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ORIGINAL RESEARCH

A combined analysis of five observational studies evaluating the efficacy and tolerability of bimatoprost/timolol fixed combination in patients with primary open-angle glaucoma or ocular hypertension

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Objective: The aim of this study was to evaluate the safety and efficacy of a fixed combination of bimatoprost 0.03% and timolol (BTFC) in a clinical setting, in a large sample of patients with primary open-angle glaucoma or ocular hypertension and insufficient intraocular pressure (IOP) lowering on prior therapy.

Methods: Patient data were combined (n = 5556) from five multicenter, observational, non-controlled, open-label studies throughout Europe. Patients were identified from 830 sites in Austria, France, Germany, The Netherlands, and Switzerland. Assessments were made at baseline, 6 weeks (in Austrian, German and Swiss centers), and 12 weeks in all centers.

Results: BTFC lowered mean IOP from baseline by 5.4 mmHg over the 12-week duration of the studies ($P < 0.0001$). At study entry, 92.9% of patients were receiving another ocular hypotensive medication. In patients with no previous treatment (n = 311), BTFC reduced IOP by –9.1 mmHg, corresponding to a reduction from baseline of 36.4% ($P < 0.0001$). In patients receiving prior therapy of a prostaglandin analog, a β-blocker, or a fixed combination, BTFC reduced IOP by a further 24.5%, 25.9%, and 21.4%, respectively. The majority of patients (90.3%) reported no adverse events. The most common adverse events were conjunctival hyperemia (3.2%) and eye irritation (2.8%). BTFC was rated as "good" or "very good" by 92.5% of physicians and 88.0% of patients. Most patients (96.3%) were equally or more compliant with BTFC than with their previous treatment.

Conclusion: In routine clinical practice, BTFC achieved consistent IOP lowering in both previously treated and untreated patients with primary open-angle glaucoma or ocular hypertension. BTFC was associated with significant IOP reductions, good tolerability, and good compliance.

Keywords: bimatoprost 0.03%, intraocular pressure, ocular hypotensive medication, prostaglandin analog, β-blocker

Introduction

Elevated intraocular pressure (IOP) increases the risk that patients with ocular hypertension (OHT) will develop primary open-angle glaucoma (POAG)[1] and that those with glaucoma will experience disease progression.[2–5] Risk factors for progressive loss of visual field in glaucoma include increased age, corneal thickness, female sex, abnormal baseline anticardiolipin antibody levels as well as raised IOP.[1,2] However, lowering

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IOP is currently the only proven method for preserving visual function and reducing the rate of progression in glaucoma disease.[5–7] In a Canadian observational study to determine the impact of risk factors on the rates of visual field change in glaucoma, a reduction in median IOP of 20% in patients who progressed was associated with a significant 70% decrease in the median rate of visual field progression.[7]

While single medications that lower IOP are common first-line therapy for POAG and OHT patients, monotherapy does not adequately control IOP long-term for many patients, thus multiple therapies are required.[4] The addition of one or more drugs to the therapeutic regimen (adjunctive therapy) increases the dosing frequency, which has been associated with reduced patient persistence, leading to poor adherence.[8] Advantages of fixed combination (FC) therapy over therapy with unfixed combinations may include greater convenience, fewer side effects, and thus better tolerability, leading to improved patient compliance.[8,9]

The FC of bimatoprost 0.03% and timolol 0.5% (BTFC; Ganfort®, Allergan, Irvine, CA, USA) provides greater IOP reduction than prostaglandin monotherapy[10] and is as effective as its individual components used adjunctively.[11] Compared with its individual components as monotherapy in patients with bilateral glaucoma or OHT, BTFC achieved significantly greater reduction in IOP than bimatoprost 0.03% or timolol alone.[12] In randomized clinical trials, BTFC provided greater overall IOP reduction from baseline compared with latanoprost/timolol (LT) or travoprost/timolol (TT) FC.[13–15] These trials were included in a meta-analysis of 20 clinical trials that suggested BTFC had a greater overall ability to lower IOP than LTFC or TTFC.[16] Reports of treatment with BTFC in clinical practice have confirmed significant IOP reductions as well as good adherence and tolerability.[17] The present combined analysis of five studies aimed to assess the safety and IOP-lowering efficacy of BTFC in routine clinical practice in a large number of patients with POAG or OHT with insufficient IOP lowering on prior therapy.

Methods

Study design

This was a combined analysis of five multicenter, prospective, observational, non-interventional, non-randomized, open-label studies (Figure 1). A total of 830 sites in Austria, France, Germany, The Netherlands and Switzerland were identified. Patients were treated with BTFC at a dose determined by the treating physician and guided by the summary of product characteristics, which recommends that BTFC is applied daily to each affected eye.[18] There was no washout period for patients on prior therapy before the beginning of BTFC treatment, as this was an observational study.

The primary efficacy outcome was mean change in IOP (measured using contact tonometry) in each eye from baseline to the end of the study (approximately 12 weeks, based on routine clinical practice). Efficacy was also assessed in terms of target IOP, which was individually set for each patient by their treating physician, and a physician-reported assessment of BTFC in terms of IOP reduction using a four-point scale: "very good," "good," "moderate," and "poor." The visit schedule was based on routine clinical practice in each country: three visits were arranged in Austria, Germany, and Switzerland (a baseline visit, a follow-up visit at 6 weeks, and a final visit), and two visits in France and The Netherlands (baseline and final visit). All patients were assessed at the first visit (baseline) and the end of the study period, scheduled for week 12. At the first visit, additional information was recorded, including demographics, previous therapy, and reasons for changing to BTFC.

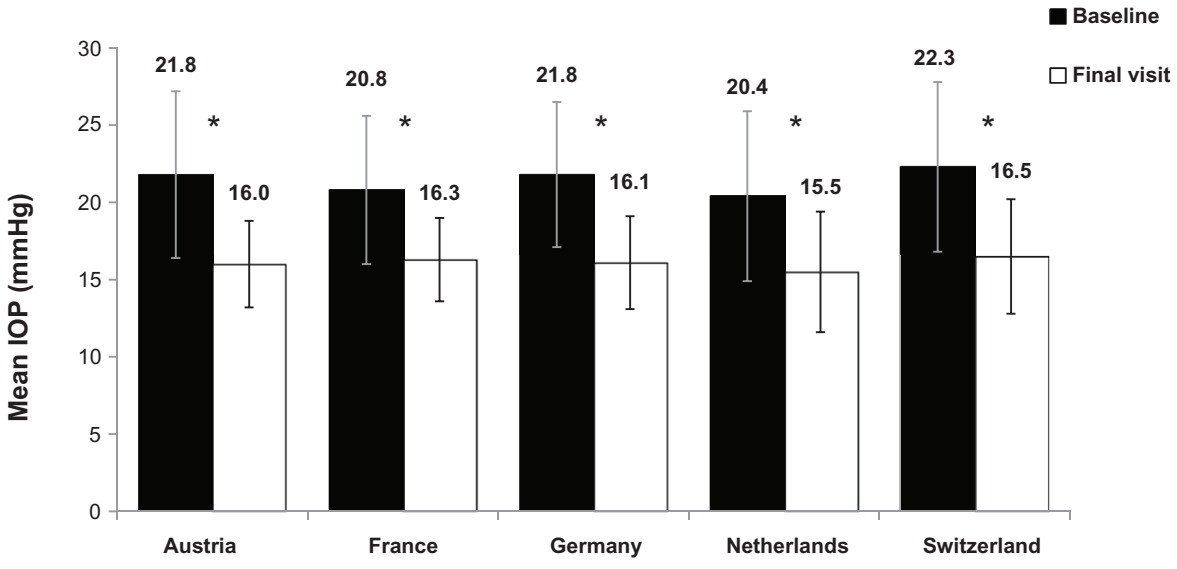
All adverse events (AEs) were recorded as free-text entries, using a questionnaire. Symptoms were categorized by Medical Dictionary of Regulatory Activities (v 14.1) preferred term, and causality between AEs and treatment was rated as "definite," "probable," "possible," "improbable," "no relation," "not assessable," or "unknown." Tolerability was assessed by both patient and physician using a four-point scale: "very good," "good," "moderate," and "poor." For patients who had received previous treatment, compliance with BTFC was compared with prior therapy and rated by physicians as "better," "equal," or "worse."

Patients

Patients included in the studies had a diagnosis of POAG or OHT established by their treating physician according to local criteria. Patients were eligible for inclusion regardless of whether they had received prior IOP-lowering therapy.

Analysis

Analyses of patient demographic and safety data were performed on the safety population, defined as all patients with any data documented. Change in IOP from baseline was calculated using data from all patients with complete data at both baseline and final visit. Data entry and analyses used the statistical software package SAS (v 9.1; SAS Institute, Cary, NC, USA) and Medidata software (Medidata, Konstanz, Germany). Data quality checking allowed implausible data to be excluded from the analysis. Summary statistics included mean and median values, standard deviations (SDs),



	Austria	France	Germany	Netherlands	Switzerland
n (right eye)	346	744	1786	666	592
n (left eye)	345	734	1789	668	594

Figure 1 Mean intraocular pressure (IOP) at baseline and final visit according to country, for patients with complete data only.
Notes: Error bars indicate standard deviations. *$P < 0.0001$, baseline versus final visit.

minimum and maximum ranges, frequency distributions, and interquartile ranges. Change in IOP from baseline to final visit was analyzed using a two-sided paired *t*-test, taking as the null hypothesis that IOP did not change after 12 weeks of study treatment. A P value < 0.05 was considered statistically significant.

Results

All five studies took place between June 2008 and June 2011. In total, 5556 patients were recruited: 392 from Austria (40 sites), 1940 from France (231 sites), 1862 from Germany (339 sites), 698 from The Netherlands (84 sites), and 664 from Switzerland (136 sites). Slightly more patients were female (54.9%) than male, and the mean age of participants was 67.6 ± 11.9 years (71.7% were >60 years old). Mean baseline IOP was 21.2 mmHg (Table 1) and most had a diagnosis of POAG (77.8%).

Mean time between enrollment and final study visit was 15.8 ± 8.25 weeks. BTFC was prescribed once a day for each eye (in 93.3% of patients), as would be expected given the licensed use of this agent;[18] 2.7% received it twice daily (not licensed) and frequency was not stated for the remainder.

Prior therapy

Prior to switching to BTFC, 5164 patients (92.9%) were recorded as taking other medication at study entry (Table 2). The remaining 392 (7.1%) either received no previous IOP-lowering therapy or had no information available regarding prior medication. Most of the patients on prior therapy had previously received timolol (2420; 46.9%) either as monotherapy or in combination with other therapies. Of the 5154 patients on prior therapy, 3291 (63.7%) were taking a monotherapy, 1410 (27.3%) were taking two therapies, and 463 (9.0%) were taking three or more therapies.

The most frequent reasons (more than one option could apply) given by physicians for switching to BTFC were insufficient IOP lowering on prior therapy (80.9%), progression of glaucoma-related damage (26.5%), unacceptable tolerability of prior therapy (11.9%), and lack of compliance with prior therapy (9.0%).

Table 1 Patient demographic data at baseline (n = 5556)

	Mean ± SD	n	%*
Age (years)	67.6 ± 11.9	5396	
Male		2469	44.4
Female		3050	54.9
Mean IOP (all patients), mmHg			
Right eye	21.2 ± 4.9	5432	
Left eye	21.2 ± 5.2	5421	
Diagnosis			
POAG		4324	77.8
OHT		1421	25.6
Patients on prior therapy		5164	92.9

Note: *Percentages may total more or less than 100%, due to missing data or selection of more than one option for some patients.
Abbreviations: IOP, intraocular pressure; OHT, ocular hypertension; POAG, primary open-angle glaucoma; SD, standard deviation.

Table 2 Prior medications taken by >2% of patients at study entry, among those whose prior therapy was documented (n = 5164)*

Medication	n	%	Active agent(s)
Xalatan®	1477	28.6	Latanoprost (0.005%)
Lumigan®	584	11.3	Bimatoprost (0.03%)
Travatan®	540	10.5	Travoprost (0.004%)
Cosopt®	498	9.6	Dorzolamide (0.2%), timolol (0.5%)
Xalacom®	422	8.2	Latanoprost (0.005%), timolol (0.5%)
Azopt®	280	5.4	Brinzolamide (1%)
Timolol	258	5.0	Timolol (0.1%, 0.25%, 0.5%)
Tim-Ophtal®	256	5.0	Timolol (0.1%, 0.25%, 0.5%)
DuoTrav®	241	4.7	Travoprost (0.004%), timolol (0.5%)
Alphagan®	184	3.6	Brimonidine (0.1%, 0.15%)
Timoptol®	178	3.4	Timolol (0.1%, 0.25%, 0.5%)
Trusopt®	158	3.1	Dorzolamide (2%)
Carteol®	153	3.0	Carteolol (1%)
Combigan®	141	2.7	Brimonidine (0.2%), timolol (0.5%)
Timoptic®	121	2.3	Timolol (0.1%, 0.25%, 0.5%)

Note: *Some patients previously received more than one intraocular pressure-lowering medication.

Effect on IOP

Baseline mean (±SD) IOP for the subset of patients with complete data for first and final visits was 21.4 ± 4.9 mmHg (n = 4134) and 21.5 ± 5.2 mmHg (n = 4130) for the right and left eyes, respectively. These values are similar to those shown in Table 1 for all recruited patients with baseline IOP data. At the final visit, mean IOP in this set of patients was reduced to 16.1 ± 3.3 mmHg and 16.0 ± 3.2 mmHg in the right and left eyes, respectively. This corresponds to a mean reduction in both eyes of −5.4 mmHg ($P < 0.0001$).

In patients with complete data for evaluation of efficacy (n = 1033), the target IOP as defined by the investigator was reached or bettered in 876 patients (84.8%). In 167 patients (16.2%), the IOP decreased but the target was not reached and 59 (5.7%) had no change or increased IOP.

The mean IOP reduction from baseline was similar across the five countries included in the studies: −5.8, −4.5, −5.7, −4.9, and −5.8 mmHg for centers in Austria, France, Germany, The Netherlands, and Switzerland, respectively (Figure 1). This reduction between first visit and final visit was significant for all patients with complete data across all the European countries ($P < 0.0001$).

The largest IOP reduction (−9.1 mmHg, mean of both eyes) was seen in patients (n = 311, right eye; n = 308, left eye) who had received no previous therapy ($P < 0.0001$), corresponding to a reduction of 36.4% in IOP from baseline (Figure 2A). However, BTFC also significantly reduced IOP in patients who had received prior monotherapy of a β-blocker (−5.6 mmHg) or the prostaglandin analogs latanoprost (−5.2 mmHg), travoprost (−5.7 mmHg), or bimatoprost 0.03% (−4.7 mmHg); $P < 0.001$ for all comparisons (Figure 2A). BTFC also produced additional IOP lowering in patients with complete data who had received prior therapy with other FCs, including dorzolamide/timolol FC (−4.7 mmHg), LTFC (−4.2 mmHg), TTFC (−4.4 mmHg), and brinzolamide/timolol FC (−2.2 mmHg) (Figure 2B). The overall mean reduction in these patients was −4.5 mmHg, corresponding to a reduction of 21.4% in IOP from baseline. All additional IOP reductions for patients on prior FC therapy were significant ($P < 0.0001$), except for the small number of patients (n = 9) previously taking brinzolamide/timolol FC.

Physicians rated the overall efficacy of BTFC on IOP reduction as "very good" or "good" in 88.7% of those patients for whom the evaluation data were available (n = 3111).

Tolerability and AEs

The majority of patients (5015/5556, 90.3%) did not report any AEs during treatment with BTFC (Table 3). AEs were recorded for 541 patients (9.7%), and the most common were conjunctival hyperemia (3.2%) and eye irritation (2.8%) (Table 3). Where evaluation data were available, BTFC tolerability was rated as "very good" or "good" by 92.5% of physicians (n = 4196) and 88.0% of patients (n = 4102) at week 12.

Three patients (0.05%) experienced serious adverse drug reactions. One patient was hospitalized for circulatory collapse, which was rated as possibly related to study treatment. A second patient experienced life-threatening dyspnea immediately after instillation of BTFC, which the physician rated as probably related to study treatment. These reactions are also sometimes seen as a response to β-blocker therapy. A third patient suffered from conjunctival hyperemia and eye pruritus, classified as medically important by the physician, but with no recorded assessment of causal relation to treatment.

Physicians rated compliance as "better than" or "equal to" previous treatment in 96.3% of those patients with evaluation data (n = 3823).

Discussion

These five observational studies aimed to evaluate the safety and efficacy of BTFC in routine clinical practice. In this pooled analysis of data from 5556 patients with POAG or OHT from 830 sites in five countries, patients treated with BTFC achieved a mean IOP reduction from baseline of 25% over a 12-week period. This reduction in IOP was statistically

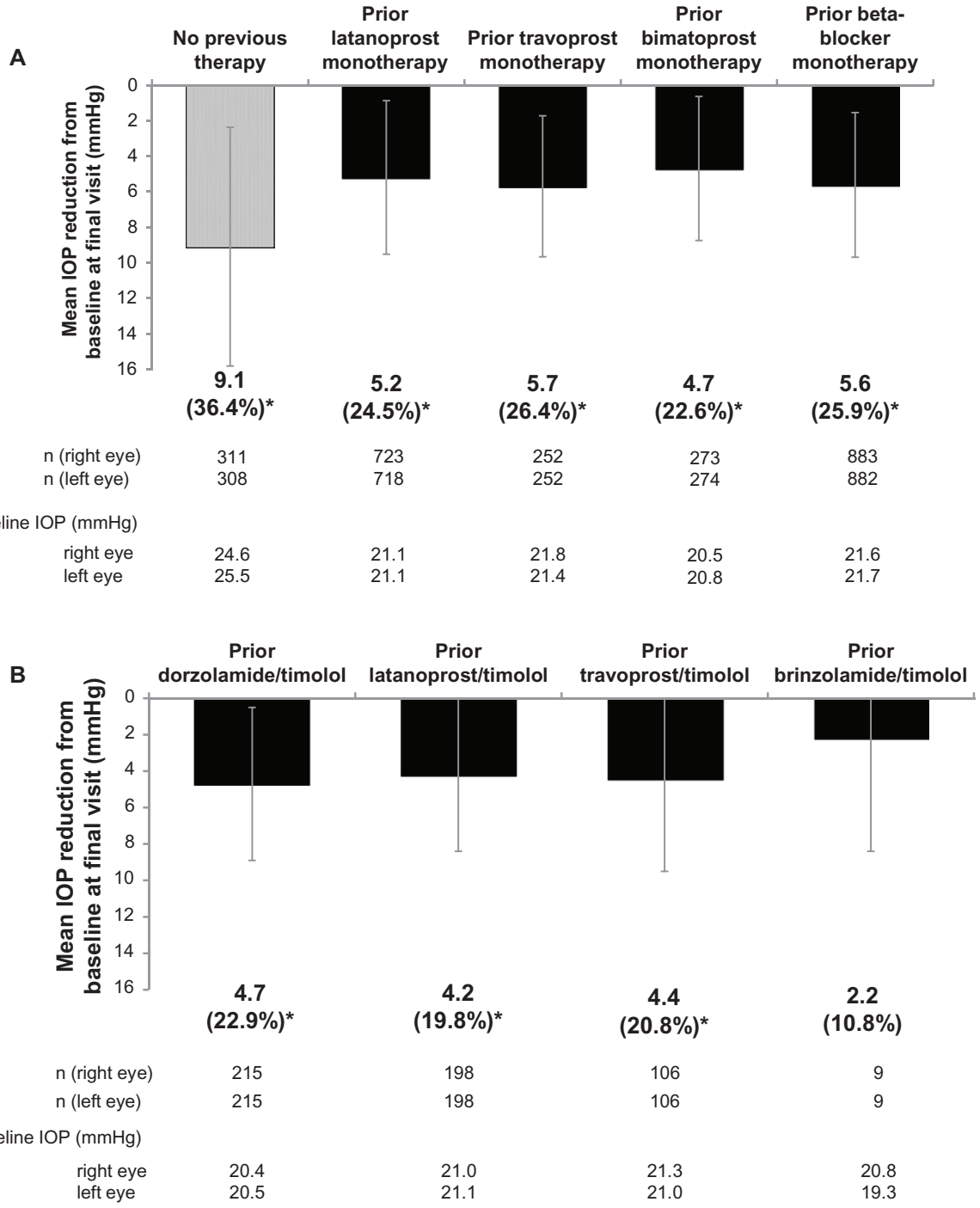


Figure 2 Mean intraocular pressure (IOP) reductions at final visit in (**A**) patients with no previous therapy or previous monotherapy and (**B**) patients with previous fixed combination therapy.

Notes: Bars represent the mean of right and left eye mean IOP differences from baseline. Error bars indicate standard deviations. Only data from patients with complete data are shown. *$P < 0.0001$, baseline versus final visit.

significant ($P < 0.001$). Similar mean IOP reductions were observed in all five European countries included in the study, thus it seems likely that these results would be borne out in similar populations in other European countries.

Most patients were switched to BTFC by their physician due to insufficient IOP lowering on their previous therapy (80.9%), and target IOP was reached or bettered in ~85% of patients, most of whom (92.9%) were taking prior medication at the time of study entry. Significant reductions from baseline IOP were observed: 36.4% for no prior therapy, 25.9% for prior β-blocker monotherapy, 24.4% for prior prostaglandin monotherapy, and 21.4% for prior FC therapy.

Table 3 Adverse events experienced by ≥0.1% of patients in the total population (n = 5556) classified according to Medical Dictionary for Regulatory Activities (v 14.1) preferred term

Adverse event	n	%*
All adverse events	541	9.7
Conjunctival hyperemia	177	3.2
Eye irritation	158	2.8
Eye pain	41	0.7
Eye pruritus	38	0.7
Dry eye	27	0.5
Skin hyperpigmentation	25	0.4
Eyelash growth	24	0.4
Foreign body sensation	23	0.4
Headache	22	0.4
Dizziness	19	0.3
Eye allergy	18	0.3
Increased lacrimation	18	0.3
Blurred vision	11	0.2
Conjunctival irritation	10	0.2
Dyspnea	10	0.2
Abnormal sensation in eye	8	0.2
Asthenopia	8	0.1
Erythema of eyelid	8	0.1
Drug intolerance	6	0.1
Eye edema	6	0.1
Photophobia	6	0.1
Reduction in visual acuity	6	0.1

Note: *Some patients (n = 150) recorded > 1 adverse event.

Treatment with BTFC was also well tolerated, with ~90% of patients experiencing no AEs, and compliance was rated as better than or equal to previous treatment by ~96% of physicians.

This combined analysis includes a German observational study of 1862 patients in which continuation of BTFC therapy beyond the end of the study was 82.9%.[17] In that study, an IOP ≤ 16 mmHg was achieved by over half (56.2% right eyes, 54.8% left eyes) of the total patient population and in over a quarter of eyes studied (left and right); IOP was reduced further to ≤14 mmHg by week 12.

Three independent clinical trials have shown that BTFC has greater overall ability to lower IOP than LTFC or TTFC.[13,15,19] In a meta-analysis that included those trials, IOP reduction from baseline was significantly greater with BTFC at all time points (9 am, noon, 4 pm, and diurnal curve) compared with TTFC and at 9 am, 4 pm, and over the diurnal curve compared with LTFC.[16] Results from large clinical trials on the relationship between risk of progression and IOP[1,2] suggest that the rate of progression may be reduced by as much as 10%–15% per mmHg of further IOP reduction.[20] If so, modest reductions in IOP may result in considerable gains over an extended period, and the addition of one or more medications to achieve this extra IOP reduction may have significant benefits for the patient's quality of life. This combined analysis of five observational studies demonstrates that BTFC can achieve additional IOP lowering in patients who have received prior therapy (monotherapy, adjunctive therapy, or FC) when used in clinical practice. Compared with their components used adjunctively, FCs are associated with less side effects and improved adherence.[21]

These studies were all open label and observational, and therefore have inherent limitations that affect interpretation of the results. Their design was uncontrolled and there was no washout period between the prior medications and the switch to BTFC. The studies were of relatively short duration, and although this was sufficient to evaluate changes in IOP levels, it was inadequate for evaluating long-term safety. Finally, the method of recording data using free-text entry may have allowed errors that could be difficult to detect. Nevertheless, combining data from five substantial studies provides a large body of data on the safety and efficacy of BTFC in clinical practice. The results confirm the findings of randomized clinical trials and demonstrate that BTFC is an effective choice for patients with POAG and OHT who have not achieved sufficient IOP lowering on their current therapy.

Disclosure

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