the Worse (Left) Eye by Treatment Group, Mean (SD)

Measure	Lifitegrast (n = 25)*	TPP (n = 25)
Eye discomfort (visual analog scale)†		
Baseline	65.38 (18.84)	57.96 (21.37)
Day 42	41.73 (25.69)	29.12 (23.74)
CFB to day 42	−22.76 (30.29)	−28.84 (33.46)
Burning		
Baseline	1.40 (1.00)	1.28 (0.84)
Day 42	1.09 (0.97)	1.00 (0.91)
CFB to day 42	−0.32 (0.99)	−0.28 (1.02)
Stinging		
Baseline	1.28 (1.17)	1.08 (0.91)
Day 42	0.73 (0.88)	0.40 (0.76)
CFB to day 42	−0.50 (1.22)	−0.68 (0.95)
Foreign body sensation		
Baseline	1.44 (0.92)	1.40 (1.00)
Day 42	1.18 (1.05)	0.72 (0.79)
CFB to day 42	−0.27 (1.45)	−0.68 (0.69)
Dryness		
Baseline	2.36 (0.70)	1.88 (0.83)
Day 42	1.41 (0.91)	1.40 (0.71)
CFB to day 42	−1.05 (0.79)‡	−0.48 (0.96)
Pain/soreness		
Baseline	0.56 (0.77)	0.88 (1.01)
Day 42	0.55 (0.80)	0.52 (0.77)
CFB to day 42	0.00 (0.82)	−0.36 (0.70)
Photophobia		
Baseline	1.28 (1.06)	1.64 (1.22)
Day 42	1.14 (1.08)	1.24 (1.13)
CFB to day 42	−0.18 (0.85)	−0.40 (0.76)

*Data were available for n = 22 patients in the lifitegrast group at day 42 except as noted (3 patients withdrew before day 42 because of the lack of efficacy).

†Data were available for n = 21 patients in the lifitegrast group at day 42 (data for 1 patient were not collected because of a site error).

‡$P < 0.05$ for comparison between groups in CFB to day 42 based on the pooled *t* test.

Findings for Objective Assessments

Both treatments improved MMP-9 scores compared with baseline (Table 2). There was no significant difference between groups in CFB to day 21 for any objective measure.

There was no significant difference between groups in CFB to day 42 in lipid layer thickness, a coprimary outcome measure. Two measures improved more from baseline to day 42 with lifitegrast compared with TPP: corneal staining [mean (SD) difference, 0.67 (0.97), pooled t = 2.35; $P = 0.0230$] and eyelid redness [mean (SD) difference, 0.40 (0.51), pooled t = 2.64; $P = 0.0115$]. There was a trend toward greater improvement in BCVA [mean (SD) difference in CFB to day 42, 0.09 (0.16), Satterthwaite t = 1.92; $P = 0.0638$] and meibomian gland patency [mean (SD) difference, 1.21 (2.23), pooled t = 1.85; $P = 0.0713$] with lifitegrast versus TPP. There was no difference between groups for MMP-9 analyzed either on a continuous (0–4) scale or as positive/negative.

TABLE 2. Change in Objective Assessments From Baseline to Day 42 in the Worse (Left) Eye by Treatment Group, Mean (SD)

Measure	Lifitegrast (n = 25)*	TPP (n = 25)
Lipid layer thickness†		
Baseline	88.71 (16.09)	79.28 (17.09)
Day 42	83.48 (17.48)	79.67 (16.75)
CFB to day 42	−3.67 (21.12)	1.25 (15.69)
BCVA (Snellen visual acuity, LogMAR scores)		
Baseline	0.19 (0.18)	0.17 (0.26)
Day 42	0.26 (0.28)	0.14 (0.23)
CFB to day 42	0.07 (0.20)	−0.03 (0.11)
MMP-9		
Baseline	2.20 (1.32)	2.68 (0.80)
Day 42	1.50 (1.47)	1.80 (1.50)
CFB to day 42	−0.86 (1.61)	−0.88 (1.72)
Meibomian gland patency		
Baseline	4.84 (2.93)	5.44 (2.08)
Day 42	6.05 (2.84)	5.28 (2.59)
CFB to day 42	1.05 (2.55)	−0.16 (1.91)
MGD score		
Baseline	2.08 (0.49)	1.84 (0.55)
Day 42	1.77 (0.97)	1.92 (0.81)
CFB to day 42	−0.32 (0.89)	0.08 (0.76)
Bulbar conjunctival injection (conjunctival redness)‡		
Baseline	0.64 (0.45)	0.70 (0.41)
Day 42	0.16 (0.32)	0.52 (0.58)
CFB to day 42	−0.48 (0.42)	−0.21 (0.67)
Corneal fluorescein staining (superficial punctate keratitis)		
Baseline	1.48 (1.00)	0.84 (0.85)
Day 42	1.00 (1.27)	0.96 (0.98)
CFB to day 42	−0.55 (0.80)§	0.12 (1.09)
Eyelid redness‡		
Baseline	1.00 (0.00)	1.00 (0.00)
Day 42	0.23 (0.43)	0.63 (0.58)
CFB to day 42	−0.77 (0.43)§	−0.38 (0.58)

*Data were available for n = 22 patients in the lifitegrast group at day 42 except as noted (3 patients withdrew before day 42 because of the lack of efficacy).

†Data were available for n = 21 patients in the lifitegrast group and n = 24 patients in the TPP group at day 42 (the device was unable to calculate values for 1 patient in each group).

‡Data were available for n = 24 patients in the TPP group at day 42 (data for 1 patient were not collected because of a site error).

§$P < 0.05$ for comparison between groups in CFB to day 42 based on pooled t test.

Safety and Tolerability

No adverse events were reported during the study.

DISCUSSION

This is the first published study comparing lifitegrast and TPP for treatment of ocular surface disease. In this study of patients with inflammatory MGD, both lifitegrast and TPP generally improved symptoms and signs of DED over 6 weeks. In between-group comparisons, lifitegrast improved eye dryness scores, corneal staining, and eyelid redness from baseline to day 42 significantly more than TPP. TPP-treated patients did not experience significantly better outcomes on any measure compared with lifitegrast-treated patients. Notably, this was true even for markers of obstructive MGD including lipid layer thickness, meibomian gland patency, and MGD score.

Previous studies had demonstrated the efficacy of lifitegrast in patients with DED[19–22] and the efficacy of TPP in patients with MGD.[8–14] MGD is often considered a disease of gland obstruction. However, in this first head-to-head study of lifitegrast versus TPP in patients with inflammatory MGD, treatment with an antiinflammatory agent (lifitegrast) led to significant improvements in patient symptoms and signs when compared with TPP.

This study had a number of limitations. The sample size was small and differed somewhat on measures of signs and symptoms at baseline, which may have limited sensitivity to detect differences between groups. Three patients discontinued in the lifitegrast group, which further limited sample size and also created an imbalance between groups. In addition, patients were selected to have evidence of both MGD and inflammation. Findings may differ in other patient samples selected to have either MGD or inflammatory DED. Further study is needed to distinguish patients most likely to benefit from lifitegrast, TPP, or a combination of therapies.

Despite the limitations of this study, the pattern of findings in favor of lifitegrast compared with TPP is striking. Based on the findings of this study, treatment for inflammatory MGD should include lifitegrast ophthalmic solution 5%.

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