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12-week study comparing the fixed combination of brimonidine and timolol with concomitant use of the individual components in patients with glaucoma and ocular hypertension

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PURPOSE. *To evaluate the efficacy and safety of fixed-combination brimonidine tartrate 0.2%/timolol 0.5% ophthalmic solution dosed BID and demonstrate non-inferiority to concomitant use of brimonidine tartrate 0.2% BID and timolol 0.5% BID in glaucoma and ocular hypertension patients with intraocular pressure (IOP) uncontrolled on monotherapy.*
METHODS. *Randomized, multicenter, double-masked, parallel-group study involving 371 patients with inadequate IOP control (IOP from 22 to 34 mmHg) after ≥3 weeks of run-in on any monotherapy. Patients were treated with fixed-combination brimonidine/timolol BID (fixed-combination group, n=188) or concomitant brimonidine BID and timolol BID (concomitant group, n=183). IOP was assessed pre-dose and 2 hours after morning dosing at weeks 2, 6, and 12.*
RESULTS. *A total of 355 patients (96%) completed the study. Patient demographics, run-in monotherapy, and baseline mean IOP on monotherapy were comparable between treatment groups. During follow-up, the mean reduction from baseline IOP was significant ($p<0.001$) at all time points and ranged from 4.4 to 5.3 mmHg in each group. Brimonidine/timolol fixed combination was as effective as concomitant therapy with respect to mean IOP and mean change from baseline IOP at all time points and visits. Between-group differences were ≤0.35 mmHg for mean IOP and ≤0.30 mmHg for mean change from baseline IOP; none were significant. No unexpected side effects were associated with the fixed combination. Both treatments were well tolerated with no difference in adverse events between groups.*
CONCLUSIONS. *Brimonidine/timolol fixed-combination therapy is as safe and effective as concomitant treatment with the individual components. Its simplified dosing regimen has the potential to improve compliance. (Eur J Ophthalmol 2005; 15: 581-90)*

KEY WORDS. *Brimonidine, Fixed combination, Glaucoma, Intraocular pressure, Timolol*

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INTRODUCTION

Recent randomized controlled trials have proven that treatment to reduce intraocular pressure (IOP) is important to limit the progression of glaucoma and slow the loss of visual function (1-3). In the Early Manifest Glaucoma Trial (2) and the Ocular Hypertension Treatment Study

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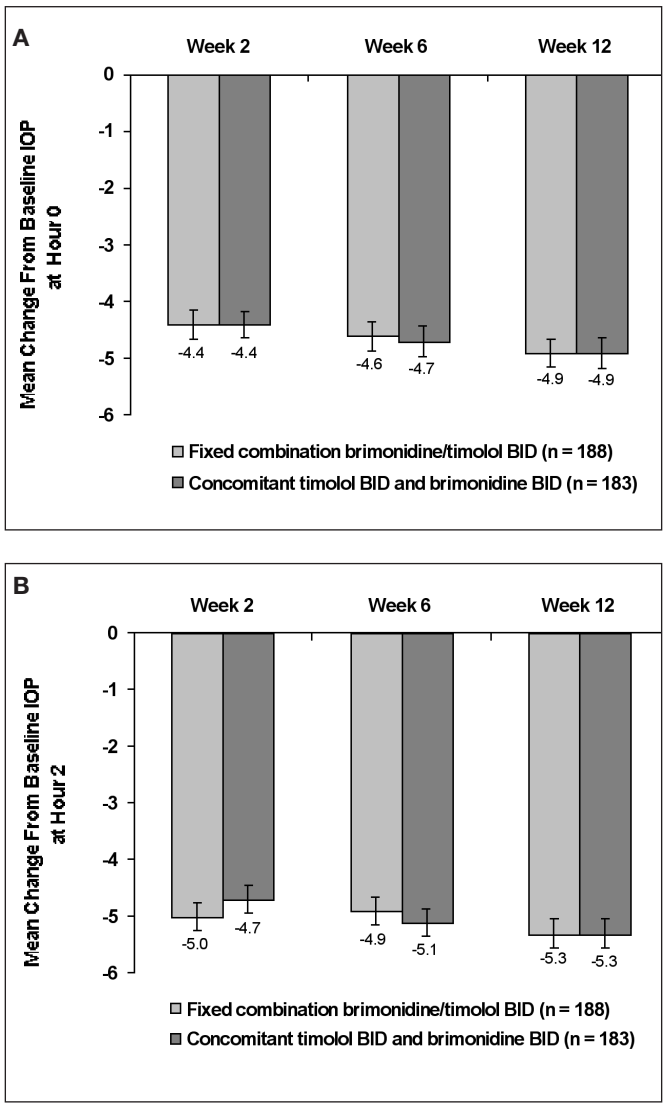

Fig. 1 - *Mean change from baseline intraocular pressure (IOP) on run-in monotherapy at all follow-up measurements for the intent-to-treat population at* **(A)** *hour 0 and* **(B)** *hour 2. Differences between groups (combination – concomitant) ranged from -0.30 to 0.14 mmHg, and none were statistically significant (p≥0.345). Results were similar for the per-protocol population. Error bars represent SEM.*

(4), each 1 mmHg of IOP lowering corresponded to approximately a 10% reduced risk of progression. In the Advanced Glaucoma Intervention Study, progression was minimized in patients with consistently low IOP (5). These studies have shown that lower target pressures provide the best protection of the visual field in glaucoma. The preferred initial treatment is usually monotherapy with an IOP-lowering medication. Many patients, however, do not achieve low target pressures with a single medication. When more than one IOP-lowering medication is needed, adjunctive medication with a complementary mechanism of action is most likely to provide additive IOP lowering.

The alpha-adrenergic receptor agonist brimonidine is a well established IOP-lowering medication that has a dual mechanism of action.

It lowers IOP both by increasing uveoscleral outflow and by reducing aqueous production (6). Brimonidine has been shown to effectively reduce IOP when used concurrently with multiple medications including beta-blockers (7-10). In Europe, brimonidine is licensed for use both as monotherapy and as adjunctive therapy with a beta-blocker.

The nonselective beta-adrenergic antagonist timolol is a commonly used topical beta-blocker. Timolol reduces IOP by inhibiting aqueous production (11). In clinical studies only the prostaglandin-related class of IOP-lowering medications has provided larger IOP reductions than timolol (12). Timolol drops are usually comfortable and well tolerated.

Compliance with therapy is a major issue affecting treatment success, particularly in chronic diseases that have no symptoms in early stages, such as glaucoma. Use of multiple medications and complicated regimens is inconvenient for patients and associated with reduced compliance (13, 14). Adjunctive therapy with a topical ophthalmic medication may be particularly inconvenient, because patients must wait between instillation of separate drops to avoid washout. A fixed combination that contains two medications in a single bottle is more convenient to use and may improve compliance (15). Use of a fixed combination is also likely to decrease the daily exposure of the ocular surface to preservative that is potentially damaging (16, 17).

A new fixed combination of brimonidine 0.2% and timolol 0.5% has been developed to allow treatment with both medications with a single drop. The new formulation combines the active medications at their maximally effective concentration in a vehicle preserved with benzalkonium chloride (BAK). Purite, the nontoxic preservative used in the brimonidine-Purite 0.15% formulation, was not used because it is incompatible with timolol.

The objectives of this study were to evaluate the efficacy and safety of treatment with the brimonidine/timolol fixed combination compared with concomitant use of brimonidine and timolol and to demonstrate non-inferiority of the fixed combination to concomitant use of the component medications.

METHODS

Study design

This was a 12-week, multicenter, double-masked, parallel-group study comparing the fixed combination of brimonidine tartrate 0.2%/timolol 0.5% dosed twice daily with concurrent twice-daily administration of brimonidine tartrate 0.2% and timolol 0.5% in patients with glaucoma or ocular hypertension (OHT) who had elevated IOP on monotherapy. The study was carried out at 22 centers in 7 countries and was conducted in compliance with the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP) and the Declaration of Helsinki, 1996. All patients provided written informed consent prior to participation in the study.

Patients

The study enrolled glaucoma and OHT patients with elevated IOP in at least one eye while on monotherapy. Eligible patients were at least 18 years old; had a diagnosis consistent with any of the following: chronic open-angle glaucoma, chronic angle-closure glaucoma with a patent iridotomy, pseudoexfoliative glaucoma, pigmentary glaucoma, or OHT; had IOP ≥22 mmHg and ≤34 mmHg in at least one eye at baseline (hour 0) after a minimum of 3 weeks on monotherapy; required bilateral treatment to lower IOP; and had best-corrected visual acuity of 20/100 or better in each eye. Women of child-bearing potential were required to have a negative urine pregnancy test. Primary exclusion criteria included uncontrolled systemic disease, previous allergy or sensitivity to any component of any study medication, contraindication to brimonidine or timolol treatment, anticipated alteration of existing systemic chronic therapy that could have a substantial effect on IOP, active ocular disease other than glaucoma or OHT (mild blepharitis, cataract, age-related macular degeneration, and diabetic retinopathy were allowed at the discretion of the investigator), need for chronic use of other ocular medications during the study, functionally significant visual field loss within the last year, corneal abnormalities that precluded accurate IOP measurements, and any condition or situation that, in the investigator's opinion, may have put the patient at significant risk, confounded the study results, or interfered significantly with the patient's participation in the study.

At the screening visit, patients naïve to IOP-lowering therapy began treatment with a single IOP-lowering medication chosen by the investigator. Patients on monotherapy with any IOP-lowering medication continued on this therapy. Patients on multiple-drug therapy discontinued all but one medication chosen by the investigator. Patients on a combination product discontinued the product and began monotherapy chosen by the investigator. Washout of any previous IOP-lowering medication and run-in with monotherapy were performed concurrently. If

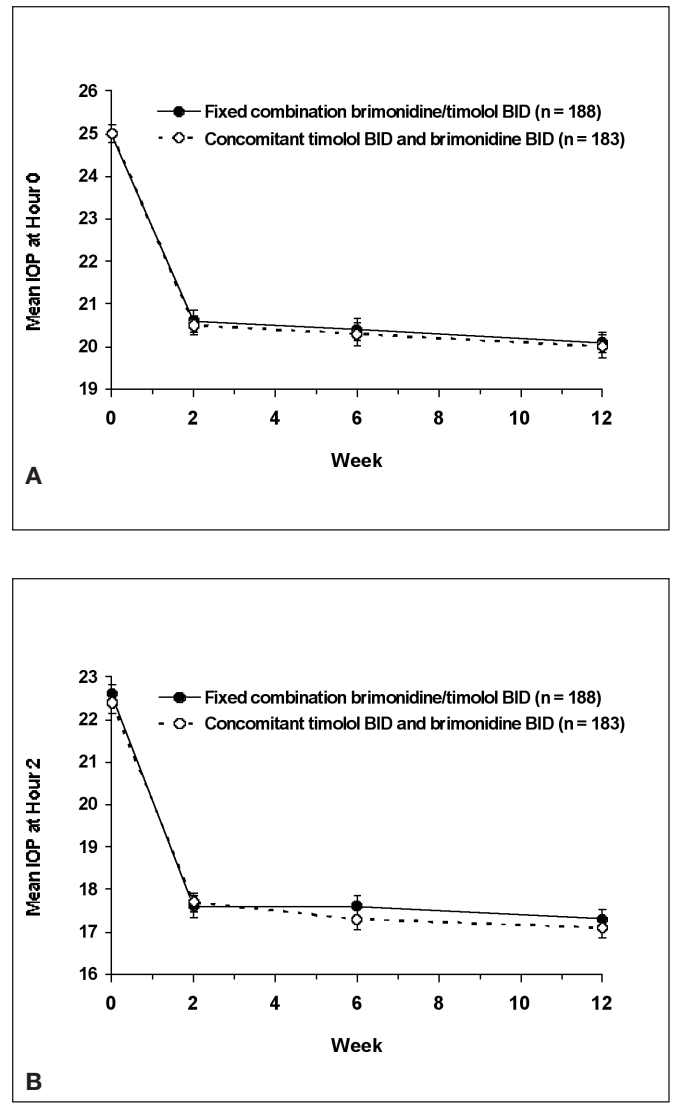

Fig. 2 - *Mean intraocular pressure (IOP) for the intent-to-treat population at* **(A)** *hour 0 and* **(B)** *hour 2. Differences between groups (combination – concomitant) ranged from -0.05 to 0.35 mmHg, and none were statistically significant (p≥0.274). Similar results were found for the per-protocol population. Error bars represent SEM.*

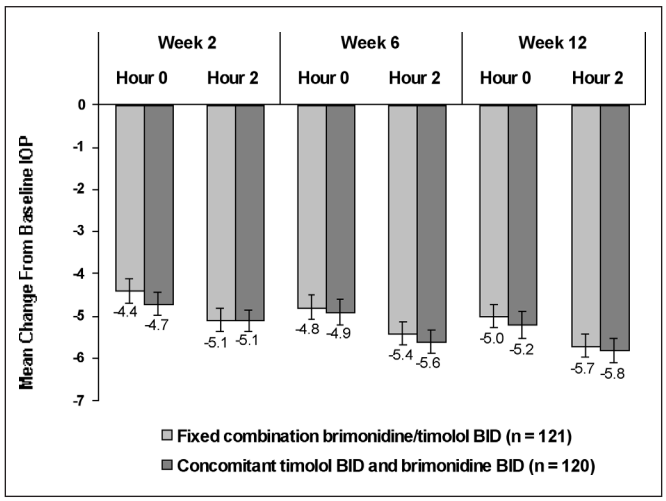

Fig. 3 - *Mean change from baseline intraocular pressure (IOP) on run-in monotherapy for the subgroup of patients whose run-in medication was a beta-blocker. Analysis of results for the intent-to-treat population is shown. Baseline mean IOP was comparable between treatments (at hour 0: combination, 25.0 mmHg; concomitant, 24.9 mmHg, p=0.985; at hour 2: combination, 22.7 mmHg; concomitant, 22.6 mmHg, p=0.802). Differences between treatments (combination – concomitant) ranged from 0.11 to 0.33 mmHg; none were statistically significant (p≥0.374). Results were similar for the per-protocol population. Error bars represent SEM.*

topical beta-blockers, prostaglandins, or combination products were discontinued, the washout/run-in period was at least 4 weeks. If any other IOP-lowering medication was discontinued, the washout/run-in period was at least 3 weeks. All patients were run-in on monotherapy for at least 3 weeks. Patients were then seen at the baseline study visit and IOP was measured at hour 0 (9:30 am ± 1 hr). Patients with IOP ≥22 mmHg and ≤34 mmHg in one or both eyes at that time were eligible for study entry.

Intervention and outcome measures

Following measurement of IOP at hour 0 at baseline, patients were randomly assigned to one of the two treatment groups in the ratio 1:1, following stratification according to site and prior run-in monotherapy (beta-blocker, carbonic anhydrase inhibitor [CAI], prostaglandin, or other). The fixed-combination treatment group received brimonidine tartrate 0.2%/timolol 0.5% ophthalmic solution BID and brimonidine/timolol vehicle BID. The concomitant treatment group received brimonidine tartrate 0.2% ophthalmic solution BID and timolol 0.5% ophthalmic solution BID. All formulations used in the study were preserved with BAK. Both patients and investigators were masked to the treatment. Study medications were supplied in color-coded, identically appearing bottles. The concomitant group was given timolol in a blue-labeled bottle and brimonidine in a yellow-labeled bottle. The combination group was given fixed-combination brimonidine/timolol in a blue-labeled bottle and vehicle control in a yellow-labeled bottle. Patients were instructed to instill one drop of each medication in each eye in the morning (between 8:30 and 10:30 am) and evening (between 8:30 and 10:30 pm), using the medication in the blue-labeled bottle first and waiting 15 minutes before instilling the drop from the yellow bottle. Follow-up study visits were scheduled at weeks 2, 6, and 12.

Efficacy was evaluated using IOP measurements taken using a Goldmann applanation tonometer affixed to a slit lamp at hour 0 (trough effect) and hour 2 (peak effect) at baseline and weeks 2, 6, and 12. At each time point, IOP was measured twice for each eye, and if the measurements differed by more than 2 mmHg, a third measurement was taken. IOP was recorded as the mean of two measurements or the median of three measurements.

Patients were instructed not to instill medications on the morning of study visits. Medications were instilled at the office immediately following the hour 0 IOP measurement. The last dose of the run-in monotherapy was administered at baseline (Day 0), and study treatment was commenced in the evening of Day 0. The last instillation of study treatment was at week 12 after the hour 0 IOP measurement.

The primary safety outcome measure was the incidence of adverse events. Other safety parameters included pulse rate, blood pressure, biomicroscopy, ophthalmoscopy, cup:disc ratio, visual acuity, visual fields, and laboratory tests (hematology, chemistry, and urinalysis).

Data analysis

Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test. Ordinal variables were analyzed using the Wilcoxon rank-sum test. A two-way analysis of variance (ANOVA) with factors for treat-

ment and investigator, together with the 95% confidence interval (CI) on the between-group difference, was used to compare changes in IOP between groups. Within-group changes in IOP from baseline were evaluated using the paired t-test.

For patients with a single eye eligible for study, IOP in that eye was used in all analyses. For patients with both eyes eligible for study, efficacy analyses used IOP in the worse eye (eye with higher IOP at baseline, hour 0, or the right eye if the eyes had equivalent IOP).

The primary efficacy measure was the mean change from baseline IOP at hour 0, week 12, based upon the intent-to-treat (ITT) study population consisting of all randomized patients. Missing values were replaced by the last observation carried forward (LOCF) to the corresponding time point (ie, hour 0 or hour 2). IOP was analyzed using a strategy of combined tests of non-inferiority and superiority. The fixed combination was determined to be non-inferior to concomitant brimonidine and timolol when the upper limit of the 95% CI on the difference in mean change from baseline IOP (fixed combination minus concomitant) was <1.5 mmHg. The CI was constructed using the error term from the two-way ANOVA. Secondary efficacy measures included mean change from baseline IOP at other follow-up time points, mean IOP, mean change from baseline IOP, and mean IOP for the per-protocol (PP) patient population (all patients with no major protocol violations; data collected after minor protocol violations affecting IOP were excluded), within-group change from baseline IOP for both the ITT and PP patient populations, and the percentage of patients achieving target IOP levels from 12 to 22 mmHg (in steps of 1 mmHg) in the ITT population with LOCF for missing data. Subgroup analyses of efficacy measures for patients who were run-in on beta-blockers were also included in the statistical plan for the study. Additional post hoc analyses evaluated the percentage of patients achieving an average IOP at all time points in categories of <14 mmHg, 14 to 17.5 mmHg, and >17.5 mmHg in the ITT with LOCF population (similar to the analysis performed in the seventh report of the Advanced Glaucoma Intervention Study (1) and the percentage of patients who reached and maintained a ≥20% decrease from baseline IOP at all follow-up measurements in the ITT with LOCF population.

TABLE I - PATIENT CHARACTERISTICS

	Combination therapy (n=188)	Concomitant therapy therapy (n=183)	Between-group p value
Age, yr, mean ± SD	58.5±12.8	59.6±12.2	0.386
Sex, n (%)			0.134
Male	77 (41.0)	61 (33.3)	
Female	111 (59.0)	122 (66.7)	
Race, n (%)			0.748
Black	4 (2.1)	5 (2.7)	
Non-black	184 (97.9)	178 (97.3)	
Diagnosis, n (%)			0.159
Glaucoma	146 (77.7)	144 (78.2)	
Ocular hypertension (OHT)	34 (18.1)	37 (20.2)	
1 eye glaucoma/1 eye OHT	8 (4.3)	2 (1.1)	
Iris color, n (%)			0.811
Dark (brown or black)	142 (75.5)	136 (74.3)	
Light (all other colors)	46 (24.5)	47 (25.7)	
Run-in monotherapy, n (%)			0.828
Beta-blocker	121 (64.4)	120 (65.6)	
Brimonidine	28 (14.9)	30 (16.4)	
Carbonic anhydrase inhibitor	20 (10.6)	19 (10.4)	
Prostaglandin or prostamide	17 (9.0)	12 (6.6)	
Other	2 (1.1)	2 (1.1)	
Baseline mean IOP on monotherapy, mmHg, mean ± SD			
Hour 0	25.0±3.0	25.0±3.0	0.616
Hour 2	22.6±3.1	22.4±3.4	0.384

IOP = Intraocular pressure

The planned enrollment of the study, 330 patients, was chosen to give a power of 85% to establish non-inferiority of the fixed combination to concomitant therapy in the subgroup of patients run-in on a beta-blocker, assuming 60% of patients would be run-in on a beta-blocker, an attrition rate of 15%, a two-tailed type I error rate of 0.05, a common SD of 3.2, and a non-inferiority margin of 1.5 mmHg.

RESULTS

Patient characteristics and disposition

A total of 371 patients met the entry criteria and were enrolled in the study. Most patients (97.3%) were white, and the majority (62.8%) were female. There were no significant differences in demographic characteristics, medical or ophthalmic history, ophthalmic diagnosis, baseline mean IOP, or run-in monotherapy between treatment groups (Tab. I). Beta-blockers were the most commonly used run-in monotherapy: 65.0% of patients were run-in on a beta-blocker, 15.6% on brimonidine, 10.5% on a carbonic anhydrase inhibitor, 7.8% on a prostaglandin or prostamide, and 1.1% on another medication.

Study completion rates were high in both treatment groups (94.1% for the combination group and 97.3% for the concomitant group). Patients in the combination group discontinued from the study due to adverse events (n = 4), loss to follow-up (n = 4), protocol violations (use of prohibited medication, n = 1), and other reasons (n = 2).

Patients in the concomitant group discontinued from the study due to adverse events (n = 2), loss to follow-up (n = 1), protocol violations (use of prohibited medication, n = 1), and personal reasons (n = 1).

IOP-lowering efficacy

In the ITT patient population with LOCF, both fixed-combination and concomitant therapy provided statistically and clinically significant mean IOP reductions from monotherapy-treated baseline at each follow-up time point at each visit ($p<0.001$). There were no significant between-group differences in the mean change from baseline IOP. At hour 0 (trough effect), the mean IOP reduction ranged from 4.4 mmHg to 4.9 mmHg in each treatment group (Fig. 1A). The mean IOP reduction at hour 2 (peak effect) ranged from 4.9 mmHg to 5.3 mmHg in the fixed-combination group and from 4.7 mmHg to 5.3 mmHg in the concomitant group (Fig. 1B). Based on least square estimates, the between-group difference in mean change from baseline IOP (combination minus concomitant) ranged from -0.30 mmHg to 0.14 mmHg ($p\geq0.345$) over all follow-up measurements. At week 12, the mean change from baseline IOP at hour 0 (the primary efficacy endpoint) was -4.9 mmHg for both groups, and the upper limit of the 95% CI for the difference between groups (combination minus concomitant) was 0.79, demonstrating non-inferiority of the fixed combination to concomitant therapy. Similarly, at all other time points during follow-up, the IOP-lowering effect of the fixed combination was non-inferior to that of concomitant therapy, with the upper limit

TABLE II - TREATMENT-RELATED ADVERSE EVENTS

	Combination therapy	Concomitant therapy	Between-group p value
Overall incidence	38 (20.2)	26 (14.2)	0.126
Individual adverse events*			
Eye pain	10 (5.3)	7 (3.8)	0.491
Headache	9 (4.8)	8 (4.4)	0.848
Eye pruritus	8 (4.3)	4 (2.2)	0.260
Conjunctival hyperemia	6 (3.2)	5 (2.7)	0.794
Visual disturbance	4 (2.1)	5 (2.7)	0.748
Asthenia	4 (2.1)	3 (1.6)	>0.999
Oral dryness	4 (2.1)	2 (1.1)	0.685
Allergic conjunctivitis	3 (1.6)	2 (1.1)	>0.999
Burning sensation in eye	2 (1.1)	4 (2.2)	0.444
Somnolence	3 (1.6)	1 (0.5)	0.623

Values are n (%).
*All individual adverse events possibly, probably, or definitely associated with treatment that were reported for ≥1% of patients are listed

of the 95% CI of the difference (combination minus concomitant) consistently ≤0.83 mmHg.

Analysis of mean IOP for the ITT patient population also showed comparable IOP lowering between treatment groups and non-inferiority when comparing the effect of the fixed combination to that of concomitant therapy (Fig. 2). Mean IOP at follow-up measurements ranged from 17.3 mmHg to 20.6 mmHg in the fixed-combination group and 17.1 mmHg to 20.5 mmHg in the concomitant group. The between-group differences ranged from -0.05 mmHg to 0.35 mmHg (p≥0.274), with the upper limit of the 95% CI of the difference (combination minus concomitant) being ≤0.97 mmHg at all time points and visits.

The PP patient population included 88.4% of enrolled patients: 88.3% (166/188) of patients in the combination group and 88.5% (162/183) of patients in the concomitant group. Analyses of mean change from baseline IOP and mean IOP for observed cases in the PP patient population also showed that the fixed combination met the criterion for non-inferiority to concomitant therapy at all time points and follow-up visits. These results confirmed those for the ITT patient population and consequently, the robustness of the conclusion that the fixed combination was non-inferior to (i.e., as effective as) concomitant therapy.

Subgroup analyses were performed to determine whether the type of run-in medication affected the results. The study was powered to detect differences between treatments for the patient subgroup run-in on a beta-blocker. The results in this subgroup reproduced the findings in the overall population (Fig. 3). Mean reductions from baseline IOP at the hour 0 and hour 2 measurements at weeks 2, 6, and 12 ranged from 4.4 mmHg to 5.7 mmHg in the combination group and 4.7 mmHg to 5.8 mmHg in the concomitant group. No significant differences were found between treatment groups. The fixed combination was non-inferior to and as effective as concomitant therapy at all time points at all follow-up visits. Analysis of the patient subgroups run-in on a CAI, prostaglandin, or other medication also showed similar mean changes from baseline IOP between treatment groups.

An additional efficacy analysis evaluated the percentage of patients in each treatment group who achieved target pressures. The findings were comparable between treatment groups. At trough effect (hour 0) on week 12, 33.0% of patients in the combination group and 37.2% of patients in the concomitant group achieved an IOP of ≤18 mmHg. At peak effect (hour 2) on the same visit, 70.2% of patients in the combination group and 70.5% of patients in the concomitant group achieved an IOP of ≤18 mmHg. The percentage of patients who achieved an average IOP ≤17.5 mmHg over all follow-up measurements (29.3% in the combination group, 29.5% in the concomitant group) was comparable between treatment groups.

Safety analyses

Fixed-combination therapy and concomitant therapy showed similar safety profiles, and both were well tolerated. The overall incidence of adverse events, regardless of causality, was comparable between groups (30.3% in the combination group and 24.6% in the concomitant group). Most adverse events were mild or moderate in severity. One or more treatment-related adverse events, identified by the investigator as possibly, probably, or definitely related to treatment, were reported for 20.2% of patients in the combination group and 14.2% in the concomitant group (p=0.126). Ocular pain, ocular pruritus, and headache were the most commonly reported treatment-related adverse events (Tab. II). There were no significant between-group differences in the incidence of any particular adverse event.

No unexpected or serious treatment-related adverse events were reported. The adverse event profiles associated with the treatments were predictable from the previously reported safety profiles of brimonidine and timolol used alone and concomitantly. There were no reports of bradycardia or hypotension in either treatment group.

Treatment-related adverse events led to few discontinuations in either group (4/188, 2.1% of patients in the fixed combination group and 2/183, 1.1% of patients in the concomitant therapy group, p=0.685). One additional patient in each group discontinued due to an adverse event unrelated to treatment (in each case, hypertension). Allergic conjunctivitis was the most common adverse event leading to discontinuation (two fixed-combination patients and one concomitant therapy patient).

There were no clinically relevant mean changes from baseline in any laboratory, hematology, chemistry, or urinalysis parameter in either treatment group. No clinically or statistically significant changes in mean blood pressure or pulse rate were seen during the study. Changes from baseline were unremarkable for visual acuity, visual fields, and cup:disc ratio in each group. The most frequently reported findings on biomicroscopy were conjunctival erythema and follicles. There were no statistically significant between-group differences for these or any other biomicroscopic or ophthalmoscopic findings.

DISCUSSION

The results of this study demonstrate that the new brimonidine/timolol fixed combination is as effective as concomitant therapy with brimonidine and timolol in reducing IOP in patients with IOP uncontrolled on monotherapy. The difference in efficacy, as measured by mean IOP and mean change from baseline IOP, between the fixed combination and concomitant administration of the component drugs was consistently less than 1 mmHg. Further, the fixed combination was safe and well tolerated, and it is conveniently dosed with a single drop twice daily. This simplified dosing regimen could have a positive effect on compliance.

Statistically significant and clinically relevant mean decreases in IOP were achieved when patients on monotherapy were switched to either the brimonidine/timolol fixed combination or concomitant therapy. The additional IOP lowering obtained ranged from 4.4 mmHg to 5.3 mmHg in both treatment arms. The magnitude of this IOP reduction from baseline on monotherapy compares favorably to mean decreases from timolol-treated baseline IOP seen with the latanoprost/timolol fixed combination and the timolol/dorzolamide fixed combination in previously reported studies (18, 19).

Administration of drugs together in a fixed combination is not necessarily as effective as concomitant administration of the separate drugs. Previous studies of the timolol/dorzolamide fixed combination and the latanoprost/timolol fixed combination did not consistently demonstrate non-inferiority of the fixed combination to concomitant treatment with the components (19, 20). In contrast, in the present study, non-inferiority of the fixed combination of brimonidine and timolol to concomitant therapy with the component drugs was demonstrated for both mean change from baseline IOP and mean IOP using the upper limit of the 95% CI of the difference between means approach and a criterion for non-inferiority of 1.5 mmHg.

At the time the study was designed, clinical significance was assumed only for between-group differences >1.5 mmHg. Non-inferiority studies of the fixed combinations of timolol/dorzolamide and latanoprost/timolol also used a 1.5 mmHg criterion for non-inferiority (19, 20). However, smaller differences in IOP-lowering efficacy may also be clinically relevant.

In the Early Manifest Glaucoma Trial, each 1 mmHg of IOP lowering decreased the risk of disease progression by approximately 10%, suggesting that a difference of 1 mmHg could be clinically significant. In the present study, non-inferiority of the fixed combination to concomitant use of the component drugs was demonstrated even using the stricter criterion for non-inferiority of a 1.0 mmHg difference between therapies.

The upper limit of the 95% CI for the difference between treatments consistently fell below 1.0 mmHg at all time points and all visits.

It is particularly important to evaluate results for the per-protocol patient population in non-inferiority studies. The primary reasons that patients were excluded from the PP population in our study were an inadequate run-in period on monotherapy and non-compliance with the run-in monotherapy at the baseline visit.

Efficacy results for the ITT with LOCF population were fully reproduced using observed values in the PP population. The brimonidine/timolol fixed combination was non-inferior to concomitant therapy for both mean IOP and mean change from baseline IOP at all time points and all visits in both analyses. Thus the conclusion that brimonidine/timolol fixed combination is as effective as concomitant brimonidine and timolol is robust.

In the Advanced Glaucoma Intervention Study, patients who consistently met a target IOP of <18 mmHg showed less progression of field loss than patients who failed to reach the target IOP at one or more visits (1). For patients in the present study, mean baseline IOP at hour 0 was 25.0 mmHg on monotherapy, and an IOP reduction of approximately 30% from monotherapy-treated baseline would be required for the average patient to reach a target IOP <18 mmHg on the two-drug regimen.

Thus, only a low percentage of patients in each treatment group would be expected to consistently achieve IOP <18 mmHg throughout follow-up. Nonetheless, a remarkable number of patients (29.3% in the combination group, 29.5% in the concomitant group) achieved an average IOP ≤17.5 mmHg over all follow-up measurements.

At hour 0 on the final study visit, 33.0% of patients in the combination group and 37.2% in the concomitant group had achieved an IOP of ≤18 mmHg. These results demonstrate that the combination of brimonidine and timolol provides IOP control for many patients who are uncontrolled on monotherapy.

Safety and tolerability evaluations of the brimonidine/timolol fixed combination were favorable. The side effect profile associated with the fixed combination was consistent with the side effect profiles of the individual components used alone and concomitantly.

There were no significant differences between treatment

groups in the incidence of adverse events, and adverse events led to few discontinuations from treatment. In clinical practice, a fixed-combination product offers several advantages over concomitant therapy:

Dosing is easier and more convenient when brimonidine and timolol are administered in a single drop.

There is no need to wait between instillation of drops, and the potential problem of washout or dilution of the first drug by application of the second is avoided.

The increased convenience may result in better patient compliance, an important concern because patient noncompliance is a primary reason for failure of medical therapy. Finally, chronic use of multiple glaucoma medications has been associated with subclinical ocular surface inflammation and an increased failure rate of subsequent trabeculectomy (21).

BAK, the preservative used most commonly in ophthalmic medications, has deleterious effects on the ocular surface and may be primarily responsible for the toxicity associated with chronic glaucoma treatment (17). Corneal exposure to BAK can be reduced by coadministration of brimonidine and timolol in a single drop.

In conclusion, the results of this study have demonstrated that the new fixed combination of brimonidine and timolol is as effective, safe, and well tolerated as concomitant therapy with the component drugs.

Use of the fixed combination formulation will decrease ocular exposure to BAK and may improve patient compliance. Concurrent therapy with brimonidine and timolol can be replaced with the new brimonidine/timolol fixed combination with confidence.

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All patients in the study provided informed consent.

The study was conducted in accordance with the applicable Independent Ethics Committee (IEC) regulations in each participating country. All investigators obtained written IEC approval between December 2000 and June 2001 prior to initiating the study.

F.J. Goñi and the other investigators in the Brimonidine/Timolol Fixed Combination Study Group have no proprietary interests in the brimonidine/timolol fixed combination or the study sponsor, Allergan Ltd.

I.J. Bossowska and A.M. Ingram are employees of Allergan Ltd.

Statistical analysis for this study was performed by Didier Ill, MSc, Biostatistics Department, Allergan Ltd.

APPENDIX

Members of the Brimonidine/Timolol Fixed Combination Study Group:

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