Introduction

Intraocular pressure (IOP) is the critical factor influencing the progression of glaucomatous optic nerve damage. Large-scale multicenter studies, including the Advanced Glaucoma Intervention Study (AGIS), the Collaborative Initial Glaucoma Treatment Study (CIGTS), the Ocular Hypertension Treatment Study (OHTS), and the Early Manifest Glaucoma Trial (EMGT), have shown that IOP reduction is effective in counteracting the progression of glaucomatous visual field loss. Furthermore, these and other clinical studies suggest that a target IOP of 21 mmHg, which corresponds to two standard deviations (SD) above the mean IOP of normal eyes (1, 2), is not sufficient to prevent visual field loss in eyes with primary open-angle glaucoma (POAG); this is because the visual field of most advanced glaucomatous eyes remains stable only when the mean IOP is maintained at <15 mmHg (3, 4) or <18 mmHg (5) for long follow-up periods. This implies that the target IOP for preventing the further progression of glaucomatous optic neuropathy might be <21 mmHg. However, it has also been suggested that the progression of glaucomatous optic neuropathy in POAG eyes is more dependent upon other clinical factors, such as circulatory abnormalities and immune responses. Eid *et al.* (6) found no relationship between IOP reduction and the stability of the visual field in eyes treated medically for long follow-up periods. In the present study, we examined whether the progression of visual field defects in POAG eyes with IOPs that were maintained, on average, at <21 mmHg were dependent upon the IOP levels.

Methods

Patients with POAG whose IOP and visual fields were followed up regularly for ≥5 years were included in this retrospective study. Individuals whose baseline visual field defects were measured between 1981 and 2000 at Kumamoto University Hospital, and at Nippon Telegraph and Telephone Corporation West Kyushu General Hospital, were enrolled in the study. We defined the outcomes of the second visual field tests as the baseline data for visual field loss. If the reliability values (fixation losses, false-positive responses, or false-negative responses) were ≥50%, the data obtained in the third or subsequent test that fitted our criteria served as the baseline. We enrolled the patients who received visual field tests at least once a year. The visual field defects were evaluated using the AGIS scores, ranging from 0 (no defect) to 20 (end-stage defect) as described previously (7). Patients with baseline scores of 1 to 16 were enrolled in the study, whereas those with scores of ≥17 were excluded. Between 1981 and 2003, measurements were made using Humphrey visual field analyzers with a full-threshold strategy set for the central 30-2 threshold test. We analyzed 52 test locations, corresponding to areas within the central 24-2 threshold, which did not include sites above or below the center of the blind-spot.

During the follow-up as well as at the baseline, patients were treated with medicine and surgeries for IOP lowering. The IOP levels were evaluated using a Goldmann Applanation Tonometer on a slit-lamp biomicroscope. Initially, the IOP values measured at visits made over a period of 3 months were averaged, and the 3-month average values were then averaged over 1 year; this value was designated as

the average IOP for the year. All of the average yearly IOPs were then averaged, and this value was designated as the average IOP level.

The exclusion criteria were as follows: eyes with a baseline visual acuity of <0.2 in decimal notation according to the Landolt C chart; eyes with an average IOP level of >21 mmHg over the entire follow-up period; and eyes with significant associated visual acuity changes due to senile cataract or other ocular diseases, or due to intraocular surgery (including cataract surgery). POAG cases in which the IOP levels >21 mmHg were not recorded at any time before or during the follow-up periods including the 24-h IOP hospital examinations, and with or without IOP lowering treatment, were defined as normal tension glaucoma (NTG). POAG cases in which IOP levels >21 mmHg were recorded at least once, including at times other than during the follow-up period, were defined as POAG with high pressure. To categorize the eyes with POAG into subgroups based upon the IOP levels, the number of years during which the highest IOP was ≥18 mmHg was determined for each case. Eyes that were classified as POAG with high pressure were classified as either ≤3 years (group A) or ≥4 years (group B). By contrast, NTG eyes were classified as either 0 years (group C) or ≥1 year (group D). To evaluate the probability of progression of the visual field defects during the follow-up period in each group, we calculated Kaplan–Meier survival curves. We defined a deterioration of ≥4 points according to the AIGS criteria as progression of the visual field defects. It is known that 5% of eyes deteriorate by ≥4 points due to inter-test fluctuations [7]; thus, worsening of the visual field defects by ≥4 points was not classified as progression if the visual field defects were classed as less severe in

subsequent tests.

In addition, we evaluated the enlargement of the cup on the basis of the vertical cupping/disc (C/D) ratios. The vertical C/D ratios calculated from the drawings in the clinical records were expressed as decimal values with intervals of 0.1. We analyzed the C/D ratios at the baseline and at the last examination.

Results

In total, 70 eyes with POAG with high pressure and 30 eyes with NTG met the criteria for inclusion in the study. In 14 of 30 eyes with NTG, the 24-h IOP hospital examinations were performed, showing no IOP levels of >21 mmHg. The mean ± SD values for age, follow-up period, IOP level at baseline, and average IOP level during follow-up are presented in Table 1. During the follow-up period, all the eyes and 27 eyes were treated with anti-glaucomatous drugs and glaucoma surgeries, respectively. The mean ± standard error (SE) visual field defect scores at baseline and at the last examination for the 100 eyes were 6.3±0.4 and 8.0±0.5, respectively. This difference was statistically significant (p<0.0001, Wilcoxon paired signed rank test). The distribution of each score is 14 eyes in 1 point, 9 eyes in 2 points, 11 eyes in 3 points, 8 eyes in 4 points, 10 eyes in 5 points, 5 eyes in 6 points, 6 eyes in 7 points, 8 eyes in 8 points, 2 eyes in 9 points, 9 eyes in 10 points, 4 eyes in 11 points, 4 eyes in 12 points, 3 eyes in 13 points, 1 eye in 14 points, 2 eyes in 15 points and 4 eyes in 16 points. The baseline scores for the POAG eyes with high pressure (6.5±0.5) and NTG (5.8±0.7) had increased to 8.1±0.6 and 7.8±0.8, respectively, by the time of the last examination,

thereby demonstrating statistically significant progression ($p<0.0001$, Wilcoxon paired signed rank test).

An analysis of the relationship between the average IOP levels during the follow-up period and the increase in visual field defect scores (Fig. 1) showed that high average IOP levels and increased scores were weakly but significantly correlated ($r=0.21$, $p=0.037$, Pearson's correlation coefficient test). In addition, we divided POAG eyes into two groups; high IOP group (average IOP levels of ≥16 mmHg; $n=36$) and low IOP group (average IOP levels of <16 mmHg; $n=64$). The comparison of two groups showed that the increases in the visual field scores of high IOP group (2.5±0.5) were significantly greater ($p=0.031$, Mann Whitney-U test). More specifically, in the high pressure group, the increases in the visual field scores for eyes with IOP levels ≥16 mmHg (2.4±0.5; $n=34$) were greater ($p=0.012$, Mann Whitney-U test) than those for eyes with IOP levels <16 mmHg (0.9±0.4; $n=36$). We further divided the NTG group into two subgroups (≥13.8 mmHg or <13.8 mmHg) based on the median values of the average IOP levels, because only two eyes had average IOP levels ≥16 mmHg. However, no significant difference was found between the increases in scores in these two subgroups: 1.3±0.6 ($n=15$) for the <13.8 mmHg group versus 2.8±0.7 ($n=15$) for ≥13.8 mmHg group ($p=0.073$, Mann-Whitney U test; Fig. 2).

In addition, a comparison of the visual field score changes in groups A and B, and groups C and D (Fig. 3), revealed that the increases in groups B (2.4±0.5; $n=32$) and D (3.2±0.7; $n=13$) were significantly greater ($p=0.014$, Mann-Whitney U test) than those in groups A (0.9±0.3; $n=38$; $p=0.013$, Mann-Whitney U test) and C (1.1±0.5;

n=17; p=0.014, Mann-Whitney U test). A Kaplan–Meier analyses of the relationship between IOP levels and progression of visual field defects (Fig. 4) indicated that the 5-year survival ratios were 89.5% in group A and 84.4% in group B, and the 10-year survival ratios were 83.5% in group A and 44.5% in group B, indicating a poorer prognosis for group B (p=0.047, log rank test). By contrast, although the same comparisons of groups C and D showed values of 76.9% and 76.5%, respectively, at 5 years, and of 0% and 76.5%, respectively, at 10 years, the difference was not significant (p=0.466, log rank test).

Also, to examine correlation between IOP fluctuation and the progression of visual filed defect, we analyzed the relationship between AGIS score change and the mean value of yearly IOP ranges in all the POAG eyes. But, no statistical significance was shown (p=0.80, Pearson's correlation coefficient test).

At baseline, the vertical C/D ratios of 0.8 or less were shown in 56 of 100 eyes. Of 56 eyes with the C/D ratio of $\leq$ 0.8, the C/D ratio increased by $\geq$0.2 during the follow-up period in 18 eyes, and increased by <0.2 in 38 eyes. The increase of $\geq$0.2 was associated with a worse prognosis in the visual field defect score (3.8±0.9 versus 1.0±0.3; p=0.0055, Mann-Whitney U test). Among the POAG eyes with high pressure, those with increases of C/D ratio $\geq$0.2 had higher average IOP levels than those with increases of <0.2 (17.6 ±2.1 mmHg versus 15.9 ±2.1 mmHg; p=0.017, Mann-Whitney U test). However, there was no significant difference between the average IOP levels of the two groups of NTG eyes (14.4 ±1.7 mmHg; $\geq$ 0.2 versus 14.2 ±1.3 mmHg; < 0.2; p=0.91, Mann-Whitney U test).

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	60	110
Age (years)		63.8 ± 12.9	61.6 ± 13.2	56.8 ± 15.3
Follow-up (years)		7.4 ± 1.3	6.4 ± 1.5	7.8 ± 1.7
IOP (mmHg)	Baseline	17.9 ± 3.6	13.9 ± 1.8	17.0 ± 3.5
	Average	15.6 ± 2.7	13.6 ± 1.5	15.0 ± 2.5

± standard deviation

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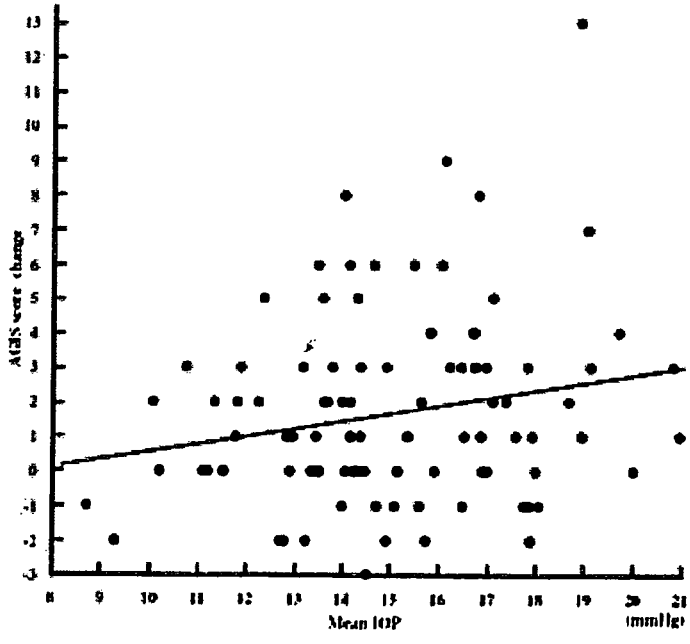

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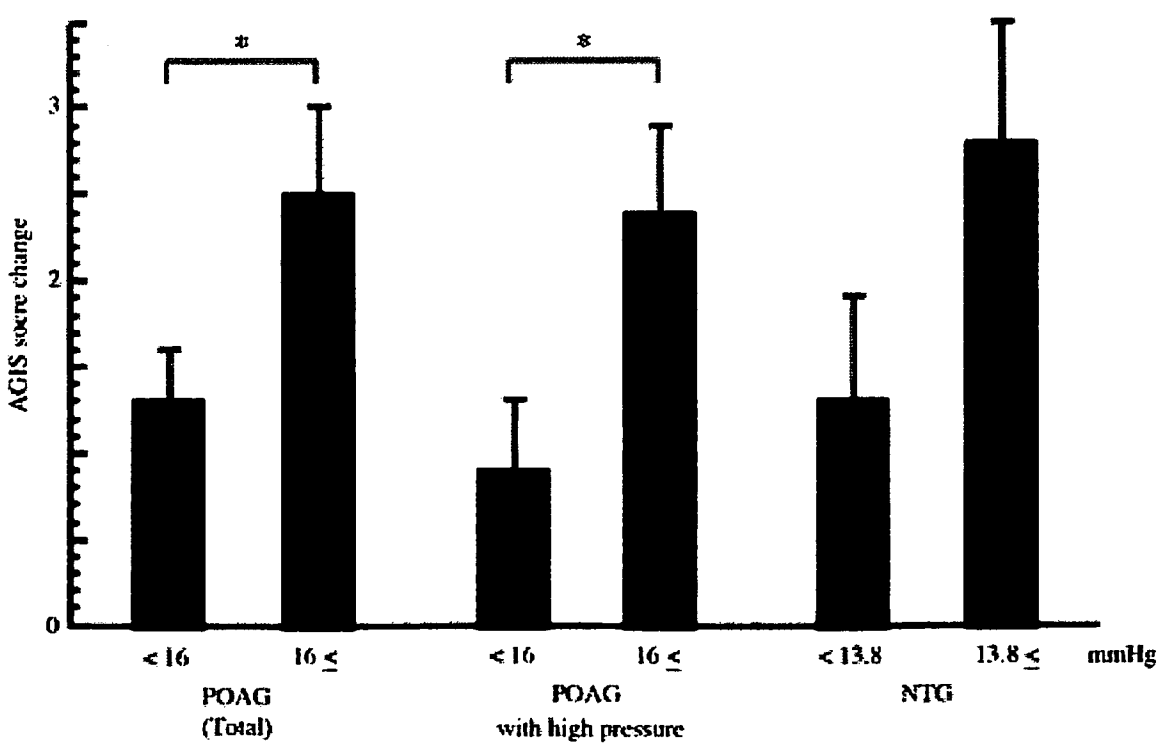

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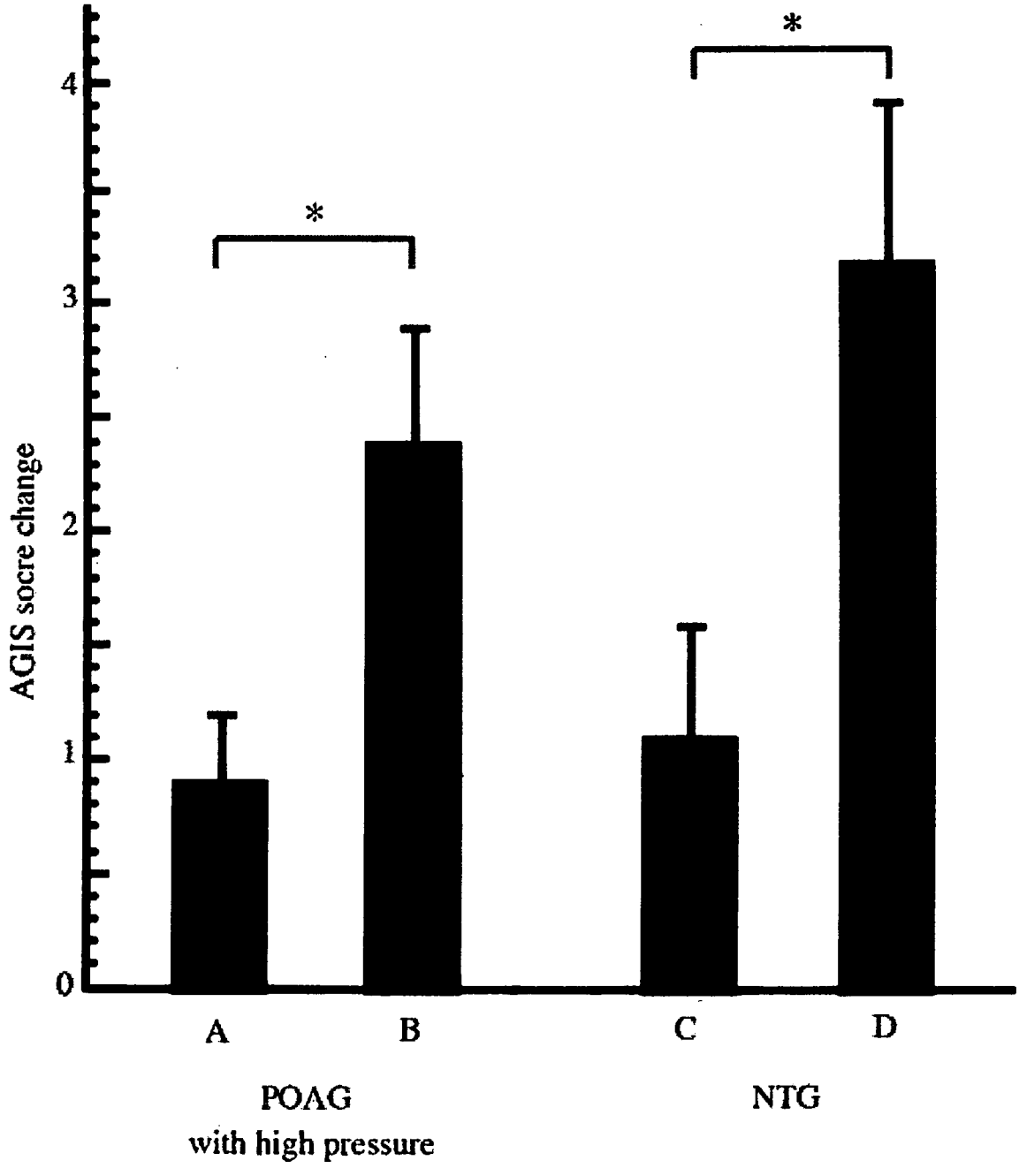

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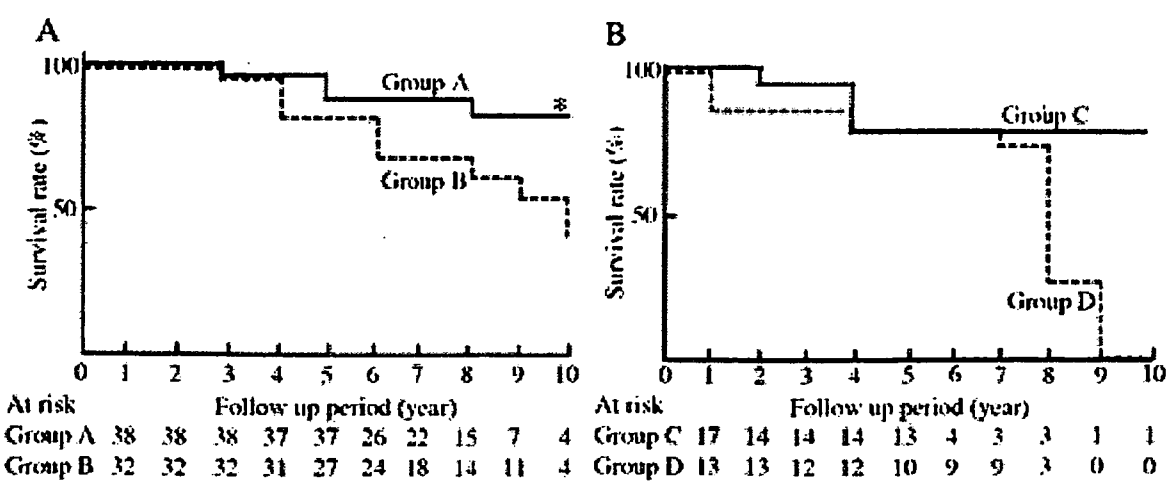

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Intraocular Pressure Elevation after Injection of Triamcinolone Acetonide: A Multicenter Retrospective Case-Control Study

MASARU INATANI, KEIICHIRO IWAO, TAKAHIRO KAWAJI, YOSHIO HIRANO, YUICHIRO OGURA, KAZUYUKI HIROOKA, FUMIO SHIRAGA, YORIKO NAKANISHI, HIROYUKI YAMAMOTO, AKIRA NEGI, YUKA SHIMONAGANO, TAIJI SAKAMOTO, CHIEKO SHIMA, MIYO MATSUMURA, AND HIDENOBU TANIHARA

• 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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From the Department of Ophthalmology and Visual Science, Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan (M.I., K.I., T.K., H.T.); Department of Ophthalmology and Visual Science, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan (Y.H., Y.O.); Department of Ophthalmology, Kagawa University Faculty of Medicine, Miki, Japan (K.H., F.S.); Department of Organs Therapeutics, Division of Ophthalmology, Kobe University Graduate School of Medicine, Kobe, Japan (Y.N., H.Y., A.N.); Department of Ophthalmology, Faculty of Medicine, Kagoshima University Graduate School of Medicine and Dental Sciences, Kagoshima, Japan (Y.S., T.S.); and Department of Ophthalmology, Kansai Medical University, Moriguchi, Japan (C.S., M.M.).

Inquiries to Masaru Inatani, Department of Ophthalmology and Visual Science, Kumamoto University Graduate School of Medical Sciences, 1-1-1, Honjo, 860-8556 Kumamoto, Japan; e-mail: inatani@fc.kuh.kumamoto-u.ac.jp

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