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Original article

Assessing the safety and efficacy of switching to brinzolamide/timolol fixed combination as a replacement therapy in patients with uncontrolled intraocular pressure in Taiwan

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ABSTRACT

Purpose: The objective of this study is to assess the safety and efficacy of switching to brinzolamide 1% and timolol 0.5% fixed combination (BTFC) from prior pharmacotherapy in patients with open-angle glaucoma (OAG) or ocular hypertension (OH) in Taiwan.

Methods: This was a multicenter, open-labeled, interventional prospective study. The 8-week study involved patients with OAG or OH with uncontrolled intraocular pressure (IOP) and consisted of three study visits to the clinical site. Patients were instructed to discontinue their prior medications at the first visit, prior to starting the study medication. Enrolled patients were dosed with BTFC twice daily in both eyes for 8 weeks. IOP measurements and safety evaluations were conducted at both Week 4 and Week 8.

Results: A total of 74 patients were enrolled. The overall mean IOP reductions from baseline after Week 8 of BTFC was 3.45 mmHg (15.42%); when subgrouped by prior medication class (β-blockers vs. non-β-blockers), the reduction in mean IOP after transitioning to BTFC at Week 8 was as follows: subgroup β-blockers were 3.23 mmHg (14.9 %) and non-β-blockers were 3.58 mmHg (15.25%). All mean IOP changes from baseline were statistically significant ($p < 0.001$). Of the 69 patients (per protocol population) who were switched to BTFC regardless of prior therapy, 37 (53.6%) patients at Week 4 and 38 (55.1%) patients at Week 8 had IOP $\leq$ 18 mmHg. No treatment-related serious adverse events were reported in this study.

Conclusion: The results of this study demonstrated the potential benefit of using BTFC as a replacement therapy in order to ensure adequate IOP control. BTFC administered twice daily was safe and effective in patients with uncontrolled IOP in Taiwan.

1. Introduction

Glaucoma is a progressive optic neuropathy characterized by degeneration of retinal ganglion cells, cupping of the optic nerve heads, and visual field defects often related to elevated intraocular pressure (IOP). The disease affects 70 million people worldwide and is the second most common cause of blindness. It is estimated that by the year 2020, this number will rise to around 79.6 million.[1]

Topical IOP-lowering medications remain the primary treatment option for a majority of glaucoma patients. In many glaucoma patients, treatment with a single therapeutic agent (monotherapy) is often ineffective in providing long-term control of IOP, and these patients eventually require the addition of another IOP-lowering medication adjunctive to their current regimen to achieve adequate IOP control. A significant number of patients with ocular hypertension (OH) or open-angle glaucoma (OAG) will require more than one medication to achieve adequate control of IOP. Nearly 40% of patients in the Ocular Hypertension Treatment Study required two or more medications to achieve a 20% reduction in IOP.[2] Adjunctive therapy involving multiple medication bottles adds complexity to the treatment regimen when compared with

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single-agent monotherapy and may introduce a washout effect if coadministered drops are not spaced adequately in time.[3] The requirement of more than one therapy to control IOP is inconvenient to the patient and often leads to noncompliance. Fixed combinations (FCs) of commonly coadministered IOP-lowering agents have been developed to minimize these issues, offering simplification of the dosing regimen and elimination of the washout effect.[4,5]

Topical carbonic anhydrase inhibitors (e.g., AZOPT®—brinzolamide 1%) and beta-adrenergic blocking agents (e.g., timolol 0.5%) have been used adjunctively to treat elevated IOP in patients with glaucoma and OH, who cannot achieve target IOP on a single therapeutic regimen. Clearly, the ability to combine two medications in a single formulation should enhance patient compliance, while maintaining better IOP control than a single therapeutic regimen.[6]

Brinzolamide 1% and timolol 0.5% fixed combination (BTFC) (AZARGA®, Alcon Laboratories, Inc., Fort Worth, TX, USA) was approved for the reduction of elevated IOP in patients with OAG or OH for whom monotherapy provides insufficient IOP reduction. Although several clinical studies have been conducted to assess the safety and efficacy of BTFC, more studies are needed to determine its IOP-lowering effect in patients who cannot achieve target IOP while on a single or multiple therapeutic regimen.[6] The objective of this open-label, 8-week study was to assess the safety and efficacy of switching to BTFC from prior pharmacotherapy in patients with OAG or OH in Taiwan.

2. Methods

2.1. Patients

This was an open-label, 8-week, multicenter study in patients with OAG or OH. Patients were recruited from the outpatient clinic in the Department of Ophthalmology at the Veterans General Hospital (Taipei, Taichung, and Kaoshiung), Taiwan, from July 2011 to March 2012. Eligible patients were 20 years of age or older with bilateral OAG or OH. Eligible patients had to have a baseline IOP of between 19 and 35 mmHg while being on either a single therapeutic agent or two separate ocular hypotensive agents, and they required a change from their current hypotensive medications to BTFC to achieve target IOP. They required to have a best-corrected visual acuity of 6/60 (1.0 LogMAR) or better in each eye. Patients were excluded from this study if they had any of following conditions: a closed or barely open anterior chamber angle; a history of ocular surgery or ocular inflammation within the past 3 months; any history of ocular filtering surgery, severe trauma, or argon laser trabeculoplasty; current use of contact lenses or oral ocular hypotensive agents; known hypersensitivity to any components of the study medications; participation in another clinical study within 1 month prior to the screening visit; progressive retinal or optic nerve disease from any cause; a history of, or at risk for, uveitis or cystoid macular edema; a history of ocular herpes simplex; use of systemic medications known to affect IOP, which have not been on a stable course for 7 days prior to screening visit/baseline visit, or an anticipated change in the dosage during the course of the study; bronchial asthma or a history of bronchial asthma, bronchial hyperreactivity, or severe chronic obstructive pulmonary disease that would preclude the safe administration of a topical beta-blocker; a history of (or current) severe, unstable, or uncontrolled cardiovascular, hepatic, or renal disease that would preclude the safe administration of a topical beta-blocker; hyperchloremic acidosis; any clinically significant, serious, or severe medical or psychiatric condition; women who were pregnant or lactating; participation in any other investigational study within 30 days prior to the screening visit; best-corrected visual acuity worse than 6/60 in either eye; and any abnormality preventing reliable applanation tonometry in either eye. Approval from the appropriate regulatory authorities and ethics committees was obtained for each center, and all patients provided signed informed consent prior to study entry. The investigation was conducted according to the guidelines of the Declaration of Helsinki.

2.2. Protocol

Evaluations included medical and ocular history, best-corrected Snellen visual acuity, refraction, slit-lamp examination, ophthalmoscopy through dilated pupils, visual field testing with an automated perimetry threshold program, and IOP measurement by Goldmann applanation tonometry. Previously treated patients were instructed to discontinue their prior medications, without a washout period at baseline prior to the switch period. All patients were given one drop of BTFC twice daily in both eyes. Follow-up visits were conducted after 4 and 8 weeks of treatment. We took bilateral IOP measurements for each patient at the same time of the scheduled visits to avoid diurnal variations. Study procedures that were repeated at each follow-up visit included review of symptomatology, and direct observation and collection of reports of adverse events (AEs). AEs were summarized by system organ class (SOC), preferred term, severity, and relationship to the study medication using number and percentage. Any AE that occurred during the study was rated and recorded.

2.3. Statistical analysis

Efficacy was evaluated by calculating the mean IOP change from baseline to each follow-up visit. Only patients with no missing IOP measurements for all three visits were eligible for efficacy evaluation. Analyses were performed for both intent-to-treat (ITT) and per protocol (PP) data sets, with the PP data set providing the primary inference. SAS for Windows version 6.12 (SAS Institute, Inc., Cary, NC, USA) was used for the efficacy evaluation.

3. Results

3.1. Patient demography

This study was conducted from July 2011 to March 2012. Of the 74 enrolled patients, 69 were included in the PP analysis. Table 1 presents the number of safety population, ITT patients, and

Table 1
Baseline characteristics of patients.

Demographics	Number (%)
Safety population	74 (100)
Gender	
Male	32 (43.2)
Female	42 (56.8)
Diagnosis	
OAG	59 (80)
Ocular hypertension	15 (20)
ITT population	73 (98.6)
PP population	69 (93.5)
Discontinued from the study	5 (6.76)
Reasons for discontinuation	
Uncontrolled IOP	0 (0.0)
Personal reasons	1 (20.00)
Poor compliance	1 (20.00)
Adverse events	3 (60.00)
Lost to follow-up	0 (0.0)

IOP = intraocular pressure; ITT = intent to treatment; OAG = open-angle glaucoma; PP = per protocol.

patients who completed the 8-week follow-up visit and who were eligible for PP analysis. The median age of these patients was 60 years and 43% were male. Enrolled patients were diagnosed with either primary OAG (80%) or OH (20%). Of the five discontinued patients, three were discontinued from the study due to AEs (Table 1).

3.2. Evaluation of efficacy

The mean IOP at baseline for these patients was 22.0 ± 2.58 mmHg. Following a switch to BTFC, patients had a mean IOP of 18.54 ± 2.86 mmHg at Week 4 and 18.55 ± 3.08 mmHg at Week 8—a mean IOP decrease of 3.46 mmHg (15.29%) and 3.45 mmHg (15.42%) from baseline ($p < 0.0001$) at Week 4 and Week 8 visit, respectively (Table 2). Among the patients who were switched to BTFC regardless of prior therapy, 37 (53.6%) at Week 4 and 38 (55.1%) at Week 8 had IOP ≤18 mmHg.

3.3. Prior beta-blocker therapy

The mean IOP in this group was reduced from 21.77 ± 2.07 mmHg at baseline to 18.38 ± 2.70 mmHg at Week 4 and 18.54 ± 2.98 mmHg at Week 8. The mean change in IOP was −3.38 mmHg (−15.49%) at Week 4 and −3.23 mmHg (−14.90%) at Week 8. The observed mean change was statistically significant at both the visits ($p < 0.0001$). Among the patients who were switched from a beta-blocker to the BTFC, 15 (57.7%) patients at Week 4 and 15 (57.7%) patients at Week 8 had IOP ≤18 mmHg.

3.4. Prior non-beta-blocker therapy

For patients who switched from any medication class other than beta-blockers to BTFC, the mean IOP was reduced from 22.14 ± 2.87 mmHg at baseline to 18.63 ± 2.98 mmHg at Week 4 and 18.56 ± 3.17 mmHg at Week 8. The mean change in IOP was −3.51 mmHg (−15.16%) at Week 4 and −3.58 mmHg (−15.25%) at Week 8. The observed mean change was statistically significant at both the visits ($p < 0.0001$). The non-beta-blocker group included patients on a prior treatment regimen that included brinzolamide 1% ($N = 7$), dorzolamide 2% ($N = 8$), FC of dorzolamide 2%/timolol 0.5% ($N = 1$), prostaglandin analogs (bimatoprost 0.03%, latanoprost 0.005%, or travoprost 0.004%) ($N = 11$), FC of prostaglandin analogues (PGA)/timolol 0.5% ($N = 3$), FC of brimonidine 0.2%/timolol 0.5% ($N = 2$), brinzolamide 1% + timolol 0.5% ($N = 4$), dorzolamide 2% + timolol 0.5% ($N = 4$), or PGA + timolol 0.5% ($N = 3$).

3.5. Safety evaluation

All 74 enrolled patients were evaluable for safety (Table 3). There were total 18 (24.32%) patients who reported AEs. Majority of the AEs belonged to the SOC "eye disorders" ($n = 11$; 14.86%). All the AEs were considered as either mild or moderate in intensity. A total of 13 (72.22%) patients experience at least one of the following AEs that were deemed related to the study drug: palpitations, dry eye, eye discharge, foreign body sensation in eyes, ocular hyperemia, blurred vision, and nausea. Three patients were discontinued from the treatment due to dry eye, blurred vision, or foreign body sensation in eyes. There were no deaths or serious AEs in the study.

4. Discussion

This open-label, multicenter, interventional study was aimed at assessing the safety and efficacy of switching to AZARGA (BTFC), as a replacement therapy in patients with uncontrolled IOP in Taiwan. Of the total 74 patients enrolled in the study, 69 completed the study. Of the five discontinued patients, three were discontinued from the study due to AEs related to the study drug. Overall, the study drug was well tolerated. The most common AE was blurred vision. All the AEs were mild to moderate in intensity. Fifteen patients had mild and three had moderate AEs. All the three patients who had moderate AEs belonged to the SOC "eye disorders"; 2twopatients had moderately blurred vision and one had foreign body sensation in eyes, moderate in intensity. No serious AEs or deaths were reported in the study. The most commonly reported AEs belonged to the SOC "eye disorders" ($n = 11$; 14.86%).

In Manni's study,[7,8] the most common adverse ocular effects of the BTFC and FC of dorzolamide/timolol were blurred vision, eye pain, and irritation. Blurred vision occurred more commonly in the brinzolamide/timolol group than in the dorzolamide/timolol group (3.6% vs. 0.5%), which was thought to be due to the suspension formulation. Ocular pain (6.5% compared with 2.7%) and irritation (10.6% compared with 2.7%) occurred more commonly in the dorzolamide/timolol group than in the brinzolamide/timolol group. Other ocular reactions included foreign body sensation and hyperemia. Overall, the dorzolamide/timolol group had a significantly greater number of reported side effects (23% vs. 14.1%),[8,9] demonstrating that the BTFC might be better tolerated.

Table 2
Efficacy of brinzolamide/timolol fixed combination treatment—per protocol and subgroup analysis.

	Baseline	Week 4	Week 8
Per protocol population (N = 69)			
Mean IOP ± SD (mmHg)	22.00 ± 2.58	18.54 ± 2.86	18.55 ± 3.08
Mean IOP Change (%)		−3.46 (−15.29%)	−3.45 (−15.42%)
p		<0.0001	<0.0001
Number and percentage of patients having IOP <18 mmHg, *N* (%)		37 (53.6)	38 (55.1)
Subgroup of prior medication			
β-Blockers (*N* = 26)			
Mean IOP ± SD (mmHg)	21.77 ± 2.07	18.38 ± 2.70	18.54 ± 2.98
Mean IOP Change (%)		−3.38 (−15.49%)	−3.23 (−14.9%)
p		<0.0001	<0.0001
Number and percentage of patients having IOP <18mmHg, *N* (%)		15 (57.7)	15 (57.7)
Any class (non-β-blockers) (*N* = 43)			
Mean IOP ± SD (mmHg)	22.14 ± 2.87	18.63 ± 2.98	18.56 ± 3.17
Mean IOP Change (%)		−3.51 (−15.16%)	−3.58 (−15.25%)
p		<0.0001	<0.0001
Number and percentage of patients having IOP <18 mmHg, N (%)		22 (51.2)	23 (53.5)

IOP = intraocular pressure; SD = standard deviation.

Table 3
Ocular and systemic adverse events—safety population ($N = 74$).

	No (%)
Number of patients with Adverse Events	18 (24.32)
Mild	15 (83.33)
Moderate	3 (16.67)
Serious	0 (0)
Ocular adverse event	11 (14.86)
Dry eye	1 (1.35)
Eye discharge	1 (1.35)
Foreign body sensation in eyes	2 (2.70)
Ocular hyperemia	9 (12.2)
Vision blurred	5 (6.76)
Systemic adverse event	9 (12.16)
Palpitations	1 (1.35)
Nausea	1 (1.35)
Abdominal pain upper	1 (1.35)
Insomnia	3 (4.05)
Pruritus	3 (4.05)

Among the patients who were switched from prior beta-blocker monotherapy to study drug, a significant reduction in mean IOP was observed at subsequent visits from baseline; the mean change in IOP was −3.38 mmHg at Week 4 and −3.23 mmHg at Week 8 ($p = 0.0002$ at Week 4 and $p = 0.0009$ at Week 8). When switched to BTFC, more than half of the enrolled patients had an IOP ≤18 mmHg at the subsequent study visits (53.6%, 37/69 at Week 4; 55.1%, 38/69 at Week 8). The subgroup analysis did not show any relevant difference in the mean change in IOP between two subgroups (patients switched to BTFC from either beta-blockers or non-beta-blockers) at Weeks 4 and 8. Similarly, no discernible difference was observed in the percentage of patients having IOP ≤18 mmHg at the subsequent study visits between the two subgroups: 51.2%, 22/43 at Week 4; 53.5%, 23/43 at Week 8 in the non-beta-blocker group and 57.7%, 15/26 at Week 4; 57.7%, 15/26 at Week 8 in beta-blocker group. The non-beta-blocker group included patients on a prior treatment regimen that included an α-2 agonist, a carbonic anhydrase inhibitor, a prostaglandin analog, or other combinations (fixed or unfixed). Due to the small sample size of this subgroup, these non-beta-blocker classes were not analyzed individually.

Various studies have evaluated the efficacy of the BTFC therapy.[7] In a double-masked, randomized, parallel-group, multicenter study with a 6-month follow-up, a BTFC was compared with either brinzolamide 1% or timolol 0.5%. The BTFC reduced IOP by approximately 8.0 mmHg from baseline (29.6%). For timolol 0.5% (dosed twice daily) and brinzolamide 1% (dosed twice daily), the IOP reduction from baseline ranged from 5.7 to 6.9 mmHg (22.8–26.1%) and from 5.1 to 5.6 mmHg (18.9–20.8%), respectively. The BTFC was most effective at lowering IOP at all visits and time points. These results showed that the FC was superior in IOP-lowering efficacy compared with each of its individual components.[10] Results of our study were similar to those of the previously published BTFC study, assessing efficacy where patients switched from a prior therapy.[11]

Limitations of this study include the following: lack of a control group due to its open-label design, small sample size for the subgroup analysis, lack of monitoring of the patient's compliance prior to enrolling in the study and during the course of the study; only one time point of the IOP measurement taken at baseline, Week 4, and Week 8 visits; and lack of a washout period prior to study initiation that could introduce bias due to potential side effects of previous glaucoma medications.

To conclude, the results of this study showed that BTFC may be a safe and efficacious treatment alternative when Taiwanese patients with either OAG or OH are unable to achieve target IOP while on their current pharmacotherapy. The results were comparable to those of the previously conducted studies.

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