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Efficacy and safety of bimatoprost in patients with uncontrolled glaucoma as alternative to filtration surgery

M. VETRUGNO[1], C. SBORGIA[1], E. BALESTRAZZI[2], C. BIANCHI[3], A. CAPOROSSI[4], M. NARDI[5], A. RAPISARDA[6], G. TASSINARI[7], L. ZEPPA[8]

[1]Department of Ophthalmology, University of Bari, Bari
[2]Department of Ophthalmology, University of L'Aquila, L'Aquila
[3]Private Hospital Villa Aprica, Como
[4]Department of Ophthalmology, University of Siena, Siena
[5]Department of Ophthalmology, University of Pisa, Pisa
[6]Eye Hospital, Siracusa
[7]Eye Hospital, Bologna
[8]Eye Hospital, Avellino - Italy

PURPOSE. To evaluate the efficacy and safety of bimatoprost 0.03% as an alternative to filtration surgery in patients with uncontrolled glaucoma.
Design. Interventional study.
METHODS. A total of 83 consecutive patients (83 eyes) awaiting glaucoma surgery were enrolled in eight ophthalmic centers. Reasons for listing were inadequate intraocular pressure (IOP) control despite medical therapy and documented progression of visual field loss. All patients discontinued the previous treatment and were switched to bimatoprost 0.03% QD (one drop at 9 pm). The primary efficacy outcome was a 20% IOP reduction from baseline at each timepoint. IOP was measured at day 7, day 30, day 60, and day 90 of treatment; less than 20% IOP reduction was considered as a failure.
RESULTS. An IOP reduction of at least 20% was achieved in 74 patients (89.1%) after 7 days and in 64 patients (86.5%) after 30 days. Sixty-two patients (74.6%) maintained IOP readings 20% lower than baseline after 60 and 90 days. In these patients, visual field indices improved in 8 eyes (13%), and remained unchanged in 54 eyes (87%). Ocular side effects were conjunctival injection (15.6%), burning sensation (9.6%), foreign body sensation (4.8%), and eyelash growth (2.4%).
CONCLUSIONS. This preliminary study shows that bimatoprost 0.03% could represent a useful therapeutic tool that might defer filtration surgery. (Eur J Ophthalmol 2005; 15: 477-81)

KEY WORDS. Bimatoprost, Efficacy, Compassionate use, Filtering surgery

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INTRODUCTION

According to the European Glaucoma Society guidelines, medical therapy of primary open-angle glaucoma (POAG) should follow progressive steps to obtain the lowest intraocular pressure (IOP), which is likely to prevent further visual field loss and maintain normal visual function (1).

Today, a wide range of options for medical therapy is available, and maximum tolerated medical therapy (MTMT) is often enough before surgery.

According to Realini and Fechtner (2), MTMT can be

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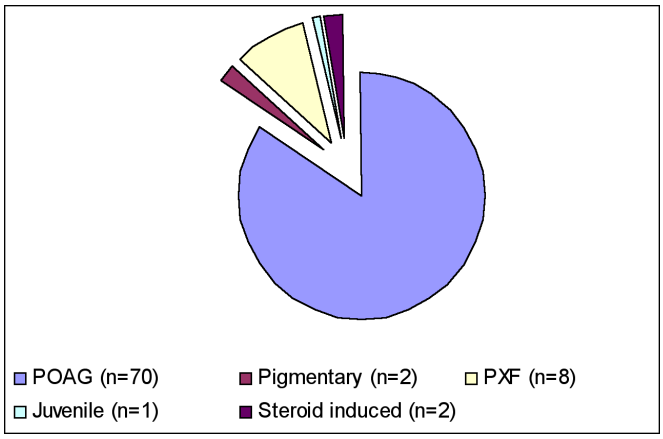

Fig. 1 - Demographic data (intent-to-treat population) I: Diagnosis. POAG = Primary open angle glaucoma; PXF = Pseudoexfoliative glaucoma.

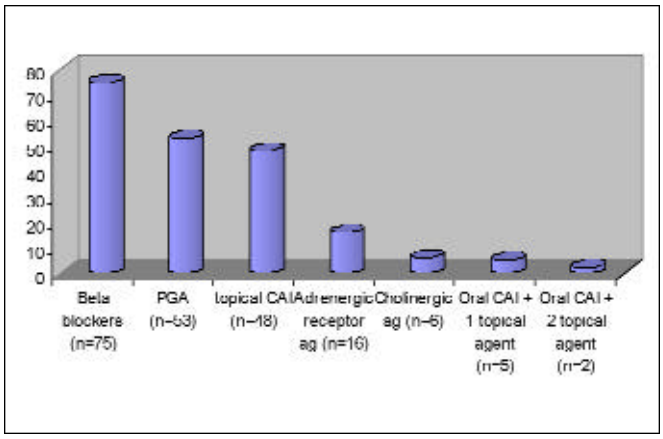

Fig. 2 - Demographic data (intent-to-treat population) II: Frequencies of patients receiving antiglaucoma medication. Some patients were taking dual therapy. PGA = Prostaglandin analogues; CAI = Carbonic anhydrase inhibitors; ag = Agonists.

defined as the point at which it makes no sense to add more medication, but this decision-making process in glaucoma management is often difficult, because of drug availability, different health care management systems, the medical history of the patient, life expectancy, intolerance to treatment, systemic and/or local side effects, or poor compliance.

Some centers have adopted a more interventional approach to glaucoma management and filtering surgery is contemplated at an early stage (3).

As of today, there are no controlled clinical trials (4) that show that trabeculectomy can accomplish IOP control without the costs and side effects of medical therapy, and therefore medical therapy remains the mainstay for glaucoma management.

Studies indicate that prostamide analogues, such as bimatoprost, can be more effective in lowering IOP than timolol (5, 6), latanoprost (7, 8), travoprost (9), and combination therapy (10).

Parrish et al (11) found a comparable ability to reduce IOP among bimatoprost, travoprost, and latanoprost. Bimatoprost has also been shown to be effective in latanoprost nonresponder patients (12-14).

The aim of this study was to evaluate whether bimatoprost can lower IOP when MTMT fails. When this study was conducted, bimatoprost was not commercially available in Italy and it was decided to administer it for 3 months on a compassionate basis to a group of patients who were listed for surgery and the waiting time was known to exceed 2 months.

MATERIALS AND METHODS

From April 2002 to July 2002, eight ophthalmic centers participated in this prospective multicenter study. As bimatoprost was administered on a compassionate basis, no ethical committee approval was needed. All patients scheduled for glaucoma filtering surgery who were facing waiting times of at least 2 months were considered eligible for this study, and a written informed consent was obtained from each.

The inclusion criteria were any of the following: POAG; pigmentary, pseudoexfoliative, and juvenile glaucoma; IOP >24 mm Hg on MTMT regimen; any progression of visual field loss (Humphrey 30-II full threshold); intolerance to MTMT; or poor compliance with MTMT. For this reason, we included patients who were on only one topical drug. A total of 101 patients were included. Prior the enrollment, we excluded 18 patients: 10 because of rapidly evolving field loss, i.e., visual field loss >5 dB as expressed by Humphrey parameter mean defect (MD), documented by at least two consecutive examinations in the last 6 months, or macula-threatening scotomata as they were fast-tracked to surgical intervention and not facing long waiting times; 3 considered suitable for laser trabeculoplasty (because of their poor compliance even to a single medication); and 5 who expressed preference for surgery.

After selection, a total of 83 patients were enrolled in the study. All the patients were instructed to stop all previous glaucoma medications (both topical and oral, if that was the case) and received topical bimatoprost 0.03%

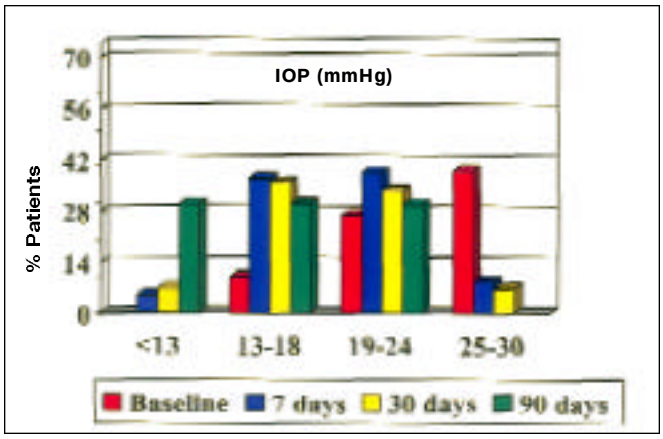

Fig. 3 - Distributions of the intraocular pressure (mmHg) measures at each timepoint.

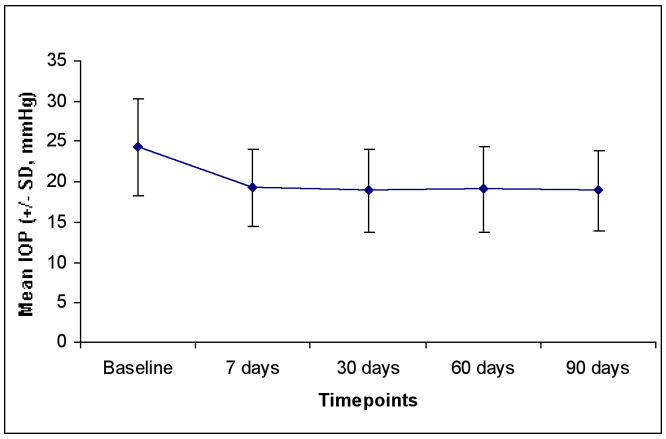

Fig. 4 - Mean (± standard deviation) intraocular pressure at each timepoint

(Lumigan), daily, 1 drop at bedtime. Patients started the new regimen without a wash-out period. IOP measurements were taken at baseline (the time of entering the study, when the MTMT was replaced with the bimatoprost treatment), and after 7, 30, 60, and 90 days. The primary efficacy outcome measure was change in IOP measured from baseline. If the IOP was at least 20% lower than the MTMT baseline, the patients were to continue with bimatoprost treatment; otherwise they were re-enlisted for surgery.

RESULTS

A total of 83 eyes (83 patients) were enrolled in the study. Mean age was 66 ± 11.5 years, 50 men and 33 women. Figure 1 shows the percentage of the different types of glaucoma included in the study. Figure 2 shows the percentage of patients receiving each of the different IOP-lowering medications at baseline. Seven patients were taking only one antiglaucoma agent, 56 patients were on two, and 20 were on three ocular hypotensive agents. Moreover, 7 patients were also taking systemic carbonic anhydrase inhibitors (CAIs).

After 7 days on bimatoprost monotherapy, IOP readings 20% lower than baseline were obtained in 74 patients (89.1%), while the IOP was outside target in 6 patients and 3 patients developed intolerance to bimatoprost. Thirty days after commencing bimatoprost, a further 10 patients were excluded (9 patients were not within target IOP levels, 1 patient due to conjunctival hyperemia) while 64 patients (86.5%) still reached the target of at least 20% IOP lowering. After 60 days, 2 more patients were excluded from the study and listed for surgery as the IOP fell short of the target.

The 17 patients who discontinued from the study because they did not reach the 20% IOP reduction were treated before entering the study as follows: fixed combination (timolol + dorzolamide) + prostaglandins in five cases, fixed combination (timolol + dorzolamide) + systemic CAIs in seven cases, beta blockers + adrenergic agonists in three cases, and beta blockers + cholinergic agonists in two cases. All the remaining 62 patients (74.6%) completed the study at the endpoint (90 days) with IOP controlled within target levels. In summary, 83 patients entered the study, 62 patients completed 3 months of bimatoprost replacement therapy, 4 patients discontinued due to adverse effects, and 17 discontinued for lack of efficacy (not reaching at least 20% drop in IOP).

Figure 3 shows the distributions of the IOP at each timepoint. Figure 4 shows mean IOP at each timepoint: bimatoprost reduced IOP from 24.3 (±6) mmHg at baseline to 19.3 (±4.8) mmHg (after 7 days), 18.9 (±5.1) mmHg (after 30 days), 19.1 (±5.3) mmHg (after 60 days), and 18.9 (±4.9) mmHg (after 90 days). IOP recorded at each timepoint was significantly lower than baseline ($p<0.0001$ at analysis of variance test with Tukey–Kramer post test). Statistical analysis showed no differences among mean IOPs at different timepoints. After 90 days, 29% of patients reached a target IOP below 13 mmHg, and 29%

TABLE I - THE SUCCESS RATE OF BIMATOPROST REPLACEMENT OF PREVIOUS THERAPY

Previous number of drugs	**Bimatoprost success rate** %
1	92.8
2	83.3
3	77.5
Fixed combination	75

more patients were within 13 and 18 mmHg. Table I shows the success rate of the replacement of the previous therapy with bimatoprost.

The overall incidence of ocular side effects in patients on bimatoprost was as follows: conjunctival injection in 13 eyes (15.6%), burning sensation in 8 eyes (9.6%), foreign body sensation in 4 eyes (4.8%), and eyelash growth in 2 eyes (2.4%). However, only 4 patients (4.8%) discontinued the treatment with bimatoprost because of ocular side effects.

DISCUSSION

IOP is a primary risk factor for glaucoma and the main target for therapy. It has been shown that each mmHg of IOP lowering will reduce risk for progression of glaucoma by 10% (4). For this purpose, every effort has to be made to optimize IOP control. Although there is no absolute consensus on the definition of a clinical responder, a 15 to 20% IOP reduction is often used to define a clinically relevant response to a glaucoma medication (4).

Bimatoprost has been recently introduced as a new prostamide-analogue drug, and has been shown to be more effective than beta-blockers (5, 6) and comparable to (11) or more effective than (7-9) other similar compounds. It is not clear whether bimatoprost acts on a different target than prostaglandin analogues, but it has been shown that bimatoprost lowers IOP in patients who are nonresponders to latanoprost (12-14). Our study confirms the above findings.

Studies of shifts in surgical rates in patients with glaucoma have been recently performed in Scotland (15, 16), the United States (17), and France (18). After 1994, with the introduction of new classes of drug, surgery rate decreased by 45.9% in Scotland, 22% in the United States, and 47% in France. In our study, bimatoprost monotherapy delayed surgical intervention in 74.6% of patients, after 3 months. This finding may have a major implication on waiting lists, overall costs, incidence of complications, and quality of life of the patient.

It can be argued that keeping patients on a different form of treatment after they were considered in need for surgery is open to criticism. Another point to consider is that we do not for how long the efficacy of bimatoprost is guaranteed, and further studies are needed. Finally, the increased acceptability of a monotherapy versus MTMT might bias our results as compliance is more likely to be maintained with our protocol than with MTMT, or it can be improved after the information to patients that surgery would be needed, if the last medical therapy fails. Nevertheless, a remarkable result was that about 30% of patients reached IOP levels <13 mmHg, and about 30% of patients reached IOP levels between 13 and 18 mmHg. These data are relevant in consideration that reducing IOP at the lowest target might reduce the risk for glaucoma progression (4).

Bimatoprost monotherapy was associated with a number of side effects such as itching and conjunctival injection (9, 10).

In summary, in a group of surgical candidates, with IOP uncontrolled by various regimens of MTMT, 3 months of replacement treatment with bimatoprost delayed surgery in 74.6% of the subjects. Our findings confirm a recent report on the efficacy of replacing MTMT with prostaglandins (19). Bimatoprost might represent an alternative to surgery in patients with MTMT, although longer follow-up is needed to confirm these data.

Reprint requests to:
Prof. Michele Vetrugno
Department of Ophthalmology
University of Bari
Piazza Giulio Cesare, 11
70124 Bari, Italy
m.vetrugno@oftalmo.uniba.it

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