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GLAUCOMA

One-year efficacy of adjunctive use of Ripasudil, a rho-kinase inhibitor, in patients with glaucoma inadequately controlled with maximum medical therapy

Hiroshi Inazaki[1] · Satoshi Kobayashi[1] · Yoko Anzai[1] · Hisayoshi Satoh[1] · Shimpei Sato[1] · Maiko Inoue[1] · Shin Yamane[1] · Kazuaki Kadonosono[1]

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Abstract
Purpose The aim of this study was to evaluate the one-year efficacy, ability to lower intraocular pressure, and tolerability of ripasudil, a rho-kinase inhibitor, in patients with glaucoma inadequately controlled with maximum medical therapy.
Methods This prospective, non-comparative, interventional case-series study included 39 patients with primary open-angle glaucoma inadequately controlled with maximum medical therapy before treatment with ripasudil. Ripasudil was administered twice per day as adjunctive therapy to ongoing glaucoma treatment. The primary endpoint was the degree of intraocular pressure reduction after 12 months of treatment; the secondary endpoints were the incidence of adverse events.
Results We examined 39 eyes. The intraocular pressure reduction (given as the relative percentage of intraocular pressure reduction) from baseline was −2.6 mmHg (−15.5%; 95% confidence interval, −1.1 to −3.9 mmHg; $P < 0.001$) after 12 months of treatment. The adverse events were conjunctival hyperemia (all patients), blepharitis (three), allergic conjunctivitis (two), punctate keratitis (two), and ophthalmalgia (one).
Conclusions Treatment with ripasudil decreased intraocular pressure in patients with glaucoma that was poorly controlled with maximal medical therapy, and it was well-tolerated.

Keywords Rho-kinase inhibitor · Ripasudil · Maximum medical therapy · Adjunctive therapy · Add-on therapy · Primary open-angle glaucoma

✉ Hiroshi Inazaki
t156007f@yokohama-cu.ac.jp

[1] Department of Ophthalmology and Micro-technology, Yokohama City University School of Medicine, 4-57 Urafune-cho, Minami-ku, Yokohama, Kanagawa 232-0024, Japan

Introduction

Although filtering surgery is more effective than medical therapy for lowering intraocular pressure (IOP), medical therapy is typically used to treat glaucoma [1]. Many types of antiglaucoma medications are currently available. Nevertheless, because of the occurrence of adverse events or poor responses to the medications, glaucoma cannot be successfully controlled even with the use of these medications. A study on ocular hypertension treatment [2] indicated that patients usually need two or more medications to achieve the target IOP. Therefore, antiglaucoma medications that have novel mechanisms of action are necessary [3].

Ripasudil (0.4%) (GLANATEC®; Kowa Company, Ltd., Nagoya, Japan) is a new rho-kinase inhibitor that lowers IOP by modulating the actin cytoskeleton and altering the conventional outflow of the aqueous humor [4–6]. This mechanism of action is different from that of other antiglaucoma medications [4–9]. In 2014, ripasudil became available in Japan. Some researchers have reported the efficacy of ripasudil monotherapy and combination therapy using ripasudil and prostaglandins (PGs) and/or β-blockers [10–13]. The reported percent IOP reduction after 52 weeks of treatment was as follows: −19.3% (monotherapy), −13.8% (PG + ripasudil), −17.2% (β-blocker + ripasudil), and −9.9% (fixed combination of PG and β-blocker + ripasudil). These percentages were the percent IOP reduction if ripasudil was added to an existing treatment regimen. We previously reported the safety and efficacy of ripasudil administration as an adjunct to maximum medical therapy (three or four types of eye drops) for 3 months [14]. The IOP reduction after 3 months was −15.5% (Table 1). However, the long-term safety and efficacy of ripasudil have not yet been studied. In this study, we reported the results of our

Table 1 Summary of studies evaluating Ripasudil

Study	Study design	Drugs	Periods (weeks)	IOP reduction(mmHg)		relative %	No. of patients	Diagnosis (%)
				peak	traf	IOP reduction		
Clinical trial phase III	multicenter, randomized	Ripasudil(monotherapy)	8	−4.0	−2.9	−17.6	107	POAG (40.8), OHT (59.1)
JapicCTI-111,564 Tanihara et al. [12]	double-masked, parallel group comparison studies	Ripasudil + latanoprost	8	−3.2	−2.2	−13.0	208	POAG (60.8), OHT (39.2)
		Ripasudil + timolol	8	−2.4	−2.9	−13.6	205	POAG (48.1), OHT (51.9)
Tanihara et al. [13]	multicenter, prospective, open-label study	Ripasudil(monotherapy)	52	−3.7	−2.6	−19.3	111	POAG (58.4), OHT (38.2), XFG (3.5)
		Ripasudil + latanoprost	52	−2.4	−1.4	−13.8	46	POAG (74.2), OHT (24.2), XFG (1.6)
		Ripasudil + timolol	52	−3.0	−2.2	−17.2	42	POAG (68.3), OHT (26.7), XFG (5.0)
		Ripasudil + combination drug (latanoprost and timolol)	52	−1.7	−1.7	−9.9	46	POAG (71.2), OHT (22.0),XFG (6.8)
Inazaki et al. [14]	non-comparative prospective case series study	Ripasudil +3 or 4 kinds of drugs (PGs, β-blocker,CAI,α-2 stimulator)	12	−2.8		−15.5	35	POAG(100)
Sato et al. [15]	retrospective	Ripasudil +	24	−1.9 (POAG) −0.5 (NTG) −3.8 (SG) −0.1 (XFG) −2.9 (DG)		−6.5 −2.3 −19.1 −2.1 −11.4	92	POAG(46.7),NTG(30.4),SG(10.8), XFG(7.6), DG(4.3)

IOP = intraocular pressure; POAG = primary open angle glaucoma; OH = ocular hypertension; NTG = normal tension glaucoma; XFG = exfoliation glaucoma; DG = developmental glacucoma; SG = Secondary glaucoma

prospective analysis of the safety and efficacy of ripasudil that was added to the treatment regimen of patients with poorly controlled glaucoma receiving maximum medical therapy.

Materials and methods

We conducted a prospective, non-comparative, case-series study at the Yokohama City University Medical Center in Yokohama, Japan.

The inclusion criteria were as follows: Japanese men or women with primary open-angle glaucoma (POAG), 20 years of age or older, inadequately controlled IOP despite treatment with three or four drugs, IOP of less than 35 mmHg, and an IOP difference of less than 2 mmHg between any two eligibility visits. We fixed the target IOP at 18 mmHg in the early phase, 15 mmHg in the intermediate phase, and 12 mmHg in the late phase, according to Anderson's classification [15]. We defined inadequately controlled IOP as a failure to decrease the IOP to the target value using existing medical therapy.

The exclusion criteria were as follows: presence of secondary, steroid-related, or traumatic glaucoma, and narrow angles defined as grade 2 or less according to the Shaffer classification as assessed using gonioscopy. We also excluded patients who had undergone ocular surgeries, including cataract surgery within the previous year, retinal laser treatment, selective laser trabeculoplasty, glaucoma surgery, or Nd:YAG laser posterior capsulotomy within the previous 90 days, or eyelid surgery within the previous 120 days. Patients with a corrected visual acuity worse than 20/200 in either eye or with severe visual field defects were also excluded. Patients were instructed not to take medications that may affect IOP, including corticosteroids; not to wear contact lenses; and not to change the dosage of the antiglaucoma drugs between follow-up visits.

One drop of ripasudil was instilled into the target eye twice daily, at 8 a.m. and 8 p.m., for 12 months. Ripasudil instillation was added to the existing glaucoma treatment regimen.

We evaluated the IOP-lowering effect of ripasudil and the incidence of adverse events associated with the drug after each month of treatment. The IOP was measured using a Goldmann applanation tonometer at 10 a.m. during every visit. The tonometry was performed in a masked manner, with one person reading the tonometer and the other setting the tonometer dial.

To evaluate the safety of ripasudil instillation, we performed ophthalmologic examinations, during which we examined the eyelids, palpebral and bulbar conjunctivae, anterior chamber, iris, cornea, and lens using slit-lamp microscopy. We also performed a fundus examination, visual acuity test, and visual field examination. Four levels of hyperemia were defined, and cases were scored according to the presence of hyperemia on a four-point scale: none (0), mild (1), moderate (2), and severe (3). Mild hyperemia was the expansion of a few vessels, moderate hyperemia was the expansion of many vessels, and severe hyperemia was the expansion of all vessels. Hyperemia was documented by digital pictures; the information was obtained from medical records.

We calculated the change in IOP (relative percent IOP reduction) after 12 months of treatment from baseline at time-matched points and used it as the primary endpoint. The secondary endpoint was the incidence of adverse events. One eye per patient was included in the efficacy analysis. If both eyes received ripasudil, the one with the higher baseline IOP was chosen for the analysis. If the IOP in both eyes was the same, the right eye was chosen for analysis.

Statistical analysis of the IOP differences between different follow-up dates was performed using a two-tailed Student's *t*-test for paired data. Eyes were divided into three groups (study eyes, ripasudil-treated fellow eyes, and ripasudil-untreated fellow eyes). IOP differences at 12 months among the three groups were determined with a Friedman test. The statistical significance level was set at $P \leq 0.05$, and the 95% confidence intervals (CIs) were calculated for the IOP differences. The IOP values were expressed as means ± standard deviation. The statistical analyses were performed using BellCurve for Excel Ver. 2.02 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

The study was designed and conducted in accordance with the principles of the Declaration of Helsinki and was approved by the institutional review board of our center. All participants received complete information regarding the study protocol and written informed consent was obtained from each participant before enrollment in the study.

Results

Enrollment for this study began on December 1, 2014, and the follow-up was completed by November 30, 2016. Of the 39 patients enrolled, 27 received the medication in both eyes. Twenty-seven patients (27/39) completed the study treatment.

The baseline characteristics of the patients are shown in Table 2. The medications that the patients were taking at the time of study enrollment are shown in Table 3. No patient changed their medication or took oral carbonic anhydrase inhibitors, pilocarpine, or similar miotics during the study period. The mean IOP values at baseline and after 1, 3, 6, 9, and 12 months of treatment were 17.9 ± 4.5 mmHg, 16.1 ± 5.0 mmHg, 15.6 ± 4.1 mmHg, 15.4 ± 3.9 mmHg, 15.3 ± 4.1 mmHg, and 15.3 ± 4.5 mmHg, respectively.

The degrees of decrease in peak IOP values from baseline measured after each month of treatment are shown in Fig. 1. The IOP reductions (relative percent IOP reduction) from baseline after 1, 3, 6, 9, and 12 months of treatment were −1.8 mmHg (−10.0%; 95% CI, −0.6 to −3.0 mmHg;

Table 2 Demographic characteristics of the participants

Characteristic	Value
Number of eyes (patients)	39 (39)
Age, yrs. (mean ± SD)	70.4 ± 11.3
Sex (male/female)	16/23
Baseline IOP (mean ± SD), mmHg	17.8 ± 4.4
Baseline IOP (fellow eye) (mean ± SD), mmHg	17.0 ± 4.1
Baseline MD (mean ± SD)	−10.1 ± 5.6
Baseline logMAR BCVA (mean ± SD)	0.34 ± 0.58
lens status (phakic eye/pseudo phakic eye)	21/18
Laser trabeculopasty	0
Iridotomy	0
Number of medications (mean)	3.64 (3–4)
Fellow eye status (ripasudil-treated eye / no ripasudil-treated eye)	27/12

IOP = intraocular pressure; BCVA = best-corrected visual acuity; MD = mean deviation; logMAR = logarithm of the minimum angle of resolution; SD = standard deviation

$P < 0.001$), −2.3 mmHg (−12.8%; 95% CI, −1.2 to −3.6 mmHg; $P < 0.001$), −2.6 mmHg (−14.5%; 95% CI, −2.0 to −4.6 mmHg; $P < 0.001$), −2.5 mmHg (−13.9%; 95% CI, −2.0 to −4.6 mmHg; $P < 0.001$), and −2.6 mmHg (−14.5%; 95% CI, −2.0 to −4.6 mmHg; $P < 0.001$), respectively. The reductions after 1, 3, 6, 9, and 12 months of treatment were all statistically significant. The predefined target IOP was achieved in 28.2% (11/39) of patients after 12 months of treatment.

The mean IOP values in ripasudil-treated fellow eyes at baseline and after 1, 3, 6, 9, and 12 months of treatment were 17.1 ± 4.1 mmHg, 15.6 ± 4.0 mmHg, 16.0 ± 5.1 mmHg, 15.3 ± 4.5 mmHg, 15.7 ± 5.8 mmHg, and 14.7 ± 3.7 mmHg, respectively.

The mean IOP values in ripasudil-untreated fellow eyes at baseline and after 1, 3, 6, 9, and 12 months of treatment were 14.8 ± 2.7 mmHg, 14.3 ± 3.2 mmHg, 14.3 ± 2.6 mmHg, 14.3 ± 2.8 mmHg, 13.2 ± 2.6 mmHg, and 13.5 ± 3.0 mmHg, respectively. In ripasudil-untreated fellow eyes, the reductions in the IOP values relative to the values at baseline were not statistically significant at all timepoints. There was a significant difference between the treated eye group and untreated fellow eye group at 12 months after treatment.

Table 4 lists the adverse events observed in more than one patient in this study. The most frequent adverse event was conjunctival hyperemia, which was observed in all patients. The hyperemia was mild, but occurred after every instillation and persisted for approximately 2 h. After 2 h of instillation, the conditions of hyperemia were none (ten patients), mild (28 patients), moderate (one patient), and severe (zero patients). The average hyperemia score was 0.76 ± 0.48.

Three patients (3/39) developed blepharitis. Two patients (2/39) developed allergic conjunctivitis and punctate keratitis. One patient (1/39) developed ophthalmalgia. Blepharitis occurred from 3 to 6 months after the start of the study. Figure 2 shows blepharitis due to ripasudil.

Twelve patients could not complete the study. Seven patients had insufficient IOP reduction during the study. They required glaucoma surgery or selective laser trabeculoplasty, and dropped out. Three patients had blepharitis. One patient had ophthalmalgia, and one patient developed conjunctive hyperemia. The adverse events improved after discontinuation of ripasudil.

Table 3 Detail of medication before ripasudil instillation

Medication	No. of eyes
PG+(β + CAI) + α2	23
(PG + β) + CAI + α2	3
PG + β + CAI + α2	1
PG + β + CAI	3
PG + CAI + α2	2
PG+(β + CAI)	2
(PG + β) + CAI	2
(PG + β) + α2	2
β + CAI + α2	1

PG = prostaglandin analogs; β = beta-blockers; CAI = carbonic anhydrase inhibitor; α2 = α2-adrenergic agonists

() means combination drugs. Combination drug was defined as two drugs

Discussion

In this study, our results revealed the significant IOP-lowering effects of ripasudil administered as an adjunctive therapy to existing maximum medical therapy in patients with POAG. Based on previous results that demonstrated the 3-month

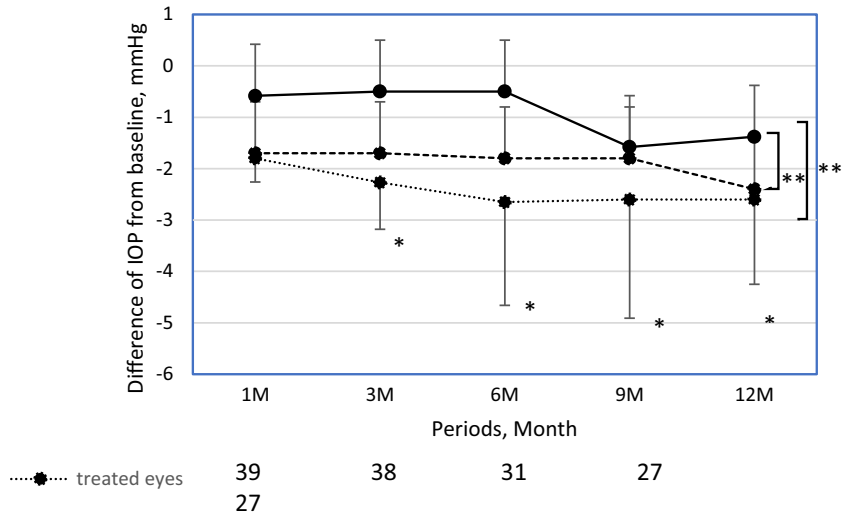

Fig. 1 Graphical representation of the differences in intraocular pressure (IOP) relative to the baseline value after 1, 3, 6, 9, and 12 months of ripasudil treatment in addition to maximum medical therapy. We divided patients into three groups: study eyes (group 1), ripasudil-treated eyes (group 2), and ripasudil-untreated eyes (group 3). At 12 months after treatment, IOP data were analyzed using the Friedman test. Further IOP decrease by ripasudil treatment was observed at all time-points (*$P < 0.001$; paired *t*-test) compared to the baseline level. At 12 months, there was a significance difference between groups 1 and 3, and between groups 2 and 3. (**$P < 0.05$; Friedman test)

efficacy of ripasudil as an adjunctive therapy [14], we conducted studies of long-term administration of ripasudil as adjunctive therapy to existing maximum medical therapy. The mean IOP reduction from baseline was −2.6 mmHg (−15.5%) after 12 months of treatment.

As seen in Table 1, the degree of IOP reduction following monotherapy with ripasudil for 52 weeks was −3.7 mmHg (−19.3%). The IOP reduction following the addition of ripasudil to latanoprost for 52 weeks was −2.4 mmHg (−13.8%), while the decrease after addition of ripasudil to timolol for 52 weeks was −3.0 mmHg (−17.2%), and the decrease after addition of ripasudil to a fixed combination of latanoprost and timolol for 52 weeks was −1.7 mmHg (−9.3%) [12, 13]. Thus, the IOP-lowering effect of ripasudil decreased as the number of ongoing medications increased. Nevertheless, the additive IOP-lowering effect found in our study (−2.6 mmHg, − 15.5%) was larger than that of the combination therapy of ripasudil with PGs and β-blockers. A study by Tanihara et al. [13] included various types of glaucoma, such as POAG, ocular hypertension, and exfoliation glaucoma, which may explain why the IOP reduction of our study was greater than that observed in other studies.

Ripasudil is a new rho-kinase inhibitor that was approved for the treatment of glaucoma. Rho-kinase inhibitors induce basic cellular changes, such as cytoskeletal rearrangement and

Table 4 Adverse Events

Symptom or Sign	Number of Patients (%) ($n = 39$)
Conjunctival hyperemia	39(100%)
Blepharitis	3(7.7%)
Allergic conjuncivitis	2(5.1%)
Panctate keratitis	2(5.1%)
Ophthalmalasia	1(2.6%)

Symptom or sign that occurred in more than one patient are listed

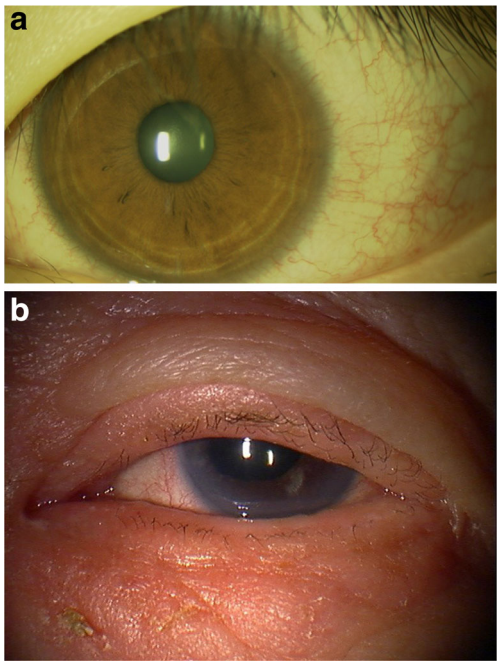

Fig. 2 Photographs showing adverse events of a one-year treatment with ripasudil. (a) Conjunctival hyperemia 30 min after instillation. The hyperemia peaked in severity 15 min after the instillation. At 2 h after instillation, the hyperemia resolved and the eyes returned to the pre-instillation state. (b) Blepharitis

cell adhesion, cell contraction, cell motility, and cell-cell contact in the trabecular meshwork and Schlemm canal that modulate the conventional outflow of aqueous humor [4–9]. Based on this, we believed that the addition of ripasudil to the existing maximum medical therapy would have an IOP-lowering effect.

The incidence of conjunctival hyperemia as an adverse effect was 100% (39/39) in this study. However, the conjunctival hyperemia was not severe and resolved in all patients within 2 h after drug instillation (Fig. 2). The occurrence of hyperemia precluded the administration of ripasudil in only one patient. Other adverse events included blepharitis (3/39), allergic conjunctivitis (2/39), punctate keratitis (2/39), and ophthalmalgia (1/39). Although previous studies [10–13] of ripasudil showed similar incidences of adverse events, the occurrence of blepharitis increased during long-term administration. In our previous study [14], blepharitis only occurred in one patient for 3 months. It has been indicated that a delayed type (type 4) hypersensitivity may cause blepharitis. Since a type 4 allergy sensitization may occur 6 to 12 months after initial exposure, blepharitis due to ripasudil might occur during this period. A study by Omichi et al. reported a nonclinical safety assessment of ripasudil [16]. K-115 (ripasudil) caused very slight erythema in pigs. In addition, K-115 was found to have less sensitizing potential, did not function as an antigen for type 1 allergies, and had no influence on increased vascular permeability in animals. Although ripasudil did not affect nonclinical tests of that study, it may have long-term effects.

Approximately 30% of the patients in this study dropped out due to insufficient IOP reduction or adverse events. Although five patients (12.8%) could not continue therapy with ripasudil, the adverse events were not severe. Thus, ripasudil appears to be safe even when used with maximum medical therapy.

Steven et al. reported that the persistence rates of a prostaglandin analog were from 58% to 68% at 12 months. A study by Kashiwagi et al. reported that the persistence rate of latanoprost monotherapy was approximately 60.8% at 12 months [17]. The patient's persistence with medication use was associated with younger age, the number of medications, and the hospital size [18]. A study by Nordstrom et al. reported that nearly half of the studied glaucoma patients discontinued all topical ocular hypotensive therapy within 6 months [19]. Our study demonstrated longer continuance than other reports, which indicates that even adjunctive therapy with ripasudil may have good adherence and safety.

We attempted to determine the IOP-lowering effect and safety of ripasudil in patients already receiving maximum medical therapy. While the duration of our previous study was short, this study examined the one-year efficacy of IOP decrease and tolerability. However, one limitation was that this was a small case study that was not randomized. This limited the results, and a study including more patients cases is needed. The effect of ripasudil is unknown in other subtypes of glaucoma such as exfoliation glaucoma, secondary glaucoma, and steroid-related glaucoma. Thus, further evaluation of the IOP-lowering effects of ripasudil therapy is necessary.

In conclusion, a one-year treatment with ripasudil in patients already on maximum medical therapy might significantly decrease IOP and may help reduce glaucoma surgery, at least for one year. Although the adverse side effects of blepharitis and conjunctive hyperemia were observed, the drug was otherwise well tolerated.

Compliance with ethical standards

Funding No funding was received for this research.

Conflicts of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; or expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments, or with comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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