Discussion

Our study demonstrated that, among POAG eyes with mean IOP levels of ≤21 mmHg, the AGIS scores for those with mean IOPs of ≥16 mmHg were significantly worse than for those with mean IOPs of <16 mmHg. To be more specific, eyes with high-pressure POAG underwent IOP-dependent progression of their visual field defects, whereas the progression of visual field defects in the NTG eyes was not significantly dependent upon their mean IOPs (although the AGIS score of the eyes with high mean IOP levels was greater). Moreover, the frequency of IOP levels of ≥18 mmHg was associated with worsening of the visual field defects.

Several criteria have been used previously to score the glaucomatous visual field defects visualized by a Humphrey field analyzer. The scoring used in the CIGTS resulted in two-fold more-frequent progression than the scoring in the AGIS, highlighting the more variable scoring in the former (8). Because the scoring in the Collaborative Normal-Tension Glaucoma Study (CNTGS) was used to compare the treatment and non-treatment groups, the criteria of the progression shows high sensitivity and variability to minimize any risk to eyes in the untreated group. In the present retrospective study, the AGIS scoring was adopted because of its lower variability. However, due to fluctuations in the AGIS scoring criteria, 5% of eyes in which visual field tests are performed twice will show a deterioration of ≥4 points in one or other of the tests (7, 9). In the present study, 10% of the eyes showed a deterioration of ≥4 points from the baseline score, but recovered during the follow-up

period. Although after the initial test, the baseline score was determined using visual field test data with high reliability, fluctuations of ≥4 points seemed to be frequent during the long follow-up period. We therefore established that the visual field defect had progressed by confirming that the poor scores were not reversed in subsequent tests. The criteria used revealed that the 10-year-survival rate was only 44.5% in the eyes with POAG with high pressure when IOP levels of ≥18 mmHg were detected in 4 of the 10 years of follow-up; this showed that maintaining IOP levels of <21 mmHg is not sufficient to prevent the progression of visual field defects in the majority of POAG eyes. The AGIS group (9) also demonstrated that frequent IOP levels of ≥18 mmHg caused marked deterioration of the score. Based on visual field data obtained by the Goldmann perimetry technique over 15 years of follow-up, Shirakashi *et al.* (4) showed that IOP levels much below 21 mmHg are favorable for preventing further progression of visual field defect in eyes with POAG. Earlier, Mao *et al.* (10) reported that ~50% of POAG eyes with mean IOP values of between 17 and 21 mmHg suffered progressive glaucomatous changes. Taken together, these findings indicate that further lowering of IOP is effective in preventing the progression of visual field defects in eyes with IOP levels of <21 mmHg.

We found that the defects increased more in NTG eyes with high mean IOP values than in those with low mean IOP values, although this difference was not statistically significant. An analysis of a larger number of NTG eyes might thus be needed to determine the relationship between mean IOP levels and progression in NTG eyes. Alternatively, the progression in NTG eyes might be more dependent upon the

maximum IOP levels than the mean IOP levels, as the present study showed that the visual field defects progressed more in NTG eyes that experienced maximum IOPs of ≥18 mmHg than in other NTG eyes. The CNTGS group (11) found that a 30% reduction of IOP was effective in preventing further visual field loss in NTG eyes. However, the CNTGS enrolled NTG eyes with IOPs of ≤24 mmHg. The absence of a clear effect of the mean IOP on the progression of visual field defects in the present study might have been due to the lower IOP levels. In addition, no significant relationship was observed between the enlargement of optic-disc cupping and the mean IOP levels in eyes with NTG, reflecting less IOP-dependent progression of visual field defects.

We enrolled visual field data with the reliability values of less than 50%, indicating the inclusion of low reliable visual field data for the analyses. Retrospectively, we could not collect enough number of visual field tests with the reliability values of less than 33% because of no immediate re-tests against the patients with the reliability values of 33 to 50%. Therefore, we could not analyze the visual field tests using more sensitive scoring system such as CIGTS and CNTGS. Further prospective study may detect more sensitive progression of visual field defect than our retrospective study using AGIS scoring did.

In conclusion, IOP-dependent progression of visual field defects occurs in eyes with POAG maintained at IOP levels of ≤21 mmHg. POAG eyes that experience IOP levels of >21 mmHg show more clear-cut IOP-dependence than do NTG eyes. Our results suggest that further lowering of the IOP is beneficial for POAG eyes maintained at ≤21 mmHg.

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Figure Legends

Figure 1. Progression of visual field defects is correlated to mean IOP levels. High average IOP levels and increased scores were weakly but significantly correlated (r=0.21, p=0.037, Pearson's correlation coefficient test).

Figure 2. Progression of visual field defects is dependent upon mean IOP level. In the POAG with high pressure group, visual field defects progressed more in eyes with mean IOPs of ≥16 mmHg. However, in the NTG group, there was no significant difference in visual field defect progression between the two subgroups, based on the median value of the average IOP levels (13.8 mmHg). The error bars represent the standard errors. *p<0.05 (Mann Whitney-U test).

Figure 3. Progression of visual field defects is dependent upon maximum IOP level. In the POAG with high pressure group, the visual field defects in group B (≥18 mmHg in ≥4 years) progressed significantly more than those in group A (≥18 mmHg in ≤3 years). In the NTG group, the visual field defects in group D (≥18 mmHg maximum IOP) progressed significantly more than those in group C (≤18 mmHg maximum IOP). The error bars represent the standard errors. *p<0.05 (Mann Whitney-U test).

Figure 4. Kaplan–Meier survival analysis based on maximum IOP levels. In the POAG with high pressure group, group A showed significantly less progression of visual field

defects than group B, whereas there was no statistically significant difference between groups C and D of the NTG group. The number of eyes at risk in each year during follow up period was shown under the graph. *$p<0.05$ (log rank test).

Table1
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Table 1: Patient data

		POAG with high pressure	NTG	Total
Number of eyes		50	50	100
Age (years)		53.5 ± 12.0	61.6 ± 13.2	56.8 ± 13.2
Follow up (years)		7.4 ± 1.7	6.4 ± 1.5	7.9 ± 1.7
IOP (mmHg)	Baseline	17.9 ± 3.6	13.9 ± 1.9	17.0 ± 3.5
	Average	15.6 ± 2.7	11.6 ± 1.5	15.0 ± 2.5

± standard deviation

Figure1
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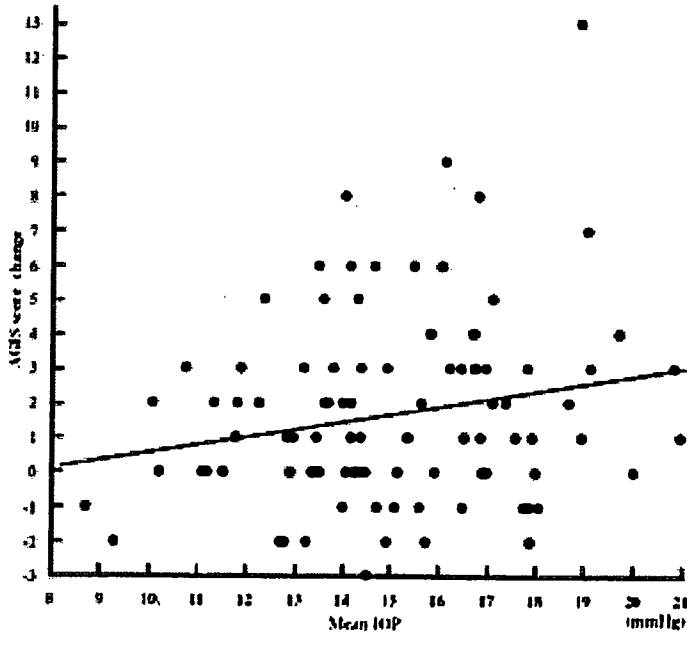

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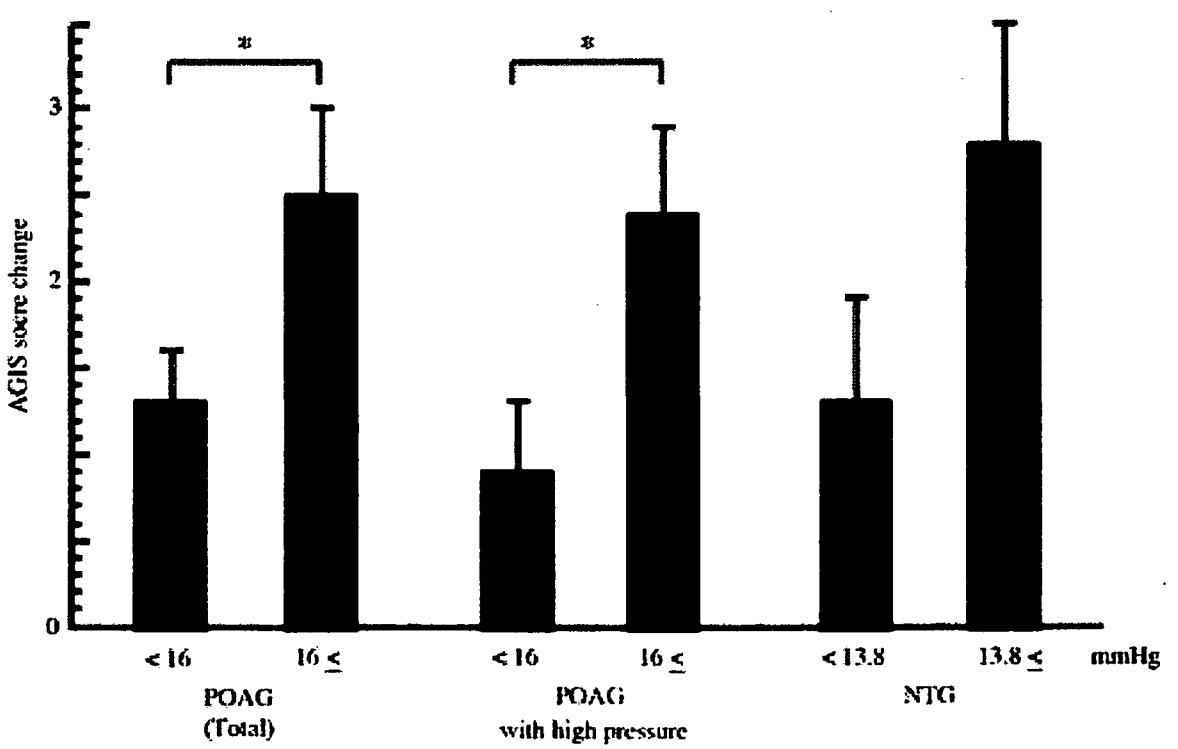

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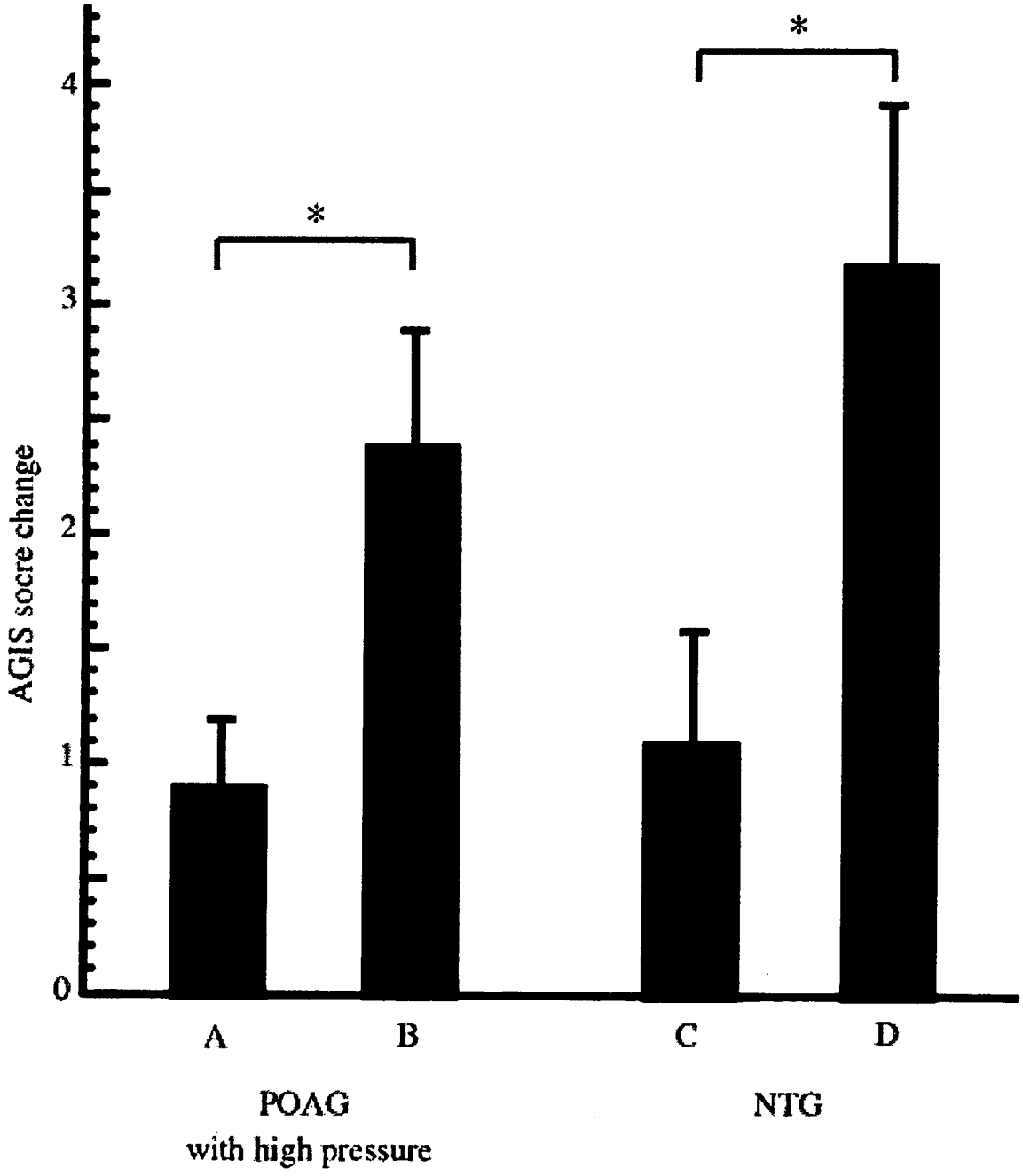

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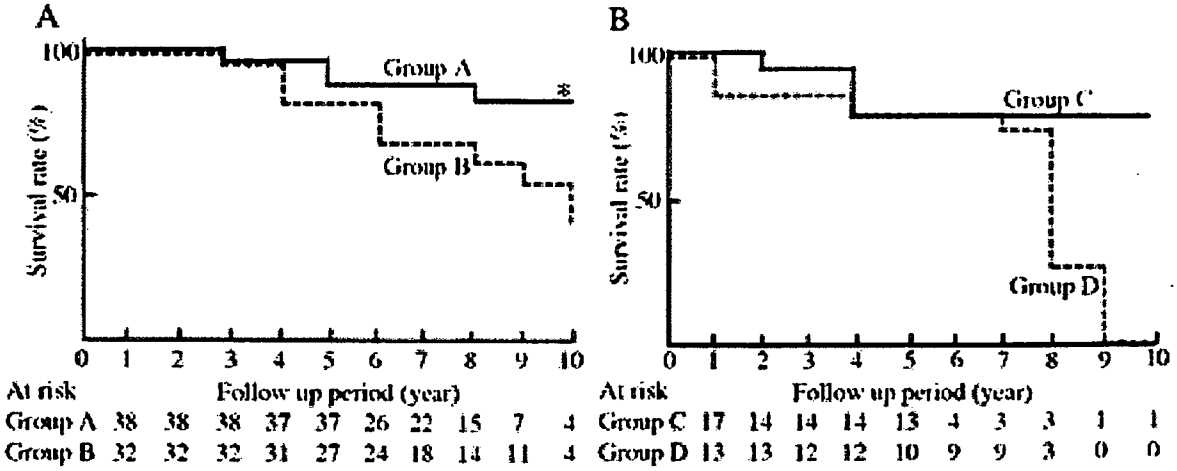

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Intraocular Pressure Elevation after Injection of Triamcinolone Acetonide: A Multicenter Retrospective Case-Control Study

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• PURPOSE: To determine the risk factors for intraocular pressure (IOP) elevation after the injection of triamcinolone acetonide (TA).

• DESIGN: Retrospective interventional case-control study.

• METHODS: SETTING: Multicenter. PATIENT POPULATION: Four hundred and twenty-seven patients. OBSERVATION PROCEDURES: Intraocular pressure levels after TA treatment by the sub-Tenon capsule injection (STI; 12 mg, 20 mg, or 40 mg), intravitreal injection (IVI; 4 mg or 8 mg), or the combination of STI (20 mg) and IVI (4 mg), and IOP levels after two TA treatments. MAIN OUTCOME MEASURE: Risk factors for IOP levels of 24 mm Hg or higher.

• RESULTS: Younger age (hazards ratio [HR], 0.96/year; $P < .0001$), IVI (HR, 1.89/year; $P < .0001$), and higher baseline IOP (HR, 1.15/mm Hg; $P = .003$) were identified as risk factors. Dose dependency was shown in STI-treated eyes (HR, 1.07/mg; $P = .0006$), as well as after IVI (HR, 1.64/mg; $P = .013$). The combination of STI and IVI was a significant risk factor (HR, 2.27; $P = .003$) compared with STI alone. In eyes receiving two TA treatments, IVI (HR, 2.60; $P = .010$), higher IOP elevation after the first injection (HR, 1.18/mm Hg; $P = .011$), and increased dosage of STI (HR, 1.07/mm Hg; $P = .033$) were risk factors.

• CONCLUSIONS: Younger age, higher baseline IOP, IVI, and increased TA dosage were associated with TA-induced IOP elevation. IOP elevation after repeated TA injection was frequently associated with eyes treated with IVI, high IOP elevation after the first injection, and high doses of STI. (Am J Ophthalmol 2008;xx: xxx. © 2008 by Elsevier Inc. All rights reserved.)

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TRIAMCINOLONE ACETONIDE (TA) IS COMMONLY USED to treat various vitreoretinal diseases. TA limits the impact of corticosteroids on ocular tissues, thereby minimizing the side effects associated with systemic steroid therapy.[1–5] However, many patients who have received intravitreal injection (IVI) of TA or the sub-Tenon capsule injection of TA (STI) encounter intraocular pressure (IOP) elevation,[6–13] which can develop into glaucoma.[14,15] The prevalence of TA-induced IOP elevation is reportedly between 18% and 50%.[7,13,16–19] This wide range of values might be explained by the following: variation between definitions of IOP elevation; the TA dose and the method of administration; whether patients have previously received TA injections; patient background characteristics, including history of glaucoma or ocular hypertension; and administration of steroids. Several reports have suggested an increased prevalence of TA-induced IOP elevation in younger patients.[1,7,15,20] Therefore, we retrospectively investigated the risk factors for IOP elevation in patients receiving TA at six Japanese clinical centers, based on a standardized definition of TA-induced IOP elevation.

METHODS

• PATIENTS: This retrospective interventional case-control study was approved by the Institutional Review Board of Kumamoto University Hospital (Kumamoto, Japan). We reviewed the medical records of patients receiving TA by STI (12 mg, 20 mg, or 40 mg), IVI (4 mg or 8 mg), or simultaneous administration by STI (20 mg) and IVI (4 mg) at the following six clinical centers in Japan: Kumamoto University Hospital (Kumamoto), Nagoya City University Hospital (Nagoya), Kagawa University Hospital (Miki), Kobe University Hospital (Kobe), Kagoshima University Hospital (Kagoshima), and Kansai Medical University Hospital (Moriguchi). Data from patients who received TA between 1 April 2002 and 31 March 2006 AQ: 1

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TABLE 1. Patient Data Before Triamcinolone Acetonide Treatment in < 24 mm Hg and ≥ 24 mm Hg Groups

Characteristic (n = 427)	Eyes with < 24 mm Hg (n = 377) n (%)	Eyes with ≥ 24 mm Hg (n = 50) n (%)	*P* Value
Male gender	228 (60.5)	30 (60.0)	.948
Mean age (years)	65.8 ± 11.2	57.1 ± 17.5	.006*
Diabetes mellitus	203 (53.8)	17 (34.0)	.008*
Hypertension	137 (36.3)	18 (36.0)	.963
Cataract surgery	141 (37.4)	17 (34.0)	.638
Vitrectomy	88 (23.3)	14 (28.0)	.475
IVI included	69 (18.3)	25 (50.0)	<.0001*
Mean IOP at baseline (mm Hg)	13.8 ± 3.1	15.1 ± 3.1	.010*

IOP = intraocular pressure; IVI = intravitreal injection of triamcinolone acetonide.
*$P < .05$.

were included in the analyses. If both eyes were treated with TA, the eye that was treated first was investigated. The exclusion criteria were as follows: eyes that had received intraocular surgery within three months before TA treatment; eyes with a history of glaucoma or uveitis; eyes that had shown > 21 mm Hg IOP levels; and patients who had been treated with steroids. Eyes treated with a second TA injection within the follow-up period were included in the analyses. If the TA dose administered in the second injection was different from that in the first, the eyes were included in the analysis of the first injection, but excluded from the analysis of the second.

• MAIN OUTCOME MEASURE AND OBSERVATION PROCEDURE: The main aim of this study was to investigate the risk factors for IOP elevation after TA treatment. The IOP levels after TA treatment were derived from patients' medical records. If any ocular surgeries were performed, IOP data from before the surgeries were evaluated. If an additional dose of TA was administered after the first injection, the IOP data at the first TA injection were evaluated until the second injection. The IOP levels were also evaluated between two weeks and a maximum of 12 months after the second injection. The baseline IOP was defined as the IOP level on the day of TA injection or at the last examination before the TA injection. The IOP data were mainly selected from records obtained by measurement using noncontact pneumotonometry. In line with previous reports,[6,15] we defined an IOP of 24 mm Hg or higher after TA treatment as elevated IOP induced by TA treatment. Furthermore, if IOP levels of 24 mm Hg or higher were shown by the noncontact pneumotonometer, they were re-examined using a Goldmann applanation tonometer on a slit-lamp biomicroscope, and the value shown by the tonometer was used as the IOP. Eyes for which the medical records did not indicate whether re-examination by tonometry had been performed were excluded from the study.

The following variables were assessed as potential risk factors for elevated IOP: gender; age; history of diabetes mellitus, hypertension, cataract surgery, or vitrectomy; dose and route of TA administration (12 mg, 20 mg, or 40 mg by STI; 4 mg or 8 mg by IVI; or a combination of 20 mg by STI and 4 mg by IVI); and baseline IOP. These factors were compared between patients with less than 24 mm Hg and those with 24 mm Hg or higher IOP. Potential risk factors for IOP levels of 24 mm Hg or higher after additional treatment were as described above. The maximal IOP minus baseline IOP (ΔIOP) values after the first treatment and the interval between the first and the second treatment were also assessed.

• STATISTICAL ANALYSIS: Data analysis was performed using the JMP version 6 statistical package program (Cary, North Carolina, USA). The Mann–Whitney *U* test and the Chi-square test (or the Fisher exact test) were used for the univariate analyses. To confirm the effects of the risk factors and identify the hazard ratios (HRs) for TA-induced IOP elevation, multivariate Cox proportional hazards regression analysis was performed. The multivariate factors were selected from among the variants with a probability (*P*) value of less than .30 shown by univariate analysis. A *P* value less than .05 was considered statistically significant.

RESULTS

IN TOTAL, 427 EYES SATISFIED THE STUDY CRITERIA. ALL OF the eligible patients were Japanese. The diagnoses for the TA-treated eyes were as follows: age-related macular degeneration (67 eyes), other choroidal neovascular diseases (34 eyes), retinal vein occlusion (131 eyes), diabetic retinopathy (180 eyes), and other retinal diseases related to cystoid macular edema (15 eyes). Of these, 319 eyes were treated by one TA injection, and 108 eyes were treated with an additional TA injection. In total, 50

TABLE 2. Risk Factors for Elevated Intraocular Pressure Elevation of ≥ 24 mm Hg After Triamcinolone Acetonide Treatment—Cox Proportional Hazards Analysis

Variable	Hazards Ratio for ≥ 24 mm Hg	*P* Value
Model 1: All eyes treated with triamcinolone acetonide injection (n = 427)		
Age (years)	0.96 (0.95 to 0.98)	<.0001*
Diabetes mellitus	0.76 (0.55 to 1.02)	.068
IVI included	1.89 (1.41 to 2.52)	<.0001*
IOP at baseline (mm Hg)	1.15 (1.05 to 1.27)	.003*
Model 2: Eyes with STI only (n = 333)		
Age (year)	0.96 (0.94 to 0.99)	.003*
Diabetes mellitus	0.91 (0.60 to 1.38)	.647
STI (mg)	1.07 (1.03 to 1.12)	.0006*
IOP at baseline (mm Hg)	1.31 (1.13–1.52)	.0003*
Model 3: Eyes with IVI only (n = 57)		
Age (year)	0.98 (0.94 to 1.03)	.393
Diabetes mellitus	0.91 (0.47 to 1.61)	.760
IVI (mg)	1.64 (1.09 to 3.39)	.013*
IOP at baseline (mm Hg)	1.03 (0.85 to 1.27)	.765
Model 4: Eyes with 20 mg of STI or 20 mg of STI plus 4 mg of IVI (n = 201)		
Age (year)	0.95 (0.92 to 0.98)	.003*
Diabetes mellitus	0.75 (0.41 to 1.29)	.306
Plus 4 mg of IVI	2.27 (1.33 to 4.02)	.003*
IOP at baseline (mm Hg)	1.28 (1.07 to 1.55)	.008*

IOP = intraocular pressure; IVI = intravitreal injection of triamcinolone acetonide; STI = sub-Tenon capsule injection of triamcinolone acetonide.
Hazards ratio is shown with 95% confidence interval.
*$P < .05$.

(11.7%) of the 427 eyes had an elevated IOP of 24 mm Hg or higher. IOP elevation of 24 mm Hg or above started 0.5 month after the injection in 12 eyes, after one month in nine eyes, after two months in 19 eyes, after three months in nine eyes, and after six months in one eye. Patient data before TA injection for the group with IOP elevation of less than 24 mm Hg and the group with 24 mm Hg or T1 higher are shown in Table 1. The patients within the 24 mm Hg or higher group were younger, were less likely to have a history of diabetes mellitus, had a greater incidence of IVI administration of TA, and had higher baseline IOP values. The multivariate Cox proportional hazards regression showed that younger age (HR, 0.96 per year; 95% confidence interval [CI], 0.95 to 0.98; $P < .0001$), the inclusion of IVI (HR, 1.89; 95% CI, 1.41 to 2.52; $P < .0001$), and higher baseline IOP (HR, 1.15 per mm Hg; 95% CI, 1.05 to 1.27; $P = .003$) were risk factors for IOP T2 elevation (Table 2; Model 1).

We also examined whether IOP elevation after TA injection was dose-dependent. In eyes treated by STI (n = 333), one of 36 eyes (2.8%), six of 164 eyes (3.7%), and 18 of 133 eyes (13.5%) showed IOP values of 24 mm Hg or higher after doses of 12 mg, 20 mg, and 40 mg by STI, respectively. Cox proportional hazards regression analysis of the 333 eyes identified younger age (HR, 0.96 per year; 95% CI, 0.94 to 0.99; $P = .003$), a higher dose administered by STI (HR, 1.07 per mg; 95% CI, 1.03 to 1.12; $P = .0006$), and higher baseline IOP (HR, 1.31 per mm Hg; 95% CI, 1.13 to 1.52; $P = .0003$) as risk factors (Table 2; Model 2). In eyes treated by IVI (n = 57), one of 18 eyes (5.6%) and 14 of 39 eyes (35.9%) were associated with IOP of 24 mm Hg or higher after doses of 4 mg and 8 mg by IVI, respectively. Cox proportional hazards regression analysis of the 57 eyes showed that a higher dose administered by IVI (HR, 1.64 per mg; 95% CI, 1.09 to 3.39; $P = .013$) was a risk factor. However, neither younger age (HR, 0.98 per year; 95% CI, 0.94 to 1.03; $P = .393$) nor higher baseline IOP (HR, 1.03 per mm Hg; 95% CI, 0.85 to 1.27; $P = .765$) were significant risk factors (Table 2; Model 3). Additionally, 10 of 37 eyes (27.0%) were associated with an IOP of 24 mm Hg or higher after simultaneous administration by STI (20 mg) and IVI (4 mg). In eyes treated with 20 mg by STI, or with both 20 mg by STI and 4 mg by IVI (n = 201), younger age (HR, 0.95 per year; 95% CI, 0.92 to 0.98; $P = .003$), the addition of 4 mg by IVI (HR, 2.27, 95% CI, 1.33 to 4.02; $P = .003$), and baseline IOP (HR, 1.28 per mm Hg; 95% CI, 1.07 to 1.55; $P = .008$) were identified as risk factors (Table 2; Model 4).

TABLE 3. Data Before the Second Triamcinolone Acetonide Treatment in < 24 mm Hg and ≥ 24 mm Hg Groups

Characteristic (n = 108)	Eyes of < 24 mm Hg (n = 92) n (%)	Eyes of ≥ 24 mm Hg (n = 16) n (%)	*P* Value
Male gender	53 (57.6)	10 (62.5)	.714
Mean age (years)	63.1 ± 11.0	55.6 ± 17.8	.279
Diabetes mellitus	50 (54.3)	8 (50.0)	.748
Hypertension	42 (45.7)	3 (18.8)	.044*
Cataract surgery	33 (35.9)	6 (37.5)	.900
Vitrectomy	24 (26.1)	5 (31.3)	.667
IVI included	4 (4.3)	4 (25.0)	.004*
Mean IOP at baseline (mm Hg)	13.8 ± 3.0	13.5 ± 2.4	.900
ΔIOP after the 1st injection (mm Hg)	3.0 ± 3.2	5.8 ± 2.1	<.0001*
Interval between 1st and 2nd injections (months)	5.2 ± 3.2	5.1 ± 3.2	.841

IOP = intraocular pressure; IVI = intravitreal injection of triamcinolone acetonide; ΔIOP = maximal IOP minus baseline IOP.
*$P < .05$.

TABLE 4. Risk Factors for Elevated Intraocular Pressure of ≥ 24 mm Hg After Second Triamcinolone Acetonide Injection—Cox Proportional Hazards Analysis

Variable (n = 108)	Hazards ratio for ≥ 24 mm Hg	*P* Value
Model 1: All the eyes treated with repeated TA injections (n = 108)		
Age (years)	0.99 (0.95 to 1.02)	.410
Hypertension	0.71 (0.33 to 1.29)	.276
IVI included	2.60 (1.30 to 4.83)	.010*
ΔIOP after 1st injection (mm Hg)	1.18 (1.04 to 1.30)	.011*
Model 2: Eyes with repeated STIs (n = 100)		
Age (years)	1.03 (0.98 to 1.08)	.247
Hypertension	0.82 (0.37 to 1.58)	.557
STI (mg)	1.07 (1.01 to 1.18)	.033*
ΔIOP after 1st injection (mm Hg)	1.45 (1.17 to 1.85)	.0006*

IVI = intravitreal injection of triamcinolone acetonide; STI = sub-Tenon capsule injection of triamcinolone acetonide; ΔIOP = maximal IOP minus baseline IOP.
Hazards ratio is shown with 95% confidence interval.
*$P < .05$.

Of the 108 eyes treated with a second injection, 16 (14.8%) had IOP elevation to 24 mm Hg or higher. Data before the second TA treatment for the group with elevation of less than 24 mm Hg and the group with T3 elevation of 24 mm Hg or higher are shown in Table 3. The 24 mm Hg or higher group included fewer patients with histories of hypertension, more eyes treated with the inclusion of IVI, and higher ΔIOP after the first injection. Cox proportional hazards regression analysis showed that the inclusion of IVI (HR, 2.60; 95% CI, 1.30 to 4.83; P = .010) and higher ΔIOP after the first injection (HR,1.18 per mm Hg; 95% CI, 1.04 to 1.30; P = .011) were risk factors for IOP elevation after the additional TA injection T4 (Table 4; Model 1). In eyes treated with two STI injections (n = 100), an increased dose administered by STI (HR, 1.07 per mg; 95% CI, 1.01 to 1.18; P = .033) and higher ΔIOP after the first injection (HR, 1.45 per mm Hg; 95% CI, 1.17 to 1.85; P = .0006) were shown to be risk factors (Table 4; Model 2).

DISCUSSION

THIS STUDY INVESTIGATED THE RISK FACTORS OF IOP ELEvation following topical TA injection. Cox proportional hazards regression analysis of 427 eyes showed that younger age (HR, 0.96 per year; 95% CI, 0.95 to 0.98), TA treatment including IVI (HR, 1.89; 95% CI, 1.41 to 2.52),

and higher baseline IOP (HR, 1.15 per year; 95% CI;1.05 to 1.27) were risk factors for elevated IOP of 24 mm Hg or higher. These risk factors were also observed in the 201 eyes treated with either 20 mg by STI or a combination of 20 mg by STI and 4 mg by IVI. TA dose dependency for the frequency of IOP elevation was identified by multivariate analyses for 333 eyes treated by STI (1.07 per mg; 95% CI, 1.03 to 1.12) and 57 eyes treated by IVI (1.64 per mg; 95% CI, 1.09 to 3.39). Moreover, multivariate analyses in eyes after two TA treatments showed that TA treatment including IVI, higher ΔIOP after the first TA injection, and a higher dose administered by STI were risk factors.

Several reports have discussed the rates of IOP elevation after TA injection, and have identified potential risk factors. Retrospective studies examining IVI-induced IOP elevation reported that treatment with 20 mg by IVI induced IOP of more than 21 mm Hg in 112 of 272 patients (41.2%),[1] and that 4 mg by IVI induced IOP elevation by 30% or more in 267 of 528 eyes (50.6%),[12] IOP elevation to 24 mm Hg or higher in 36 of 89 patients (40.4%),[6] and IOP elevation to more than 21 mm Hg, or by more than 5 mm Hg, in 26 of 60 patients (43.3%).[20] These results indicate that higher baseline IOP values[6,12] and younger age[1,20] are risk factors for IVI-induced IOP elevation.

By contrast, retrospective studies of STI-induced IOP elevation showed levels equal to or more than 6 mm Hg, or IOP levels of more than 20 mm Hg, in nine of 49 eyes (18.4%),[13] and IOP elevation of equal to or more than 5 mm Hg in 19 of 43 eyes (44.2%).[8] In our previous retrospective study, 40 mg by STI induced high IOP of 24 mm Hg or above in 26 of 115 eyes (22.6%).[15] Younger age[15] and a history of diabetes mellitus[13] are reported risk factors for STI-induced IOP elevation. However, to determine in detail the influence of risk factors, including the dose and route of TA administration, it will be necessary to carry out statistical analysis on a larger number of eyes treated with TA at multiple clinical centers. In this meta-study, to determine the TA-induced IOP elevation more exactly, we excluded eyes with other risk factors for IOP elevation, such as glaucoma, ocular hypertension, uveitis, steroid administration, and recent histories of intraocular surgery. Moreover, TA-induced IOP elevation obtained using noncontact pneumotonometry was confirmed using a Goldmann applanation tonometer. Taken together, our retrospective results reflect the detailed characterization of TA-induced IOP elevation.

No previous large-scale clinical studies have confirmed the risk factors for TA-induced IOP, or examined the effects of the amount of TA administered and the interaction between STI and IVI. The present study not only confirmed that younger age and higher baseline IOP risk factors,[1,6,12,20] but also revealed that IVI induces IOP elevation more frequently than STI, as well as demonstrating the dose dependency for TA-induced IOP elevation. However, no correlations with gender, medical history of hypertension, diabetes mellitus, cataract surgery, or vitrectomy were observed in the analyses for the risk factors. Although some reports have shown that diabetes mellitus is a risk factor for corticosteroid-induced IOP elevation,[13,21] others have shown that it is not significant. A previous randomized diabetes mellitus clinical trial conducted by Palmberg[22] showed that the history of diabetes mellitus was not associated with glaucoma. Our results seem to agree with this. In addition, it could be speculated that the lens and the vitreous affect the diffusion of TA in the ocular tissue; however, no reports (including our present results) suggest that the histories of cataract surgery and vitreous surgery influence TA-induced ocular hypertension.

Interestingly, IVI and ΔIOP are risk factors for IOP elevation in eyes treated with repeated TA injections. IOP elevation is also frequently associated with a higher dose of repeated STI treatment. There are some reports concerning IOP elevation after repeated TA injection.[6,7,12] A study that retrospectively investigated 43 eyes treated repeatedly with 20 to 25 mg by IVI showed that no eyes with 21 mm Hg or less after the first TA injection exhibited more than 21 mm Hg after the second TA injection.[24] By contrast, another study previously reported that 28 of 43 eyes (65.1%) treated with a second TA injection showed an IOP elevation of 30% or more, which was not observed at the first TA injection.[12] In our present study, 15 of 16 eyes with IOP elevation after the second TA injection did not exhibit IOP elevation after the first TA injection. Our present data appear to agree with the latter study, although it showed that the risk factors for IOP elevation after the second TA injection were higher baseline IOP and male gender.[12]

The study presented here has several limitations. First, it shows the risk factors for IOP elevation and not for TA-induced visual field loss attributable to severe TA-induced ocular hypertension. We could not retrospectively quantify visual field loss in eyes with TA-induced IOP elevation because of the association with retinal macular diseases. Second, we did not statistically analyze the duration of IOP elevation in this study. In total, 44 of 50 eyes with IOP elevation in this study showed reversible IOP elevation, whereas six eyes were associated with persistent ocular hypertension in spite of anti-glaucomatous medical treatments. They were treated with trabeculectomy (two eyes) and trabeculotomy (four eyes), which is a surgical procedure effective for corticosteroid-induced glaucoma.[15,23] The six eyes included three treated with 8 mg by IVI, one treated with 4 mg by IVI, one treated with 4 mg by IVI plus 20 mg by STI, and one treated with 40 mg by STI. Persistent IOP elevation might be associated with IVI or high-dose treatment by STI. Third, it remains to be determined whether glaucoma and ocular hypertension are risk factors, as we excluded patients suffering from these disorders from the present study. Such patients might be more susceptible to TA-induced

IOP elevation. Actually, few cases with past histories of glaucoma and ocular hypertension were treated with TA injection. In our clinical centers, TA injection might have been avoided in the patients associated with glaucoma or ocular hypertension. Fourth, we could not evaluate worldwide differences as we only analyzed data from Japanese patients.

In conclusion, our case-control study indicates that younger patients, those with a higher baseline IOP, and those receiving higher doses of TA or intravitreally administered TA are more susceptible to corticosteroid-induced IOP elevation. Greater IOP elevation after the first injection is associated with frequent IOP elevations after the second TA injection.

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Intraocular Pressure–Lowering Effects and Safety of Topical Administration of a Selective ROCK Inhibitor, SNJ-1656, in Healthy Volunteers

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Objective: To investigate the effects and safety of topical administration of an ophthalmic solution of a selective Rho-associated coiled coil-forming protein kinase (ROCK) inhibitor, SNJ-1656, 0.003% to 0.1%, in healthy male adult volunteers.

Design: Randomized, double-masked, group-comparison, phase 1 clinical study. In the initial single-dose trial, 45 healthy volunteers were randomly subdivided into 5 groups and treated with SNJ-1656 in concentrations of 0.003%, 0.01%, 0.03%, 0.05%, and 0.1% in stepwise fashion. In the repeated-instillation trial, 36 healthy volunteers were assigned to receive SNJ-1656 ophthalmic solution at the following concentrations and dosages: 0.05% once daily, 0.1% once daily, 0.05% twice daily, or 0.1% twice daily. In our studies, the administration of the solution and subsequent examinations (including intraocular pressure [IOP] measurements) were performed in a double-masked fashion.

Results: After single-dose instillation of placebo or SNJ-1656, 0.003%, 0.01%, 0.03%, 0.05%, and 0.1%, the changes in IOP from the baseline were −0.91, −1.18, −1.48, −2.20 ($P = .04$ vs placebo), −1.48, and −1.98 mm Hg, respectively, at 2 hours, and −0.63, −0.95, −1.79, −2.26 ($P = .01$ vs placebo), −1.95, and −3.00 ($P < .001$ vs placebo) mm Hg, respectively, at 4 hours. Significant IOP reductions after repeated instillation were also found. On slitlamp examination during the trial, there were no significant adverse findings except hyperemia of the bulbar and palpebral conjunctiva after instillation.

Conclusion: This clinical study demonstrated that SNJ-1656 ophthalmic solution is a safe topical agent effective in reducing IOP in human eyes.

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NUMEROUS DRUGS TO lower intraocular pressure (IOP) have been developed and used to treat glaucoma. Among them, prostaglandin analogues and adrenergic α_1-receptor antagonists have been shown to lower IOP by increasing uveoscleral (unconventional) outflow of aqueous humor,[1,2] whereas adrenergic β-receptor blockers, α_2-receptor agonists, and carbonic anhydrase inhibitors have been shown to reduce IOP by inhibiting aqueous humor production.[3-5] Pilocarpine and other miotic agents are believed to reduce IOP by increasing transcanalicular (conventional) aqueous outflow caused by contraction of the ciliary muscle (CM).[6] However, no IOP-lowering drugs directly modulating conventional outflow have been used clinically to treat glaucoma.

Rho guanosine triphosphatase, a member of the Rho subgroup of the Ras superfamily, participates in signaling pathways that lead to formation of actin stress fibers and focal adhesions.[7] Rho is also involved in diverse physiological functions associated with cytoskeletal rearrangement related to cell shape, cell motility, cytokinesis, and smooth muscle contraction.[8] Recently, several putative target molecules of Rho have been identified as Rho effectors, including Rho-associated coiled coil-forming protein kinase, termed p160ROCK, and its isoform, ROKa/Rho kinase/ROCK II.[9,10] ROCK has been shown to be expressed in ocular tissues, including the trabecular meshwork (TM) and CM.[11] In our previous study,[11] we demonstrated that instillation of Y-27632, a selective ROCK inhibitor, significantly reduced IOP, of which mechanism was attributed to improved outflow.[11-13] Inhibition of ROCK activity has been shown to induce alterations in TM cellular responses such as migration, adhesion, and changes in cell shape.[11] Another selective ROCK inhibitor, Y-39983, 4-[(1*R*)-1-aminoethyl]-*N*-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl) benzamide monohydrochloride, is 30-

fold more potent in inhibiting ROCK activity and has similar IOP-lowering effects at lower concentrations than Y-27632.[14]

The purpose of this clinical trial was to investigate the IOP-lowering effects and safety of SNJ-1656, an ophthalmic solution of Y-39983, in a single-dose trial and a prolonged repeated-instillation trial. We report herein the first results, to our knowledge, of a clinical trial of an ophthalmic solution consisting of a selective ROCK inhibitor in human eyes.

METHODS

We conducted this clinical trial as a randomized, double-masked, group-comparison, phase 1 clinical study in accordance with the ethical principles of the Declaration of Helsinki. Included in this study were healthy Japanese male volunteers, aged 20 to 35 years. Subjects with any history of ocular disease (including glaucoma), ocular surgery, or severe ocular trauma considered inappropriate for participation were excluded from the study. In addition, we excluded subjects with a history of liver, kidney, heart, digestive organ, or respiratory organ disorders; hematological diseases; or drug hypersensitivity. The subjects were considered eligible to participate if they had no abnormalities on ocular examination (including IOP) in either eye on screening by ophthalmologists. Subjects with a corrected visual acuity of less than 20/20, a cup-disc ratio of 0.6 or more in both eyes, or a difference in the cup-disc ratio of 0.2 or more between the eyes were excluded. Body weight was required to be within 80% to 120% of standard body weight value, calculated with the formula:

(Height in Centimeters − 100) × 0.9 kg.

During the trial, subjects were prohibited from continuing all medical treatment and from wearing contact lenses. Smoking and ingestion of caffeine, alcohol, and grapefruit were also prohibited during the trial.

First, the single-dose trial of SNJ-1656 and placebo ophthalmic solution (vehicle of SNJ-1656) was conducted in stepwise fashion from July 6 to September 17, 2005, at Osaka Clinical Pharmacological Institute, Osaka. The study was begun at step 1 (SNJ-1656, 0.003%, and placebo). After the safety of the ophthalmic solution was confirmed by physician interviews, physical examinations, ophthalmologic monitoring, and laboratory tests, step 2 (SNJ-1656, 0.01%, or placebo) was started, followed in turn by steps 3 (SNJ-1656, 0.03%, or placebo), 4 (SNJ-1656, 0.05%, or placebo), and 5 (SNJ-1656, 0.1%, or placebo). Nine subjects for each step (6 in the test drug group and 3 in the placebo group) were included. SNJ-1656 (or placebo) was topically administered in both eyes at 9 AM. Intraocular pressure was measured with noncontact tonometry before instillation and at 1 (10 AM), 2 (11 AM), 4 (1 PM), 8 (5 PM), 12 (9 PM), and 24 (9 AM the following day) hours after instillation.

To investigate the safety of prolonged repeated administration of SNJ-1656, a 7-day repeated-instillation trial was conducted from January 14 to April 1, 2006, at Osaka Clinical Trial Hospital, Osaka. The study was conducted in stepwise fashion from steps 1 (SNJ-1656, 0.05%, or placebo once daily), 2-1 (SNJ-1656, 0.1%, or placebo once daily), 2-2 (SNJ-1656, 0.05%, or placebo twice daily), and 3 (SNJ-1656, 0.1%, or placebo twice daily). However, steps 2-1 and 2-2 were concurrently conducted because the daily exposure of drug in the 0.05% twice daily group is the same as that in the 0.1% once daily group. Nine subjects for each step (6 in the test drug group and 3 in placebo group) were included. Twice-daily instillation was performed in both eyes of the subjects at 9 AM and 9:30 PM during the first 6 days and 9 AM on the seventh day. Once-daily instillation was performed in both eyes at 9 AM on all 7 days. The IOPs were measured with noncontact tonometry before instillation and at 1 (10 AM), 2 (11 AM), 4 (1 PM), 8 (5 PM), and 12 (9 PM) hours after instillation in the morning during the 7-day trial and remeasured on the eighth day at 24 hours (9 AM the following day) after the last instillation.

To evaluate the safety of SNJ-1656, ophthalmologic findings and physiological conditions were examined during the trials. The palpebral and bulbar conjunctiva, cornea, anterior chamber, iris, and lens were examined with slitlamp microscopy at 9 AM, 10 AM, 1 PM, 5 PM, and 9 PM daily during the trial. Also, the ocular findings were scored according to the following criteria: 0 indicates no significant changes; 0.5, slight changes regarded as physiological; 1, mild changes requiring no treatment; 2, moderate changes requiring any treatment; and 4, severe changes requiring hospitalization. Pupil diameter was measured at constant illumination at 9 AM, 10 AM, 11 AM, 5 PM, and 9 PM. General physiological factors, including blood pressure, pulse, and body temperature, were also monitored at 9 AM, 10 AM, 1 PM, 5 PM, and 9 PM. Electrocardiograms were obtained at 9 AM and 11 AM. Ocular examinations included determination of best-corrected visual acuity, retinal fundus examination, full-field flash electroretinography (LE-1000; Tomey, Nagoya, Japan), examination of the corneal and conjunctival surfaces with fluorescein and rose bengal dye, the Schirmer lacrimal test, corneal endothelial cell count with a specular microscope (Noncon Robo Pachy SP-9000, Konan Medical Inc, Tokyo), determination of corneal thickness using pachymetry (Noncon Robo Pachy SP-9000), and hematological and urine examinations, all performed at 9 AM. In the repeated-instillation trial, slitlamp examination, Schirmer lacrimal and rose bengal tests, the measurement of pupil diameter, and the monitoring of physiological factors were performed on the first, third, fifth, and seventh days of the trial. An electrocardiogram was obtained on the first, second, fourth, sixth, and seventh days. All examinations were reperformed on the last day of the trial and 1 week after the trial. Slitlamp photography was performed at baseline and whenever abnormal findings were obtained on slitlamp examination results. If volunteers experienced abnormal ocular symptoms, the volunteers indicated them on the patient data sheets. To minimize the adverse effects of SNJ-1656 in the subjects, the study was performed in ascending order from steps 1 to 5 in the single-instillation trial and steps 1, 2-1, 2-2, and 3 in the repeated-instillation trial.

In our studies, the ophthalmological solution was administered and subsequent examinations (including IOP measurements) were performed in a double-masked fashion. Unless otherwise indicated, data are expressed as mean±SD.

RESULTS

IOP-LOWERING EFFECT IN SINGLE-DOSE TRIAL

In the single-instillation trial of SNJ-1656, the mean IOP at baseline was 14.05±2.53 mm Hg for the placebo group and, for the SNJ-1656 groups, 14.08±1.44 mm Hg for 0.003%, 13.73±1.49 mm Hg for 0.01%, 13.73±2.18 mm Hg for 0.03%, 13.19±1.35 mm Hg for 0.05%, and 13.42±2.73 mm Hg for 0.1%, with no significant differences among the groups. The IOP levels in eyes administered SNJ-1656 first decreased and then returned to baseline levels by 24 hours after instillation (**Figure 1**A). The change in IOP from the baseline was −0.91, −1.18, −1.48, −2.20, −1.48, and −1.98 mm Hg at 2 hours and −0.63, −0.95, −1.79, −2.26, −1.95, and −3.00 mm Hg at