

Intraocular Pressure-lowering Effect and Safety of Travoprost 0.004% and Latanoprost 0.005% for the Treatment of Chronic Angle Closure Glaucoma

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Aim: To compare the intraocular pressure-lowering efficacy and safety of travoprost 0.004% with latanoprost 0.005% for patients with chronic angle closure glaucoma.

Patients and Methods: 320 patients with chronic angle closure glaucoma, who had previously undergone laser peripheral iridotomy, were randomised to receive travoprost 0.004% once daily ($n = 161$) or latanoprost 0.005% ($n = 159$) once daily for 12 weeks. Efficacy and safety evaluations were conducted on day 2, and weeks 2, 6, and 12.

Intraocular pressure measurements were performed at 9.00 am and 4.00 pm, except at the week 6 visit, when the intraocular pressure was measured at 9.00 am only.

Results: Mean intraocular pressure reductions from baseline were up to 9.1 mm Hg (95% confidence interval, -9.7, -8.4) and 7.9 mm Hg (95% confidence interval, -8.5, -7.3) with travoprost and latanoprost, respectively. Pooled intraocular pressure data for the 12-week period suggested that travoprost was more efficacious than latanoprost at 9.00 am, but this was not statistically significant. At 4.00 pm, pooled intraocular pressure data for the intent-to-treat analysis demonstrated a statistically superior reduction for travoprost compared with latanoprost ($p = 0.0196$). Travoprost 0.004% also demonstrated significantly greater intraocular pressure reduction from baseline than latanoprost in the per protocol analysis at 4.00 pm ($p = 0.0162$). Up to 71% of patients treated with travoprost and up to 63% of patients treated with latanoprost achieved a target intraocular pressure of <18 mm Hg during the 12-week study period. No treatment-related serious adverse events were reported in either group.

Conclusion: Both travoprost and latanoprost are effective for control of intraocular pressure in patients with chronic angle closure glaucoma. Travoprost 0.004% provided equal or greater intraocular pressure control than latanoprost 0.005%. Once daily administration was well tolerated by patients with chronic angle closure glaucoma.

Key Words: Glaucoma, angle-closure, Latanoprost, Travoprost

Asian J Ophthalmol 2006;8(1):13-19

Introduction

Population based studies suggest that approximately 67 million people worldwide have glaucoma.¹ Angle closure glaucoma (ACG) is as common as open angle glaucoma (OAG), but the majority of ACG occurs in Asia.¹ ACG is a leading cause of blindness in East Asia.²⁻⁶ In chronic ACG (CACG), gradual angle closure and a decrease in aqueous humor outflow through the angle may lead to persistent intraocular pressure (IOP) elevation, even after peripheral iridotomy, and long-term medical therapy may be required.⁷

Few adequately described randomised and controlled clinical trials have assessed the efficacy of therapeutic treatment for CACG.⁸ In a preliminary study by Chew et al, the IOP-lowering effect of latanoprost 0.005% was compared with timolol 0.5% for 32 patients with CACG.⁹ Patients who were diagnosed with glaucomatous optic neuropathy with a compatible visual field defect and at least 6 clock hours of synechial angle closure on gonioscopy were randomised and treated for 2 weeks. After 2 weeks of treatment, the IOP was lowered by 8.8 mm Hg (34%) in the latanoprost group compared with 5.7 mm Hg (23%) in the timolol group. In another study by Hung et al, latanoprost was added adjunctively to the conventional regimens of β -blockers and pilocarpine for 26 patients with residual ACG.⁷ The IOP reduction ranged from 4.8 mm Hg (21%) at 1 week to 8.9 mm Hg (36%) at 1 year after latanoprost was added to the conventional regimens. In a randomised double-masked multicentre 12-week study of latanoprost compared with timolol for patients with CACG, latanoprost 0.005% once-daily produced significantly greater IOP reduction than timolol 0.5% instilled twice daily.¹⁰

The mechanism of action of prostaglandin analogues in angle closure remains to be established. Recently, a new

prostaglandin analogue travoprost 0.004% has become available. In clinical studies of patients with OAG or ocular hypertension (OH), travoprost once-daily reduced diurnal mean IOP significantly more than timolol twice daily¹¹ and produced additional IOP reductions when used as an adjunct to timolol.¹² Results from a 12-month randomised study in patients with OAG or OH demonstrated equal or superior IOP reductions with travoprost compared with latanoprost.¹³ Travoprost showed greater IOP-lowering efficacy 20 hours post-dose.¹³ The present study was designed to compare the IOP-lowering efficacy and safety of travoprost compared with latanoprost for patients with CACG.

Patients and Methods

Patients

This was a randomised double-masked parallel-group multicentre study that compared the efficacy and safety of travoprost with latanoprost for patients with CACG for whom surgical peripheral iridotomy was insufficient to provide adequate IOP control. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice. Twenty two investigational sites in Australia, Hong Kong, Korea, Malaysia, Peru, The Philippines, Singapore, Taiwan, and Thailand were approved by their respective institutional review boards or ethics committees before initiating the study.

All patients signed and dated an approved written informed consent form prior to any study-related procedures or changes in ocular medical treatment. Eligible patients were aged 18 years or older and had unilateral or bilateral CACG with a mean IOP of 21 to 30 mm Hg in at least 1 eye at the eligibility visit. CACG was defined as optic neuropathy and/or a visual field defect together with gonioscopy demonstrating that the trabecular meshwork was not visible

for at least 180° and evidence of peripheral anterior synechiae (PAS) in association with chronically elevated IOP with indentation.⁹ As one of the criteria for evaluation, patients had undergone peripheral iridotomy at least 1 month prior to the screening visit.

Patients were excluded from the study if they had any of the following conditions: ocular trauma that damaged the anterior chamber angle in the study eye; ocular infection or ocular inflammation (except inflammation occurring in connection with peripheral iridotomy) in the study eye within 3 months of entry into the study; best-corrected visual acuity (BCVA) worse than 0.6 logMAR in either eye; refractive surgery, intraocular surgery (except for peripheral iridotomy or laser peripheral iridoplasty), or argon laser trabeculoplasty in the study eye within 3 months of entry into the study; severe central visual field loss in either eye; hypersensitivity to any components of the study medications; use of a long-term medication that may affect IOP, with less than 1 month stabilised dosing regimen prior to the screening visit; use of a steroid or non-steroidal anti-inflammatory drug less than 1 month before the screening visit; severe asthma or bronchial respiratory disease; and any abnormality preventing reliable applanation tonometry in either eye. Women who entered the study were either postmenopausal for at least 1 year or were unable to become pregnant due to a previous surgical sterilisation procedure. Women who had childbearing potential were excluded from the study.

In addition, patients were excluded if they had participated in another clinical trial within 30 days of commencing this study or were unable to safely discontinue their current ocular hypotensive medications for the washout period of 5 days to 4 weeks, depending on their pre-study medication. Contact lens wearers were also excluded.

Methods

Patients were assessed for eligibility according to the inclusion and exclusion criteria at the screening visit, which took place between 5 days and 4 weeks before the baseline eligibility visit, depending on the previous medication. At the screening visit, systemic and ocular medical histories were obtained and gonioscopy using a Goldmann or Koeppel lens was performed. The angular width of the anterior angle recess was graded for 4 quadrants using the Shaffer classification. Each quadrant was represented by a number ranging from 0 (closed) to 3 (wide open). The presence of PAS was determined using indentation gonioscopy with a Zeiss 4-mirror lens. A goniogram describing the extent and distribution of PAS was completed for each patient. An automated visual field examination was performed at the screening visit unless a documented test had been done within 12 weeks of the screening visit. Patients who qualified for entry into the study at the screening visit discontinued their ocular hypotensive medication. The minimum washout periods for ocular hypotensive drugs were 4 weeks for prostaglandin analogues or topical β -blockers, 2 weeks for adrenergic agonists, and 5 days for miotics and carbonic anhydrase inhibitors. Patients who were not using an ocular hypotensive medication had the eligibility visit at least 3 days after the screening visit. To minimise potential risk to patients due to IOP elevation during the washout period, investigators were able to substitute a miotic or an oral/topical carbonic anhydrase inhibitor for a β -blocker, prostaglandin analogue, or adrenergic agonist. The washout period for a miotic or carbonic anhydrase inhibitor was a minimum of 5 days.

At the eligibility visit, bilateral IOP measurements were obtained at 9.00 am and 4.00 pm. Patients were eligible when their mean IOP was 21 to 30 mm Hg in at least 1 eye at both time points. Eligible patients

were then randomised in a 1:1 ratio into 2 parallel treatment groups, according to a computer-generated allocation schedule, to receive either travoprost 0.004% or latanoprost 0.005%.

After the eligibility visit, patients continued to the double-masked treatment phase with subsequent visits at day 2, and weeks 2, 6, and 12. Bilateral IOP measurements were conducted with a Goldmann applanation tonometer at 9.00 am and 4.00 pm, except at the week 6 visit, where IOP measurements were performed at 9.00 am only. Two IOP measurements were taken and averaged. If the difference between the first and second reading was greater than 4 mm Hg, a third reading was taken and the 2 nearest readings were averaged. BCVA using the logMAR scale and slit-lamp biomicroscopy to examine deposition of pigment on the corneal endothelial layer or the lens capsule or any abnormalities of the conjunctiva, cornea, anterior chamber, iris, or lens were performed at every visit. Fundus examination to assess the vitreous, retina, macula, choroids, and optic nerve head was conducted at the screening and week 12 visits.

During the study, adverse events, defined as any change from baseline in a patient's ophthalmic or medical health, as identified by observations made by the investigator or complaints solicited from patients, were monitored regardless of whether they were treatment related. Serious adverse events were classified as death, admission to hospital, prolonged hospital admission, events that the investigator considered to be life-threatening, sight-threatening, or disabling, or those associated with a congenital anomaly. Any adverse events that occurred during the study were rated and reported by the investigator.

Unopened study medications were stored under refrigeration and protected from light. Once opened, study medications were stored at room temperature. Study

medications were provided in identical coded bottles. Eligible patients were instructed to instil 1 drop of the assigned study medication into each eye once daily at 9.00 pm, starting on the day of the eligibility visit and continuing for 12 weeks. Written instructions were provided to all patients. During the study period, no other topical IOP-lowering medication was permitted in either eye and no systemic medication with the potential to affect IOP could be commenced or undergo a change in dosage. If patients experienced an acute increase in IOP, as judged by the investigator, they were to be withdrawn from the study and an appropriate rescue medication was prescribed.

Statistical tests were conducted using the patients' worse eye for analysis. The patients' worse eye was defined as the eye with the higher IOP at 9.00 am on the day of the eligibility visit. When both eyes had equal IOPs, the worse eye was the eye with the higher IOP at 4.00 pm on the day of the eligibility visit. If both eyes were still equal at 4.00 pm, the right eye was selected for analysis.

A sample size of 142 evaluable patients per treatment group was calculated as sufficient to detect a 1.5 mm Hg greater IOP reduction with travoprost than latanoprost at a 95% 2-sided confidence interval (CI) with 90% power. These estimates were based on a standard deviation for IOP of 3.5 mm Hg and a 2-sample *t* test at the 0.05 significance level, which were derived from historical data for OAG clinical studies. 320 patients were enrolled in the study to ensure a sufficient number of evaluable patients per protocol. A strategy of combined tests of non-inferiority and superiority suggested by Morikawa and Yoshida¹⁴ was employed for the comparison between the 2 treatment groups. The difference between the treatment groups in IOP reduction from baseline during 12 weeks of therapy at 2 times, 9.00 am and 4.00 pm, was estimated

by least squares means from a repeated measures analysis of variance (ANOVA). For the differences in daily IOP reduction between groups an upper limit of the 95% CI of <1.5 mm Hg indicated non-inferiority of travoprost with respect to latanoprost, whereas an upper limit of the 95% CI of <0 mm Hg would have indicated superiority of travoprost.

Intent-to-treat and per protocol data sets were used for the statistical analyses. The intent-to-treat data set included all patients who received at least 1 dose of the study medication, while the per protocol data set included all patients who received the study medication, completed at least 1 on-therapy scheduled visit, and satisfied protocol inclusion/exclusion criteria. The non-inferiority hypothesis was tested using the per protocol data set and verified with the intent-to-treat data set. For patients who withdrew from the study and for missing data, the last observations were carried forward to impute values in the intent-to-treat data set. No last-observed data were imputed in the per protocol analyses. The secondary efficacy variables were the proportion of patients who achieved target IOP levels between treatment groups on the basis of the percentage of patients whose IOPs decreased to the target levels of 18, 17, 16 and 15 mm Hg. These criteria were included to be consistent with previous reports.¹¹⁻¹³

Analyses of safety parameters were conducted using ANOVA, Mantel-Haenszel chi squared tests, Pearson chi squared tests, or Fisher's exact tests, depending on the variable being analysed. Both efficacy and safety analyses were performed using the Statistical Analysis System for Windows version 6.12 (SAS Institute, Inc, Cary, USA).

Results

Patients' Demographics

320 patients were enrolled in the study. 161 patients were treated with travoprost

Table 1. Patients' characteristics.

	Travoprost 0.004% (n = 161)	Latanoprost 0.005% (n = 158)	p Value
Age (SD) [years]	63.9 (9.2)	62.4 (8.6)	0.389
Sex (%)			
Male	55 (34.2)	51 (32.3)	0.721
Female	106 (65.8)	107 (67.7)	
Race (%)			
Caucasian	2 (1.2)	2 (1.3)	1.000
Asian	145 (90.1)	143 (90.5)	
Other*	14 (8.7)	13 (8.2)	
Iris colour (%)			
Brown	159 (98.8)	156 (98.7)	0.185
Hazel	2 (1.2)	0 (0.0)	
Blue	0 (0.0)	2 (1.3)	

* Reported as Mestizo or Indian

0.004% and 159 patients were treated with latanoprost 0.005%. One patient in the latanoprost treatment group had no on-therapy data and was excluded from the intent-to-treat analysis. Seven patients (4 in the travoprost group, including 1 excluded from the intent-to-treat analysis and 3 due to non-qualifying IOP, and 3 in the latanoprost group, including 1 due to contraindicated concomitant medication and 2 due to non-qualifying IOP) were excluded from the per protocol analysis. Twenty four patients (15 in the travoprost group and 9 in the latanoprost group) discontinued the study prematurely. The major reasons for discontinuation were inadequate control of IOP (4 in the travoprost group and 3 in the latanoprost group), adverse events (6 in the travoprost group and 1 in the latanoprost group), and administrative or other reasons (5 in the travoprost group and 5 in the latanoprost group). For the patients who discontinued the study or missed a visit, but who were evaluable for the intent-to-treat analysis, the last available (on-therapy) 9.00 am IOP measurement was carried forward to impute all subsequently missed 9.00 am IOP measurements. Likewise, the last available (on-therapy) 4.00 pm IOP measurement was carried forward to impute all subsequently missed 4.00 pm IOP measurements.

Of the 319 patients in the intent-to-treat analysis, 106 (33.2%) were men and

213 (66.8%) were women. The demographic and baseline characteristics are presented in Table 1. The patients were predominantly Asian (288; 90.3%), with 4 (1.3%) Caucasian and 27 (8.5%) other (Mestizo or Indian). The mean age was 63.2 years and ranged from 32 to 82 years; 176 patients (55.2%) were younger than 65 years at enrolment. There were no statistically significant differences between the treatment groups for age, sex, race, or iris colour (Table 1).

Efficacy Evaluation

Baseline mean IOP was similar between the treatment groups at 9.00 am (25.4 mm Hg; SD, 3.0 mm Hg for travoprost; and 25.0 mm Hg; SD, 2.9 mm Hg for latanoprost) and at 4.00 pm (24.5 mm Hg; SD, 2.9 mm Hg for travoprost; and 23.9 mm Hg; SD, 2.8 mm Hg for latanoprost). There were no statistically significant differences between the baseline IOP readings for the 2 treatment groups.

Mean IOP reductions in the per protocol analysis ranged from 7.4 to 9.1 mm Hg for travoprost and from 6.6 to 7.9 mm Hg for latanoprost throughout the study. In the intent-to-treat analysis, mean IOP reductions ranged from 7.4 to 9.0 mm Hg for travoprost and 6.6 to 7.9 mm Hg for latanoprost.

According to the per protocol data, travoprost produced mean IOP reductions of 8.2 mm Hg (32.4%) at 9.00 am and 7.7 mm Hg (31.6%) at 4.00 pm for all visits pooled over the 12-week treatment period, compared with 7.6 mm Hg (30.5%) at 9.00 am and 6.7 mm Hg (27.9%) at 4.00 pm for latanoprost (Figure 1). The

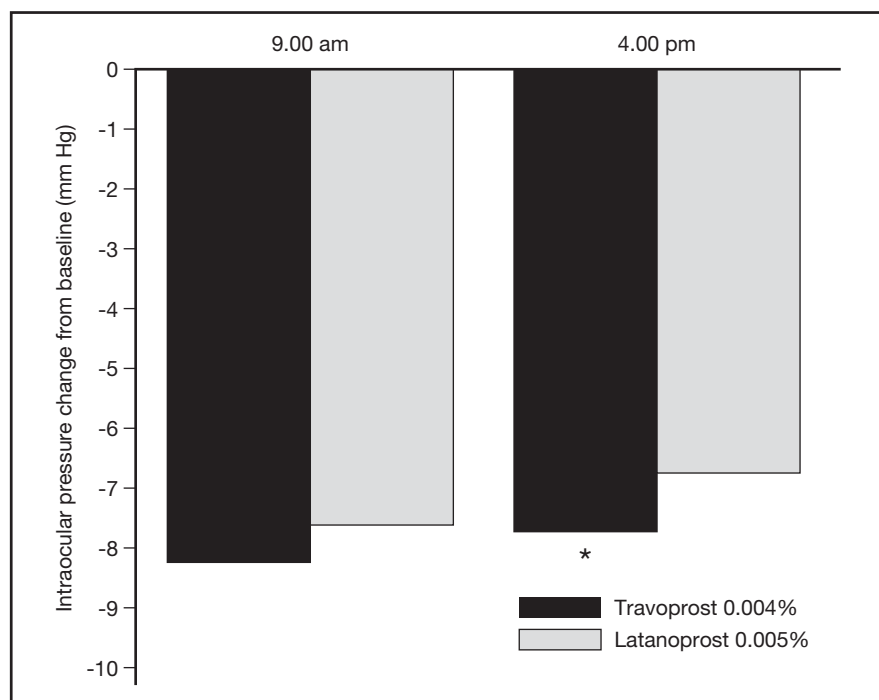


Figure 1. Mean intraocular reductions for travoprost and latanoprost at 9.00 am and 4.00 pm after 12 weeks (pooled per protocol data).

* $p = 0.0162$

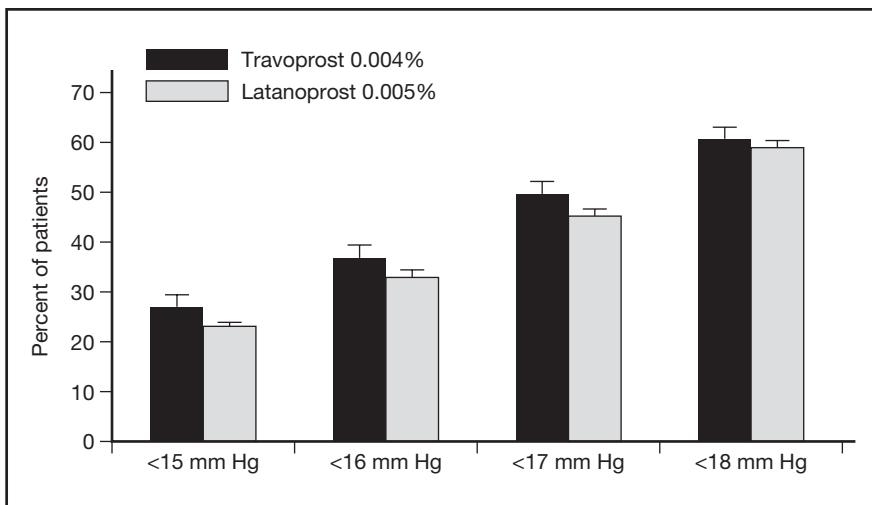


Figure 2. Percent of patients with intraocular pressure less than 18, 17, 16, and 15 mm Hg (pooled per protocol data).

difference in mean IOP reductions between travoprost and latanoprost at 4.00 pm in the pooled per protocol data was statistically significant ($p = 0.0162$). As the upper 95% confidence limit (-0.4) was less than zero in the per protocol analysis, it was appropriate to conduct tests of superiority based on the intent-to-treat analysis. Mean IOP reductions at 9.00 am were 8.1 mm Hg (31.9%) for travoprost and 7.7 mm Hg (30.8%) for latanoprost in the pooled intent-to-treat analysis. Mean IOP reductions at 4.00 pm were 7.7 mm Hg (31.4%) for travoprost and 6.7 mm Hg (28.0%) for latanoprost in the pooled intent-to-treat analysis. This difference was statistically significant ($p = 0.0196$).

Patients were considered to have a clinically relevant response to treatment if their IOP decreased to less than 18 mm Hg.¹⁵ After 12 weeks of therapy, up to 71% of patients in the travoprost group and up to 63% of patients in the latanoprost group achieved this response. When examining the pooled data at IOP levels lower than 17, 16, and 15 mm Hg, more patients in the travoprost treatment group achieved a response than in the latanoprost group (Figure 2). At an IOP level of <15 mm Hg, up to 28.9% of patients responded to travoprost and up to 24.2% responded to latanoprost.

Safety Evaluation

320 patients were evaluated for the safety analysis. No deaths or other treatment-related serious adverse events were reported during the study. Two patients in the latanoprost group experienced 4 serious adverse events (infection and rectal disorder in 1 patient, and retinal haemorrhage and blurred vision in the other patient) that were not related to the study drug and did not interrupt their participation in the study. Seven patients discontinued the study due to adverse events; 6 in the travoprost group and 1 in the latanoprost group. Adverse events were mostly mild to moderate with 1 exception (severe corneal abrasion in the travoprost group), generally resolved with or without treatment, did not usually interrupt patient participation in the study, and were not age dependent.

The most frequent ocular adverse events in the travoprost group were ocular hyperaemia (36.0%), ocular discomfort (9.3%), ocular pruritus (6.2%), cells (3.7%), and foreign body sensation (2.5%). For the latanoprost group, the most frequent ocular adverse events reported were ocular hyperaemia (11.3%), cells (2.5%), ocular discomfort (2.5%), foreign body sensation (2.5%), and blurred vision (2.5%). All other adverse events occurred at an incidence of less than 2%.

Discussion

This study evaluated the safety and efficacy of travoprost 0.004% compared with latanoprost 0.005% for patients with CACG. The results demonstrated that both travoprost 0.004% and latanoprost 0.005% were effective for producing statistically significant reductions in IOP from baseline at all treatment visits during the 12-week study period. This supports previous study results demonstrating the efficacy of a prostaglandin analogue for the treatment of CACG in a controlled, double-masked study.¹⁰ These results are also consistent with the findings reported in the study of patients with OAG by Netland et al, which compared travoprost 0.004% with latanoprost 0.005%.¹³

In the current study of patients with CACG, pooled intent-to-treat data from the treatment groups showed that, at 4.00 pm, the mean IOP reduction for travoprost was significantly greater than for latanoprost 20 hours after treatment ($p = 0.0196$). Up to 71% of patients in the travoprost group and up to 63% of patients in the latanoprost group achieved a clinically relevant response to treatment (<18 mm Hg).

The safety profile of travoprost in the present study was similar to that previously reported in patients with OAG or OH.¹¹⁻¹³ In the present study, both travoprost and latanoprost were well tolerated locally and systemically. The most frequently reported adverse event in both treatment groups was ocular hyperaemia. Hyperaemia associated with travoprost and latanoprost was reported as an adverse event based on patient complaints. No quantitative measurement of hyperaemia intensity was made in this study. In the studies by Goldberg et al¹¹ and Netland et al,¹³ prostaglandin hyperaemia was mild in intensity with an average grade of less than 0.5 on a 5-unit scale of hyperaemia and generally resolved without treatment. Hyperaemia reported with the prostaglandin analogues did not pose any safety concern for patients in

these studies,^{11,13} or in the present study. Iris discolouration was reported in less than 1% of patients in each treatment group and, not surprisingly, was lower than the rate reported for longer term studies of travoprost and latanoprost in patients with OAG or OH.^{11-13,16-20} Clinically relevant changes in visual fields and disc cupping were not anticipated in a study of 12 weeks duration and were measured for safety reasons.

The mechanism of action of the prostaglandin analogues travoprost and latanoprost in eyes with angle closure is unknown. Prostaglandin analogues may enhance aqueous access to the ciliary body via the open part of the anterior chamber angle. Alternatively, these agents may facilitate aqueous flow through the peripheral anterior synechiae to the ciliary body.⁷ The current study indicates that the IOP-lowering efficacy of travoprost is equal to or greater than latanoprost for ACG, which is the most prevalent form of glaucoma in Asian populations.

The inclusion criteria for the previous studies^{9,10} and the present study were chosen for reasons of patient safety. Patients with a less severe form of CACG, for whom the anterior chamber angles were only partly closed, were enrolled. In the present study, a quantitative assessment of PAS was also not included. The relationship between the configuration of the drainage angle and IOP-lowering efficacy of latanoprost was evaluated in 137 patients in a 12-week treatment study.²¹ The percent change in IOP produced by latanoprost was not correlated with the mean angle width or the extent of PAS, indicating that prostaglandin analogues may be considered as a therapeutic option for eyes with clinically closed angles.

The aims of the management of ACG primarily include control of IOP and prevention of further angle closure. Laser peripheral iridotomy is usually performed to treat

pupillary block in CACG and has been accepted as first-line treatment.⁸ However, iridotomy alone does not cure CACG or sufficiently reduce IOP in all patients.⁸ Medical therapies are often required and are an effective clinical intervention for the management of CACG. Latanoprost 0.005% once daily and timolol 0.5% twice daily are recommended for the treatment of patients with primary ACG (PACG) in an evidence-based update of interventions for ACG.⁹ The term PACG used by Saw et al⁸ is equivalent to the term CACG used in this report.

The present study results support travoprost 0.004% as a therapeutic choice for the medical treatment of patients with CACG. Travoprost 0.004% offers clinically significant IOP-lowering efficacy, and ocular and systemic safety in a once-daily dosing schedule that favours improved patient compliance. Travoprost produces equal or superior IOP reduction for patients with CACG when compared with latanoprost. Both drugs are at least as effective for patients with CACG as for patients with OAG or OH and are well tolerated locally and systemically by patients with CACG.

Acknowledgements

This study was sponsored by Alcon Research Ltd, Fort Worth, Texas, USA. The members of the Travatan CACG Study Group are: I Goldberg, J Rait, Australia; SP Hui, J Chua, Hong Kong; NH Baek, YJ Hong, C Kee, Korea; G Arumugam, RA Rahman, Malaysia; MA Tenorio, EM Vargas, Peru; M Agulto, The Philippines; PTK Chew, S Seah, V Yong, Singapore; DW Lu, JW Hsieh, SC Wu, Taiwan; and A Euswas, Y Leelachaikul, P Pachimkul, P RojanaPongpun, N Ruangvaravate, Thailand.

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