• Clinical Research •

Efficacy and safety of bimatoprost in glaucoma and ocular hypertension in non-responder patients

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Abstract

• AIM: To establish the efficacy and safety of bimatoprost 0.03% monotherapy in glaucoma and ocular hypertension (OHT) patients with inadequate intraocular pressure (IOP) on current therapy.

• METHODS: Pre- and post-switch IOPs were analyzed for 59 consecutive patients who were switched from current therapy to bimatoprost monotherapy between 2011-2015. Demographic information, diagnosis, and any adverse events were recorded. Change in IOP post-pre switch was analyzed using a 2-sided Student's paired *t*-test at the 5% significance level.

• RESULTS: There was a statistically significant mean reduction in IOP at the first follow up visit, which was maintained at subsequent follow up visits for patients regardless of diagnosis, or pre-switch treatment (*P*<0.001). Subgroup analysis also demonstrated a statistically significant mean reduction in IOP when looking at OHT patients only, as well as patients with any diagnosis switched from latanoprost monotherapy to bimatoprost monotherapy (*P*<0.001).

• CONCLUSION: This is the largest independent data set which supports switching glaucoma patients with poor response to current treatment onto bimatoprost monotherapy before considering other adjuvant medical or more invasive therapy.

• KEYWORDS: glaucoma; ocular hypertension; bimatoprost; latanoprost

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INTRODUCTION

Glaucoma is a complex neurodegenerative condition estimated to effect 64.3 million people worldwide in 2013, a number that is predicted to rise to 111.8 million by 2040[1]. The only modifiable risk factor in the treatment of glaucoma to date is the reduction of intraocular pressure (IOP)[2]. Prostaglandin analogues (PGAs; bimatoprost, latanoprost, Travaprost) are commonly the first line agents used to lower IOP in primary open angle glaucoma (POAG), and ocular hypertension (OHT)[3]. Although the precise mechanism of action of these drugs is not known, it is widely accepted that they act to increase aqueous outflow *via* two pathways; uveoscleral outflow increase by extracellular matrix remodeling[4], and trabecular outflow increase[5].

Meta-analyses have shown bimatoprost 0.03% to be equivalent in its IOP lowering efficacy when compared to Travaprost, or Latanoprost[6]. In recent years however, there has been a small, but growing body of Allergan sponsored literature[7-14], as well as independent studies[15-18] supporting the use of Bimatoprost in patients with OHT, normal tension glaucoma (NTG), and POAG who are deemed 'non-responders' on their current treatment. The largest independent study currently in the literature consisted of 46 patients with POAG or OHT and found no significant benefit from a switch to bimatoprost monotherapy[17].

We present an independent observational study of glaucoma and OHT patients with inadequate IOP control on current therapy that were switched to bimatoprost 0.03% monotherapy.

SUBJECTS AND METHODS

Consecutive 'non-responder' patients with IOPs above their target IOP on current treatment were prospectively identified by the lead glaucoma consultant between July 2011 and Jan 2015. These patients were switched from their current IOP lowering agent to bimatoprost 0.03% monotherapy only.

Data collection was carried out retrospectively, through case note review and clinical electronic data base searches. Information on patient demographics, diagnosis, pre-switch treatment, pre-switch IOP, IOP at all available post-switch clinics, as well as any adverse events were recorded.

To be included patients required a minimum of one follow up visit; documentation of pre- and post-switch IOP recordings, pre-switch therapy and documentation of any adverse events. Any participants with active ocular disease except glaucoma or receiving ocular treatment which may affect the IOP were excluded. The structure of the study is shown in Figure 1.

This study was approved by the institutional review board and followed the regulations of the Personal Information Protection and Electronic Documents Act and the Good Clinical Practice Guidelines of the Declaration of Helsinki.

Change in IOP post-pre switch was analyzed using a 2-sided Student's paired *t*-test at the 5% significance level for left eye and then for right eye (to assess consistency).

RESULTS

Adequate follow up data for analysis was obtained for a total of 59 consecutive patients following the clinical records search. Patient demographics are detailed in Table 1. The majority of patients had OHT as their working diagnosis, with over half on monotherapy with latanoprost before being switched to bimatoprost. The mean pre-switch IOP for all study patients regardless of diagnosis was 23.4 mm Hg.

Intraocular Pressure Effects of Bimatoprost Monotherapy at First Follow up The average time between switch to bimatoprost and the first follow up appointment was 104±44d. The mean reduction in IOP from pre-switch IOP at this time point for right eyes was: -4.24 mm Hg; 95%CI (-5.49 to -2.1); P<0.001 (n=58), and the mean reduction in IOP at this time point for left eyes was: -4.42 mm Hg; 95%CI (-5.4 to -2.45); P<0.001 (n=59).

At the first follow up visit, 16 (27%) of patients were deemed to have unsatisfactory IOP, and were either switched to other therapy, or listed for selective laser trabeculoplasty. The remaining 33 (55.9%) patients remained on bimatoprost monotherapy, as their IOP was deemed satisfactory.

Subgroup Analysis

Ocular hypertension patients switched to bimatoprost The mean reduction in IOP for OHT patients at first follow up appointment for right eyes (n=47) was -4.11 mm Hg; 95%CI (-5.62 to -2.59); P<0.001. The mean reduction in IOP for OHT patients at first follow up appointment for left eyes (n=48) was -4.52 mm Hg; 95%CI (-5.67 to -3.37); P<0.001.

Patients switched from latanoprost monotherapy to bimatoprost monotherapy For patients with any diagnosis, switched from latanoprost monotherapy to bimatoprost monotherapy (n=37), the mean reduction in IOP at first follow up appointment was -5.27 mm Hg; 95%CI (-6.87 to -3.67); P<0.001 for right eyes, and -5.27 mm Hg; 95%CI (-6.56 to -3.98); P<0.001 for left eyes.

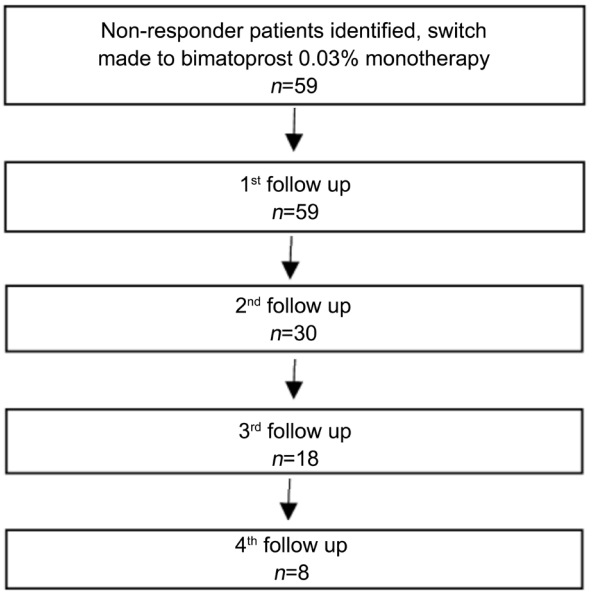

Figure 1 Study structure.

Table 1 Baseline characteristics of study patients *n* (%)

Characteristics	Values
Age (a)	
Mean (range)	64 (42-88)
Sex	
M	31 (53)
F	28 (47)
Race	
Caucasian	23 (39)
Black	24 (41)
Asian	12 (20)
Diagnosis	
OHT	43 (73)
POAG	6 (10)
NTG	4 (7)
PAC-OHT	5 (8)
PACG	1 (2)
IOP-lowering Rx	
Latanoprost	39 (66)
Travoprost	11 (19)
Travoprost/Timolol combination drop	3 (5)
Latanoprost+Dorzolamide/Timolol combination drop	2 (3)
Dorzolamide+Travoprost/Timolol combination drop	2 (3)
Brinzolamide+Bimatoprost/Timolol combination drop	1 (2)
Latanoprost/Timolol combination drop	1 (2)
Mean Pre-switch IOP (mm Hg)	
Right eye	23.2±4.4
Left eye	23.3±3.7

Intraocular Pressure Effects of Bimatoprost Monotherapy at Second Follow up Second follow up appointment data were available for 30 patients. The average time from switch to bimatoprost to second follow up appointment was 320±109d. The mean reduction in IOP from pre-switch IOP at this time point for right eyes was: -6.31 mm Hg; 95%CI (-8.58 to -4.04); P<0.001 (n=30), and the mean reduction in IOP at this time point for left eyes was: -7.95 mm Hg; 95%CI (-8.75 to -5.25); P<0.001 (n=30).

Table 2 Mean IOP at each follow-up visit

IOP	Pre-switch (*n*=59)	1st follow up (104±44d; *n*=59)	2nd follow up (320±109d; *n*=30)	3rd follow up (490±145d; *n*=18)	4th follow up (708±160d; *n*=8)
Mean IOP (mm Hg)	23.2	18.9	16.6	15.5	16.8
Range	14-34	10-27	10-37	8-20	13-24

The summary of mean IOP at each follow up visit can be found in Table 2.

Adverse Events Of all patients in the study, four adverse events were recorded; three patients reported increased conjunctival hyperaemia post-switch from Travaprost, and treatment was discontinued. Another patient reported frequent headaches associated with the switch to bimatoprost, but in this case, these side effects were deemed minor, and the patient continued on bimatoprost monotherapy.

DISCUSSION

We present the largest independent data set published to date following the progress of patients switched to bimatoprost 0.03% monotherapy due to inadequate response to previous therapy. Our findings suggest that for some patients with glaucoma who fail to respond adequately to mono, dual, and triple medical therapy, bimatoprost 0.03% appears to offer statistically, and clinically significant additional IOP reduction. For over 55.9% of non-responder patients a switch to bimatoprost monotherapy provided adequate IOP response at first follow up. As demonstrated by our long-term follow up data, the initial IOP reductions seen appear to be sustained, or even modestly improved by 10mo.

Our subgroups analyses show that there is a statistically significant reduction in IOP in OHT patients who are switched from any current treatment to bimatoprost monotherapy. This is important, as the aim with OHT patients should always be to achieve adequate control using medical monotherapy, and bimatoprost appears to allow this to occur in patients not responding to other therapy.

The second subgroup analysis compared latanoprost monotherapy to bimatoprost monotherapy in patients with a mixture of diagnoses; again, a statistically significant reduction in IOP was seen upon switch, suggesting that non-responders to latanoprost monotherapy should always have a trial switch to bimatoprost monotherapy before moving onto dual medical therapy, or selective laser trabeculoplasty.

To date, latanoprost remains the most commonly prescribed first line PGA in patients with OHT and POAG, and this is confirmed by our baseline patient demographics. Incidence of latanoprost nonresponse has been reported to be as high as 28.1% in the Japanese population[19]. A mixture of industry sponsored[9-10,13], and independent[15-16] short- and long-term studies have demonstrated an additional IOP lowering effect of bimatoprost when compared to latanoprost.

A number of reasons have been put forward for bimatoprost's additional IOP lowering efficacy when compared with other PGAs; PGAs such as latanoprost are pro-drugs that require de-esterification to yield an active drug. It has been speculated that poor de-esterification of latanoprost could explain the cohort of latanoprost non-responders[15]. PGAs act primarily *via* prostaglandin $F_{2\alpha}$ prostanoid receptors[20], whereas there is *in vitro,* and *ex vivo* evidence based on ahuman anterior segment model that bimatoprost acts on a distinct prostamide receptor in the trabecular meshwork, increasing outflow by approximately 40%[21].

Results from our small observational study support switching glaucoma patients with poor response to current treatment onto bimatoprost monotherapy before considering other adjuvant medical or more invasive therapy. The benefits of this approach include sustained IOP reduction on monotherapy, avoidance of increased cost and side effects of poly-pharmacy, and improved patient compliance due to simplicity of regime.

While the exact mechanisms by which Bimatoprost produces its additional IOP lowering effects on non-responders remains to be elucidated, there is a growing body of evidence that this prostamide appears to exhibit additional IOP lowering efficacy when compared to other PGAs.

Weaknesses of this study include a relatively small patient cohort of 59, and non-blindness of examiners to the patient's treatment. It is also noted that patient compliance to a single medication regimen may be better than to a multi-medication regimen.

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