European Journal of Ophthalmology / Vol. 19 no. 1, 2009 / pp. 66-71

Efficacy of the fixed combinations of bimatoprost or latanoprost plus timolol in patients uncontrolled with prostaglandin monotherapy: A multicenter, randomized, investigator-masked, clinical study

M. CENTOFANTI[1,2], F. ODDONE[1], M. VETRUGNO[3], G. MANNI[1,2], P. FOGAGNOLO[1], L. TANGA[1], P. FERRERI[3], L. ROSSETTI[4]

[1]Fondazione G.B. Bietti–IRCCS, Roma
[2]Dipartimento di Biopatologia e Diagnostica per Immagini, Università di Roma Tor Vergata, Roma
[3]Dipartimento di Oftalmologia e Otorinolaringoiatria, Università di Bari, Bari
[4]Clinica Oculistica, Dipartimento di Medicina, Chirurgia e Odontoiatria, Università di Milano, Ospedale San Paolo, Milano - Italy

PURPOSE. *To compare the efficacy and tolerability of a once-daily evening dose of bimatoprost/timolol fixed combination (BTFC) with that of a once-daily evening dose of latanoprost/timolol fixed combination (LTFC) in patients not controlled with prostaglandins analogues monotherapy.*
METHODS. *A total of 82 patients on prostaglandin analogues monotherapy were enrolled in this prospective, multicenter, investigator masked, clinical study and were randomized to either BTFC (n=47) or LTFC (n=35) topical therapy once at night for 12 weeks. The primary endpoint of the study was to compare the mean daily intraocular pressure (IOP) reduction from baseline between the two treatment arms. Secondary endpoints included the mean daily IOP at 1 and 3 months compared to baseline and the percentage of patients showing a mean IOP reduction from baseline greater than or equal to 15% or 20%.*
RESULTS. *Mean IOP at baseline was 22.7±2.0 and 22.1±2.6 mmHg in the BTFC and LTFC groups, respectively (p=0.23). Both treatments were effective in reducing the IOP from baseline. The mean IOP reduction was significantly greater in the BTFC group than in the LTFC group (–21.4% vs –13.7%, p<0.001). A higher percentage of patients in the BTFC group showed a mean IOP reduction from baseline ≥15% (72.3% vs 40.0%) and ≥20% (61.7% vs 17.1%) compared to patients in the LTFC group.*
CONCLUSIONS. *Both BTFC and LTFC were more effective versus the monotherapy with prostaglandin analogues. BTFC demonstrated higher performance than LTFC in terms of relative IOP reduction. (Eur J Ophthalmol 2009; 19: 66-71)*

KEY WORDS. *Bimatoprost, Latanoprost, Timolol, Fixed combination*

Accepted: August 14, 2008

INTRODUCTION

Glaucoma is a leading cause of irreversible blindness (1). The only effective and clinically proved means of managing the condition is to reduce the intraocular pressure (IOP) (2) and among topical hypotensive agents prostaglandin analogues are widely recognized as the most effective available. Although topical therapy with a single hypotensive drug remains the first line choice (3), in a large number of patients to reach the target IOP it is

1120-6721/066-06$25.00/0

necessary to use a combination of medications; as many as 40% of patients with glaucoma are treated with a combination of drugs (4). In this setting, a fixed combination preparation may improve both the compliance and the quality of life (European Glaucoma Society. Terminology and Guidelines for Glaucoma. 2nd ed. Savona, Italy: DOGMA Srl; 2003). In addition, theoretically safety might be increased by using a fixed combination product because of limiting the exposure to benzalkonium chloride, the preservative in most eyedrops, which has been shown to be irritating for the conjunctiva (5).

The ß-adrenergic receptor antagonist timolol has been shown to provide excellent additivity with other ocular hypotensive drugs (6-8). Bimatoprost, a prostaglandin derivative, has been shown to lower IOP by facilitating uveoscleral outflow of aqueous humor and to be more effective than timolol (9) and to be as effective as latanoprost or travoprost (10, 11) or to give better IOP control than latanoprost (12). Recently, the fixed combination bimatoprost/timolol, a new IOP lowering combination that combines bimatoprost 0.03% and timolol 0.5%, has been introduced in the market.

The purpose of this study is to compare the efficacy and tolerability of a once-daily evening dose of bimatoprost/timolol fixed combination (BTFC) with that of a once-daily evening dose of latanoprost/timolol fixed combination (LTFC) in patients with open angle glaucoma (OAG) not controlled with prostaglandins analogues monotherapy.

METHODS

This 12-week prospective, multicenter, investigator masked, clinical study was carried out at three Italian eye research centers. The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and its amendment of October 2000 (Edinburgh, UK) and ethics committee approval was obtained from each center.

Patients diagnosed with OAG and 18 years or older who fulfilled the eligibility requirements detailed below and signed an informed consent at the screening visit were included.

Inclusion criteria were a diagnosis of OAG (including pseudoexfoliative and pigmentary glaucoma), topical monotherapy with prostaglandin analogous since at least 3 months before the study enrollment, and IOP not satisfactorily controlled (>21 mmHg) or, as judged by the physician, a target IOP not reached. OAG was defined as the presence of reproducible defects in at least two reliable Humphrey SITA-standard visual fields tests (GHT outside normal limits, and PSD p<5%) with corresponding optic nerve head defects as judged ophthalmoscopically by the physician.

Ocular exclusion criteria were closed/barely open anterior chamber angles (ACA) or history of acute angle closure (the ACA was viewed by means of the Goldmann 1-mirror lens; Shaffer grading was used, and grades II, III, and IV were included; grades 0 and I were excluded), ocular surgery or argon laser trabeculoplasty within the last 3 months, ocular inflammation/infection occurring within 3 months before the pretrial visit, refractive surgery, neovascular glaucomas, hypersensitivity to benzalkonium chloride or to any other component of the trial drug solutions.

General exclusion criteria were inability to adhere to treatment/visit plan, contraindications to the use of ß-blockers, use of any systemic drugs known to affect IOP, pregnancy, nursing, or, if applicable, nonuse of adequate contraception.

The study visit plan included a screening visit during which patients were checked for eligibility, and baseline visit where eligible patients stopped their current treatment and were randomized 1.5:1 to start either BTFC once at night or LTFC once at night (10:00 PM ± 1 h). Each patient was allocated to one of the two treatment groups according to a computer-generated randomization code. After baseline, two follow-up visits were performed at 4 and 12 weeks.

At baseline and at each follow-up visit a complete ophthalmologic evaluation was performed and IOP was measured at 10:00 AM, 12.00 PM, and 4:00 PM. The average of two consecutive Goldmann applanation IOP readings was reported at each time point (or the median of three readings if the first two were not within 2 mmHg). IOP was reported and analyzed for the study purposes as the mean of the three daily measurements for each visit (mean IOP). The incidence or increase of ocular hyperemia during the study was evaluated by self-report from the patients. All evaluations and IOP measurements were performed in each center by the same well-trained evaluator masked for the patient's treatment arm.

The primary endpoint of the study was to compare the mean daily IOP reduction from baseline between the two treatment arms after 3 months of therapy. The secondary endpoints were 1) the mean daily IOP at 1 and 3 months

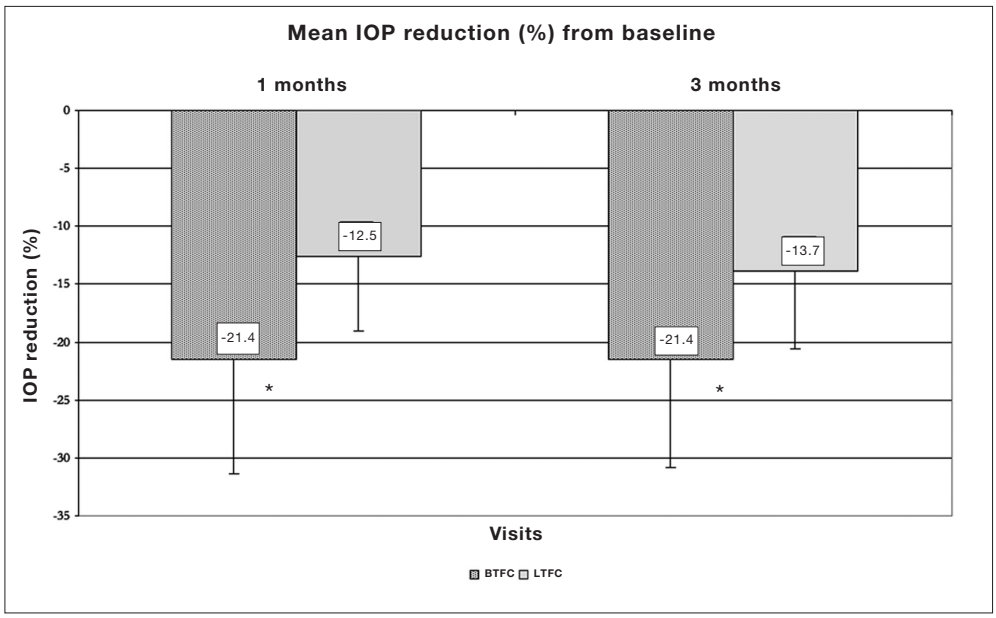

Fig. 1 - *Intraocular pressure reduction from baseline at 1 and 3 months. *p<0.001.*

compared to baseline, 2) the percentage of patients showing a mean IOP reduction from baseline greater or equal to 15% or 20% after 3 months of treatment, and 3) the difference in the incidence of study drug–related side effects.

An intent to treat (ITT) approach was used to analyze data and in case of missing values the last observation available was carried forward (LOCF). Data were described by means ± standard deviations (SD) and 95% confidence intervals (95% CI). One-way analysis of variance with Dunnett correction for multiple comparison was used to analyze follow-up IOP data within each group and independent *t*-test was used, after normality of data was checked and confirmed by Shapiro-Wilk test, to compare the percentage mean IOP reductions from baseline between groups. Chi-square and Fisher exact tests were used to compare categorical variables between groups. p<0.05 was considered statistically significant.

TABLE I - DEMOGRAPHIC CHARACTERISTICS OF ENROLLED PATIENTS

	BTFC	LTFC	p
n	47	35	—
Age, yr	64.1±9.4	65.6±10.7	0.6
Sex, M/F	24/23	16/19	0.1

BTFC = bimatoprost plus timolol fixed combination; LTFC = latanoprost 0.005% plus timolol 0.5% fixed combination.

RESULTS

A total of 82 patients were enrolled in the study: 47 were randomized to BTFC and 35 to LTFC. All patients completed the study. Patients' main characteristics are summarized in Table I.

TABLE II - MEAN DAILY INTRAOCULAR PRESSURE AT BASELINE AND AT EACH FOLLOW-UP VISIT

	Baseline		1 month			3 months		
	Mean	95% CI	Mean	95% CI	p*	Mean	95% CI	p*
BTFC	22.7	22.1–23.3	18.0	17.1–18.9	<0.001	17.9	17.1–18.7	<0.001
LTFC	22.1	21.2–23.0	19.3	18.5–20.1	<0.001	19.0	18.2–19.7	<0.001

*Statistical significance versus baseline.
BTFC = bimatoprost plus timolol fixed combination; LTFC = latanoprost 0.005% plus timolol 0.5% fixed combination.

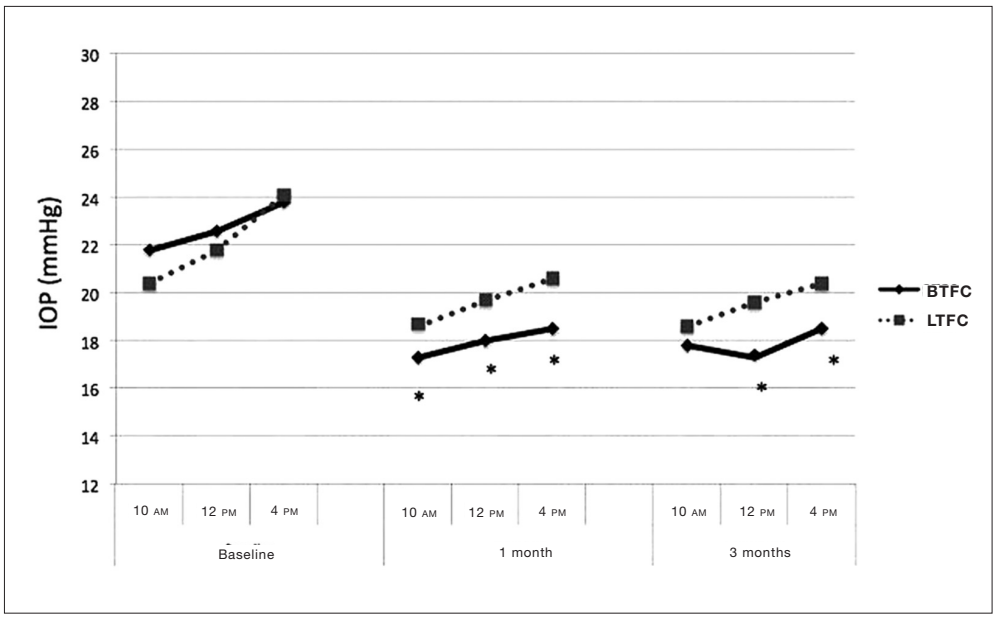

Fig. 2 - *Comparison of intraocular pressure between BTFC and LTFC groups at each single time point of each visit of the study. BTFC = bimatoprost + timolol fixed combination; LTFC = latanoprost + timolol fixed combination. *Differences at each time point between groups with p<5%.*

Before study enrollment, within the BTFC group, 17% of patients were on bimatoprost 0.03%, 27.7% on travoprost 0.004%, and 55.3% on latanoprost 0.005% monotherapy. Within the LTFC group, 20% of patients were on bimatoprost 0.03%, 40% on travoprost 0.004%, and 40% on latanoprost 0.005%. Mean IOP at baseline was similar between groups (22.7±2.0 and 22.1±2.6 mmHg in the BTFC and LTFC group, respectively, p=0.23).

Mean IOP and IOP at each time of the day was significantly decreased after 1 and 3 months of treatment compared with the baseline in both groups (Tabs. II and III). The mean IOP reduction from baseline after 3 months of treatment was significantly greater in the BTFC group than in the LTFC group (–21.4% vs –13.7%, p<0.001) as shown in Figure 1. A breakdown comparison of the data based on the individual time points of each follow-up visit is presented in Figure 2. BTFC provided lower IOPs compared to LTFC at six out of six follow-up time points of the study, and although only five out of six reached statistical significance this is consistent with the mean IOP data.

A higher percentage of patients in the BTFC group showed a mean IOP reduction from baseline: ≥15% (72.3% vs 40.0%, p<0.003) and ≥20% (61.7% vs 17.1%, p<0.001) compared to patients in the LTFC group.

Both treatments were well tolerated although a higher percentage, even if not statistically significant, of patients in the BTFC arm self-reported an increase of ocu-

TABLE III - MEAN INTRAOCULAR PRESSURE (95% CI) AT EACH TIME POINT OF THE STUDY

	Baseline	1 month	p	3 months	p
BTFC					
10 AM	21.8 (21.3–22.4)	17.3 (16.4–18.2)	<0.001	17.8 (17.0–18.5)	<0.001
12 PM	22.6 (21.9–23.2)	18.0 (17.1–18.9)	<0.001	17.4 (16.4–18.4)	<0.001
4 PM	23.8 (22.8–24.8)	18.5 (17.3–19.6)	<0.001	18.5 (17.5–19.6)	<0.001
LTFC					
10 AM	20.4 (19.5–21.3)	18.7 (17.8–19.6)	0.013	18.6 (17.7–19.6)	0.0105
12 PM	21.8 (20.9–22.6)	19.7 (18.8–20.7)	<0.0023	19.6 (18.7–20.5)	0.001
4 PM	24.1 (22.7–25.5)	20.6 (19.6–21.6)	<0.001	20.4 (19.4–21.3)	<0.001

BTFC = bimatoprost plus timolol fixed combination; LTFC = latanoprost 0.005% plus timolol 0.5% fixed combination.

lar hyperemia not associated with ocular symptoms (10.6% vs 5.7%, p=0.69). No patients discontinued the study and no serious adverse events were recorded throughout the study.

DISCUSSION

In this study, we evaluated the efficacy and safety of BTFC and LTFC both once-daily evening dosed in patients with OAG not controlled with prostaglandin analogues monotherapy.

Our results showed that both treatments provided a significant reduction of mean diurnal IOP from baseline after 1 and 3 months of therapy, although BTFC showed a significantly higher IOP lowering effect when compared to LTFC both considering the mean IOP at each visit and the IOP at each single time point of the follow-up.

Moreover, patients treated with BTFC were more likely to show IOP reductions greater than 15% and 20% from baseline compared to LTFC-treated patients.

The goal of glaucoma treatment is to maintain quality of life at a sustainable cost and quality of life is closely linked with visual function. Today the only approach proven to be efficient in preserving visual function in glaucoma is to lower the IOP although there is no IOP level that is safe for each patient and it is not possible to assess accurately and in advance the IOP level at which no further damage will occur in each individual patient. The principal drawback of this concept is that we know whether the selected target IOP was inadequate only after the patient's condition declines.

According to the EGS guidelines, the first approach to lower the IOP should be based on a single topical drug and, if the target IOP is not reached, provided that this drug demonstrates to be effective, a second drug can be associated to the first. Combination therapy offers some advantages, usually measured in terms of IOP reduction, and some drawbacks, mainly represented by an increase in the number of daily drops to be administered with consequent increased risk of lack of compliance and side effects. In this scenario, when a combination therapy is required it is crucial to choose the treatment regimen that offers the greatest chance to maximize the advantages and minimize the drawbacks of the combination therapy, or in other words the treatment regimen that allows maximizing the IOP lowering effect while minimizing the number of daily drops, therefore reducing the risk of side effects and lack of compliance.

Among the families of IOP lowering drugs, prostaglandin analogues have been demonstrated to be more effective in lowering the IOP, followed by the nonselective ß-blockers (13).

The results of our study show that, although both BTFC and LTFC were more effective than monotherapy with prostaglandin analogues, BTFC had slightly higher performance than LTFC in terms of relative IOP reduction.

Our results are in agreement with the results of a recently published prospective randomized single-masked clinical study where a significantly higher IOP-lowering effect of BTFC compared to LTFC was reported (14).

Usually the threshold of response to a topical therapy is set to 15% or 20% IOP reduction and in our study the BTFC allowed reduction of IOP more than 15% and 20% from the baseline in a higher proportion of patients compared to the LTFC treatment.

The choice of a fixed combination of drugs when a combination therapy is required allows minimization of some of the aforementioned drawbacks of combination therapy, mainly through a positive influence on the dosing schedule, improved compliance, and ultimately quality of life, and as previous studies showed similar efficacy for the unfixed and fixed combination of bimatoprost (15) and latanoprost (16) with timolol the fixed option should be preferred.

Among the limitations of the present study, the study was not double-masked and lasted over a relatively short period of time, although it is likely that 3 months might be enough to evaluate differences in IOP lowering efficacy between two different treatments. Further studies are required to assess the long-term efficacy of these drug combinations considering the potential long-term drift of the ß-blocker. Moreover, the higher proportion of patients at baseline treated with latanoprost monotherapy in both groups, and the potential presence of low-responders or no-responders to latanoprost among these patients, might have led to an overestimation of the BTFC treatment effect compared to that of LTFC throughout the follow-up. Finally, patients entering a clinical study show better compliance, which might explain better performance of drugs in trials compared to clinical practice (17).

No significant differences regarding safety were recorded between the two treatments during the study, although BTFC treatment was associated with a higher in-

cidence of self-report of ocular hyperemia not associated with other ocular symptoms.

In conclusion, this study suggests that LTFC and BTFC both given once daily in the evening effectively reduce the IOP in patients with OAG not well controlled with prostaglandins. Moreover, BTFC showed significantly greater IOP reduction performance compared to LTFC, although other studies are necessary to confirm this difference in the longer term.

ACKNOWLEDGEMENTS

The study was supported by an unrestricted grant by Allergan.

None of the authors has proprietary interest in the drugs involved in this study.

Reprint requests to:
Marco Centofanti, MD, PhD
Via Livenza, 3
00198 Roma, Italy
marco.centofanti@fastwebnet.it

REFERENCES

1. Quigley HA. Number of people with glaucoma worldwide. Br J Ophthalmol 1996; 80: 389-93.
2. The Advanced Glaucoma Intervention Study (AGIS). 4. Comparison of treatment outcomes within race. Seven-year results. Ophthalmology 1998; 105: 1146-64.
3. Alward WLM. Medical management of glaucoma. N Engl J Med 1998; 339: 1298-307.
4. Lundberg LU, Thygesen J, Damgaard-Jensen L, Serup L, Kessing SV. Glaucoma patients treated by practicing ophthalmologists in Denmark. Estimated number of patients and the extent of visual field defects. Ugeskr Laeger 2000; 162: 3028-33.
5. Manni G, Centofanti M, Oddone F, Parravano M, Bucci MG. Interleukin-1beta tear concentration in glaucomatous and ocular hypertensive patients treated with preservative-free nonselective beta-blockers. Am J Ophthalmol 2005; 139: 72-7.
6. Arici MK, Sayici M, Toker M, et al. A short-term study of the additive effect of timolol and brimonidine on intraocular pressure. Eye 2002; 16: 39-43.
7. Bucci MG for the Italian Latanoprost Study Group. Intraocular pressure lowering effects of latanoprost monotherapy versus latanoprost or pilocarpine in combination with timolol: a randomized, observer-masked multicenter study in patients with open-angle glaucoma. J Glaucoma 1999; 8: 24-30.
8. Diestelhorst M, Nordmann J-P, Toris CB. Combined therapy of pilocarpine or latanoprost with timolol versus latanoprost monotherapy. Surv Ophthalmol 2002; 47 (Suppl): S155-61.
9. Sherwood M, Brandt J, for the Bimatoprost Study Groups 1 and 2. Six-month comparison of bimatoprost once-daily and twice-daily with timolol twice-daily in patients with elevated intraocular pressure. Surv Ophthalmol 2001; 45 (Suppl): S361-8.
10. Parrish RK, Palmberg P, Sheu WP, for the XLT study group. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. Am J Ophthalmol 2003; 135: 688-703.
11. Orzalesi N, Rosseti L, Bottoli A, Fogagnolo P. Comparison of the effects of latanoprost, travoprost, and bimatoprost on circadian intraocular pressure in patients with glaucoma or ocular hypertension. Ophthalmology 2006; 113: 239-46.
12. Noecker RS, Dirks MS, Choplin NT, Bernstein P, Batoosingh AL, Whitcup SM. A six-month randomized clinical trial comparing the intraocular pressure lowering efficacy of bimatoprost and latanoprost in patients with ocular hypertension or glaucoma. Am J Ophthalmol 2003; 135: 55-63.
13. Van Der Valk R, Webers CA, Schouten JS, Zeegers MP, Hendrikse F, Prins MH. Intraocular pressure-lowering effects of all commonly used glaucoma drugs: a meta-analysis of randomized clinical trials. Ophthalmology 2005; 112: 1177-85.
14. Martinez A, Sanchez M. A comparison of the safety and intraocular pressure lowering of bimatoprost/timolol fixed combination versus latanoprost/timolol fixed combination in patients with open-angle glaucoma. Curr Med Res Opin 2007; 23: 1025-32.
15. Hommer A. A double-masked, randomized, parallel comparison of a fixed combination of bimatoprost 0.03%/timolol 0.5% with non-fixed combination use in patients with glaucoma or ocular hypertension. Eur J Ophthalmol 2007; 17: 53-62.
16. Diestelhorst M, Larsson LI. A 12-week, randomized, double-masked, multicenter study of the fixed combination of latanoprost and timolol in the evening versus the individual components. Ophthalmology 2006; 113: 70-6.
17. Gossec L, Tubach F, Dougados M, Ravaud P. Reporting adherence to medication in recent randomized controller trials of 6 chronic disease: a systematic literature review. Am J Med Sci 2007; 334: 248-54.