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Late-Onset Ocular Hypotensive Effect of Ripasudil on Primary Open-Angle Glaucoma

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Purpose: We evaluated the late-onset ocular hypotensive effect of ripasudil after long-term administration in real-world clinical data and investigated its associated factors in primary open-angle glaucoma (POAG).

Patients and Methods: We reviewed the clinical patients with POAG who newly started ripasudil without changes of treatment. Enrolled eyes were assigned to two groups: positive group with the late-onset effect and negative group. Eyes that show the late-onset effect 6 months after starting ripasudil were defined as positive. Logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the late-onset effect.

Results: We enrolled 74 eyes of 74 patients with POAG (age, 67.5 ± 10.9 years; mean deviation, −11.2 ± 5.9 dB) and followed them for 14.2 ± 5.0 months. Among them, 12 (16.2%) eyes were assigned to the positive group. Retinal nerve fiber layer (RNFL) thickness (73.4 ± 12.9 vs 64.0 ± 9.8 μm, $P = 0.04$) and primary IOP (18.8 ± 4.1 vs 15.8 ± 4.3 mmHg, $P = 0.01$) before starting ripasudil were higher in the positive group than in the negative group. The late-onset effect was associated with higher IOP (OR, 1.22; 1.01–1.48) and thicker RNFL (2.76; 1.15–6.63).

Conclusion: Some patients with POAG showed the late-onset IOP-lowering effect of ripasudil, and its associated factors were higher IOP and thicker RNFL. The addition of ripasudil may offer potential benefits particularly for early-stage glaucoma with thicker RNFL.

Keywords: ripasudil, ROCK-inhibitor, glaucoma, ocular hypertension, intraocular pressure

Introduction

Glaucoma is the second leading cause of blindness worldwide,[1] and the total number of cases of glaucoma is estimated to rise to 111.8 million in 2040.[2] Elevated intraocular pressure (IOP) is considered the most important and only clinically modifiable risk factor for the development and progression of glaucoma.[3] Therefore, improving our understanding of IOP-lowering strategies for patients with glaucoma is clinically important.

Rho-associated protein kinase (ROCK) inhibitors are widely used to lower IOP in glaucoma and ocular hypertension. These ocular hypotensive agents affect the cytoskeleton of both the trabecular meshwork and Schlemm's canal cells, lowering IOP through a direct effect on the conventional outflow pathway. By decreasing the density of actin stress fibers, they induce the relaxation of the trabecular meshwork and cause disruption of the actin bundles, thereby leading to the expansion of the internal space in the trabecular meshwork.[4–6] In other words, these agents increase the conventional outflow of the aqueous humour.[5,7] Ripasudil (Glanatec, Kowa Company, Ltd., Aichi, Japan), which is a ROCK inhibitor, was approved in Japan in 2014 as an IOP-lowering treatment for glaucoma and ocular hypertension.[8] Many clinical studies have shown its efficacy and safety in patients with primary open-angle glaucoma (POAG).[9–12]

Recently, an additional late-onset ocular hypotensive effect of ripasudil after long-term topical treatment was demonstrated.[12,13] In these reports, a gradual decrease of IOP was observed approximately 6 months after starting ripasudil in addition to temporary IOP-lowering effect. This late-onset effect in patients with POAG is presumed to be

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induced by extracellular matrix (ECM) remodeling of the conventional outflow pathway caused by ripasudil.[13] However, another observational study reported no significant difference in IOP between 1 to 6 months and 12 to 24 months after starting ripasudil.[14] To date, the late-onset ocular hypotensive effect of ripasudil has been controversial in the real-world data, and its associated factors remains unknown.

In this study, we aimed to elucidate the late-onset ocular hypotensive effect of ripasudil in patients with POAG. Furthermore, we explored its clinically associated factors contributing to the effect.

Material and Methods

Study Population

We retrospectively reviewed the clinical patients with POAG who visited the Jikei University Hospital and newly started ripasudil between January 2018 and December 2019. Among them, we excluded patients with (1) infrequent follow-up, (2) short follow-up period (<6 months), (3) change of treatment (switching eyedrops, intraocular surgery, or laser treatment) within 3 months before or 6 months after starting ripasudil, (4) secondary glaucoma (such as uveitis), which was difficult to evaluate IOP-lowering effects of ripasudil. We analyzed one randomly chosen eye per patient.

Ethics

This study was approved by the ethics committee of the Jikei University School of Medicine [approval number: 33–119 (10,734)]. The study design followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients as a broad consent (opt-out).

Ophthalmologic Examinations

The enrolled patients underwent general ophthalmologic examinations, which included spherical equivalent measurement, best-corrected visual acuity evaluations using a Landolt C chart, IOP measurements using Goldmann applanation tonometry, slit-lamp biomicroscopy, fundus photography, visual field measurements using the Humphrey Visual Field Analyzer (Carl Zeiss Meditec, Inc). 30–2 Swedish interactive threshold algorithm standard program, and optical coherence tomography (OCT) measurements using Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA). OCT measurements included the average circumpapillary retinal nerve fiber layer (RNFL) thickness, and the average macular ganglion cell layer (GCL) thickness. All patients underwent IOP measurements at certain times, either in the morning or in the afternoon.

Glaucoma Diagnosis

The criteria for glaucoma diagnosis were the presence of glaucomatous optic neuropathy and visual field defect consistent with the optic nerve change.[15] Glaucomatous optic neuropathy was diagnosed when (1) the vertical cup-to-disc ratio of the optic nerve head was 0.7 or more; (2) the rim-to-disc ratio at the superior portion (11- to 1-o'clock positions) or the inferior portion (5- to 7-o'clock positions) was 0.1 or less; (3) the difference in the vertical cup-to-disc ratio was 0.2 or more between both eyes; or (4) RNFL defects in continuity with thinned rim were found.

Glaucomatous visual field defect was diagnosed based on the Anderson-Patella criteria, when (1) the glaucoma hemifield test results were outside normal limits; (2) pattern deviation probability plots in the upper or lower hemifield showed a cluster of 3 or more non-edge contiguous points having sensitivity with a probability of less than 5%, of which at least 1 point had a probability of less than 1%; or (3) a pattern standard deviation outside the 95% normal confidence limits was noted.

Definition of the Late-Onset Effect

All eyes were categorized into two groups: positive group (with late-onset effect) and negative group (without late-onset effect). Classification was based on IOP trends after ripasudil initiation: early (1–6 months), middle (4–9 months), and late (7–12 months). Cases were assigned to the positive group if IOP showed a continuous decrease: *primary IOP > early IOP > middle IOP > late IOP* (Figure 1). Cases not meeting these criteria were classified as negative. This approach excluded cases with inconsistent trends, such as IOP rebound before IOP reduction in the late period.

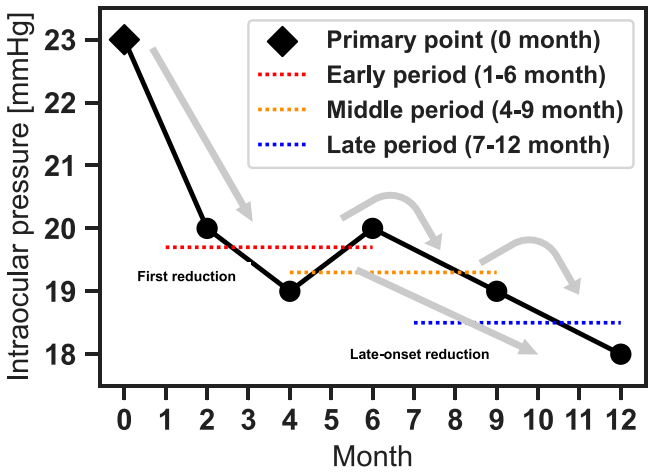

Figure 1 Definition of the positive group of the late-onset effect In this Figure 1, IOP means intraocular pressure. An example case in this figure shows a constant IOP decline trend "primary IOP (before starting ripasudil) > early IOP > middle IOP > late IOP", and is assigned to the positive group. Eyes who do not satisfy this definition are determined to be the negative group. The diamond shape in this figure shows the primary IOP, and the circles indicate the other measurement points of IOP. Three colored horizontal lines represent the mean IOP in the early period, in the middle period, and in the late period, respectively. The widths of lines represent the lengths of these periods.

Statistical Analyses

We compared the patient backgrounds of these two groups regarding the following: sex, age, intraocular lens implantation, number of eye drops, spherical equivalent and best-corrected visual acuity, thicknesses of the RNFL and GCL in OCT measurements, mean deviation (MD) and pattern standard deviation determined in visual field test, and primary IOP. Continuous variables were presented as mean ± standard deviation. The Mann–Whitney *U*-test was used to compare continuous variables between the two groups. The chi-squared test and Fisher's exact test were used to compare categorical data as nominal scales. To explore associated factors on the late-onset ocular hypotensive effect, logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the late-onset effect. Multivariable logistic models included statistics that were statistically significant ($P < 0.05$) in the univariable analysis or clinically essential. All statistical analyses were performed using Python 3.10.8.

Results

We enrolled 105 eyes of 74 patients who newly started ripasudil between January 2018 and December 2019. We randomly chose one eye per patient, and analyzed 74 eyes of 74 patients (mean age, 67.5 ± 10.9 years; male, 62.0%). The mean follow-up period was 14.2 ± 5.0 months.

The 74 eyes were divided into two groups: the positive group showing the late-onset effect and the negative group not showing the effect. 12 (16.2%) eyes were assigned to the positive group and 62 (83.8%) to the negative group. IOP trends in each of the two groups are shown in Figure 2. The differences in characteristics between the positive and negative groups are shown in Table 1. Statistically significant differences were observed between the two groups in primary IOP (18.8 ± 4.1 vs 15.8 ± 4.3 mmHg, $P = 0.01$), RNFL thickness (73.4 ± 12.9 vs 64.0 ± 9.8 μm, $P = 0.04$).

To identify the associated factors on the late-onset effect, a univariable logistic regression was first performed. As shown in Table 2, the analysis revealed that primary IOP and RNFL thickness were associated with the late-onset effect (OR 1.15 (95% CI; 1.01 to 1.31); and 1.10 (1.01 to 1.19), respectively). Regarding the remaining variables, MD showed a modest, although not significant, association with the outcome (OR 1.09 (0.99 to 1.21); P = 0.08). Subsequently, we performed multivariable logistic regression analysis using various combinations of primary IOP, RNFL thickness, and MD values as explanatory variables, and three models were created (Table 3). In model 1, the OR of primary IOP was 1.22 (1.01 to 1.48) and the OR of RNFL thickness was 1.11 (1.01 to 1.21), both of which were significant. In model 2, the OR of primary IOP was 1.33 (1.06 to 1.65). Overall, RNFL thickness and primary IOP significantly were associated with the occurrence of the late-onset effect.

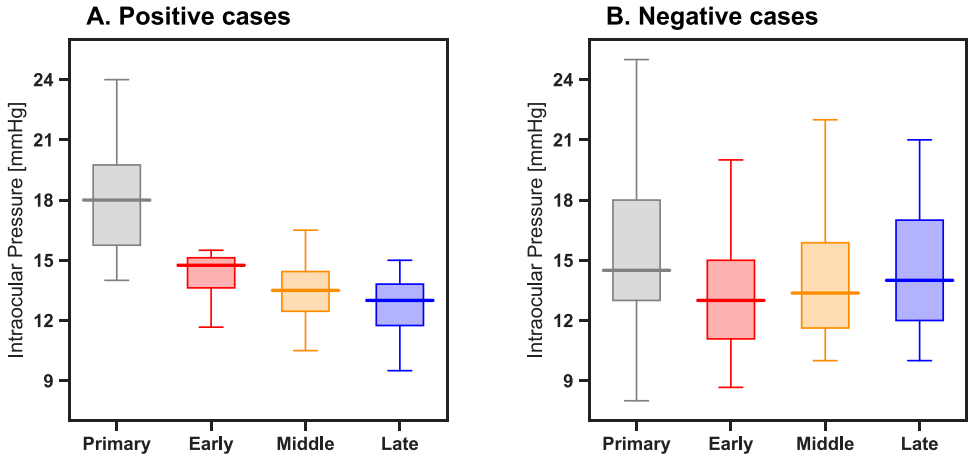

Figure 2 Time courses of intraocular pressure variations in patients with open-angle glaucoma. **(A** and **B)** show the stratified visualization of intraocular pressure (IOP) trends in positive and negative cases, respectively. The trends are presented at four time points: the primary point (before starting ripasudil), the early period (1–6 months after starting ripasudil), the middle period (4–9 months after), and the late period (7–12 months after). The median and interquartile range (IQR) of IOP in each term are depicted as colored boxplots. In the positive group (**A**), the median of the IOP is 18.0 (IQR; 4.0) mmHg at the primary point, 14.8 (1.5) mmHg in the early period, 13.5 (2.0) mmHg in the middle period, and 13.0 (2.1) mmHg in the late period. In the negative group (**B**), the median of the IOP is 14.5 (IQR; 5.0) mmHg at the primary point, 13.0 (3.9) mmHg in the early period, 13.4 (4.2) mmHg in the middle period, and 14.0 (5.0) mmHg in the late period.

Discussion

In this study, we evaluated the late-onset effect of ripasudil in 74 eyes of 74 patients with POAG who visited Jikei University Hospital between January 2018 and December 2019. The positive group with the late-onset effect included 12 (16.2%) eyes. The differences in patient backgrounds between the positive (12 eyes) and negative (62 eyes) groups were statistically significant in terms of primary IOP and RNFL thickness. These clinical factors were also significant in multivariable analyses.

Table 1 Characteristics of Patients

		Total (n = 74)	Positive (n = 12)	Negative (n = 62)	*P* value
Observation period, month		14.2 ± 5.0	14.3 ± 4.6	14.1 ± 5.2	0.79[a]
Sex, n	**Male**	46 (62.2%)	6 (50.0%)	40 (64.5%)	
	Female	28 (37.8%)	6 (50.0%)	22 (35.5%)	0.35[a]
Age, years		67.5 ± 10.9	64.2 ± 12.7	68.1 ± 10.5	0.29[b]
Lens	**Phakia**	53 (71.6%)	9 (75.0%)	44 (71.0%)	
	Iol	21 (28.4%)	3 (25.0%)	18 (29.0%)	1.00[a]
Eyedrop, n	**One**	4 (5.4%)	1 (8.3%)	3 (4.8%)	
	Two	6 (8.1%)	2 (16.7%)	4 (6.5%)	
	Three	27 (36.5%)	5 (41.7%)	22 (35.5%)	
	Four	37 (50.0%)	4 (33.3%)	33 (53.2%)	0.30[a]
BCVA, logmar		0.3 ± 0.5	0.1 ± 0.1	0.3 ± 0.5	0.21[b]
SE, diopter		−3.6 ± 3.7	−4.6 ± 4.7	−3.5 ± 3.4	0.48[b]
Oct	**RNFL, μm (n)**	65.6 ± 10.8 (54)	73.4 ± 12.9 (9)	64.0 ± 9.8 (45)	**0.04**[b]
	GCL, μm (n)	58.5 ± 12.3 (48)	64.8 ± 15.9 (8)	57.2 ± 11.3 (40)	0.26[b]
Hfa	**MD, dB (n)**	−14.9 ± 7.9 (50)	−11.2 ± 8.0 (11)	−16.0 ± 7.6 (39)	0.08[b]
	PSD, dB (n)	11.0 ± 3.3 (45)	10.3 ± 4.3 (10)	11.2 ± 3.0 (35)	0.92[b]
Primary IOP, mmhg		16.3 ± 4.4	18.8 ± 4.1	15.8 ± 4.3	**0.01** [b]

Note: [a]Fisher exact test; [b]Mann–Whitney *U*-test. Boldface values indicate statistical significance with P < 0.05. Continuous variables are presented as mean ± standard deviations.

Abbreviations: n, number; IOL, intraocular lens; BCVA, best corrected visual acuity; logMAR, logarithm of minimum angle of resolution; SE, spherical equivalent; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer; GCL, ganglion cell layer; HFA, Humphrey visual field analyzer; MD, mean deviation; PSD, pattern standard deviation; IOP, intraocular pressure.

Table 2 Univariable Logistic Regression

		OR (95% CI)	*P* value
Sex, n	**Male**	0.55 (0.16 to 1.91)	0.35
Age, years		0.97 (0.91 to 1.02)	0.25
Lens	**Iol**	0.81 (0.20 to 3.36)	0.78
Eyedrop, n	**One**	Reference	
	Two	1.5 (0.09 to 25.4)	0.78
	Three	0.68 (0.06 to 8.00)	0.76
	Four	0.36 (0.03 to 4.39)	0.43
		P for trend	0.17
BCVA, logMAR		0.14 (0.01 to 1.64)	0.12
SE, diopter		0.92 (0.79 to 1.08)	0.30
OCT	**RNFL, μm**	1.10 (1.01 to 1.19)	**0.03**
	GCL, μm	1.05 (0.99 to 1.12)	0.12
HFA	**MD, dB**	1.09 (0.99 to 1.21)	0.08
	PSD, dB	0.92 (0.75 to 1.13)	0.45
Primary IOP, mmHg		1.15 (1.01 to 1.31)	**0.04**

Note: Boldface values indicate statistical significance with P < 0.05.
Abbreviations: OR, odds ratio; CI, confidential interval; n, number; IOL, intraocular lens; BCVA, best corrected visual acuity; logMAR, logarithm of minimum angle of resolution; SE, spherical equivalent; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer; GCL, ganglion cell layer; HFA, Humphrey visual field analyzer; MD, mean deviation; PSD, pattern standard deviation; IOP, intraocular pressure.

Table 3 Multivariable Logistic Regression with Primary IOP, RNFL and MD

	Model 1 (n = 54)		Model 2 (n = 50)		Model 3 (n = 35)	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Primary IOP (mmHg)	1.22 (1.01 to 1.48)	**0.04**	1.33 (1.06 to 1.65)	**0.01**		
RNFL (μm)	1.11 (1.01 to 1.21)	**0.02**			1.07 (0.98 to 1.17)	0.14
MD (dB)			1.07 (0.96 to 1.19)	0.23	1.03 (0.93 to 1.15)	0.54

Note: Boldface values indicate statistical significance with P < 0.05.
Abbreviations: OR, odds ratio; CI, confidential interval; n, number; IOP, intraocular pressure; RNFL, retinal nerve fiber layer; MD, mean deviation.

A thicker RNFL was associated with the late-onset effect, suggesting that this effect would be achieved in relatively early-stage glaucoma. Degeneration and increased ECM in the trabecular meshwork, along with the pharmacological effects of ripasudil, may explain this finding.[16,17] One mechanism is ECM stretching due to elevated IOP, which increases matrix metalloproteinase activity and alters ECM protein expression levels.[18,19] The other mechanism involves the biochemical effects of transforming growth factor-β2 (TGF-β2), which is more abundant in the aqueous humor of patients with glaucoma, on the ECM.[20] An ex vivo study showed that TGF-β2 decreased the outflow facility, thereby likely to affect the ECM.[21] In addition, an in vivo study in rhesus macaques showed that the ECM structure changed with increasing age.[22] In the human eye, analysis using anterior-segment OCT also suggested age-related structural changes in the ECM.[23] Thus, in early-stage glaucoma, ECM degeneration is likely less severe, as it progresses with age. Turning to the pharmacological effects of ROCK inhibitors, they reduce cell tension, stiffness, and ECM synthesis in the trabecular meshwork and Schlemm's canal by regulating contractility, fibrosis, permeability, and cellular behaviors.[24–26] In the long term, ripasudil induces ECM remodeling in the conventional outflow pathway, potentially leading to late-onset IOP

reduction.[13] Altogether, we speculate that ripasudil is more effective in early-stage glaucoma, where milder ECM degeneration makes gradual remodeling and late-onset IOP reduction more achievable.

A higher IOP before starting ripasudil was related to the late-onset effect. Although elevated IOP is one of the causes of ECM degeneration in the trabecular meshwork and Schlemm's canal and seems a negative factor for the late-onset effect,[18,19] it was positively related to this effect in our study. In general, the effect of glaucoma medication is greater in patients with elevated IOP.[27] The same may be true for the late-onset effect of ripasudil. Nevertheless, further analysis of this mechanism is warranted.

While previous prospective studies suggested that ripasudil had a late-onset effect on overall IOP reduction,[12,13] our results showed that the late-onset effect was not observed in most of the patients, but only in some patients (16.2%). This may be because most patients in our study had late-stage glaucoma, where the mean RNFL thickness was 64.8 μm, the mean MD was −11.0 dB, and the mean number of glaucoma medications was 3.3. As ripasudil is usually the third or fourth drug choice, retrospective studies inevitably include many late-stage cases. In a previous study observing the late-onset IOP-lowering effect, 33.1% of the enrolled patients had ocular hypertension,[12,13] and hence, the characteristics of those patients were different from those of ours. This may be one of the reasons for these contrasting results. On the other hand, in another retrospective study, the late-onset effect was not obtained overall when comparing the early period (1–6 months) and the late period (12–24 months).[14] The mean number of glaucoma medications was 2.8, which suggested that most of the patients probably had the same stage of glaucoma as that in our patients. This is probably why their results were similar to those of our study. These facts are also consistent with our hypothesis that the late-onset effect is limited to patients with relatively early-stage glaucoma.

Our study had some limitations. (1) As ripasudil is usually used as the third, fourth, or fifth drug, most patients already have late-stage glaucoma. This led to the small number of patients with early-stage glaucoma. Therefore, further investigation on early-stage glaucoma is warranted to confirm and validate our findings. (2) We did not obtain information on the duration of glaucoma treatment. Since the treatment duration can serve as a surrogate marker for the disease duration, it is likely to reflect the state of ECM degeneration. Further discussion on the late-onset effect of ripasudil, taking this information into account, is desirable. (3) The number of IOP measurement points (once every 2–3 months) was limited in this retrospective study.

In conclusion, our study revealed that the late-onset effect was not observed in most of the patients, but only in some patients (16.2%). Our results did not show the late-onset effect as an overall trend, and this finding may be attributed to patient backgrounds. In our study, patients with the late-onset effect were characterized by a thicker RNFL. This finding indicates that patients with preserved RNFLs, which probably reflects early-stage glaucoma, are more likely to benefit from the additional efficacy of ripasudil. Furthermore, a higher IOP was associated with the late-onset effect. We believe that our results will serve as a crucial step toward more effective use of IOP-lowering eye drops for glaucoma patients and a more detailed understanding of the mechanisms of ROCK inhibitors on the conventional outflow pathway.

Data Sharing Statement

The database used in the current study is not made public, but it will be made available from the corresponding author upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work. This paper has been uploaded to ResearchSquare as a preprint: https://www.researchsquare.com/article/rs-1682069/v1

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