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CLINICAL INVESTIGATION

Additive intraocular pressure-lowering effects of the Rho kinase inhibitor ripasudil in Japanese patients with various subtypes of glaucoma

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Abstract

Purpose The present study aimed to investigate the effectiveness of adjunctive therapy involving the Rho-associated, coiled-coil-containing protein kinase (ROCK) inhibitor ripasudil in lowering intraocular pressure (IOP) in patients with different subtypes of glaucoma, on the basis of the time of IOP measurement

Study design Retrospective study

Methods In total, 58 patients who underwent adjunctive therapy with ripasudil at a single institution were included. They were classified into a primary open-angle glaucoma (POAG) group, an exfoliation glaucoma (XFG) group, and a secondary glaucoma associated with uveitis, or steroid glaucoma (SG), group. The average IOPs within 6 months before (pre-IOP) and after (post-IOP) the addition of ripasudil were compared among the 3 groups. The IOP values of the morning-visit and afternoon-visit groups were also compared to reflect the peak effectiveness of ripasudil.

Results The IOP reductions in the POAG (n = 38), XFG (n = 6), and SG (n = 14) groups were −1.1, +0.5, and +0.5 mmHg, respectively. Significant reductions in IOP were observed in the POAG group ($P = .014$). The IOP reductions in the POAG morning-visit and afternoon-visit groups were −1.9 and +0.5 mmHg, respectively. IOP was significantly reduced in the morning-visit POAG group after treatment with ripasudil ($P = .002$). The IOP values measured during morning visits were lower than those measured during afternoon visits (IOP reduction: −1.3 mmHg; $P = .011$).

Conclusions The findings of the present study indicate that ripasudil is effective as an adjunctive therapy for lowering IOP in patients with POAG; these reductions are more significant when measured closer to the time of peak effectiveness.

Keywords Glaucoma · Intraocular pressure · Rho-kinase inhibitor · Ripasudil

Introduction

Glaucoma is a chronic, progressive neuronal disease characterized by damage to the optic nerve that eventually leads to blindness. The sole evidence-based treatment for glaucoma involves reduction of intraocular pressure (IOP) [1–3], which can be accomplished via medication, laser therapy, and/or surgical treatment [4–7]. First-line treatment typically involves the use of prostaglandin analogs (PGAs), owing to their robust efficacy in reducing IOP with once-daily treatment and without systemic side effects. However, in most cases, combined therapy involving nonantagonistic drugs with different mechanisms of action (e.g., β-blockers, carbonic anhydrase inhibitors, and α2 receptor agonists) is required owing to insufficient reduction of IOP by PGAs.

Ripasudil, a selective Rho-associated, coiled-coil-containing protein kinase (ROCK) inhibitor (Glanatec ophthalmic solution 0.4%; Kowa Pharmaceutical Company Ltd), was approved in December 2014 for the treatment of glaucoma in Japan. Ripasudil is the first drug to directly target the conventional outflow pathway by increasing aqueous humor outflow through the trabecular meshwork (TM) [8], primarily via 2 mechanisms: in the early phase (ie, within a few hours of instillation), ROCK inhibitors widen the TM

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by deforming the cytoskeleton within the TM cells and loosening the intracellular junctions within the Schlemm canal endothelium [8]; in the late phase (ie, within a few months of instillation), the extracellular matrix may reform, leading to reductions in tissue resistance, similar to findings observed in fibroblasts [9–11].

Adjunctive treatment with ripasudil, which may act via different mechanisms, may result in robust reduction of IOP without competition with other medications. Previous studies have reported positive effects from the use of ripasudil combined with latanoprost or timolol for the treatment of primary open-angle glaucoma (POAG) or ocular hypertension (OH) [12]. However, most patients with glaucoma are treated with multiple drugs, and the efficacy of ripasudil in reduction of IOP remains unclear for glaucoma types other than POAG and OH. Thus far, some reports have indicated a significant additive IOP-lowering effect of ripasudil in multiple medical therapy for POAG [13–15], but the additive effect in treatment of secondary glaucoma, including exfoliation glaucoma, has not been fully investigated [13, 16]. Because the peak IOP-lowering effects of ripasudil are observed approximately 2 h after administration [17], its IOP-lowering effects may be underestimated depending on the time of measurement. In this regard, most postmarketing studies have not considered the time of IOP measurement relative to the instillation of ripasudil. Thus, the present study aimed to evaluate the additive effect of ripasudil on IOP reduction with regard to the time of IOP measurement (morning or afternoon) in patients undergoing either monotherapy or combined therapy for the treatment of various types of glaucoma.

Patients and methods

The present study included 58 patients undergoing adjunctive therapy with ripasudil eye drops for at least 6 months, all of whom had visited our institution between May 2015 and June 2016. This retrospective study was approved by the local ethics committee of Miyata Eye Hospital and was conducted in accordance with the tenets of the Declaration of Helsinki. All study information and opportunities for refusal to participate were made publicly available, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. The patients were divided into the following 3 groups: (1) primary open-angle glaucoma (POAG) group (n = 38); (2) exfoliation glaucoma (XFG) group (n = 6); and (3) secondary glaucoma associated with uveitis or steroid glaucoma (SG) group (n = 14). Among the included patients with a history of uveitis, some presented with the glaucoma subtype associated with uveitis and some presented with steroid glaucoma; for these patients, it was difficult to manage the IOP. Therefore, patients with glaucoma associated with uveitis and patients with steroid glaucoma were included in the same group. Patients with other types of glaucoma were excluded. If the patient required adjunctive therapy for both eyes, the eye with the higher IOP was selected. No patients had switched to ripasudil from other eye drops. Patients with any active ocular surface diseases and those who used contact lenses were also excluded.

The medication scores for each patient before the addition of ripasudil eye drops were determined as follows: 1 point for a single type of eye drop, 2 points for a fixed combination of eye drops, and 2 points for an oral medication.

Intraocular pressure

The IOP was measured twice in 1 visit by use of a Goldmann applanation tonometer, and the average of the 2 measurements was regarded as the representative value. Pre-IOP and post-IOP were defined as the average IOP over the 6-month period before or after addition of ripasudil, measured at the same time over 2–3 visits within a 4-week interval. Changes in IOP were compared among the POAG, XFG, and SG groups. IOP reduction was also compared between the following 2 groups, considering the peak IOP-lowering effects of ripasudil: a morning-visit group, in which IOP was measured within 6 h of administration (reflecting the peak time), and an afternoon-visit group, in which IOP was measured ≥ 6 h after administration (reflecting the trough time).

Because we predicted that the IOP-lowering effects of ripasudil would be underestimated in the afternoon-visit group, owing to differences in the duration of the peak effect, IOP was also measured in the morning in this group.

Changes in IOP were analyzed by using paired *t* tests. The level of significance was set at $P < .05$.

Results

Patients

Fifty-eight patients (mean age: 69.8 ± 12.1 years; age range 36–90 years; 25 men, 33 women) were included in the study. Thirty-eight (65.5%), 6 (10.4%), and 14 (24.1%) patients were included in the POAG, XFG, and SG groups, respectively. No closed-angle patients were included in the XFG group. The 14 patients in the SG group comprised 12 with idiopathic anterior uveitis, 1 with cytomegalovirus uveitis, and 1 with HTLV-1-associated uveitis. Mild inflammation was observed in all the patients; 9 patients in the SG group received betamethasone sodium phosphate eye drops before the addition of ripasudil. The mean ages in the POAG, XFG, and SG groups were 68.2 ± 12.8 years, 79.3 ± 7.4 years, and 70.0 ± 9.3 years, respectively (Table 1). The mean

Table 1 Patient demographic data

	Total	POAG	XFG	SG
No. of patients	58	38	6	14
Age (mean ± SD), years (range)	69.8 ± 12.1 (36–90)	68.2 ± 12.8 (36–86)	79.3 ± 7.4 (77–86)	70.0 ± 9.3 (60–90)
Sex				
Male	25 (43.1%)	15 (39.5%)	4 (66.7%)	6 (42.9%)
Female	33 (57.9%)	23 (60.5%)	2 (33.3%)	8 (57.1%)
Medication score, mean ± SD (range)	1.9 ± 1.0 (1–5)	1.6 ± 0.8 (1–4)	2.2 ± 1.2 (1–4)	2.6 ± 1.1 (1–5)
Pre-IOP (mean ± SD), mmHg (range)	19.8 ± 4.9 (11.7–37.0)	17.7 ± 3.3 (11.7–27.0)	24.5 ± 4.6 (19.7–33.3)	23.2 ± 5.3 (14.5–37.0)

POAG primary open-angle glaucoma, *XFG* exfoliation glaucoma, *SG* secondary glaucoma

Table 2 Medication score

Score	No. of patients	Medications
1	28	PGAs
2	10*	PGAs + beta-blockers
	3	PGAs + CAIs
3	12*	PGAs + beta-blockers + CAIs
	1	PGA + CAI + brimonidine
4	3*	PGAs + beta-blockers + CAIs + brimonidine
5	1*	PGA + beta-blocker + CAI and oral medication

PGA prostaglandin analog, *CAIs* topical carbonic inhibitors

*Including fixed combinations

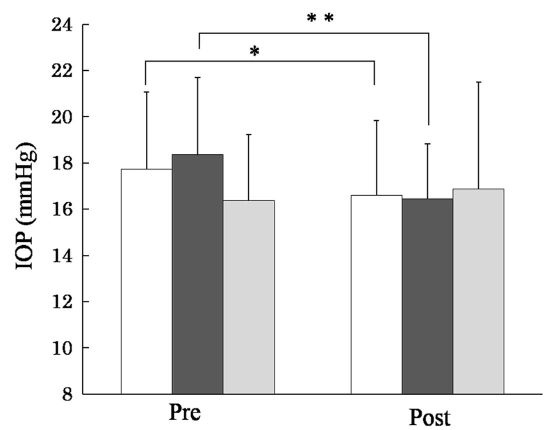

Fig. 1 Changes in intraocular pressure (IOP, mean ± SD) in the primary open-angle glaucoma (POAG) group. The post-IOP was significantly lower than the pre-IOP (n = 38) (open bar). In the morning-visit group (closed dark bar), the post-IOP was significantly lower than the pre-IOP (n = 26), whereas the pre- and post-IOPs in the afternoon-visit group did not differ significantly (closed light bar). **P* = .014, ***P* = .002

medication score was 1.9 points. Twenty-eight (48.3%), 13 (22.4%), 13 (22.4%), 3 (5.2%), and 1 (1.7%) patients exhibited scores of 1, 2, 3, 4, and 5 points, respectively (Table 2). The average medication scores in the POAG, XFG, and SG groups were 1.6, 2.2, and 2.6 points, respectively.

Intraocular pressure

The mean pre-IOP and post-IOP values in the POAG group were 17.7 ± 3.3 mmHg and 16.6 ± 3.3 mmHg, respectively. Following the addition of ripasudil, the POAG group exhibited a significant reduction in IOP (−1.1 mmHg; *P* = .014). A significant reduction in IOP (measured close to the time of peak efficacy) was also observed in the morning-visit group (n = 26) (−1.9 mmHg; pre: 18.4 ± 3.3; post: 16.5 ± 2.4 mmHg; *P* = .002). In contrast, no significant reduction in IOP (measured well beyond the duration of peak efficacy) was observed in the afternoon-visit group (n = 12) (pre 16.4 ± 2.9 mmHg; post 16.9 ± 4.6 mmHg; Fig. 1). Reductions in IOP among patients in the POAG group with premedication scores of 1, 2, 3, and 4 were −1.5 mmHg, −3.3 mmHg, −0.9 mmHg, and −4.0 mmHg, respectively. IOP reduction was observed regardless of the premedication score (Table 3). The IOP was reevaluated in 9 of the 12 patients in the POAG afternoon group who had agreed to visit in the morning, close to the time of ripasudil's peak efficacy. In these 9 patients, the mean IOP was 15.2 ± 5.0 mmHg, significantly lower than that obtained in the afternoon (−2.3 mmHg, *P* = .011; Fig. 2).

Table 3 IOP reduction in the POAG morning group, according to preaddition medication score

Score	No. of patients	Pre-adding IOP (mmHg)	Post-adding IOP (mmHg)	IOP reduction (mmHg)
1	14	17.8 ± 3.1	16.2 ± 2.7	−1.5 ± 2.9
2	6	19.9 ± 4.2	16.7 ± 2.2	−3.3 ± 2.3
3	5	17.5 ± 1.7	16.6 ± 1.8	−0.9 ± 2.0
4	1	21.5	17.5	−4.0

IOP intraocular pressure, *POAG* primary open-angle glaucoma

The XFG group exhibited no significant reduction in IOP following treatment with ripasudil (pre 24.5 ± 4.6 mmHg; post 25.0 ± 4.1 mmHg) in either the morning (pre

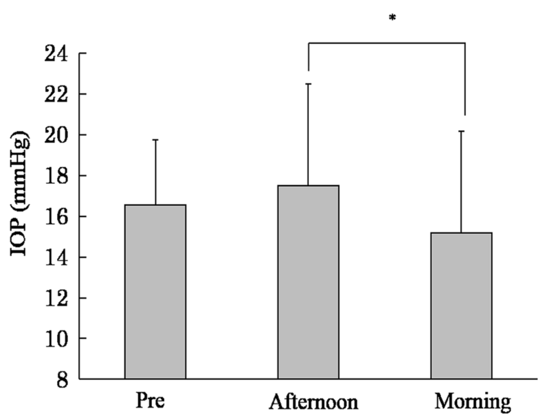

Fig. 2 Changes in the IOP values (mean ± SD) of the afternoon-visit POAG group upon remeasurement in the morning. The morning IOP values were significantly lower than the afternoon IOP values (n = 9). **P* = .011; *IOP* intraocular pressure, *POAG* primary open-angle glaucoma

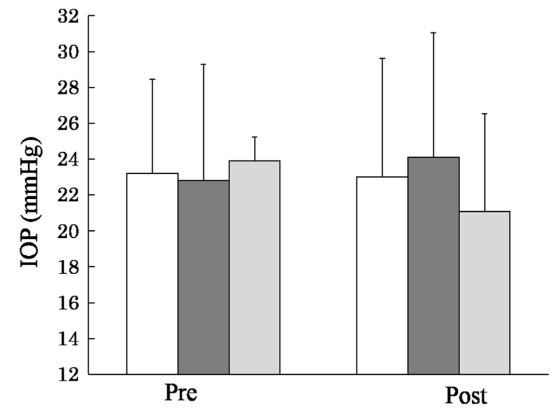

Fig. 4 Changes in intraocular pressure (IOP; mean ± SD) in the secondary glaucoma (SG) group. No significant differences in IOP were observed in either the morning or the afternoon group. All (open bar), morning-visit group (closed dark bar), afternoon-visit group (closed light bar)

24.2 ± 4.9 mmHg; post 24.0 ± 3.9 mmHg) or the afternoon (pre 26.0 mmHg; post 29.5 mmHg; Fig. 3).

In addition, the SG group exhibited no significant reduction in IOP following treatment with ripasudil (pre 23.2 ± 5.3 mmHg; post 23.0 ± 6.6 mmHg) in either the morning (pre 22.8 ± 6.5 mmHg; post 24.1 ± 6.9 mmHg) or the afternoon (pre 23.9 ± 1.3 mmHg; post 21.1 ± 5.5 mmHg; Fig. 4).

Discussion

The present study aimed to examine changes in IOP following the addition of ripasudil to the treatment regimens of patients with POAG, SG, or XFG. Although we observed a significant reduction in IOP (−1.1 mmHg, $P < .05$) in the POAG group, no significant IOP-lowering effects were observed in either the XFG or the SG group, regardless of the time of measurement. Previously, a 2-month study involving Japanese patients with POAG/OH demonstrated that adjunctive treatment with ripasudil resulted in significant reductions in IOP at the time of peak efficacy (1.6 mmHg for timolol and 1.4 mmHg for latanoprost) [12]. In addition, a 1-year study involving Japanese patients with POAG/OH and XFG revealed that IOP reduction at the time of peak efficacy was −3.7 mmHg in patients undergoing ripasudil monotherapy and −1.7 to −3.0 mmHg in patients undergoing adjunctive therapy with PGs and beta-blockers [18]. Three previous studies indicated that ripasudil had a significant IOP-lowering effect, even for POAG patients who were already undergoing maximal drug treatment [13–15, 19].

Matsumura and colleagues reported a significant IOP-lowering effect of ripasudil in 27 eyes with XFG that were treated with prostaglandin analog monotherapy for 5 months [16]. In another report, ripasudil for 6 months did not cause additive IOP reduction in patients with XFG and SG [13], but the number of patients (n = 17) was small, similar to the number in our study (n = 20), and multiple drops were already in use. Thus, an additive effect of ripasudil on XFG may not be observed. Because diurnal and daily variations in IOP in patients with XFG and SG are large [20, 21], a small number of participants may be insufficient to evaluate the effect of the drugs. Further large-scale studies are required to clarify the effect of ROCK inhibitors on glaucoma subtypes other than POAG. Ripasudil lowers IOP by relaxing TM cells, expanding the meshwork gap, and suppressing production of the extracellular matrix [8]. These effects occur via direct biochemical reactions that alter the cytoskeleton and

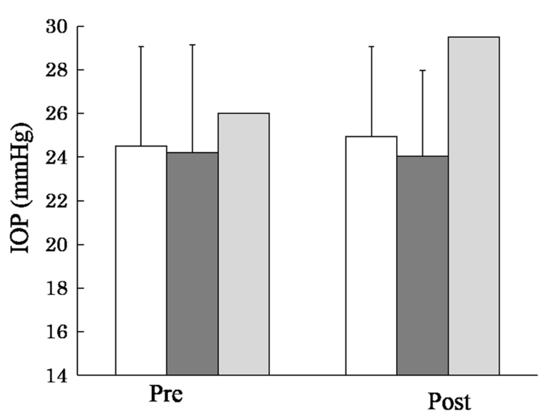

Fig. 3 Changes in intraocular pressure (IOP; mean ± SD) in the exfoliation glaucoma (XFG) group. No significant differences in IOP were observed in either the morning or the afternoon group. All (open bar), morning-visit group (closed dark bar), afternoon-visit group (closed light bar)

extracellular matrix of TM cells. This may explain the lack of effectiveness in patients with XFG and SG, in which the outflow pathways and cells may be damaged by exfoliative material and inflammation, respectively.

When patients were stratified with respect to the time of IOP measurement, greater reductions in IOP were observed in the morning-visit group than in the afternoon-visit group (−1.9 mmHg, $P < .01$). Indeed, no significant reductions in IOP were observed in the afternoon-visit group, although lower IOP values were observed among these patients when measurements were obtained in the morning. Previous studies have reported that the IOP-lowering effect of ripasudil reaches peak levels 2 h after administration and then decreases to near-trough levels by 12 h after administration [17]. Thus, we speculated that this IOP-lowering effect would not be observed in the afternoon-visit group, because IOP was measured well beyond the duration of peak efficacy. As expected, when patients in the afternoon-group underwent remeasurement of the IOP in the morning, a significant reduction of −2.3 mmHg ($P = .011$) was observed, relative to the afternoon IOP values. These findings suggest that the efficacy of ripasudil in lowering IOP may be underestimated in clinical practice, depending on the time of measurement relative to administration. Future studies should consider the measurement time, relative to ripasudil instillation, to more appropriately evaluate its efficacy in clinical practice.

In clinical settings, patients are often treated with combinations of 3 or 4 medications ("full-medication") before surgical treatment is considered. In the present study, patients treated with 3 drugs before the addition of ripasudil (n = 5) experienced an IOP reduction of 0.9 mmHg relative to the pre-IOP values. One patient treated with 4 drugs before the addition of ripasudil experienced an IOP reduction of 4.0 mmHg relative to the pre-IOP value. These findings suggest that ripasudil is effective in lowering IOP in patients treated with full medication.

The present study has some limitations. Patients with glaucoma associated with uveitis or with steroid glaucoma were included in the same group. Because complex factors involving the duration and causes of inflammation, as well as the use of steroids in patients with SG, make it difficult to manage IOP, further prospective studies are required to evaluate the efficacy of ripasudil for lowering IOP in patients with SG. In addition, because this study included a small number of cases representing each disease type at 1 hospital, it is necessary to evaluate the IOP-lowering effect of ripasudil in long-term, multicenter trials involving a large number of patients. Such studies should also examine the efficacy of ripasudil as a second drug, as the interactions between ripasudil and other drugs in multidrug combinations remain unclear.

In conclusion, the findings of the present study indicate that ripasudil is effective as an adjunctive therapy for lowering IOP in patients with POAG. Because more significant reductions in IOP were observed in the morning POAG group, future studies should consider the times of administration and measurement when evaluating the IOP-lowering effects of ripasudil.

Conflicts of interest T. Komizo, Lecture fee (Kowa); T. Ono, Lecture fees (Bayer, Kowa, Santen, Senju); A. Yagi, None; K. Miyata, Grant (Novartis, Otsuka, Santen, Senju), Lecture fees (Kowa, Novartis, Otsuka, Pfizer, Santen, Senju); M. Aihara, Grant (Alcon, Pfizer), Consultant fees (Crewt Medical Systems, Glaukos, HOYA, Otsuka, Santen, Senju, WaKamoto), Lecture fees (Abbot, Alcon, Allergan, Crewt Medical Systems, HOYA, JFC Sales Plan, Kowa, Nitten, Otsuka, Pfizer, Santen, Senju, WaKamoto).

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