LONG TERM IOP LOWERING EFFICACY OF BIMATOPROST/TIMOLOL FIXED COMBINATION: A 12 MONTH PROSPECTIVE STUDY

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ABSTRACT

Purpose: To evaluate the long-term IOP-lowering effect of an initially successful switch from prostaglandine-analog (PGA) monotherapy to bimatoprost-timolol fixed combination (BTFC)

Methods: Prospective, monocentric, open-labeled clinical trial. 30 patients with insufficient intraocular pressure (IOP) control under PGA monotherapy were screened. Following a one month run-in period of BTFC, patients who presented an effective IOP-lowering response were prospectively studied for an additional 11-month period. IOP, tolerability and safety (adverse reactions, slit lamp biomicroscopy) were further assessed at month 6 and month 12 after initiating BTFC.

Results: BTFC therapy significantly decreased IOP when compared to PGA monotherapy (PGA monotherapy: 17.3±3.8mmHg; BTFC 1 month 13.2±3.3mmHg; $p<0.05$). This decrease from PGA-monotherapy IOP was sustained throughout the timeframe (6-month: 13.5±3.6mmHg; 12-month: 13.9±2.4mmHg; $p<0.05$ in pairwise comparison). There was no statistical difference in IOP between BTFC study visits ($p>0.05$). Of the 27 patients who had a satisfactory IOP-lowering response to BTFC after one month, 18 (66.7%) still had sufficient IOP control at the 12 month study visit. Therapy was discontinued at 1 month in 3 patients (2 due to intolerance to medication and 1 failing to achieve IOP control). No intolerability was reported beyond the 1 month of BTFC therapy.

Conclusion: In the majority of patients, the initial IOP lowering effect of replacing PGA monotherapy by BTFC seems to predict a long term response to the new treatment strategy.

KEY WORDS

bimatoprost/timolol, Glaucoma, Intraocular pressure

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INTRODUCTION

Glaucoma is a chronic progressive optic neuropathy and one of the major causes of irreversible vision loss in the industrialized world (1). The mainstay of the current therapy has been to lower intraocular pressure (IOP), its main risk factor. The existing commercially available medications present a wide range of IOP lowering efficacy, adverse reactions and treatment regimens. Existing literature supports the idea of first line treatment being a monotherapy with a treatment regimen that involves a once-a-day administration (2,3). Accordingly, prostaglandin analogs (PGA) have become a popular option as first option when initiating treatment, as they have the most powerful IOP-lowering efficacy as a monotherapy and have an excellent safety profile (4-6).

Nevertheless, in 49-75% (7,8), monotherapy does not suffice to successfully control IOP. In such cases, the current guidelines from the European Glaucoma Society suggest several alternatives, from changing between monotherapy drugs to adding a second drug to the existing monotherapy class. When combining medications, the use of fixed combinations (FC) is recommend to improve compliance, tolerability and efficacy (2). Switching an insufficiently controlled glaucoma patient from a PGA-monotherapy to a PGA/timolol 0.5% FC can indeed offer a further IOP reduction while keeping the same once-a-day treatment regimen (9) (as opposed to some other fixed combinations). Bimatoprost 0.003% / timolol 0.5% FC (BTFC) has been suggested to have a higher IOP-lowering efficacy when compared to other PGA/timolol FC in several short-term studiesto confirm this finding (10-13), whereas a recent meta-analysis states that further studies would be useful (14). Indeed, this short-term additional IOP-lowering effect can be due to a (often temporary) increase in compliance as the patients may perceive that a change in therapy can decrease the likelihood of needing more invasive procedures, including surgery.

As such, whether a long term, sustained IOP-lowering effect in previously uncontrolled glaucoma patients under PGA-monotherapy can be achieved by a switch to BTFC is still unclear. Our aim is therefore to continue monitoring these patients on the longer term, to determine whether IOP lowering, tolerability and safety profile are maintained over time.

MATERIALS AND METHODS

Subjects

This prospective, open-labeled clinical trial was approved by the Institutional Review Board of the University Hospitals Leuven and adhered to the tenets of the Declaration of Helsinki. All eligible patients who agreed to participate in the study signed an informed consent prior to enrolment.

Glaucoma patients were defined as having characteristic optic disc damage (based on cup/disc ratio, thinning of neuroretinal rim, notching, nasalization of disk vessels, disk hemorrhages, etc.) and visual field defect criteria (15,16).

Target pressure calculations were made for each patient, based on maximal IOP and stage of the disease (15). Patients with open-angle glaucoma that had an insufficient IOP control under PGA monotherapy that accepted the proposed treatment change after consideration of the alternatives were screened. Only one eye was selected per patient.

Inclusion criteria:

- individuals over 18 years old
- diagnosed with open-angle glaucoma
- insufficient IOP control with PGA monotherapy
- documented favorable IOP lowering efficacy and tolerablility on a topical treatment including bimatoprost/timolol fixed combination
- willing to sign an informed consent

Exclusion criteria:

- Intolerance or contra-indication for one of the components of the bimatoprost/timolol
- Conditions (eg corneal diseases) that interfere with reliable IOP measurements
- Monophtalmic patients or with study eye's visual acuity below 1 (logMar)

Study procedures:

All eligible patients completed an ocular examination that included slit-lamp biomicroscopy, visual acuity, IOP measurement with applanation tonometry, visual field testing. Past medical history was recorded. They were instructed to discontinue their previous therapy and to administer one drop daily of BTFC for a run-in period of 1 month.

At one month of BTFC therapy, a baseline visit was performed. In addition to the previously described ocular examinations, IOP lowering efficacy was assessed. Those who had sufficient IOP control remained under BTFC treatment and were scheduled for a visit at month 6 and month 12.. At any study visit where there was an uncontrolled IOP, the patient would be discontinued from the study and other treatment strategies were initiated.

A subjective tolerability score was made, based on a short patient questionnaire that contained questions on eye redness, foreign body sensation, burning/stinging, tears, dry and blurry vision, according to the following scale: (0)=none, (1) = minimal, (2) = mild, (3) = moderate, (4) = severe. The total score was calculated as the sum of symptom scores divided by the number of symptoms (thus ranging between 0 and 4). A thorough investigation concerning adverse reactions (both ocular and systemic) was done at each consult. Furthermore patients were explicitly asked whether they experienced any complaints.

Whenever deemed necessary for the safety of the patient, additional visits would be planned outside the study visit protocol to ensure a proper follow-up.

STATISTICS

Mann-Whitney and Kruskal-Wallis tests were used to make pairwise and overall comparisons between continuous variables, respectively. Statistical significance was considered when $p < 0.05$. Values are depicted as mean ± SD unless otherwise indicated. Analyses were performed using Graphpad Prism ver. 5.0; (Graphpad Software Inc, La Jolla, CA, USA).

RESULTS

Recruitment and retention

After a one month run in period with BTFC, 27 of 30 patients achieved target IOP and were included at baseline visit. Three out of 30 patients failed the inclusion criteria: 2 patients showed signs of intolerance to BTFC and 1 patient had insufficient IOP lowering. The overall description of the patients' demographic, ocular characteristics at this baseline visit, including previous surgeries is depicted in table I. Of the patients enrolled at baseline, 19 patients concluded the 12-month study, as 4 patients were lost to follow-up and in 4 patients IOP control became sub-optimal (*Fig. 1*).

Outcome

Of the 27 patients started on BTFC, 18 patients (66.7%) presented with a successful IOP control at the 12-month visit. IOP was significantly reduced after the 1 month BTFC therapy when compared to PGA-monotherapy (PGA monotherapy: 17.3 ± 3.8 mmHg; BTFC 1 month 13.2 ± 3.3 mmHg; $p<0.05$). In percentage of IOP reduction, there was a significant reduction from the screening visit throughout the study visit (BTFC 1 month: -23.3 ± 13.9%; BTFC 6 month: -19.4 ± 21.1%; BTFC

Table I: . *Baseline characteristics of participant patients (n=27)*

Age (years)	65.6±13.7
Male/Female ratio	17/10
IOP (mmHg)	17.3±3.8
Visual Acuity (LogMar)	0.21±0.24
Visual field MD (dB)	-8.29±8.4
Type of Glaucoma diagnosis	
POAG	13
NTG	7
Secondary open-angle	7
Previous laser/surgical treatment	
Trabeculectomy	3
Laser Trabeculoplasty	2
Previous medication	
Latanoprost	20
Bimatoprost	6
Travoprost	1

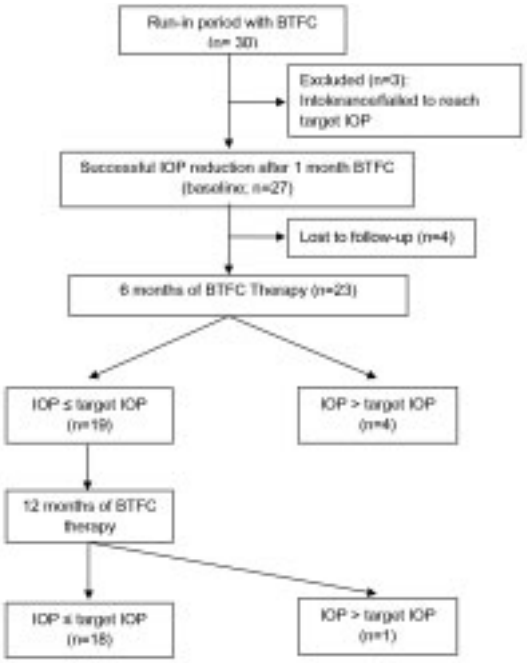

Fig. 1: Flowchart of patient progress in the 12 month study. IOP = intraocular pressure; BTFC = bimatoprost/timolol fixed combination.

12 month: -17.2 ± 18.8%; vs screening, $p<0.05$) (Fig. 2).
There was no statistical difference between IOP values of 1 month, 6 month and 12 month study visits ($p=0.35$).

Self-reported symptoms of intolerance were mild and did not change significantly over time. The overall mean score of the questionnaire was 0.80 ± 0.2 (1 month visit), 0.66 ± 0.2 (6 month visit), 0.75 ± 0.2 (12 month visit) with no statistically significant difference between the study visits ($p=0.49$). Nor were any significant differences between study visits seen for each of the separate items (pruritus, burning/stinging, blurred vision, sticky eye sensation, eye dryness sensation or foreign body sensation). A detailed description of the selfreported ocular symptoms is made in *Table II*. No systemic adverse reactions were reported.

DISCUSSION

The switch in therapy from PGA-monotherapy to a bimatoprost/timolol fixed combination had a long-term effectiveness in IOP reduction. The initial response to the new treatment was sustained throughout the 12 month study in 18 out of 30 (67%) patients. In fact, BTFC therapy led to an additional 15% decrease on average when compared to the previous PGA-monotherapy, despite the relatively low baseline pressures in our study patients. Our results are in line with previous reports on the short term efficacy of transition from PGA monotherapies to PGA/timolol FC therapies (17,18), thus suggesting that this additional IOP-lowering can be sustained in the long term. Although some reports suggest that these PGA-related FCs may possess less IOP-lowering efficacy than each of the two components separately (11), they are apparently more efficient than PGA-monotherapy, with possibly an improved ocular tolerability by decreasing ocular hyperemia (12). This ocular symptom has been widely de-

Table II: *Tolerability Evaluation of BTFC therapy*

	1 Month	*6 Month*	*12 Month*	*p-value*
Redness	0.87±1.3	0.64±1.0	0.76±1.3	0.89
Foreign body sensation	0.52±1.1	0.57±0.8	0.76±0.8	0.67
Burning/stinging	0.87±1.0	0.93±1.1	1.00±0.7	0.89
Tears	0.70±1.0	0.57±0.7	0.50±0.50	0.99
Dry	1.04±1.2	0.43±0.7	0.50±0.9	0.29
Blurry vision	0.87±1.2	0.86±1.2	1.00±1.2	0.94
Mean Score	0.80±0.2	0.66±0.2	0.75±0.2	0.49

Scores calculated from a subjective scale between 0 and 4 (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe). The total score was calculated as the sum of symptom scores divided by the number of symptoms (thus ranging between 0 and 4). Overall comparison made with Kruskal-Wallis tests.

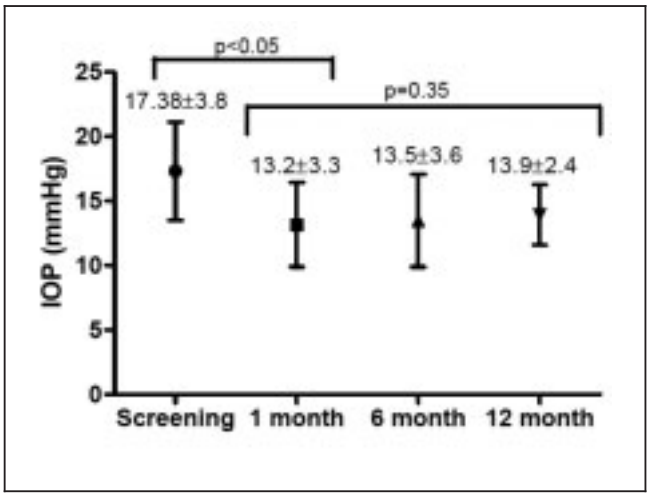

Fig. 2: Intraocular pressure (IOP) throughout the study visits. Data presented as mean±standard deviation. Mann-Whitney tests used for pairwise comparison vs screening visit ($p<0.05$ in all comparisons). No difference was found in IOP between the 3 study visits (Kruskal-Wallis test; $p=0.35$).

scribed as a side effect in PGA-related therapy regimens, and has been suggested to be a reason for patients' poor compliance and change in therapy (19). Adding a non-selective betablocker in a fixed combination appears to be beneficial by several mechanisms. One possibility is that it decreases the number of preservative-containing drops instilled into the eye when compared to non-FC, which have been consistently implicated in ocular surface disease (20,21). On the other hand, by adding a non-selective betablocker, there may be a decrease in overall neural sensitivity (22,23). Our results suggest that despite a long-term application of BTFC, patients' complaints remained mild and stable throughout the 12 month period, thus implying no cumulative negative effect on the ocular surface. Additionally, by keeping a simple, once a day treatment regimen, compliance and persistence may be sustained. Our study had a number of limitations that should be kept in mind. By aiming to keep the same therapeutic regimen, we restricted our analysis to patients under PGA-monotherapy, which led to a small case series. Additional large scale studies are still needed to further validate our conclusions. Although beyond the scope of our study, by having restricted our ocular symptom questionnaires to the period already under BTFC, the interesting point of comparing patient comfort under BTFC to the one experienced under the previous medication is not addressed in this study. Finally we used a questionnaire that has not been subjected to a specific validation study, although it was previously used in a slightly modified form in a clinical trial (24).

In conclusion, in the majority of patients, the initial IOP lowering effect of replacing PGA monotherapy by BTFC seems to predict a long term response to the new treatment strategy.

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