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ORIGINAL RESEARCH

Brinzolamide/Brimonidine Fixed Combination: Simplifying Glaucoma Treatment Regimens

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ABSTRACT

Introduction: To simplify the medical treatment of glaucoma for patients on multiple drops by introducing brinzolamide/brimonidine tartrate fixed combination (BBFC) ophthalmic suspension 1%/0.2% (SIMBRINZA®; Alcon Laboratories, Inc., Fort Worth, TX, USA) to the drop regimen and to establish its efficacy. To demonstrate that fixed combination (FC) therapies are associated with improvements in treatment adherence and persistence with reduced exposure to preservative-related ocular surface problems.

Methods: Retrospective study: 76 patients were identified as taking BBFC following a switch in treatment regimen. Intraocular pressure (IOP) prior to and 2–17.5 months (average 5.4 months) after the introduction of BBFC was measured. The change in the average number of bottles used per eye was recorded. The rate of adverse effects (AEs) of BBFC was recorded. A two-tailed paired sample *t* test was used to compare IOP prior to and after the introduction of BBFC for each eye.

Results: Mean change in IOP after BBFC introduction BBFC: − 2.76 mmHg ($p < 0.0001$). BBFC intolerance: 13%. On average there was a 0.24 reduction in the number of bottles of IOP-lowering medication used per eye ($p < 0.0064$).

Conclusion: A switch to BBFC in the drop regimen is associated with a significant drop in IOP with reduced drop burden. Instead of a third IOP-lowering medication and bottle, a practitioner should consider using BBFC + prostaglandin analogue/FC drop for effective IOP control, reduced drop burden, reduced preservative load and increased likelihood of adherence. This study promotes the concept that any treatment should principally be assessed from the patients' perspective and quality of life.

Keywords: Brinzolamide–brimonidine fixed combination; Ophthalmology; Simbrinza

INTRODUCTION

Glaucoma remains the major cause of irreversible vision loss worldwide. In 2010 it was estimated to have caused over 8 million cases of blindness, and by 2020, 79 million people worldwide will have glaucoma [1]. Glaucoma is characterised in most cases by elevated intraocular pressure (IOP), with progressive

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optic neuropathy being the main diagnostic criterion, and corresponding visual field loss [2, 3]. Currently, IOP remains the only modifiable risk factor [4].

Many topical IOP-lowering agents with different mechanisms of action are available, e.g., β-blockers, prostaglandin analogues (PGAs), carbonic anhydrase inhibitors (CAIs), α2-adrenergic agonists and parasympathomimetic agents, e.g., pilocarpine [5–7]. These medications reduce IOP by decreasing aqueous production [5], increasing aqueous outflow [5–10] or both. In contrast, PGAs work by increasing uveoscleral and trabecular meshwork outflow facility [8, 11], and α2-adrenergic agonists reduce aqueous production and augment aqueous outflow through the uveoscleral pathway [12]. Recommended first-line treatment for glaucoma is using a single IOP-lowering medication [7–13]. However, one study showed that 40% of patients need polypharmacy to reach and maintain their target IOP, and an additional 9% needed more than three medications [14]. The use of multiple drops in a chronic and often asymptomatic condition can lead to lack of persistence and non-adherence, which may ultimately decrease drug effectiveness [15]. Studies demonstrate that approximately 50% of patients have been found not to be adherent to their medication over 75% of the time [16]. Medical treatment regimens requiring separate administration of several topical agents tend to have lower persistence [17, 18].

A method of improving adherence and persistence with glaucoma drops is to use fixed-combination medications, which allow instillation of two medications in a single solution. Fixed-combination medications reduce the number of medication bottles, reduce costs and simplify the dosing regimen, all of which may increase persistence [17–19] and adherence [17, 18]. A prospective trial has shown that switching from concomitant administration of multiple separate medications to a fixed-combination therapy increases patient adherence [20]. By using fixed combinations, tolerability may be improved over the use of multiple agents by reducing the cumulative exposure to irritating preservatives [21]; therefore, the reduced ocular symptoms associated with fixed-combination medications may improve overall adherence [22].

Whilst most combination preparations contain timolol, which is a beta-blocker, there are several potential side effects of beta-blockers that can limit patient adherence and persistence with these drugs; furthermore they are contraindicated in patients with certain medical conditions, such as asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, impotence, depression, confusion and memory loss [23].

Brinzolamide 1%-Brimonidine 0.2% fixed combination/BBFC (SIMBRINZA®; Alcon Laboratories Inc, Fort Worth, TX, USA) remains the only combination preparation for glaucoma and ocular hypertension that does not contain a beta-blocker. It is a sterile, preserved ophthalmic suspension formulation with a safety profile similar to its individual components. BBFC is approved for three-times-daily dosing in the USA and two-times-daily dosing in Europe.

We estimated that > 20% of our glaucoma clinic population was on three or more separate drop bottles at one time. Our aim was to study the effect of simplifying glaucoma treatment regimens in patients taking multiple bottles of glaucoma drops (> 2) by maximising the combination preparations prescribed, thereby reducing the numbers of bottles used with the aim of improving adherence and IOP control. BBFC was used in the new treatment regimens. The purpose of this study is to assess the efficacy of the new treatment regimen and tolerability of the same over at least a 2-month period following a switch or simplification of therapy.

METHODS

The study was exempt from requiring Institutional Review Board approval as it involved the assessment of retrospective and de-identified data. No ethical issues were identified.

Patient Identification

This study was conducted through retrospective case note review for patients attending the glaucoma clinics at the Eye Ear and Mouth Unit,

Maidstone and Tunbridge Wells NHS Trust, between October 2014 and July 2016. We collected and reviewed the medical records of patients whose topical intraocular pressure (IOP)-lowering regimen had been changed to include the use of BBFC.

As a result of the recent introduction of an electronic patient record at this NHS Trust, some patients' records were in the form of paper notes and others in the form of an electronic patient record.

Inclusion Criteria

Eligible patients were aged $\geq$ 18 years, diagnosed with open angle glaucoma (OAG), including pseudoexfoliation, pigmentary glaucoma or ocular hypertension. These patients had used three or more different bottles of drops before the switch to a regimen including BBFC.

Exclusion Criteria

Patients with unobtainable or incomplete records were excluded from further analysis. Patients identified as taking BBFC drops with a follow-up period $<$ 2 months were excluded from data analysis.

Data Collection and Analysis: Outcome Criteria

For eligible patients with complete records who met all the inclusion or exclusion criteria, the following outcome criteria were obtained for each eye:

1. The IOP {as measured by Goldmann applanation tonometry (GAT)] prior to and most recently after the introduction of BBFC.
2. The time interval between the change in regimen and the most recent IOP reading.
3. The total number of IOP-lowering drop bottles used prior and subsequent to the change in regimen.
4. The number of patients unable to tolerate or persist with BBFC as a result of side effects was recorded.

In this study, the treatment regimen was changed as follows. For example, if a patient was taking latanoprost + timolol + brimonidine + brinzolamide (4 separate bottles), the treatment regimen was rationalised to latanoprost/timolol 0.5% + BBFC, thereby halving the bottle burden, but maintaining four active components in just two bottles. This has now become possible with the introduction of BBFC to the glaucoma pharmacopoeia.

Statistical Methods

Statistical analysis was performed using a two-tailed paired sample *t* test to compare IOP prior to and after the introduction of BBFC for each eye involved.

A two-tailed paired sample *t* test was used to compare the average number of IOP-lowering drop bottles prior to and after the introduction of BBFC for each eye involved.

RESULTS

A total of 85 patients were identified in the glaucoma clinics at Maidstone and Tunbridge Wells NHS Trust as taking BBFC following a switch in treatment regimen using the identification method outlined above. Patients were 18–80 years of age.

Nine patients' notes were incomplete or unobtainable.

Ten of the 76 remaining patients were unable to continue with BBFC because of intolerance (dropout rate 13%). Sixty-six of 76 (87%) patients showed continued adherence at most recent follow-up.

Six of 76 additional patients were excluded from IOP analysis; they were identified as having started BBFC without side effects, but longer than 2 months' follow-up IOP results were unavailable.

After these exclusions, 85 eyes of 60 patients subsequently underwent data analysis.

For each eye, IOP measurements prior to and 2–17.5 months (mean follow-up 5.4 months) after the introduction of BBFC were recorded.

The change in IOP after the introduction of BBFC for each eye is summarised in Fig. 1. The mean change in IOP after the introduction of BBFC was $-$ 2.76 mmHg: two-tailed paired

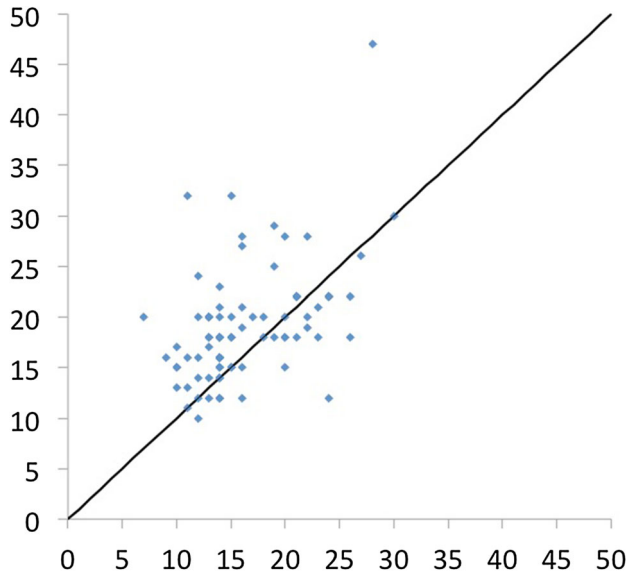

Fig. 1 Chart: IOP change (mmHg) pre (*y*-axis) and post (*x*-axis) addition of BBFC

sample *t* test; $p < 0.0001$ [95% CI for mean difference (1.59–3.94) intermediate values used in calculations: $t = 4.6861$; $df = 84$; standard error of difference = 0.590] (see Table 1).

On average there was a 0.24 reduction in the number of bottles of IOP-lowering medication used per eye after the introduction of BBFC to the drop regimen: two-tailed paired sample *t* test; $p < 0.0064$ [95% CI for mean difference (0.07–0.42) intermediate values used in calculations: $t = 2.7931$; $df = 84$; standard error of difference = 0.087].

DISCUSSION

In this study we found that reducing the bottle burden and therefore drop burden for patients with OAG and OHT not only maintained IOP control but also actually improved it. This could be related to improved compliance generally, since after the switch, a maximum of two bottles were used instead of three or more. In addition, most patients were able to tolerate the new treatment regimen that included BBFC.

The improved IOP control could also be due to the BBFC preparation. In a recent randomised clinical trial (RCT), addition of BBFC to PGA monotherapy realised a mean diurnal IOP at 6 weeks that was significantly lower compared with vehicle + PGA [(least square mean ± SE diurnal IOP was 17.1 ± 0.4 mmHg with BBFC + PGA (95% CI 16.3–17.8 mmHg) vs. 20.5 ± 0.4 mmHg with vehicle + AA (95% CI 19.8–21.2 mmHg)] [24]. The additional IOP reduction with BBFC (mean diurnal IOP reduction of 25% at week 6) was significantly greater than that with the addition of its individual components in a previous study [25].

In another study, fixed-combination brinzolamide/timolol or brimonidine/timolol added to travoprost reduced IOP from travoprost-treated baseline (20.1 mmHg) by 14 and 10%, respectively, after 3 months [26]. This suggests that BBFC added to a PGA may produce IOP reductions equivalent to those in previous studies of a three-agent treatment regimen including a β-blocker.

Table 1 IOP analysis results (see Fig. 1)

N	Pre-change IOP	Post-change IOP	Mean change in IOP	Mean change in number of bottles used per eye
85 eyes	Mean 19.0 (SD 5.69)	Mean 16.2 (SD 4.84)	Mean change in IOP − 2.76	Mean − 0.24 (0.24 reduction)

Our study was different in that it rationalised and streamlined medical treatment by reducing the drop burden (subtraction method) rather than adding drops. However, the above studies confirmed the efficacy of BBFC in combination with PGA monotherapy, which is in effect what our study patients were taking post-switch (either BBFC + PGA monotherapy or BBFC + PGA/timolol 0.5%). Our study confirmed that it is safe to rationalise treatment in this way since IOP control improved post-switch.

The mean reduction in IOP in our study (2.76 mmHg) was significant and beneficial in more than one way. For example, results of the Early Manifest Glaucoma Trial (EMGT) showed that the risk of progression decreased by 10% with each 1-mmHg decrease in mean IOP [27]. In our study, the mean IOP decrease from baseline was > 2.5 mmHg at an average of 5.4 months follow-up. In a meta-analysis of four studies ($n = 822$), mean IOP was a significant risk factor for progression [28]. Progression over 5 years occurred in $> 50\%$ with mean IOP > 20 mmHg compared with $\leq 18\%$ who had mean IOP of 13–17 mmHg [27]. In our study, mean IOP was decreased from 19 (SD 5.69) mmHg at baseline to 16 (SD 4.84) mmHg, i.e., on average < 17 mmHg, implying a reduced risk of disease progression in the long term.

The treatment regimen including BBFC was well tolerated. Thirteen per cent of patients discontinued BBFC because of adverse effects including allergic conjunctivitis, eyelid inflammation and oedema, ocular irritation and/or pain, iridocyclitis, hyperaemia, increased lacrimation and blurred vision. Patients who had been taking and tolerating brimonidine 0.2% also tolerated BBFC subsequently.

The limitations of this study are generally those of a retrospective study. As such there was no control group and no wash-out period established between drop changes. Also, the range of follow-up was wide at 2–17.5 months (mean 5.4). However, even at 2-month follow-up the pre-switch medications would have washed out giving a true indication of the post-switch IOP and tolerability. Follow-up for a longer period of time, e.g., a mean of 12 months, would help to establish the longer term efficacy and tolerability of BBFC. A future prospective randomised trial with a control group would be appropriate with diurnal IOP measurements in a masked fashion as well as quality of life assessments. Measurements of the ocular surface condition such as the ocular surface disease index, osmolarity, tear break-up time and conjunctival/corneal staining would also be valuable in such a study to examine the effect of a reduced benzalkonium chloride (BAK) load to the ocular surface [29].

CONCLUSIONS

In conclusion, rationalising topical treatment with the inclusion of the new combination preparation BBFC (subtraction method) was effective and safe. It led to a mean IOP reduction of > 2.5 mmHg at an average of 5 months' follow-up. The new treatment regimen was well tolerated in 87% of cases. There were no major adverse events beyond the known side effects of the individual components used in the treatment regimen. Therefore, clinicians are advised to try to minimise topical treatment at every opportunity and to avoid polypharmacy by prescribing more combination preparations including BBFC where possible.

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