CLINICAL SCIENCE

Unoprostone as adjunctive therapy to timolol: a double masked randomised study versus brimonidine and dorzolamide

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Aims: To compare the safety and efficacy of unoprostone, brimonidine, and dorzolamide as adjunctive therapy to timolol in patients with primary open angle glaucoma or ocular hypertension.

Methods: This was a randomised, double masked, parallel group, multicentre (14) study. After using timolol maleate 0.5% monotherapy twice a day for 2 weeks, patients (n = 146) with an early morning intraocular pressure (IOP) between 22 and 28 mm Hg, inclusively, received unoprostone isopropyl 0.15% (n = 50), brimonidine tartrate 0.2% (n = 48), or dorzolamide hydrochloride 2.0% (n = 48) twice daily as adjunctive therapy to timolol maleate 0.5% for another 12 weeks. Safety was based on comprehensive ophthalmic examinations, adverse events, and vital signs. Efficacy was based on mean change from baseline in the 8 hour diurnal IOP at week 12. Baseline was defined as values obtained after 2 weeks of timolol monotherapy.

Results: Each drug was safe and well tolerated. Burning/stinging was the most common treatment emergent adverse event. No clinically relevant changes from baseline were observed for any ophthalmic examination or vital signs. At week 12, each adjunctive therapy produced statistically significant (p<0.001) reductions from timolol treated baseline in the mean 8 hour diurnal IOP (–2.7 mm Hg, unoprostone; –2.8 mm Hg, brimonidine; –3.1 mm Hg, dorzolamide). The extent of IOP reduction did not differ significantly between unoprostone and either brimonidine (p = 0.154) or dorzolamide (p = 0.101).

Conclusion: Unoprostone was safe and well tolerated and provided a clinically and statistically significant additional reduction in IOP when added to stable monotherapy with timolol. Furthermore, unoprostone was not significantly different from brimonidine and dorzolamide as adjunctive therapy to timolol.

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Glaucoma, a group of chronically progressive neuropathies, is characterised by damage to the optic nerve and loss of visual field, primarily due to the death of retinal ganglion cells and cupping of the optic nerve head.¹ Although the exact aetiology of glaucoma has not been fully elucidated, vascular factors that reduce ocular blood flow and dysfunction of neuroprotective mechanisms are considered to be important factors in the development of the disease.^{2–6} Elevated intraocular pressure (IOP), a main characteristic of glaucomatous disease, is also considered to be a significant aetiological factor, although its exact role is currently a subject of debate.

Current treatment strategies for glaucoma and ocular hypertension (OH) are primarily aimed at lowering elevated IOP. Topical β blockers such as timolol are usually the first line of ocular hypotensive therapy. If target IOP is not reached after an appropriate period of monotherapy, combination treatments are used to achieve the desired IOP lowering effect, especially combinations of drugs with differing modes of action.⁷ Since glaucoma is a multifaceted disease, there is significant research under way to develop combination regimens that not only lower IOP but address other physiological aspects of the disease, particularly neuroprotective mechanisms and vascular dysfunction. Such an integrated approach to the physiological management of glaucoma holds great promise for advancing the field and treating patients with the disease.

In light of this, docosahexanoic acid (DHA) and its oxygenated metabolites, the docosanoids, have gained recent attention for their potentially beneficial effects on glaucomatous disease. DHA, the most abundant long chain polyunsaturated fatty acid in the human body, is well known for its posi-

tive effects on retinal and neuronal development and function.^{8,9} Furthermore, DHA delays photoreceptor apoptosis^{10,11} and maintains photoreceptor function and survival.^{12–16} DHA is also recognised for its vasorelaxing effects on the cardiovascular system.^{17–21}

Unoprostone isopropyl, a 22 carbon analogue of the naturally occurring docosanoids, possesses numerous properties of potential benefit in the physiological management of glaucoma. Specifically, unoprostone has been shown to counteract endothelin-1 induced vasoconstriction in both animal and human models,^{22–25} increase ocular blood flow and blood flow velocity in rabbits and humans,^{22,26–30} and protect against ischaemia and photoreceptor damage in rats,^{31–33} as well as against glutamate mediated neuronal death in an in vitro model.³⁴ In addition to these properties, unoprostone significantly reduces IOP.^{35,36} Recent evidence suggests that unoprostone exerts its effects by opening maxi-K⁺ channels, which may lead to vascular relaxation and/or relaxation of the trabecular meshwork, resulting in increased conventional outflow.³⁷

Since 1994, unoprostone isopropyl 0.12% ophthalmic solution has been approved in Japan and several other countries around the world for the lowering of IOP in patients with glaucoma and OH. Furthermore, the Japanese labelling for unoprostone 0.12% contains information regarding its favourable effects on ocular blood flow. Unoprostone isopropyl 0.15% ophthalmic solution has been approved in the United States and several other countries for use in the same patient population. The purpose of this study was to compare the IOP lowering efficacy and safety of unoprostone isopropyl 0.15%, brimonidine tartrate 0.2%, and dorzolamide hydrochloride 2.0%

as adjunctive therapy to timolol maleate 0.5% in patients with primary open angle glaucoma (POAG) or OH who are insufficiently responsive to timolol alone. Unlike unoprostone, which lowers IOP by increasing aqueous humour outflow, particularly conventional outflow,^{38–40} dorzolamide lowers IOP by reducing aqueous humour production,⁴¹ and brimonidine reduces aqueous humour flow and increases uveoscleral outflow.⁴² To facilitate discussion, the three combination treatments are identified only by the type of adjunctive therapy employed.

PATIENTS AND METHODS

Ethical considerations

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as amended (Somerset West, South Africa, 1996). Before the study was initiated, an institutional review board or ethics committee approved the protocol and informed consent form in compliance with US regulations and applicable local regulations. Each patient was informed of the investigational nature of the study and gave written informed consent before any study related procedures were initiated.

Study design

This was a randomised, double masked, active controlled, parallel group, multicentre study conducted at 14 investigational sites in Europe and the United Kingdom. After a 2 week, open label, monotherapy period with timolol maleate 0.5% (Timoptic), qualified patients were randomised by the sponsor in a 1:1:1 ratio to receive unoprostone 0.15% (Rescula), brimonidine tartrate 0.2% (Alphagan), or dorzolamide hydrochloride 2.0% (Trusopt) as adjunctive therapy to timolol for another 12 weeks. The randomisation schedule was computer generated using SAS Version 6.12 for Microsoft Windows and assigned an equal number of patients to each treatment group. Individual study numbers were assigned in numerical order as patients qualified for randomisation. Random assignment of patients to masked study treatment was accomplished by pre-packaging masked medication for each patient according to an investigator specific randomisation scheme. After packaging, the complete randomisation list was sealed and stored in a locked, secure location at Novartis Ophthalmics AG, Pharmacovigilance, Bülach, Switzerland.

All medications were instilled twice a day (one drop per dose) between 0700–0900 and 1900–2100 in the conjunctival cul de sac of eligible eye(s). Patients were instructed to instil double masked study medication at least 10 minutes after timolol. The first dose of masked study medication was instilled after all IOP measurements were taken at visit 2. All study medications were to be withheld on the morning of each post-screening visit until the early morning IOP was measured.

Bottles of masked study medication were identical in outward appearance and produced drops of comparable size. Study medications were labelled according to local regulatory requirements and did not reveal the identity of treatment. The identity of masked medication was concealed in a separate sealed envelope for each patient and stored at the study site. Unmasking of study medication was allowed only in the event of a medical emergency. During the course of the study, treatment was unmasked for three patients (two, unoprostone; one, dorzolamide) who experienced a serious adverse event (that is, personality disorder, corneal lesion, and retinal arterial occlusion); treatment was unmasked to determine if expedited regulatory safety reports were needed. All other envelopes were returned to the sponsor unopened.

Patients were evaluated at four visits during the study: visit 1 (week –2, screening and start of monotherapy with timolol); visit 2 (day 0, baseline/randomisation, start of adjunctive therapy); visit 3 (week 4); and visit 4 (week 12, study completion).

Patient population

The study population consisted of adult (≥ 18 years) patients (male or female, any ethnicity) with unilaterally or bilaterally elevated IOP associated with a diagnosis of POAG, OH, pseudoexfoliation glaucoma, or pigmentary dispersion glaucoma. Patients on β blocker monotherapy before entry must have used the drug for at least 4 weeks and had an IOP ≥ 22 mm Hg at screening. If patients were using more than one drug to lower IOP, their screening IOP had to be < 22 mm Hg; patients who used a β blocker as part of a multiple drug regimen must have used the drug for ≥ 4 weeks. After 2 weeks of run-in monotherapy with timolol, patients had to have an early morning IOP between 22 and 28 mm Hg, inclusively, with no more than a 5 mm Hg difference between eyes (in patients with bilateral disease). Patients also had to have an angle of at least 30° at screening (according to the Shaffer scale) and a best corrected distance visual acuity ≥ 0.1 (20/200) at screening and baseline.

Patients were excluded from the study if they (1) had been using a topical, ocular prostaglandin-type medication to control elevated IOP for a period of ≥ 3 months before screening, or had any history of its use that equalled 3 months in duration; (2) had a contraindication to β blockers, sulfonamides, or α agonists; (3) had laser or intraocular surgery within 3 months of screening or filtration surgery within 6 months of screening; or (4) were pregnant, lactating, or refused to use a reliable form of contraception during the study (for women of childbearing potential only). Patients were also excluded if their dose or regimen of an existing chronic or systemic medication with potential to affect IOP was expected to change during the trial or if new therapy was anticipated.

Safety and efficacy criteria

Ocular safety was based on comprehensive ophthalmic examinations, including best corrected distance visual acuity, ocular symptoms, ophthalmoscopy, slit lamp biomicroscopy, and visual field examination. Systemic safety was based on adverse events reporting and vital signs (brachial artery blood pressure and radial pulse). Safety evaluations were conducted at each visit, except for ophthalmoscopy and the visual fields examination, which were conducted at visits 1 and 4 only. Adverse events could have been spontaneously reported by the patient or discovered as a result of physical examination or general questioning by the investigator.

Efficacy was based on the mean change from baseline (day 0) in the 8 hour diurnal IOP at week 12; 8 hour diurnal IOP was defined as the mean of four IOP measurements taken at 0800 plus or minus 1 hour (pre-instillation, 0 hour) and 2 hours (mid-morning), 6 hours (early afternoon), and 8 hours (late afternoon) post-instillation (plus or minus 30 minutes). At each visit, IOP was measured in both eyes using Goldmann applanation tonometry. The IOP for each eye was the average of two measurements. If only one eye was eligible for the study, the value used for the efficacy analysis was the average IOP for the eligible eye. If both eyes were eligible, the value used for the efficacy analysis was the average of the four IOP measurements obtained from both eyes.

All measurements used in this study were standard and recognised as appropriate for the evaluation of the study treatment.

Statistical analysis

A sample size of 135 patients (45 per treatment group) was calculated to provide at least 80% power to detect a difference of 1.50 mm Hg in mean change from baseline in the 8 hour diurnal IOP between unoprostone + timolol and the two adjunctive comparator groups. This sample size was rounded up to 50 patients per group in order to account for potential dropouts. A difference of 1.50 mm Hg was considered to be the smallest clinically relevant difference between treatments. The

Table 1 Disposition of patients during adjunctive therapy

Category	Treatment group		
	Timolol + unoprostone	Timolol + brimonidine	Timolol + dorzolamide
Randomised to adjunctive therapy (No)	50	48	48
Completed the study (No, %)	46 (92)	46 (96)	45 (94)
Discontinued the study (No, %)	4 (8)	2 (4)	3 (6)
Protocol violation	1 (2)	0 (0)	0 (0)
Death (myocardial infarction)	0 (0)	0 (0)	1 (2)
Other adverse event	3 (6)	2 (4)	2 (4)

null hypothesis for this study was that the IOP lowering effect of unoprostone + timolol would be equal to brimonidine + timolol and dorzolamide + timolol. The alternative hypothesis was that the three adjunctive therapies would not be equal.

Safety analyses were conducted on all patients who received at least one drop of masked study medication and had at least one safety variable assessed after adjunctive therapy was initiated. Efficacy analyses were conducted on all patients who received at least one drop of masked study medication in eligible eye(s), had an IOP measurement taken at least once after the start of adjunctive therapy, and followed the protocol without significant violation. All statistical tests were two sided. Tests for main effects were considered statistically significant if they had a corresponding *p* value ≤ 0.050 ; tests for interaction effects were significant at a level of ≤ 0.100 .

For patient demographics and baseline characteristics, the Kruskal-Wallis test and Fisher's exact test were used to analyse continuous and categorical variables, respectively.

Changes from baseline (timolol treated) in brachial artery blood pressure, radial pulse, and visual acuity were tested within each treatment group using a paired *t* test and between treatment groups using a two factor analysis of variance model. Changes from baseline in the slit lamp examination, ocular symptomatology, and ophthalmoscopy were summarised but no formal statistical tests were performed. Incidences of treatment emergent adverse events considered by the investigator to be drug related were summarised by type of adjunctive therapy. Treatment emergent adverse events were defined as those events that started or worsened after the initiation of adjunctive therapy.

For the efficacy analyses, baseline was defined as IOP values measured at visit 2 (day 0, timolol treated baseline). Within each treatment group, paired *t* tests were used to determine if the observed mean (and mean percentage) changes from baseline in the 8 hour diurnal IOP differed significantly from zero. To compare between adjunctive therapies, adjusted mean changes from baseline (that is, *sas* least squares means) were calculated for each treatment group using a two factor analysis of covariance model, with treatment and study centre as factors and baseline IOP as the covariate. These mean changes from baseline were adjusted for imbalances in patient enrolment between centres and for imbalances in baseline IOP scores, and are not quite the same as the differences between the arithmetic means.

RESULTS

Patient disposition

A total of 182 patients were screened for study participation; of these, 174 patients were enrolled in the study and started monotherapy with timolol. Twenty eight patients discontinued treatment during the run-in monotherapy period, primarily because of protocol violations. At day 0, the remaining 146 patients were randomised to adjunctive therapy and received

unoprostone (50 patients), brimonidine (48 patients), or dorzolamide (48 patients) (Table 1). All patients received masked study drug as allocated. Of the 146 patients randomised, 141 were treated bilaterally and five unilaterally. Mean duration of exposure to adjunctive therapy was comparable among the three treatment groups (range 81.3–82.3 days).

Most of the patients in each treatment group completed the study (92% unoprostone; 96% brimonidine; 94% dorzolamide; these differences were not statistically significant) (Table 1). Nine patients prematurely discontinued treatment, including one patient treated with dorzolamide who died of a myocardial infarction considered unrelated to study medication. Seven patients (three, unoprostone; two, brimonidine; two, dorzolamide) discontinued because of other adverse events, and one patient (unoprostone) was withdrawn because of protocol violations.

Demographics and baseline characteristics

Overall, the three adjunctive therapies were similar with regard to demographics and baseline characteristics (Table 2); no statistically significant or clinically relevant differences were observed among treatment groups. Across treatments, the majority of patients were female (56%), and 99% were white. Mean age was 65.4 years (range 30.9–85.2 years) with a median of 67.0 years. The most common iris colours were blue (33%), brown (32%), and grey (18%). Most patients had a primary diagnosis of POAG (51%) or OH (34%). Mean duration of disease from the time of diagnosis was approximately 6 years.

Safety

Overall, each adjunctive therapy was well tolerated. Most adverse events were mild or moderate in intensity and transient in duration. A total of nine patients (three, unoprostone; two, brimonidine; four, dorzolamide) discontinued the study because of an adverse event. Of these, one patient in the dorzolamide group died as a result of myocardial infarction considered by the investigator to be unrelated to study treatment. Another patient in the dorzolamide group had retinal arterial occlusion at week 12 and was discontinued from study treatment. However, since the patient completed the planned duration of therapy, he was counted as having completed the study under patient disposition.

The majority of withdrawal events were systemic in nature, and only one event (tachycardia) led to withdrawal in more than one patient (one, dorzolamide; one, brimonidine). Aside from the fatal case of myocardial infarction, four patients withdrew from the study because of a serious adverse event. These events were personality disorder (unoprostone), corneal lesion (unoprostone), arterial thrombosis (dorzolamide), and retinal arterial occlusion (dorzolamide); all but one of these events (arterial thrombosis) was attributed to use of study medication by the investigator. Corneal lesion was reported with an incidence of 2.3% in the two pivotal monotherapy

Table 2 Patient demographics and baseline characteristics

Variable	Treatment group		
	Timolol + unoprostone (n=50)	Timolol + brimonidine (n=48)	Timolol + dorzolamide (n=48)
Sex (No, %)			
Female	23 (46)	30 (63)	29 (60)
Male	27 (54)	18 (38)	19 (40)
Ethnicity (No, %)			
White	49 (98)	48 (100)	47 (98)
Black	0 (0)	0 (0)	1 (2)
Asian	1 (2)	0 (0)	0 (0)
Age (years): mean (SD)	63.9 (10.9)	66.8 (9.7)	65.4 (10.7)
Iris colour (No, %)			
Brown	12 (24)	17 (35)	18 (38)
Hazel	3 (6)	1 (2)	1 (2)
Green	3 (6)	4 (8)	1 (2)
Blue	18 (36)	11 (23)	19 (40)
Grey	8 (16)	13 (27)	6 (13)
Other/mixed	6 (12)	2 (4)	3 (6)
Diagnosis (No, %)			
POAG	21 (42)	26 (54)	27 (56)
OH	22 (44)	16 (33)	12 (25)
PDG	0 (0)	2 (4)	0 (0)
PEX	2 (4)	0 (0)	3 (6)
Mixed*	4 (8)	3 (6)	4 (8)
Disease duration (years): mean (SD)	7.0 (6.1)	6.3 (5.7)	4.4 (3.9)

*Mixed = includes different diagnoses between eligible eyes.

studies conducted with unoprostone in the United States and Europe.⁴³ With regard to personality disorder, no other cases have been reported with unoprostone throughout the entire clinical development programme.

The overall incidence of drug related treatment emergent adverse events was generally comparable among treatment groups (range 22% to 29%), with the highest incidence occurring in patients treated with dorzolamide (29.2%). The incidences with brimonidine and unoprostone were 22.9% and 22.0%, respectively (Table 3). The percentage of patients who experienced a drug related, treatment emergent ocular event was generally comparable between the unoprostone and dorzolamide groups but somewhat lower in the brimonidine group. For systemic events, the overall incidence was several-fold lower with unoprostone (4%) versus the two comparators (15%, brimonidine; 17%, dorzolamide).

Across treatment groups, the most common drug related, treatment emergent adverse events were burning/stinging and burning/stinging upon instillation (immediate sensation of burning/stinging directly upon instillation of the study medication). The incidence of drug related burning/stinging was higher in patients treated with dorzolamide (15%) versus brimonidine (4%) or unoprostone (4%). The incidence of drug related burning/stinging upon instillation was 8%, 2%, and 0% in the unoprostone, dorzolamide, and brimonidine groups, respectively. Drug related ocular itching was only reported in the brimonidine group (8%), and taste perversion was only reported in the dorzolamide group (4%). Incidences of all other drug related, treatment emergent adverse events were generally low and comparable among treatment groups, although patients who received dorzolamide had a higher

Table 3 Summary of drug related* treatment emergent adverse events

Category	Percentage of patients (%)		
	Timolol + unoprostone (n=50)	Timolol + brimonidine (n=48)	Timolol + dorzolamide (n=48)
Overall summary:			
One or more drug related adverse events	22.0	22.9	29.2
Ocular event	18.0	10.4	22.9
Non-ocular event	4.0	14.6	16.7
Most common† drug related events:			
Abnormal vision	0.0	4.2	0.0
Burning/stinging	4.0	4.2	14.6
Burning/stinging upon drug instillation	8.0	0.0	2.1
Dry mouth	0.0	2.1	4.2
Foreign body sensation	4.0	4.2	0.0
Headache	0.0	4.2	2.1
Hypertension	0.0	4.2	0.0
Itching	0.0	8.3	0.0
Lacrimation disorder	2.0	2.1	4.2
Nausea	0.0	0.0	4.2
Tachycardia	0.0	2.1	4.2
Taste perversion	0.0	0.0	4.2
Vertigo	0.0	2.1	6.3

*Considered by the investigator to be related or possibly related to study medication.

†Events that occurred in >4% of the patients in any treatment group during adjunctive therapy.

Figure 1 Percentage change from baseline in the mean 8 hour diurnal IOP after 12 weeks of adjunctive therapy: $n = 40$, 38, and 39 for timolol combined with unoprostone, dorzolamide, and brimonidine, respectively.

incidence of vertigo (6% versus 0% and 2% for unoprostone and brimonidine, respectively).

No clinically relevant changes in comprehensive ophthalmological examinations or vital signs were observed in any treatment group during the course of the study.

Efficacy

At week 12, each adjunctive therapy produced statistically significant ($p < 0.001$) additional reductions in the 8 hour diurnal IOP over baseline values obtained after 2 weeks of monotherapy with timolol. Mean changes from baseline in the 8 hour diurnal IOP were -2.7 mm Hg, -2.8 mm Hg, and -3.1 mm Hg in the unoprostone, brimonidine, and dorzolamide groups, respectively. Likewise, mean percentage changes from baseline in the 8 hour diurnal IOP were -12.3% , -12.5% , and -14.4% (Fig 1).

Unoprostone was comparable to each adjunctive comparator in terms of mean change from baseline in the 8 hour diurnal IOP at week 12 ($\Delta = 0.62$ mm Hg, $p = 0.154$, unoprostone ν brimonidine; $\Delta = 0.71$ mm Hg, $p = 0.101$, unoprostone ν dorzolamide). Furthermore, the differences observed between unoprostone and each comparator did not reach the prospectively defined criterion for clinical significance (>1.5 mm Hg between treatments).

DISCUSSION

Treatment strategies for glaucoma are constantly evolving as more becomes known about the pathophysiology of the disease. While all treated glaucoma patients are currently given IOP lowering medications, POAG may quickly progress even when IOP is normalised,⁴⁴ and large epidemiological studies have shown approximately 30–50% of patients with glaucoma have an IOP at or below the commonly accepted threshold value of 21 mm Hg.⁴⁵ At the same time, approximately 10% of the adult population have elevated IOP without visual field loss or optic disc damage, suggesting that ocular hypertension alone may not lead to development of glaucoma.⁴⁶ None the less, large, multicentre, randomised, clinical studies of long duration have shown that lowering IOP can prevent visual field loss in some patients.^{47, 48} Given that glaucoma is a multifactorial disease, treatments should be designed to manage not only ocular hypertension but also other functional factors of the disease—namely, dysfunction of vascular and neuroprotective mechanisms. Therefore, in addition to the primary IOP lowering medications, adjunctive

therapies are needed to modulate the neurovascular aspects of glaucomatous disease.

The results of this study demonstrate that adjunctive use of unoprostone 0.15%, the first topical docosanoid approved for use in patients with glaucoma and ocular hypertension, produces a statistically significant and clinically meaningful reduction in IOP when added to stable monotherapy with timolol. Nakamatsu *et al* also showed an additive IOP lowering effect when unoprostone 0.12% and timolol were concomitantly used over a 12 week period in patients with POAG or OH who had previously received timolol monotherapy.⁴⁹ Thus, in patients who are insufficiently responsive to β blocker monotherapy, unoprostone can be used as adjunctive therapy to further lower IOP.

While the additional IOP lowering effect of unoprostone was comparable with that of brimonidine and dorzolamide, unoprostone has several unique pharmacological properties that may prove beneficial in the physiological management of glaucoma. Unoprostone has been demonstrated to positively affect ocular circulation both in animals^{22–24, 26–28} and humans.^{25, 29, 30} For example, unoprostone significantly inhibits ET-1 induced vasoconstriction,^{22–25} probably by opening the maxi-K⁺ channels.³⁷ Furthermore, unoprostone has been shown to have neuroprotective properties in different *in vitro* and *in vivo* models.^{31–34}

The results of this study show that unoprostone is safe and well tolerated as adjunctive therapy to timolol over a 3 month period. Unoprostone had no clinically notable effects on any ophthalmic examination, and only 22% of unoprostone treated patients experienced a drug related adverse event after the initiation of therapy. Most of these events were mild or moderate in intensity and transient in nature, and few events warranted cessation of treatment. The most common ocular event reported with unoprostone (burning/stinging upon instillation or otherwise) is typical of most topical glaucoma medications. In terms of systemic safety, unoprostone had no clinically relevant effect on vital signs, and few systemic adverse events were reported. Numerous studies involving unoprostone 0.12% have also demonstrated that unoprostone has an excellent safety profile when used adjunctively with β blockers (for example, timolol, carteolol),^{49–52} pilocarpine,^{50–53} carbonic anhydrase inhibitors (for example, acetazolamide),^{50–53} latanoprost,⁵⁴ and dipivefrin.^{50, 51} Furthermore, the safety of unoprostone as adjunctive therapy closely resembles that observed in monotherapy trials,^{55–61} suggesting no additional risk to patients who require multiple IOP lowering drugs.

For the most part, the three adjunctive treatments used in this study had comparable safety profiles. However, the overall incidence of drug related systemic events was several-fold lower in patients treated with unoprostone versus brimonidine and dorzolamide. In addition, the only cases of drug related ocular itching and taste perversion occurred in patients treated with brimonidine and dorzolamide, respectively. Such events are commonly associated with use of these compounds. Unoprostone is not contraindicated in patients taking monoamine oxidase inhibitors as with brimonidine, nor do patients taking the drug need to be cautious of engaging in potentially hazardous activities because of drowsiness and/or fatigue. Use of unoprostone is also not contraindicated in patients with hypersensitivity to sulfonamides, as with dorzolamide. Although burning/stinging occurred in all treatment groups, the overall incidence of burning/stinging (overall upon instillation or otherwise) was highest in patients treated with dorzolamide. Patients treated with brimonidine generally had a lower occurrence of ocular side effects than reported in other trials, especially for ocular allergy.^{62, 63} These discrepancies may possibly be due to differences in study designs or durations of exposure.

In the present study, although iris photography was not performed, no change in iris colour was reported in any

patient treated with unoprostone. Isolated cases of iris colour change have been reported in the literature for unoprostone, although the incidence is significantly less than that reported for PG analogues.^{63–69} Iris photography was performed in two long term pivotal trials with unoprostone. The incidence of iris colour change in these trials was very low (0.15%) after 12 months of therapy with unoprostone.⁷⁰ With latanoprost, for example, iris colour change occurs in 3–10% of patients treated for 6 months^{63–65} and in 11–23% of patients after 12 months of therapy.⁶⁶

In summary, the adjunctive use of unoprostone 0.15% significantly further reduces IOP in patients with primary open angle glaucoma or ocular hypertension treated with timolol alone. In addition to being comparable to both brimonidine 0.2% and dorzolamide 2.0% in terms of IOP reduction over the timolol treated baseline, unoprostone's excellent safety profile and additional vascular and neuroprotective properties position the drug as a valuable alternative for patients who require more than one type of glaucoma therapy. Further investigation may be required to confirm the role of neurovascular modulation in the treatment of glaucoma.

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