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Title: Efficacy and safety of ripasudil, a Rho-associated kinase inhibitor, in eyes with uveitic glaucoma

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Abstract

Purpose: To describe the initial experience, efficacy and safety of ripasudil hydrochloride hydrate (ripasudil), a Rho-associated kinase inhibitor eye drop, for uveitic glaucoma.

Methods: In this retrospective case series, we retrieved the clinical data of 21 eyes from 19 patients with open-angle uveitic glaucoma who were treated with ripasudil at Kobe University Hospital. We analyzed the median intraocular pressure (IOP) reductions after ripasudil treatment and collected the information on the adverse events that were encountered during the course of this treatment period.

Results: The causes of uveitis were sarcoidosis (29%), Behçet's disease (14%), Vogt–Koyanagi–Harada disease (10%), others (15%), and unclassified (33%). Of total, nineteen (90%) eyes were treated with topical, periocular, and/or systemic steroid therapies. The median number of glaucoma medications used before ripasudil treatment was 2, and the median follow-up time was 13 months. The median IOPs were 23 mmHg at baseline, 16 mmHg at 1 month, and 18 mmHg at 12 months with significant IOP reductions of −3 mmHg at 1 month and −2 mmHg at 12 months (P = 0.0050). Of total, 11 (52%) eyes with an IOP reduction ≥3 mmHg at 1 month (responders) showed a significant median IOP decrease at 12 months compared with non-responders (-5 mmHg versus 0 mmHg, P = 0.0242). Two adverse events were observed: rashes on the back and transient conjunctival hyperemia.

Conclusions: Ripasudil appears to be safe and substantially reduce IOP in eyes with uveitic glaucoma if the eye is a responder. Ripasudil could be an option for the treatment of uveitic glaucoma.

Keywords: uveitis; intraocular pressure; ocular hypertension; glaucoma; ripasudil

Introduction

Intraocular pressure (IOP) control is an important aspect of managing uveitic eyes, because the prevalence of secondary glaucoma due to uveitis (uveitic glaucoma) ranges from 8.8% to 41.8% [1-4] and eyes with uveitic glaucoma can eventually exhibit legal blindness. The mechanisms through which IOP increases in inflamed eyes are poorly understood. Prolonged intraocular inflammation, long term steroid use, and subsequent structural damage to the trabecular meshwork may be responsible for elevated IOP [5]. Histological specimens taken from patients with uveitic glaucoma revealed increased extracellular material deposition, infiltration of inflammatory cells, and occlusion of the Schlemm canal [6,7]. Furthermore, conventional outflow dysfunction may be closely related to IOP elevation in cases of uveitic glaucoma.

Ripasudil hydrochloride hydrate (brand name: Glanatec ophthalmic solution 0.4 %; Kowa Company, Ltd., Japan; hereafter referred to as ripasudil) is a Rho-associated coiled–coil containing protein kinase (ROCK) inhibitor approved in Japan in September 2014 as a second-line drug for the treatment of glaucoma or ocular hypertension. Several reports present data indicating that ripasudil lowers IOP by altering the conventional outflow facility [8-10]. For instance, Kaneko and associates conducted in vitro experiments and clearly demonstrated that ripasudil (K-115) treatment altered the morphology of trabecular meshwork cells and the permeability of the endothelial cells in the Schlemm's canal [10]. Lu and associates utilized freshly enucleated animal eyes and found that eyes perfused with a ROCK inhibitor (Y-27632) had larger effective filtration length and increased outflow facility compared with controls [8].

Accumulating evidence indicates that ripasudil lowers IOP and is well tolerated in eyes with primary open-angle glaucoma (POAG) or ocular hypertension (OHT) [11,12]. Given the

mechanism of action of ripasudil, it is expected that ripasudil substantially lowers IOP in uveitic glaucoma as well. However, to the best of our knowledge, there have been few published studies that assess the efficacy of ripasudil in eyes with secondary glaucoma due to uveitis. Therefore, the purpose of this study was to examine the efficacy and safety of ripasudil in a consecutive series of eyes with uveitic glaucoma.

Material and Methods

This retrospective study was approved by the institutional review board of Kobe University Graduate School of Medicine (UMIN000025466), and it was performed in compliance with the provisions of the Declaration of Helsinki. We reviewed the medical records of 19 patients (21 eyes) with uveitic glaucoma who received ripasudil treatment (applied twice daily) at Kobe University Hospital. In this study, ocular hypertension without a glaucomatous disc change was considered uveitic glaucoma if there was a recorded IOP of 21 mmHg or higher. Data obtained from patients' medical records included age, gender, etiology and anatomic location of uveitis, lens status, angle status, best corrected visual acuity (BCVA), IOP measured using a Goldmann applanation tonometer, visual field mean deviation (MD) measured by the Humphrey Filed Analyzer (program SITA standard 30-2; Carl Zeiss Meditec, Dublin, California), intraocular inflammation according to the National Eye Institute criteria adapted by the Standardization of Uveitis Nomenclature Working Group [13,14], medications including anti-inflammatory and anti-glaucoma drugs, and adverse events.

First, we assessed the temporal IOP changes in the patient's eyes after the commencement of ripasudil treatment, and examined subsequent IOP changes statistically at each time point after the commencement of the treatment. Second, we categorized

patients as responders and non-responders based on their response to ripasudil at 1 month. Responders were those patients with IOP decrease ≥3 mmHg at 1 month. We then compared the IOP changes at 12 months from baseline between the responders and the non-responders. Finally, we summarized the adverse events that occurred during the follow-up period.

The decimal BCVA was converted to the logarithm of the minimum angle of resolution (logMAR) for statistical analysis. Missing IOP data on were imputed using the last observation carried forward (LOCF) method (the data after discontinuation of ripasudil treatment was also considered missing data). The IOP changes over time were analyzed using the Friedman test followed by a multiple comparison test, and the IOP difference between the responders and the non-responders was analyzed using the Mann-Whitney *U*-test. Statistical analyses were performed using MedCalc v.16.8.4 software (MedCalc Software, Belgium). A P-value less than 0.05 was considered significant.

Results

Baseline characteristics of the subjects are presented in Table 1. The anterior chamber angle was open in all studied eyes. Of 21, 6 (29%) eyes were phakic and 15 (71%) were pseudophakic. Glaucomatous disc change was present in 14 (67%) eyes and absent in 7 (33%) eyes. Of 21, 4 (19%) eyes had anterior uveitis and 17 (81%) had panuveitis. The median (minimum, maximum) grades of anterior chamber cells, anterior chamber flare, and vitreal haze were 0 (0, 1), 0 (0, 0), and 0 (0, 1), respectively. The details of medical treatment for uveitis or increased IOP have been represented in Table 2. The breakdown of topical corticosteroids administered to 17 eyes were betamethasone 0.1% (53%), fluorometholone 0.1% (41%), and fluorometholone 0.02% (6%). The median (minimum,

maximum) number of eye-drop bottles was 3 (0, 4). Treatment with ripasudil was started as an add-on therapy in 11 (53%) eyes, as a substitute therapy in 7 (33%) eyes, and as a primary therapy in 3 (14%) eyes. The median (minimum, maximum) follow-up time was 13 (1, 28) months.

IOP decreased significantly after ripasudil administration, as demonstrated in Figure 1. The median (minimum, maximum) IOP was 23 (13, 46) mmHg at baseline, 16 (10, 41) mmHg at 1 month, 18 (11, 44) mmHg at 3 months, 17 (10, 44) mmHg at 6 months, and 18 (12, 44) mmHg at 12 months (P = 0.0050). The median (minimum, maximum) IOP changes were -3 (-36, +8) mmHg at 1 month, -4 (-32, +19) mmHg at 3 months, -4 (-32, +19) mmHg at 6 months, and -2 (-32, +19) mmHg at 12 months. The details of IOP changes at 1 month have been provided in Figure 2. Of total, 11 (52%) eyes attained a 10% IOP reduction from baseline at 1 month, while 5 (24%) eyes achieved a 30% IOP reduction. Of 21, 16 (76%) eyes showed an IOP reduction that was ≥1 mmHg, and 11 eyes (52%) were classified as ripasudil responders (defined as a reduction ≥3 mmHg at 1 month). The time course of IOP changes in the non-responder and responder groups has been represented in Figure 3. In the non-responder group, the median (minimum, maximum) IOP changes from baseline were -0.5 (-2, +8) mmHg at 1 month, +2 (-7, +19) mmHg at 3 months, 0 (-7, +19) mmHg at 6 months, and 0 (-9, +19) mmHg at 12 months (P = 0.0735). In the responder group, the median (minimum, maximum) IOP changes were -6 (-36, -3) mmHg at 1 month, -9 (-32, 2) mmHg at 3 months, -9 (-32, 2) mmHg at 6 months, and -5 (-32, 9) mmHg at 12 months (P < 0.0001). There was a significant difference in IOP reduction at 1 month (P = 0.0001) and 12 months (P = 0.0242) between the two groups (statistical analysis was not carried out at the other time-points).

Worsening of the intraocular inflammation was not observed in any of the subjects during the follow-up period. One patient exhibited a back rash 1 month after ripasudil treatment, and another patient complained of transient conjunctival hyperemia. Ten (48%) eyes discontinued ripasudil treatment within 12 months. The reasons for discontinuation included insufficient IOP-lowering effect in 6 (29%) eyes, a back rash in 2 (10%) eyes (1 patient), corneal surgery unrelated to ripasudil use in 1 (5%) eye, and doctor's discretion (in a case with IOP reduction and no adverse events) in 1 (5%) eye).

Discussion

This study demonstrates that ripasudil treatment effectively reduces IOP in approximately 50% of eyes with uveitic glaucoma. The overall change in IOP from baseline was -3 mmHg at 1 month, -4 mmHg at 3 months, -4 mmHg at 6 months, and -2 mmHg at 12 months. Tanihara and associates reported that ripasudil (K-115) 0.4%, as a monotherapy or additive therapy, lowered the IOP by 1.7 – 3.7 mmHg at 52 weeks in eyes with POAG or OHT [11]. Inazaki and associates prospectively examined 39 eyes with POAG that were inadequately controlled under maximum medical therapy and found that the addition of ripasudil reduced IOP by 2.6 mmHg at 12 months [12]. Moreover, we found that ripasudil is as effective in the treatment of uveitic glaucoma as is in the treatment of POAG or OHT. However, it should be noted that the drop-out rate due to inadequate IOP reduction was high and missing data may have had a large impact on the IOP values. We are hopeful that accounting for missing IOP data using the LOCF method minimized the impact and prevented a false decrease in IOP values caused by the many dropouts in the non-responder group, compared with the responder group.

In our case series examining uveitic glaucoma, responders to ripasudil (52%) showed a

much greater IOP reduction than non-responders at 1 and 12 months. As the response rate to ripasudil treatment in POAG or OHT remains unknown, we cannot assess whether the rate of 52% in our uveitic glaucoma cases is high or not. We tried to identify factors common to ripasudil responders, but the small sample size relative to the number of variables precluded us from performing a multivariate analysis. Markomichelakis and associates treated 58 eyes with uveitic glaucoma with latanoprost or dorzolamide/timolol, and reported that the responder rate was 60% in the latanoprost group and 57% in the dorzolamide/timolol group [15]. Therefore, it is not unusual that some eyes with uveitic glaucoma respond poorly to topical anti-glaucoma medications. Although the definition of responders differs among the studies, the responder rate to ripasudil in our study is comparable to that of latanoprost or dorzolamide/timolol in the aforementioned studies. As the responders in our study showed a considerable IOP reduction at 1 month after ripasudil administration (a median IOP reduction of -6 mmHg), it is important to distinguish responders from non-responders when treating uveitic glaucoma with ripasudil.

Regarding the safety of ripasudil use in patients with uveitic glaucoma, there was no exacerbation of intraocular inflammation in the studied eyes. The incidence of adverse events in our population was low. One patient exhibited a back rash and discontinued ripasudil. As the patient had a history of developing rashes in response to other medications including anti-glaucoma eye drops, this event could have been due to an allergic reaction. The other patient experienced a transient conjunctival hyperemia that was resolved without treatment. Previous reports documented adverse events associated with ripasudil including conjunctival hyperemia, eye irritation, and allergic conjunctivitis [11,12]. Conjunctival hyperemia is thought to reflect the effects of ripasudil on the conjunctival blood vessels and relaxation of the smooth muscle cells of the conjunctival blood vessels, and therefore is mild

and transient [16]. Some investigators reported a high incidence of conjunctival hyperemia, up to 100% [12], but only one patient complained of it in the current study. The difference could be attributed to the time of day the patients were typically examined. Our Uveitis Clinic is open in the afternoon and therefore intraocular ripasudil concentrations are expected to be at the trough level in most patients. Viewed together, the reported safety profiles [11,12] and the study data indicate that ripasudil appears to be a safe agent for the treatment of uveitic glaucoma. Systemic side effects were intermittent and mild, and most of the ocular side effects were mild or transient and did not exacerbate intraocular inflammation or cosmetic problems such as iris pigmentation or periorbital fat atrophy. Thus, ripasudil appears to have an advantage over other anti-glaucoma medications in terms of safety.

As corticosteroids remain the mainstay for managing inflamed eyes, steroid-induced IOP elevation frequently occurs in uveitic eyes treated with topical corticosteroids [5]. Undoubtedly, corticosteroid use was a cause of IOP increases in our cases because corticosteroid eye drops were administered to approximately 80% of the eyes at baseline and during the follow-up period, and intraocular inflammation was less severe as determined by clinical scores. As deemed necessary to control the inflammation, topical corticosteroids were not discontinued in all the cases. Therefore, we could not determine whether ripasudil is effective in either steroid-induced OHT or uveitic glaucoma, or both, which is one of the limitations of this study. However, our experience could provide useful information because uveitis specialists often encounter such cases that need continuous corticosteroid use but have a great IOP elevation. Our study has several other limitations including a retrospective study design and a small sample size. It is inevitable that patients were concomitantly treated with other IOP-lowering medications in real-world settings,

which may misrepresent the true efficacy of ripasudil. To overcome this problem, it is ideal to conduct well-designed randomized controlled trials. However, given that uveitis is an extremely complex multifactorial disease and uveitic glaucoma is relatively rare compared with POAG, the priority seems to be collecting as much clinical data as possible on the efficacy and safety of ripasudil for IOP increases in uveitic eyes. Therefore, our study would be the first step to building evidence for ripasudil treatment in patients with uveitic glaucoma.

In conclusion, ripasudil appears to substantially reduces IOP in eyes with uveitic glaucoma if the eye is a responder, and is unlikely to cause severe systemic or ocular side effects. Although predictive factors for the effects of ripasudil remain unknown, ripasudil could be an option for the treatment of uveitic glaucoma.

Compliance with Ethical Standards

Funding: No funding was received for this research.

Conflict of interest: The authors declare that they have no conflicts of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board (Kobe University Graduate School of Medicine) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Subjects' informed consent was not required since this was a retrospective review.

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Figure legends

Figure 1. Box plots of intraocular pressure (IOP) over time in all treated eyes. The IOP values at 1, 3, 4, 5, 6, 7, 8, and 12 months were significantly reduced compared with baseline. BL = baseline. * $P < 0.05$ compared with baseline.

Figure 2. Bar graphs representing the percentage of subjects with a given IOP change at 1 month. (a) percent IOP reduction from baseline. (b) absolute IOP reduction from baseline.

Figure 3. Box plots of IOP over time in the non-responder (upper graph) and responder (lower graph) groups. The IOP significantly decreased in the responder group (n=11) ($P < 0.0001$) while no significant IOP reduction was observed in the non-responder group (n=10) ($P = 0.0735$). * $P < 0.05$ compared with baseline.

Table 1. Demographic and Clinical characteristics

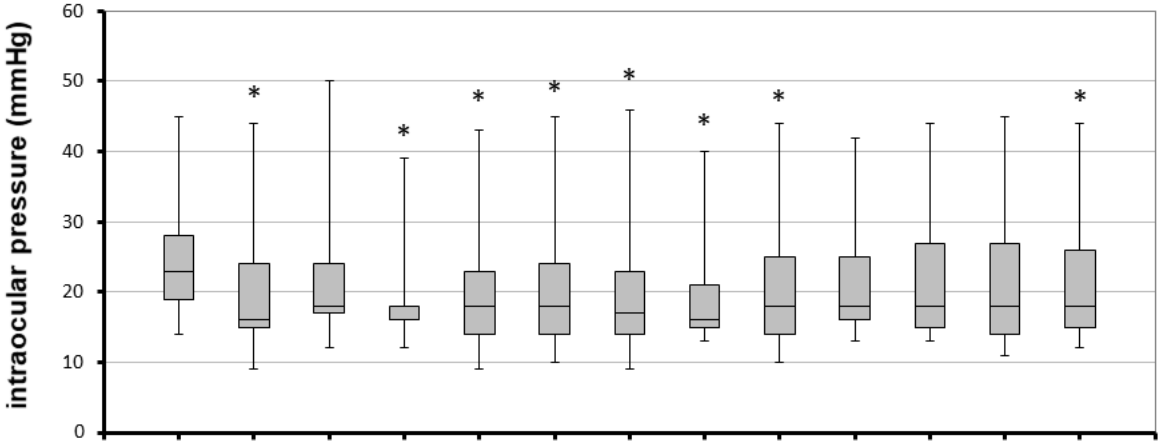
Age (years)*	69 (10, 84)
Gender (male/female)	10/9
BCVA (logMAR unit)*	0.00 (-0.176, +0.699)
Baseline IOP (mmHg)*	23 (13, 46)
Mean deviation (dB)*	-5.80 (-22.5, -0.23)
Number of glaucoma medications*	2 (0, 4)
Etiology of uveitis, n (%)	
Sarcoidosis	6 (29%)
Behçet's disease	3(14%)
Vogt-Koyanagi-Harada disease	2(10%)
Herpetic iridocyclitis	1(5%)
Cytomegalovirus iridocyclitis	1(5%)
Autoimmune retinopathy suspect	1(5%)
Unclassified	7(33%)

*Data are provided as median (minimum, maximum); BCVA, best corrected visual acuity; logMAR, *logarithm* of the minimum angle of resolution; IOP, intraocular pressure.

Table 2. Baseline details of medical treatment

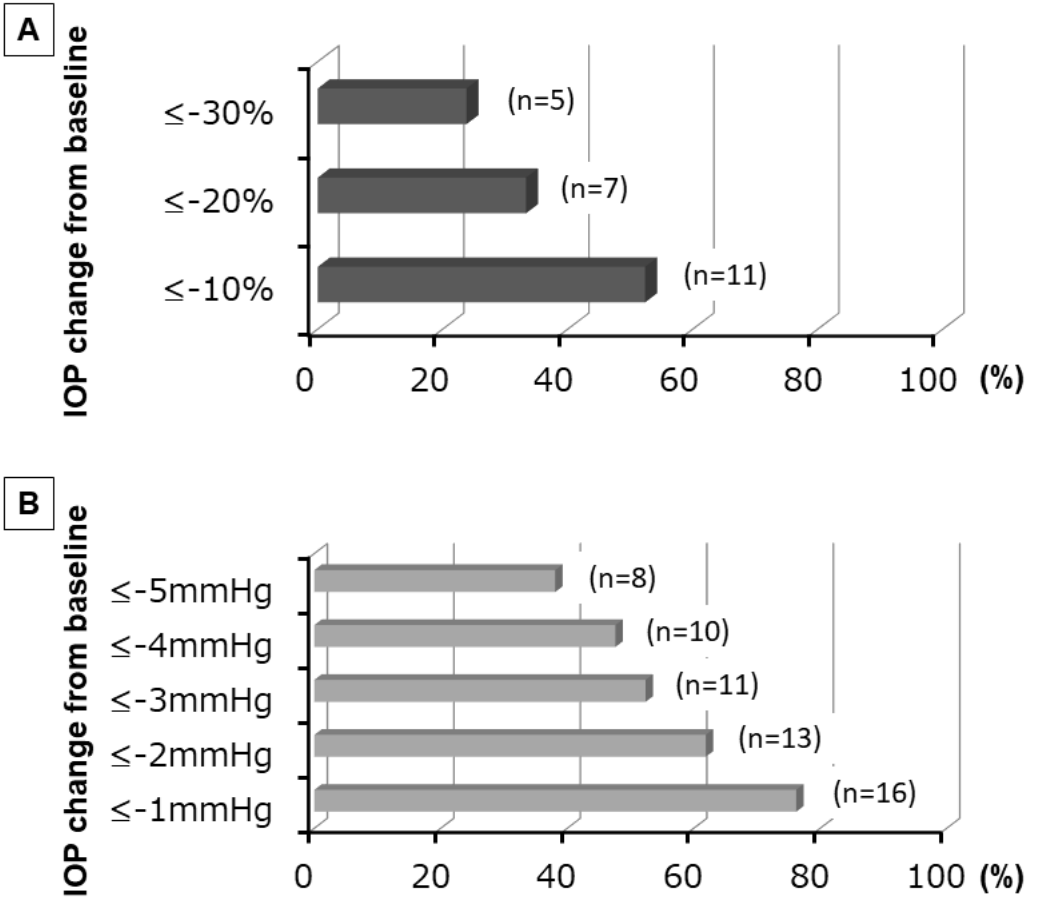
Medical treatment	Number of eyes (percentage)
Treatment for uveitis control*	
topical corticosteroids	17(81%)
systemic corticosteroids	3(14%)
periocular corticosteroids	1(5%)
systemic immunosuppressive agents	1(5%)
others	2(10%)
Eye drops for IOP controls	
PG+β+CAI	3(14%)
β+CAI	3(14%)
PG+β+CAI+α2	2(10%)
PG+β	2(10%)
PG+CAI	2(10%)
PG+α2	1(5%)
PG	1(5%)
β+CAI+α2	1(5%)
β+α2	1(5%)
β	1(5%)
α2	1(5%)
none	3(14%)

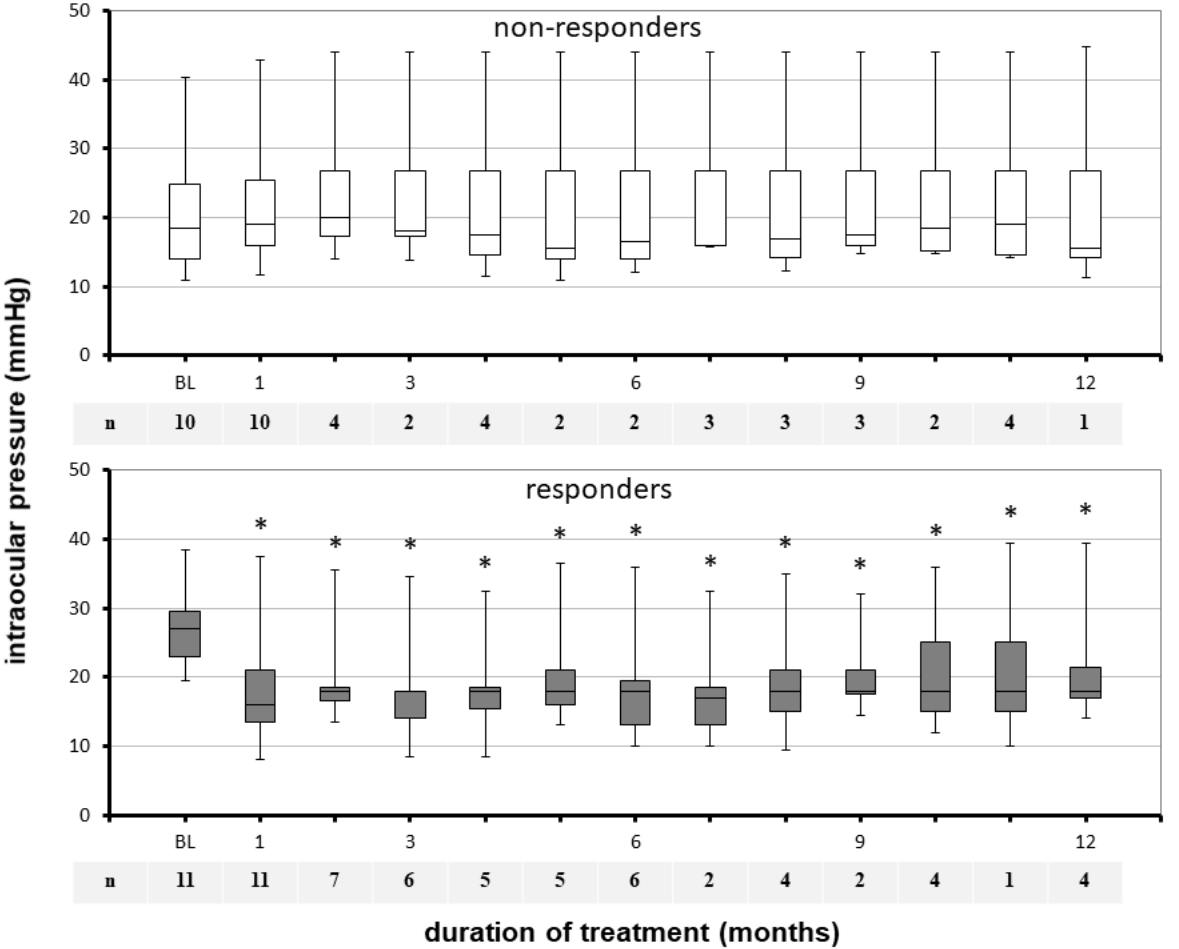
*There are overlaps among patients because some of them used multiple medications. IOP, intraocular pressure; PG, prostaglandin analogue; β, beta-blocker; CAI, carbonic anhydrase inhibitor; α2, α2 adrenergic *agonist*.



n	21	21	11	8	9	7	8	5	7	5	7	5	5

duration of treatment (months)


A
IOP change from baseline
≤-30%
≤-20%
≤-10%
(n=5)
(n=7)
(n=11)
0
20
40
60
80
100
(%)
B
IOP change from baseline
≤-5mmHg
≤-4mmHg
≤-3mmHg
≤-2mmHg
≤-1mmHg
(n=8)
(n=10)
(n=11)
(n=13)
(n=16)
0
20
40
60
80
100
(%)


non-responders
responders
intraocular pressure (mmHg)
duration of treatment (months)
BL
1
3
6
9
12
n
10 10 4 2 4 2 2 3 3 3 2 4 1
11 11 7 6 5 5 6 2 4 2 4 1 4