Adv Ther (2011) 28(8):661-670.
DOI 10.1007/s12325-011-0043-z

ORIGINAL RESEARCH

Travoprost 0.004%/Timolol 0.5% Fixed Combination in Patients Transitioning from Fixed or Unfixed Bimatoprost 0.03%/Timolol 0.5%

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Received: May 25, 2011 / Published online: July 15, 2011

ABSTRACT

Introduction: Patients with glaucoma or ocular hypertension who do not achieve target intraocular pressure (IOP) using one hypotensive agent are often transitioned to combination therapy. Travoprost 0.004%/timolol 0.5% fixed combination (TTFC) has shown efficacy in patients whose IOP is not controlled with other therapies. The goal of this study was to assess the efficacy and safety of transitioning to TTFC in patients whose IOP was uncontrolled on bimatoprost 0.03%/timolol 0.5%, administered concomitantly or as a fixed combination. ***Methods:*** This was a prospective, open-label, multicenter study of patients with open-angle glaucoma or ocular hypertension who transitioned to TTFC from fixed or unfixed bimatoprost/timolol. Patients self-administered TTFC once daily for 8 weeks, and efficacy and safety were assessed at baseline, Week 4, and Week 8. A symptom survey was administered at baseline and Week 8. Both patients and investigators reported their medication preference at Week 8. ***Results:*** A total of 105 patients were enrolled in the study. Mean IOP decreased by 16.5% from baseline after 8 weeks of TTFC therapy in the total population, 15.0% in patients transitioning from fixed-combination therapy, and 20.8% in patients transitioning from unfixed therapy ($P<0.001$ for all groups). The percentage of patients reaching target IOP (≤18 mmHg) after treatment with TTFC was 69.2% ($P<0.001$). Patients judged stinging/burning to be less severe with TTFC than with prior therapy ($P=0.029$); all other symptom frequencies and severities were similar for both treatments. Patients preferred TTFC over bimatoprost/timolol (fixed and unfixed) at a ratio of more than 4:1 (81.4% vs. 18.6%; $P<0.001$), and investigators reported a nearly five-fold preference for TTFC (83.3% vs. 16.7%; $P<0.001$). No unexpected safety concerns with TTFC were observed. ***Conclusion:*** Travoprost 0.004%/timolol 0.5% fixed combination produced a significant reduction in IOP, with

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favorable safety and tolerability profiles. Both patients and investigators strongly preferred TTFC to prior bimatoprost 0.03%/timolol 0.5% therapy.

Keywords: bimatoprost; fixed combination; glaucoma; intraocular pressure; prostaglandin analog; timolol; travoprost

INTRODUCTION

Patients with glaucoma or ocular hypertension who fail to achieve target intraocular pressure (IOP) using a single hypotensive agent are typically transitioned to combination therapy, which can be either the concomitant use of two single agents or use of a fixed-combination product.[1] Fixed-combination products have several advantages over concomitant therapy. First, they are more convenient because they are dispensed from only one bottle. In addition, fixed-combination products avoid drug washout that can occur when two drugs are administered too rapidly in succession, and they reduce patients' lifetime exposure to ocular preservatives. The European Glaucoma Society suggests that fixed-combination products be used in place of two concomitantly administered medications whenever possible.[1]

Fixed-combination travoprost 0.004%/timolol 0.5% (DuoTrav®; Alcon Laboratories [UK] Ltd., Hemel Hempstead, UK) was approved in the European Union in 2006 for the treatment of patients whose IOP is not controlled with beta-blocker or prostaglandin analog monotherapy.[2] Comprised of a prostaglandin analog and a beta-blocker, the travoprost/timolol fixed combination (TTFC) demonstrated efficacy and safety similar to that of concomitant administration of its constituents in a pooled analysis of two randomized trials, with the exception of reduced ocular hyperemia associated with TTFC (13.7% vs. 20.8%, P=0.02).[3]

The aim of the present study was to assess the efficacy and safety of transitioning to TTFC from prior therapy with bimatoprost and timolol, fixed or unfixed, in patients whose IOP was uncontrolled on these agents. Although randomized trials have been conducted comparing TTFC to other combination products under tightly controlled conditions,[4-6] the design of the present study allowed for examination of the effectiveness of TTFC under conditions similar to routine clinical practice; specifically, in situations in which patients receiving inadequate IOP control from one regimen are transitioned to another similar product.

METHODS

This prospective, open-label, multicenter transition study, conducted in Germany, Spain, and the Czech Republic, enrolled patients with open-angle glaucoma or ocular hypertension whose IOP was uncontrolled (≥19 mmHg) using bimatoprost 0.03% (Lumigan®; Allergan, Inc., Irvine, CA, USA) and timolol 0.5%, either administered concomitantly or as a fixed-combination product (Ganfort®; Allergan, Inc., Irvine, CA, USA). All patients were transitioned to TTFC, administered once daily in the evening for 8 weeks. The protocol was approved by all relevant institutional review boards in each country and the study was performed in compliance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice. All participating patients provided written informed consent.

Patient Characteristics

Eligible patients were aged ≥18 years with a clinical diagnosis of primary open-angle glaucoma, pigment dispersion glaucoma, or ocular hypertension in both eyes. Patients had to have been treated with a stable IOP-lowering

regimen of fixed or unfixed bimatoprost 0.03% and timolol 0.5% within 4 weeks prior to screening and had an IOP in both eyes considered safe by the investigator to ensure clinical stability of vision and the optic nerve throughout the study period. Patients also had to have an IOP between 19 and 35 mmHg at any time of day in one eye, which would be designated as the study eye. In the non-study eye, the IOP had to be controlled without pharmacologic therapy or on the study medication alone. Patients were required to have a best-corrected Snellen visual acuity (BCVA) of at least 20/200 in both eyes and had to be willing to discontinue the use of all ocular hypotensive medications for the entire course of the study prior to receiving the study medication. In addition, they had to be able to follow instructions and be willing and able to attend all study visits. Finally, they were required to provide informed consent prior to screening.

Patients were excluded if they met any of the following criteria: any abnormality preventing reliable applanation tonometry in either eye; any opacity or patient uncooperativeness that restricted adequate examination of the anterior chamber of either eye; risk of visual field or visual acuity worsening as a consequence of participation in the trial, in the investigator's opinion; progressive retinal or optic nerve disease from any cause other than glaucoma; corneal dystrophies in either eye; concurrent infectious/noninfectious conjunctivitis, keratitis, or uveitis in either eye; bronchial asthma or history of bronchial asthma, bronchial hyperreactivity, or severe chronic obstructive pulmonary disease that would preclude the safe administration of a topical beta-blocker; history of ocular herpes simplex; history or risk of uveitis or cystoid macular edema; history of severe allergic rhinitis; known medical history of allergy, hypersensitivity, or poor tolerance to any components of the study medication that was deemed to be clinically significant by the investigator; intraocular conventional surgery or laser surgery in either eye <3 months prior to screening; use of systemic medications known to affect IOP, which have not been on a stable course for 7 days prior to screening or an anticipated change in the dosage during the course of the study; unwillingness to accept the risk of darkened iris or eyelash changes; any clinically significant, serious, or severe medical or psychiatric condition; any condition that, in the investigator's opinion, would interfere with optimal participation in the study or present a special risk to the patient; and participation in any other investigational study within 30 days prior to screening. Women who were pregnant or lactating or of childbearing potential who were not using reliable means of birth control were also excluded from the study.

Study Design

All eligible patients completed an ocular symptom survey and then received TTFC. They were instructed to immediately discontinue their previous therapy and to administer one drop daily of the study medication at 8:00 PM for 8 weeks; thus, there was no washout period between the patient's prior ocular hypotensive regimen and the study medication. Patients were required to return at Week 4 (within 1 hour of the time of the IOP assessment at the screening/baseline visit) for IOP and safety assessments in both eyes and at Week 8 (within 1 hour of the time of the IOP assessment at the screening/baseline visit) for IOP and safety assessments and completion of the ocular symptom survey and global preference response. Investigators also completed the global preference response at the Week 8 visit for each patient. At both the Week 4 and Week 8 visits, patients must have been taking TTFC as prescribed or the visit was rescheduled.

Adverse events were noted, monitored, and evaluated throughout the study. Patients could have been excluded from the trial for any of the following reasons: uncontrolled IOP, inability to attend scheduled study visits, adverse events, personal reasons, inability to follow instructions, lost to follow-up, or noncompliance.

Assessments

Intraocular pressure was assessed using Goldmann applanation tonometry. Safety assessments were BCVA measurement with a Snellen visual acuity chart; slit-lamp examination of the eyelids, conjunctiva, cornea, iris, anterior chamber, and lens; and adverse event assessment. The ocular symptom survey comprised questions about the presence, severity, duration, and persistence of the following common ocular adverse events: dry eye, light sensitivity, tearing, burning/stinging, crusting, itching, irritation, sandy/gritty feeling, and redness. It also contained questions about ease of instillation and whether others had noticed eye redness. For the global preference question, participants and investigators were asked which medication they preferred, prior treatment (bimatoprost/timolol fixed combination or unfixed bimatoprost and timolol) or study medication (TTFC).

Study Endpoints

The primary efficacy variable was the mean change in IOP from the screening/baseline visit to the Week 8 visit for patients receiving prior bimatoprost/timolol fixed combination. Results were analyzed using a paired t-test. Assuming a standard deviation of 3 mmHg and a total of 45 evaluable patients receiving prior bimatoprost/timolol fixed combination, this study was designed to provide an 80% power to detect a 1 mmHg difference between both fixed-combination therapies.

Statistical Analysis

If both eyes of a patient qualified for the study and were treated, then the eye with the higher IOP at screening was selected for analysis. If both eyes had an equal IOP, then the right eye was selected for analysis. The percentage of patients whose IOP was reduced to ≤18 mmHg was calculated as a secondary outcome measurement using a Chi-square test. The exploratory objectives were to assess the change in the ocular symptom survey results from the screening/baseline visit to the Week 8 visit and to measure the global preference response from both patients and investigators. A one-way analysis of variance (ANOVA) test was performed to evaluate differences in the ocular symptom surveys at the screening/baseline visit and the Week 8 visit, and global preference was analyzed with a Chi-square test. Analyses were performed using the intent-to-treat (ITT) data set. All data analyses were two-sided and an α-level of 0.05 was used to declare statistical significance. Statistical analysis was performed using SAS (SAS Institute, Cary, NC, USA) by PRN Pharmaceutical Research Network, LLC (Dallas, TX, USA).

RESULTS

A total of 105 patients from nine sites throughout Germany (n=3), Spain (n=3), and the Czech Republic (n=3) were enrolled in the study and comprised the ITT population. One patient was lost to follow-up after the screening/baseline visit and was removed from further analysis. Another patient discontinued treatment at Week 4 due to intolerance of study medication, but she remained in the ITT population and last observation carried forward was employed.

Patient demographics are shown in Table 1; most patients (83.2%) had a diagnosis of primary open-angle glaucoma. Just over 75% of patients had received prior fixed-combination therapy with bimatoprost/timolol and the remainder had received unfixed therapy. The mean age of the patient population was 70.3±10.7 years (range 37-91 years). Patients had a mean baseline IOP of 21.2 mmHg.

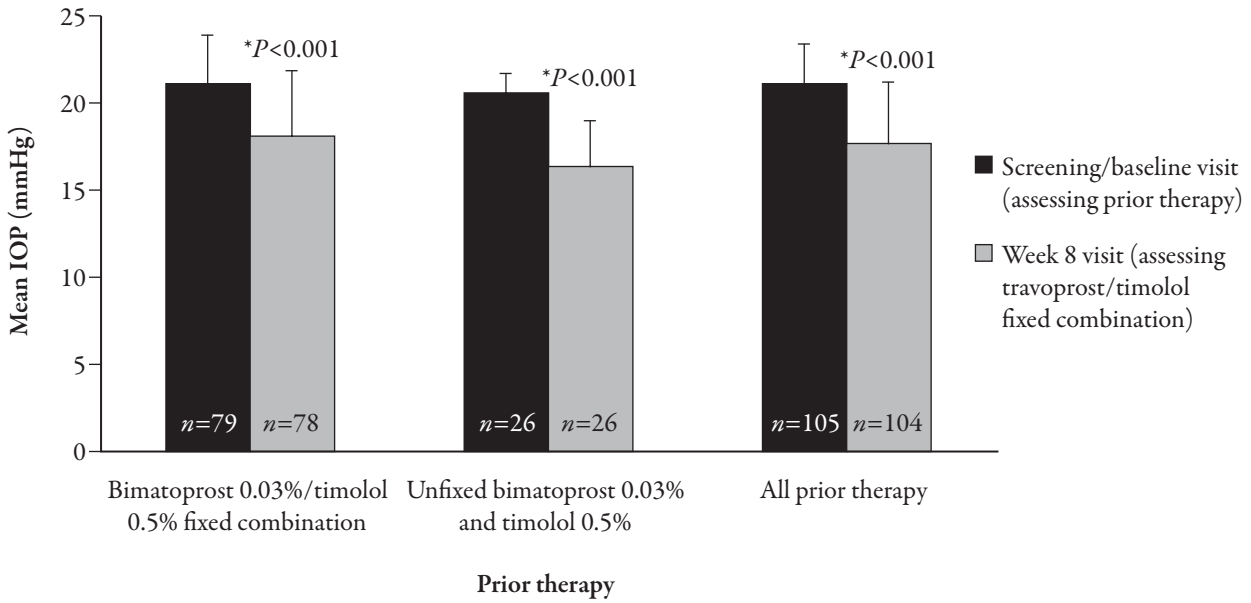
Table 1. Patient demographics of the intent-to-treat population (n=105).

Demographic	n (%)
Gender	
Female	62 (59.0)
Male	43 (41.0)
Age (years)	
≤55	9 (8.6)
56-65	20 (19.0)
66-75	42 (40.0)
≥76	34 (32.4)
Race	
White	101 (96.2)
Black	3 (2.9)
Hispanic	1 (1.0)
Diagnosis	
Primary open-angle glaucoma	88 (83.2)
Ocular hypertension	16 (15.2)
Pigment dispersion glaucoma	1 (1.0)
Prior therapy	
Bimatoprost 0.03%/timolol 0.5% fixed combination	79 (75.2)
Unfixed bimatoprost 0.03% and timolol 0.5%	26 (24.8)
Mean baseline IOP	21.2 mmHg

Change in IOP

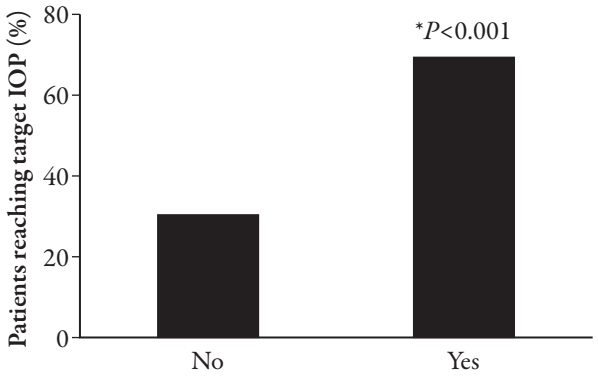
In the total population, the mean reduction in IOP after 8 weeks of treatment with TTFC was 16.5% (21.2±2.4 vs. 17.7±3.7 mmHg; P<0.001; Figure 1). The mean IOP decreased by 15.0% in patients who had previously been treated with the bimatoprost/timolol fixed combination (n=79; 21.4±2.6 vs. 18.2± 3.8 mmHg; P<0.001) and by 20.8% in patients who had previously received unfixed bimatoprost and timolol (n=26; 20.7±1.2 vs. 16.4±2.8 mmHg; P<0.001; 20.8%). The percentage of total patients reaching target IOP (≤18 mmHg) after TTFC therapy was 69.2%,

Figure 1. Mean intraocular pressure (IOP) at screening/baseline visit and after 8 weeks of therapy with travoprost/timolol fixed combination (TTFC); intent-to-treat population. *Screening/baseline visit versus Week 8 visit, paired t-test.



which was a significant improvement compared with prior therapy ($P<0.001$; Figure 2). This measurement remained statistically significant in both the prior fixed bimatoprost/timolol subgroup (65.4%; $P=0.007$) and the prior unfixed bimatoprost and timolol subgroup (80.8%; $P=0.002$).

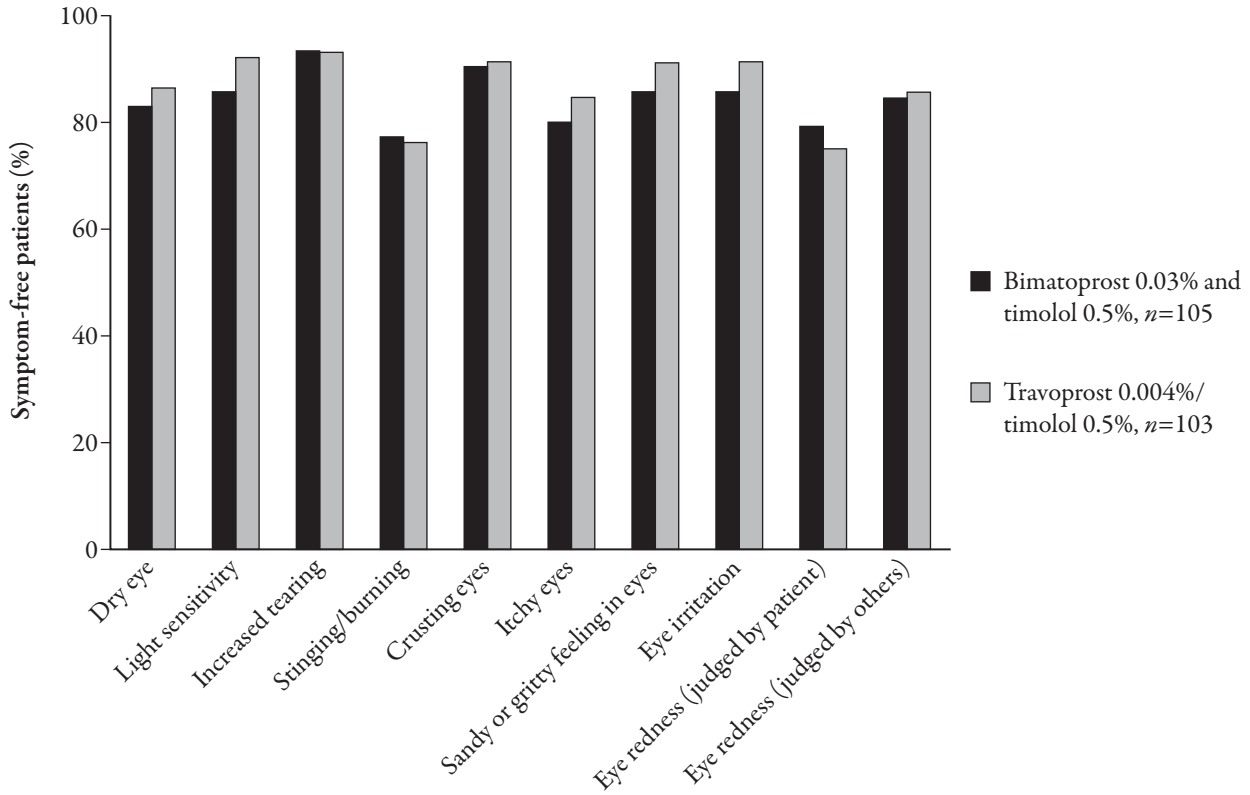
Figure 2. Percentage of patients reaching target intraocular pressure (IOP; ≤18 mmHg) after 8 weeks of therapy with travoprost/timolol fixed combination (TTFC; intent-to-treat population, $n=104$). *Bimatoprost/timolol (fixed or unfixed) therapy historical control versus travoprost/timolol fixed combination, Chi-square test.



Ocular Symptom Survey

The percentage of patients who were free of specific ocular symptoms was numerically higher across seven of the 10 symptom categories for TTFC (Week 8 visit assessment) compared with prior therapy (screening/baseline visit assessment), although none of the differences reached statistical significance (Figure 3). Stinging/burning were deemed to be less severe after treatment with TTFC ($P=0.029$ for stinging/burning); the severity of each of the other symptoms was judged to be similar between therapies. In addition, no significant differences

Figure 3. Symptom-free frequency associated with prior therapy (at screening/baseline visit) and with travoprost/timolol fixed combination (TTFC; at Week 8 visit; intent-to-treat population).



between prior therapy and study medication were noted for the persistence of symptoms or the ease of eye drop instillation (P=0.726). Examination of patient subgroups showed that the symptom profile of the prior fixed-therapy subgroup was similar to the symptom profile of the total patient population, but some differences were apparent in the subgroup who had previously taken unfixed bimatoprost and timolol. Specifically, severity of stinging/burning was not statistically different between TTFC and unfixed bimatoprost and timolol, but patients reported that eye redness was more frequently judged by others to be present while they had been taking the unfixed bimatoprost and timolol (P=0.041).

Patient and Investigator Preferences

Patients preferred TTFC over prior therapy at a ratio of more than 4:1 (81.4% vs. 18.6%; P<0.001; Figure 4). When these results were analyzed according to patient subgroup, patient ratings were more favorable for TTFC compared with unfixed bimatoprost and timolol (ratio of 12:1; 92.3% vs. 7.7%) than compared with fixed bimatoprost/timolol (ratio of 3.5:1; 77.6% vs. 22.4%). Investigators also significantly preferred TTFC over prior therapy at a ratio of nearly 5:1 (83.3% vs. 16.7%; P<0.001). Investigators preferentially rated TTFC more favorable when compared with unfixed bimatoprost and timolol (25.3:1) than with fixed bimatoprost/timolol (3.7:1).

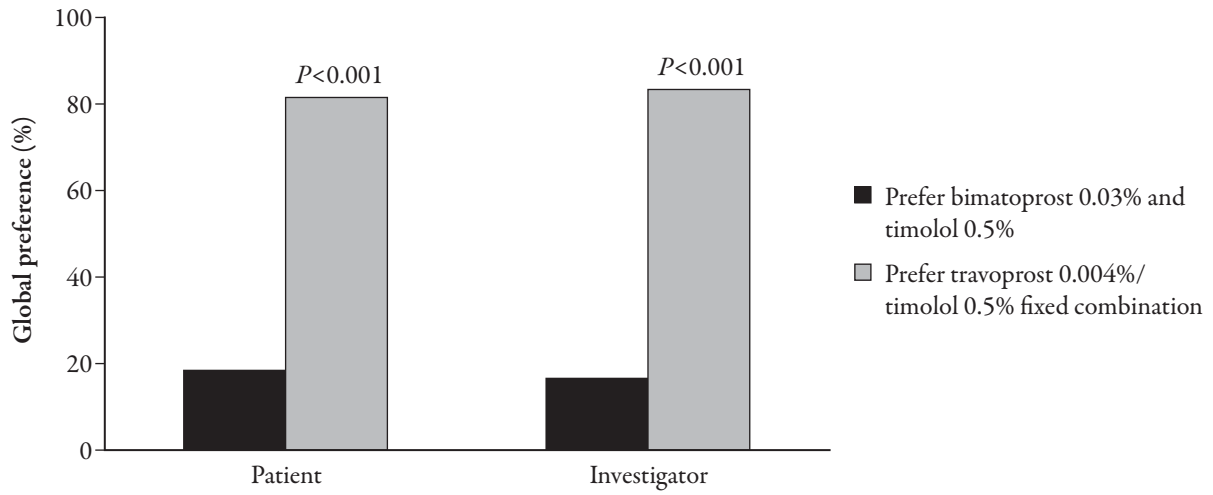
Safety

A total of 29 adverse events were reported, of which 15 were judged to be related to treatment with TTFC: ocular hyperemia, ocular burning, blurred vision, foreign body sensation, and allergic reaction (Table 2). Fourteen of the 15 treatment-related adverse events were mild in severity; one case of bilateral allergic reaction

Table 2. Travoprost 0.004%/timolol 0.5%-related adverse events in the intent-to-treat population (n=105).

Adverse event	Number of events
Total treatment-related adverse events	15
Ocular hyperemia	11
Ocular burning	1
Blurred vision	1
Foreign body sensation	1
Allergic reaction	1

Figure 4. Global preference response for the intent-to-treat patient population (n=102) and investigators (n=102).



(including hyperemia) was classified as severe and resulted in treatment discontinuation at Week 4. One event, a urinary infection preceded by itching, was deemed serious but unrelated to study medication. The BCVA did not change significantly, and the slit-lamp examination did not reveal any significant changes during the study, with the exception of a reduction in the frequency of abnormal eyelids (P=0.021) after 8 weeks of TTFC therapy.

DISCUSSION

The current study met its primary objective of demonstrating a significant reduction in mean IOP in patients who transitioned from bimatoprost/timolol fixed combination to TTFC. In addition, a significant reduction in IOP was also observed in the patient subgroup that transitioned from unfixed bimatoprost and timolol. Nearly 70% of enrolled patients reached target IOP with TTFC therapy. These findings indicate that TTFC can further reduce IOP in patients already on hypotensive therapy.

Results from the current study are consistent with results from previous studies, which have demonstrated the efficacy of TTFC in patients transitioning from prior therapies.[7-9] These transition studies have all reported clinically relevant reductions in IOP in patients transitioning from prostaglandin analog plus timolol therapy (excluding travoprost plus timolol concurrent therapy) to TTFC, ranging from 1.4 to 4.4 mmHg reductions.[7-9] These real-world clinical studies provide physicians with expectations of how patients may perform when transitioning from one regimen to another.

In addition to these transition studies examining the performance of TTFC as replacement therapy, one randomized, crossover study directly compared the efficacy of TTFC to the fixed-combination product used as prior therapy in the current study, bimatoprost/timolol fixed combination.[4] Results from this trial demonstrated that patients' mean IOP was 0.7 mmHg higher with TTFC than with bimatoprost/timolol. Although this 0.7 mmHg difference was statistically significant, it may not be clinically relevant. Several studies have demonstrated that a decrease of at least 1 mmHg is necessary to produce a clinically relevant reduction in the risk of visual field progression.[10-12] Nonetheless, this disadvantage for TTFC is somewhat in contrast to the current results, in which patients who had previously received bimatoprost/timolol fixed combination achieved a significant mean reduction in IOP of 3.2 mmHg after transitioning to TTFC.

Differences between the two studies may explain these discrepancies. For example, in the crossover study, all patients had not reached their target IOP with latanoprost/timolol fixed-combination therapy, whereas the current study enrolled patients who had not achieved target IOP while on bimatoprost/timolol combination therapy. Another potentially important difference is the requirement in the crossover study for patients to have a baseline IOP of <21 mmHg. This resulted in a mean baseline IOP of 16.5 mmHg, which is generally considered well-controlled in patients with open-angle glaucoma, raising the question of why treatment was switched to an alternate therapy under these conditions. In contrast, eligible patients in the current study had to have a baseline IOP between 19 and 35 mmHg, which resulted in a mean baseline IOP of 21.2 mmHg, clearly demonstrating that the group had uncontrolled IOP. Because of these differences in the patient populations as well as the differences in study design, it is difficult to compare these studies.

Patients in the current study judged TTFC and bimatoprost/timolol to have largely similar ocular tolerability profiles, albeit with

a significant reduction in the severity of ocular stinging/burning noted after transitioning to TTFC therapy. In addition, no unexpected safety concerns with TTFC were observed during the course of this clinical trial. Hyperemia, which is a class effect of prostaglandin analogs,[13] was reported as an adverse event in 10% of patients while on TTFC. As reported in the symptom survey, the incidence of hyperemia was not statistically different between prior therapy and TTFC therapy. Other ocular side effects common to topical ophthalmic medications, including burning, blurred vision, and foreign body sensation, were infrequently reported and were mild in severity; only one case of allergic reaction was classified as severe.

In the present study, patients clearly demonstrated a preference for TTFC over bimatoprost/timolol. Several factors may have contributed to this result, including the improved ability of TTFC to achieve the target IOP, the reduced severity of stinging and burning upon instillation of TTFC, or some other improved tolerability measure that did not reach statistical significance in the ocular symptom survey. However, another contributing factor was revealed upon examination of the preference results by prior therapy subgroups. Patients who had been on unfixed bimatoprost and timolol had a much greater preference for TTFC than did the patients who had already been taking fixed-combination therapy (92.3% vs. 77.6%). This suggests that patients prefer the convenience of a one-bottle regimen. Although this undoubtedly impacted the preference results, it does not entirely explain the imbalance, because even the patients who had been receiving bimatoprost/timolol fixed-combination therapy had a 3.5-fold preference for TTFC.

The design of the present study does present some limitations to its interpretation. First, the nonrandomized, open-label, transition design was not rigorously controlled, increasing the odds that the results could have been impacted by its design. For instance, transition studies tend to have an inherent bias toward the medication to which patients are transitioned due to the phenomenon known as regression to the mean.[14] As an example, normal fluctuations in the IOP may make it appear as if a patient has an elevated IOP with baseline medication that necessitates a change in therapy. If by the next visit, the IOP appears normalized, it is unknown whether this can be attributed to the hypotensive efficacy of the new medication or if this was simply a regression toward the mean IOP. In addition, the short-term focus of this study (8 weeks) precludes analysis of any adverse events that may appear over a longer time period. Finally, although statistics were calculated not only for the total patient population but also for individual subgroups based on prior therapy, the unfixed therapy group was underpowered due to its small sample size (n=26), making that subgroup's results not as statistically compelling. Nonetheless, both the IOP and the safety/tolerability results do corroborate those observed in the fixed bimatoprost/timolol subgroup.

In conclusion, the results of the present study suggest that physicians with patients who have not reached target IOP using bimatoprost 0.03% and timolol 0.5%, fixed or unfixed, can transition them to travoprost 0.004%/timolol 0.5% fixed combination with the expectation of further IOP reduction, a favorable safety profile, and a patient preference for the new medication. Nonetheless, because of the limitations of the design of the present study, further research is required to better understand the optimal use of TTFC in treating patients with primary open-angle glaucoma or ocular hypertension.

ACKNOWLEDGMENTS

The authors thank Jennifer Klem, PhD, who provided medical writing assistance funded by Alcon Laboratories, Inc. Maria-Luise Scherzer is the guarantor for this article, and takes responsibility for the integrity of the work as a whole.

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