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ORIGINAL RESEARCH ARTICLE

Efficacy of Ripasudil as a Second-line Medication in Addition to a Prostaglandin Analog in Patients with Exfoliation Glaucoma: A Pilot Study

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Abstract
Objective This study aimed to assess the intraocular pressure (IOP)-lowering effects of ripasudil, a Rho kinase inhibitor, as a second-line medication in patients with exfoliation glaucoma.
Methods This retrospective cohort study included patients with exfoliation glaucoma who received ripasudil as the second-line drug in addition to prostaglandin analogs, and were followed-up for at least 5 months. Twenty-seven eyes of 16 patients were enrolled; the mean (±standard deviation) age was 76.1 ± 7.2 years (range 63–91 years). Baseline IOPs were the averages of three IOP measurements performed before ripasudil treatment. Statistical analyses used the paired *t* test with the Bonferroni correction. Relevant background factors were analyzed via stepwise, multiple regression analysis.
Results The mean (±standard deviation) IOP levels prior to commencement of ripasudil, 1–2 months later, and 5–6 months later were 16.2 ± 2.1, 14.7 ± 2.8, and 13.1 ± 2.6 mmHg, respectively. These levels differed significantly ($p = 0.00019$ for 0 versus 1–2 months, 0.00087 for 1–2 vs. 5–6 months, and <0.00001 for 0 vs. 5–6 months). Stepwise multiple regression analysis on data from all 27 eyes showed that the change in IOP at 5–6 months was associated with the treatment time with prostaglandin analogs and age, but not with baseline IOP, the severity of the visual field defect, the timing of IOP measurement, or pseudophakic status.
Conclusions Ripasudil significantly lowered IOP in patients with exfoliation glaucoma, and the effect thereof increased over time within 5 months.

Key Points

Ripasudil significantly lowered intraocular pressure in patients with exfoliation glaucoma.

The effect of ripasudil was greater at 5–6 months than at 1–2 months in patients with exfoliation glaucoma.

The effect of ripasudil was associated with the treatment time with prostaglandin analogs and age in patients with exfoliation glaucoma.

1 Introduction

Lowering of intraocular pressure (IOP) is the leading therapeutic aim when treating glaucoma medically [1–3]. Currently, prostaglandin analogs are used to increase unconventional outflow, and beta-blockers are employed to reduce aqueous humor production. These drugs are representative first-line medications [4]. Carbonic anhydrase inhibitors and brimonidine serve principally as second-line drugs [5, 6]. In 2014, ripasudil, a selective Rho kinase inhibitor, was approved as a secondary anti-glaucoma medication in Japan. In clinical trials, ripasudil effectively lowered IOP when given with prostaglandin analogs, beta-

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blockers, or combinations of both of the latter drugs [7, 8]. Rho kinase inhibitors, including ripasudil, are thought to lower IOP by modulating the conventional (trans-trabecular) outflow pathway [9–12]. Recent work has shed new light on the pathogenesis of exfoliation glaucoma; common sequence variants in the lysil-oxidase-like 1 (LOXL1) gene associated with abnormal deposition of the extracellular matrix may be involved in IOP elevation [13]. Based on these findings, and insights afforded by classical studies on the outflow pathway [14], exfoliation glaucoma is now regarded as a disease in which the conventional outflow pathway is seriously aberrant [15]. Thus, in patients with exfoliation glaucoma, sensitivity to Rho kinase inhibitors may differ from that of patients with other types of open-angle glaucoma. However, few clinical studies have addressed the IOP-lowering effects of Rho kinase inhibitors in patients with exfoliation glaucoma.

Our aim was to assess the intraocular pressure (IOP)-lowering effects of ripasudil as a second-line medication in patients with exfoliation glaucoma, and to show that ripasudil, a Rho kinase inhibitor, exerts a significant IOP-lowering effect when used as a second-line medication in patients with exfoliation glaucoma. We also assessed other relevant clinical parameters.

2 Methods

2.1 Ethics, Consent, and Permissions

All procedures adhered to the tenets of the Declaration of Helsinki. This retrospective cohort study was approved by the Institutional Review Board and Ethics Committee of Kumamoto University. Each patient gave written informed consent prior to study commencement.

2.2 Patients

We retrospectively reviewed the medical records of patients treated at the Matsumura Eye Clinic, Kumamoto, Japan. Inclusion criteria were: patients with open-angle exfoliation glaucoma who received topical 0.4% ripasudil (Glanatech®; Kowa, Nagoya, Japan) as a second-line drug (in addition to a prostaglandin analog) between December 2014 and April 2016, and who were followed-up for at least 5 months. Patients were diagnosed as having open-angle exfoliation glaucoma, based on the presence of exfoliation fibrils on the iris and/or anterior lens surface associated with glaucoma optic neuropathy, observed using a slit-lamp, gonioscope, fundus scope, and a visual field test. Exclusion criterion was: eyes with any history of intraocular laser treatment or surgery other than cataract surgery.

2.3 Data Collection

Baseline IOP was the average of three IOP measurements taken prior to ripasudil treatment. IOP levels were measured via Goldmann applanation tonometry, 1–2 and 5–6 months after the addition of ripasudil to a prostaglandin analog.

2.4 Statistical Analysis

The IOP values at different time points were compared using the paired t test with the Bonferroni correction. Relevant background factors were analyzed via stepwise, multiple regression analysis. Correlations among factors were sought by calculation of Spearman's correlation coefficients. A p value <0.05 was considered statistically significant.

3 Results

Twenty-seven eyes of 16 patients with exfoliation glaucoma met the inclusion criteria; we studied seven males and nine females. Twenty eyes were treated with tafluprost, five eyes were treated with travoprost, and two eyes were treated with latanoprost before treatment with ripasudil. The mean (±standard deviation, SD) age at the time of ripasudil instillation was 76.1 ± 7.2 years (range 63–91 years). The mean (±SD) IOP prior to medical treatment was 18.8 ± 4.6 mmHg (range 10–38 mmHg). The baseline IOP prior to ripasudil treatment (thus after administration of a prostaglandin analog) was 16.2 ± 2.1 mmHg (range 9.7–19.0 mmHg). The mean (±SD) mean deviation in the Humphrey visual field test was −5.69 ± 4.80 dB (range −17.26 to −0.32 dB). The mean (±SD) treatment time with prostaglandin analogs was 5.4 ± 4.6 years (range, 0.3–18.0 years). Four eyes had histories of cataract surgery prior to ripasudil instillation. The mean (±SD) IOP levels at 1–2 and 5–6 months after addition of ripasudil were 14.7 ± 2.8 mm and 13.1 ± 2.6 mmHg, respectively; these differed significantly ($p = 0.0002$ for 0 vs. 1–2 months, 0.0009 for 1–2 vs. 5–6 months, and <0.0001 for 0 vs. 5–6 months) (Fig. 1). The percentage IOP reductions from baseline were 9.2 and 18.7% at 1–2 and 5–6 months, respectively. In 14 (52%) of the 27 eyes, the percentage IOP reduction from baseline exceeded 20%. Of those, four eyes (15%) had more than a 30% reduction in IOP from the baseline (Fig. 2). We found no significant association between the IOP levels at 1–2 and 5–6 months (Fig. 3a). Severe side effects, which required additional therapies, were not observed during the observational period.

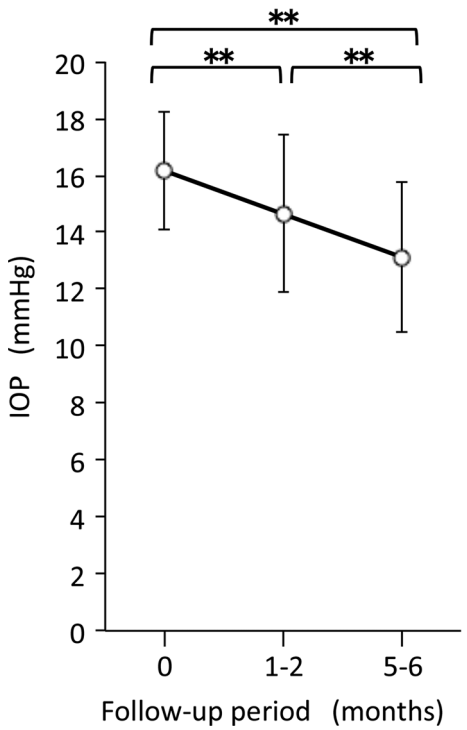

Fig. 1 Time-dependent changes in intraocular pressure (IOP) (mean ± standard deviation) to 5–6 months (M) of follow-up after ripasudil instillation. $^{**}p < 0.01$ by the paired t test with the Bonferroni correction

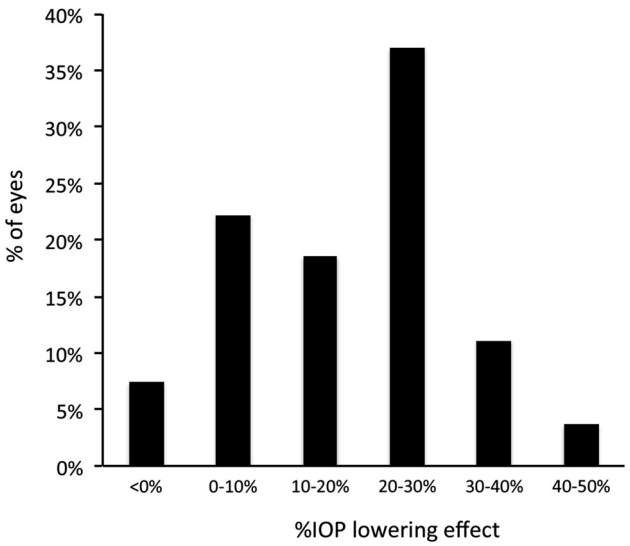

Fig. 2 Percentages of eyes by the ratios of intraocular pressure (IOP) reduction

Stepwise multiple regression analysis of data from all 27 eyes showed that the change in IOP at 5–6 months was significantly associated with the treatment time with prostaglandin analogs and age, but not with baseline IOP, the severity of the visual field defect, the timing of IOP measurement, or pseudophakic status (Table 1). Scatter plots of the IOPs of right and left eyes that both met the inclusion criteria showed that the IOP reductions in either eye were correlated ($R^2 = 0.709$, $p = 0.001$; Fig. 3b). Thus, both eyes of the same patients exhibited similar (and significant) improvement. We performed further stepwise multiple regression analysis on 17 eyes of 17 patients (those with higher IOPs) and found a significant association between IOP reduction 5–6 months after the addition of ripasudil and the treatment time with prostaglandin analogs ($t = -2.20$, $p = 0.046$), but not with age ($t^2 < 2$).

4 Discussion

In the present study, we found that ripasudil, added as a second drug to a prostaglandin analog, exerted a significant additive IOP-lowering effect. To our knowledge, this is the first report to focus on the efficacy of a Rho kinase inhibitor used to treat exfoliation glaucoma. To date, several prospective and retrospective studies have explored the IOP-lowering effects of ripasudil [7, 8, 16–20]. In our previous studies [7, 8, 16–18], we found that ripasudil lowered IOP in normal volunteers, exhibited dose-dependent efficacy in glaucomatous patients, and exerted additive IOP-lowering effects when combined with prostaglandin analogs and beta-blockers. Other clinical trials have shown that ripasudil further lowered IOP when combined with the maximal tolerable levels of prostaglandin analogs, beta-blockers, carbonic anhydrase inhibitors, and brimonidine [19, 20]. The cited studies included some patients with exfoliation glaucoma, but the numbers were small (less than ten in each study). Thus, this is the first report on the IOP-lowering effect of a Rho kinase inhibitor and the relationships thereof with clinical factors in eyes with exfoliation glaucoma.

In patients with exfoliation glaucoma, the pathogenesis of IOP elevation features principally a reduction in conventional outflow attributable to abnormal deposition of the extracellular matrix [14, 15]. The IOP-lowering mechanism of Rho kinase inhibitors involves depolymerization of the actin cytoskeleton of the trabecular meshwork and endothelial cells of Schlemm's canal [9–12]. Previous experimental studies showed that Rho kinase inhibitors affected metabolic changes in, and contraction of, the extracellular matrix in the conventional outflow route; cell contractility, adhesion, and motility; and giant vacuole formation [21–23]. Together, the data suggest that Rho kinase inhibitors improve conventional outflow by modulating cellular behavior in the trabecular meshwork and the endothelium of Schlemm's canal. Given such a mechanism of action, Rho kinase inhibitors would be expected to appropriately target exfoliation glaucoma in which the conventional outflow pathway is abnormal. The significant

Table 1 Relationships between intraocular pressure (IOP) changes at 5–6 months after ripasudil instillation, and background factors, revealed by multiple regression analysis

Background factor	*t* value	*p* value
Treatment time of prostaglandin analogs (months)	−2.47	0.021
Age (years)	2.12	0.044
Baseline IOP prior to ripasudil instillation (mmHg)	($t^2 < 2$)	N/A
Mean deviation upon Humphrey visual field analysis (dB)	($t^2 < 2$)	N/A
Time of IOP measurement	($t^2 < 2$)	N/A
Pseudophakic status	($t^2 < 2$)	N/A

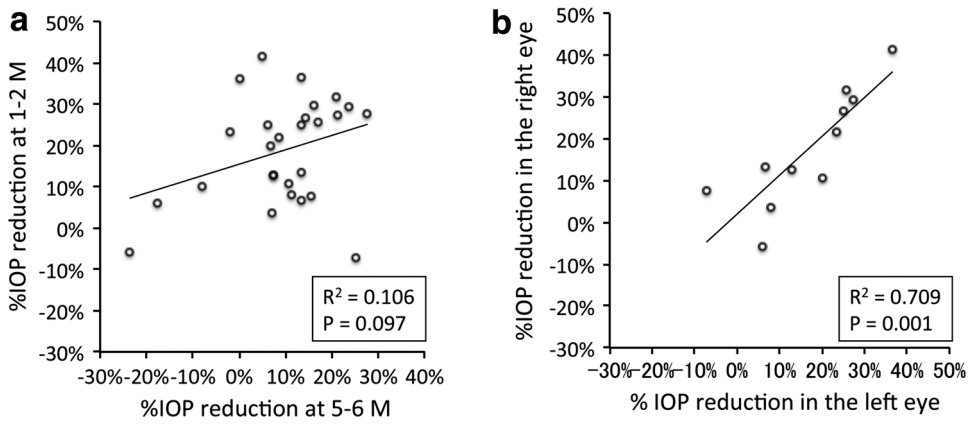

Fig. 3 Scatter plots of the percentages of intraocular pressure (IOP) reduction at 1–2 and 5–6 months (**a**) and percentage IOP reductions in *right* and *left eyes* (**b**). The lines are linear approximations. Correlations among various factors were sought by calculating Spearman's correlation coefficients (*R* values) and *p* values

IOP-lowering effect of ripasudil added to a prostaglandin analog supports this hypothesis.

We found that the change in IOP was greater 5–6 months (compared with 1–2 months) after the addition of ripasudil, suggesting that the drug exerts time-dependent IOP-lowering effects over the first 6 months in patients with exfoliation glaucoma. A 1-year clinical trial yielded similar data; the IOP-lowering effects of ripasudil increased with time and were stable. In other words, the longer the follow-up period, the lower the IOP within the follow-up period [8]. Although the previous study was mainly in primary open angle glaucoma, ripasudil may have an accumulative effect in exfoliation glaucoma. Also, we found that a shorter treatment period (potentially reflecting the time between exfoliation glaucoma onset and diagnosis) was associated with a larger change in IOP, implying that prolonged abnormality of the conventional outflow pathway in patients with exfoliation glaucoma may reduce responsiveness to Rho kinase inhibitors. Additionally, age was also a significant factor; older patients showed more IOP-lowering effects of ripasudil in the present study. Although the true nature of the interaction between age and drug effects in exfoliation glaucoma was unclear, there may have existed different pathological mechanisms between early onset and late onset patients with exfoliation glaucoma. However, no significant association between IOP change and baseline IOP, mean deviation on Humphrey visual field testing, or pseudophakic status, was evident. A previous study [8] found that baseline IOP was the only significant predictor of IOP change; age, gender, or the extent of the visual field defect were not relevant. Our results show otherwise. The discrepancies may be explained by between-study differences in glaucoma etiology and baseline IOP. The cited work [8] included principally patients with primary open-angle glaucoma and an IOP of 20 mmHg; we studied those with exfoliation glaucoma and an IOP of 16.2 ± 2.1 mmHg. Other explanations could include differences in study design, the relatively small number of cases, and/or the retrospective nature of both works. Our data should be interpreted with caution; the retrospective nature of the study may have introduced a level of bias. Thus, the observed association between baseline IOP and IOP change in patients with exfoliation glaucoma requires confirmation. Further studies with more patients are needed to identify clinical factors affecting the IOP-lowering efficacy of Rho kinase inhibitors in such patients.

No severe side effect was observed in the present study. In a previous prospective study, the most frequent side effect was hyperemia, which was observed in 55.9% of the patients with primary open-angle glaucoma or ocular hypertension after administration of ripasudil in addition to latanoprost [7]. Thus, it is assumed that the frequency and severity of ripasudil side effects would be similar in patients with exfoliation glaucoma compared with the past study. However, there was not an established interview

form in the present study, because the study was conducted in a retrospective manner. Thus, prospective studies are needed to reliably determine the safety of ripasudil in patients with exfoliation glaucoma.

5 Conclusion

Ripasudil, a selective Rho kinase inhibitor, significantly lowered IOP in patients with exfoliation glaucoma in a time-dependent manner within 5 months.

Compliance with Ethical Standards

Funding No external sources of funding were used to conduct this study.

Authorship All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for publication of this version.

Disclosures HT has received consulting fees from Kowa and MSD, and board membership fees from Senju Pharmaceutical, Santen Pharmaceutical, Alcon Japan, and Pfizer Japan. RM, TI, and AM certify that they have no conflict of interest.

Compliance with ethics guidelines All procedures followed the ethical standards of relevant committees on human experimentation (both institutional and national) and the Declaration of Helsinki of 1964, as revised in 2013. Written informed consent was obtained from all patients prior to inclusion in the study.

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