Table 4. Mean change from baseline in best-corrected visual acuity score of the study eye at the last visit in the extension phase (Group B, enrolled patients).

Visual acuity (letters)	Ranibizumab 0.3 mg $N = 28$	Ranibizumab 0.5 mg $N = 33$
Baseline		
Mean (SD)	47.9 (12.59)	50.0 (10.38)
Month 12 (start of extension phase)		
Mean (SD)	59.1 (11.69)	59.8 (15.07)
Last visit		
Mean (SD)	55.4 (17.14)	57.6 (15.36)
Change from baseline		
Mean (SD)	7.5 (19.12)	7.7 (13.02)
95% CI of the mean*	0.1, 14.9	3.0, 12.3
p-value†	0.0475	0.0019
Change from Month 12		
Mean (SD)	−3.6 (14.82)	−2.2 (7.92)
95% CI of the mean*	−9.4, 2.1	−5.0, 0.6
p-value†	0.2042	0.1186

Observed values are presented. Patients must have values at both Month 12 and last visit to be included. Baseline value is defined as the last available measurement prior to the first injection in the multiple-injection phase of the study. End of study differed between the patients and this was more evident from Month 30. Month 35 was the longest analysis point.
N = number of enrolled patients.
* Derived from t-distribution.
† Derived from paired t-test.

Nonocular AEs were observed in four patients (44.4%) in Group A (two each in the 0.3 and 0.5 mg dose groups), 19 patients (67.9%) in the 0.3 mg group and 24 patients (72.7%) in the 0.5 mg group in Group B. Nasopharyngitis was the most common AE in Group B patients (Table 6).

Adverse events potentially related to systemic VEGF inhibition were observed in four patients (14.3%) and two patients (6.1%) in the 0.3 and 0.5 mg dose groups of Group B, respectively. One patient in each dose group experienced cerebral infarction; three patients (0.3 mg dose group) and one patient (0.5 mg dose group) experienced hypertension. In Group A, AEs potentially related to systemic VEGF inhibition were observed in two patients in the 0.3 mg dose group (blood pressure increased and haematuria in one patient and hypertension in another patient).

Nonocular AEs suspected to be related to study drug were cerebral infarction, dementia and hypertension (one patient each) in 0.3 mg group, cerebral infarction and malaise (one patient each) in 0.5 mg dose group.

There were no deaths during the extension phase. Serious adverse events were reported for one of three (33.3%) patients in the 0.3 mg dose group and one of six (16.7%) patients in the 0.5 mg dose group in Group A, four patients (14.3%) in the 0.3 mg dose group and seven patients (21.2%) in the 0.5 mg dose group of Group B. Summary of ocular and nonocular SAEs is shown in Table 7. Of the SAEs, cerebral infarction (one patient each in the 0.3 and 0.5 mg dose groups of Group B) was suspected to be related to study drug and resolved with medical treatment in both patients. Four patients (two patients each from both dose groups) in Group B discontinued from the study because of SAEs. These SAEs that led to discontinuation were, however, not suspected to be study-drug related.

During the extension phase, immunoreactivity to ranibizumab (anti-ranibizumab antibodies) was not detected in patients of Group A; however, it was detected in two patients in the 0.3 mg dose group and one patient in the 0.5 mg dose group of Group B in the extension phase. In one patient in the 0.3 mg dose group, immunoreactivity to ranibizumab was detected at Month 12 (for the first time) and at study completion visit, but not at Month 24. In another patient in the 0.3 mg dose group, immunoreactivity to ranibizumab was detected at Month 24 (for the first time) and at study completion visit. In the 0.5 mg dose group, immunoreactivity to ranibizumab was detected in one patient at Month 12 (for the first time), Month 24 and at study completion visit. Of the three patients, AEs were reported in two patients. One patient in the 0.3 mg dose group experienced mild iritis as ocular AE and moderate glaucomatocyclitic crises as ocular SAE in the study eye as well as mild back injury and fall as nonocular AE. Iritis, back injury and fall were resolved without treatment and glaucomatocyclitic crises were resolved with medical treatment. One patient in the 0.5 mg dose group experienced both of conjunctival hyperaemia and intraocular pressure increased in the study eye, and both events were mild and resolved without treatment. All these events, except for intraocular pressure increased, were not suspected to be study-drug related.

Discussion

EXTEND-I was the first study with ranibizumab in Japanese patients with primary or recurrent subfoveal CNV secondary to AMD. The 6-month results indicated that monthly ranibizumab treatment significantly improved BCVA scores at Month 6 compared with baseline; the mean change (SD) observed was of +8.1 (12.65) letters and +9.0 (9.62) letters in BCVA score in the 0.3 and 0.5 mg dose groups, respectively. The improved BCVA scores at Month 6 were maintained until Month 12 by monthly treatment; the mean change (SD) observed was of +9.5 (12.79) letters and +10.5 (11.14) letters in BCVA score in the 0.3 and 0.5 mg dose groups, respectively. Monthly intravitreal injections of ranibizumab were shown to be safe and well tolerated over 12 months in Japanese patient population (Tano & Ohji 2010).

In the extension phase, the efficacy and safety of individualized flexible interval regimen (PRN regimen) of ranibizumab was assessed. In other words, the study consecutively investigated 12 monthly injections in the multiple-injection phase followed by the extension phase with PRN regimen guided by monthly BCVA score and by other ophthalmic examina-

Table 5. Best-corrected visual acuity (BCVA) of the study eye at the last visit in Group B (Enrolled patients).

BCVA	Ranibizumab 0.3 mg (N = 28)	Ranibizumab 0.5 mg (N = 33)
Loss of < 15 letters from baseline		
n (%)	24 (85.7)	32 (97.0)
95% CI of %*	67.3, 96.0	84.2, 99.9
Gain of ≥15 letters from baseline		
n (%)	9 (32.1)	9 (27.3)
95% CI of %*	15.9, 52.4	13.3, 45.5
Loss of ≥30 letters from baseline		
n (%)	1 (3.6)	1 (3.0)
95% CI of %*	0.09, 18.3	0.08, 15.8
Visual acuity < 34 letters		
n (%)	3 (10.7)	1 (3.0)
95% CI of %*	2.27, 28.2	0.08,. 15.8
Approximate Snellen equivalent of 20/200 or worse		
n (%)	4 (14.3)	2 (6.1)
95% CI of %*	4.03, 32.7	0.74, 20.2
Approximate Snellen equivalent better than 20/200 but worse than 20/40		
n (%)	18 (64.3)	20 (60.6)
95% CI of %*	44.1, 81.4	42.1, 77.1
Approximate Snellen equivalent of 20/40 or better		
n (%)	6 (21.4)	11 (33.3)
95% CI of %*	8.30, 41.0	18.0, 51.8

* Derived from the exact confidence interval. Baseline value is defined as the last available measurement prior to the first injection in the multiple dose phase of the study; N = number of enrolled patients; n = number of patients.

tions, such as slit-lamp examination, ophthalmoscopy, fundus photography, fluorescein angiography and optical coherence tomography.

The estimated number of ranibizumab injections per year in the extension phase was approximately four injections in both the dose groups, which is equivalent to one-third of the maximally possible number of injections per year. The actual injection interval during the extension phase was not fixed and varied among patients and even in individual subject. Consequently, the PRN regimen with monthly monitoring resulted in considerably less frequent injections than a monthly regimen in this study. This seems to suggest that fixed monthly injection of ranibizumab is not necessary for all patients to maintain the improved VA gained through the initial monthly injections.

Results from the extension phase show a slight, but not significant, decrease in BCVA score when the regimen was switched from monthly injections to the PRN regimen. Thus, based on the mean change in BCVA scores in both the multiple-injection phase and the extension phase, the monthly regimen seems to be more effective in obtaining the best treatment outcome in VA than PRN regimen. However, continuous monthly injections are not feasible for many patients because of the physical and psychological burden and risk of AEs such as eye infections associated with the invasive intravitreal injection procedure.

Based on the results of the pivotal randomized Phase III studies, MARINA, ANCHOR and PIER, a drug and disease model with good agreement with study data was developed to simulate BCVA outcomes by individualized flexible VA-guided regimen following the initial three consecutive monthly injections of ranibizumab (Holz et al. 2010). Individualized flexible VA-guided regimen (administered if BCVA decreased by > 5 letters) is suggested to sustain initial BCVA gains following the initial three consecutive monthly injections of ranibizumab. According to the model prediction, it was recommended that patients should be monitored with monthly visits and further treatment should be considered if BCVA decreased by > 5 letters.

As discussed in the modelling and simulation study and as observed in the present study, slight decrease in BCVA was noted during the PRN regimen in the extension phase unlike the monthly treatment regimen. Because the concept of the PRN regimen is to treat in case of deterioration, especially a decrease in BCVA score, a corresponding decline in the BCVA curve over time is expected, i.e., the observed decline in BCVA during the extension phase is imminent to the PRN regimen concept.

As a guidance for retreatment during the PRN regimen, in this study, BCVA decrease by > 5 letters between two consecutive scheduled visits (including the current visit) was applied, so that the decision of retreatment at the current visit was made on the basis of changes calculated between BCVA scores of the last and current scheduled visit, taking the other ophthalmic conditions into account. On the other hand, in SAILOR and SUSTAIN, although the applied retreatment criterion of BCVA was the same as adopted in this study, the starting point of calculation was any previous visit wherein the BCVA score was the highest, especially in SUSTAIN the previous visit was limited to the first three months (Mitchell et al. 2010). Therefore, the decrease of BCVA score by > 5 letters was less likely to occur in this study than in both SAILOR and SUSTAIN. From this perspective, if the retreatment criterion based on the previous highest score is applied, it is speculated that both the number of injection and the BCVA score are apt to increase in comparison with the criterion based on the two consecutive scheduled visits. In both this study and SUSTAIN, monitoring of BCVA scores and other ophthalmic examinations was performed monthly in the same manner; the decline of the BCVA score in the 0.3 mg dose group from Month 12 in this study and from Month 3 in SUSTAIN was almost the same (decrease of 2–3 letters) on an average. Furthermore, in SUSTAIN, the number of retreatments in 9 months of maintenance phase with PRN regimen after three consecutive monthly injection was 2.7 on average, which translates into approximately four times per year. This estimated number of retreatments per year in the SUSTAIN study is roughly the same as the estimated number of injections per year in the extension phase with the PRN regimen of this study. Thus, the

Table 6. Summary of ocular and nonocular adverse events during the extension phase.

Preferred term	Group A: Ranibizumab, 0.3 mg $N = 3$	Group A: Ranibizumab, 0.5 mg $N = 6$	Group B: Ranibizumab, 0.3 mg $N = 28$	Group B: Ranibizumab 0.5 mg $N = 33$
Ocular				
Total, *n* (%)	2 (66.7)	3 (50.0)	20 (71.4)	18 (54.5)
Asthenopia	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
Cataract	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)
Conjunctival haemorrhage	1 (33.3)	3 (50.0)	12 (42.9)	11 (33.3)
Conjunctival hyperaemia	0 (0.0)	0 (0.0)	2 (7.1)	1 (3.0)
Conjunctivitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)
Conjunctivitis allergic	0 (0.0)	1 (16.7)	0 (0.0)	1 (3.0)
Dry eye	1 (33.3)	0 (0.0)	0 (0.0)	1 (3.0)
Eye pain	0 (0.0)	0 (0.0)	2 (7.1)	0 (0.0)
Glaucomatocyclitic crisis	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)
Injection site discomfort	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)
Intraocular pressure increased*	0 (0.0)	0 (0.0)	2 (7.1)	4 (12.1)
Iritis	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)
Maculopathy	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)
Myodesopsia	0 (0.0)	1 (16.7)	0 (0.0)	2 (6.1)
Ocular hypertension	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)
Punctate keratitis	0 (0.0)	0 (0.0)	1 (3.6)	1 (3.0)
Retinal detachment#	0 (0.0)	1 (16.7)	3 (10.7)	4 (12.1)
Retinal haemorrhage†	1 (33.3)	2 (33.3)	8 (28.6)	8 (24.2)
Retinal oedema	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)
Visual acuity reduced	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)
Vitreous haemorrhage	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)
Nonocular (> 5% in any group)‡				
Total	2 (66.7)	2 (33.3)	19 (67.9)	24 (72.7)
Colonic polyp	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.1)
Dental caries	0 (0.0)	0 (0.0)	1 (3.6)	2 (6.1)
Diabetes mellitus	0 (0.0)	0 (0.0)	3 (10.7)	0 (0.0)
Fall	0 (0.0)	0 (0.0)	1 (3.6)	2 (6.1)
Gastroenteritis	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	0 (0.0)	0 (0.0)	3 (10.7)	1 (3.0)
Nasopharyngitis	1 (33.3)	1 (16.7)	5 (17.9)	8 (24.2)

N = number of enrolled patients; n = number of patients.
* Five incidences in Group B (2 from 0.3 mg; 3 from 0.5 mg) are suspected to be study-drug related.
# Serous retinal detachment in all cases.
† One incident in 0.5 mg (Group B) is suspected to be study-drug related.
‡ Full list provided in Table S1.

influence of the starting point to calculate the decrease in BCVA score for retreatment criterion on the stabilization of BCVA score may not be so large. Apart from the difference in the starting point for the PRN regimen, the duration of consecutive monthly injection before start of PRN regimen in this study and SUSTAIN was different, i.e., 12 and 3 months, respectively, and the duration of the extension phase in this study (about one and half year) and that of maintenance phase in SUSTAIN (9 months) were also different, so that it seems to be difficult to simply compare the mean change in BCVA score between these two studies. Although the starting point to calculate the decrease of BCVA for retreatment criterion still remains to be investigated, it can be argued that a more stringent retreatment criterion may lead to better results, taking into consideration the best treatment outcome obtained by monthly injection.

Recently, based on the evidence available from prospective, multicentre studies evaluating different ranibizumab treatment schedules (ANCHOR, MARINA, PIER, PrONTO, SUSTAIN and EXCITE), it was summarized that the treatment initiation with three consecutive monthly injections of ranibizumab, followed by continued monthly injections, has provided the best VA outcomes in pivotal clinical studies (Mitchell et al. 2010). Furthermore, Mitchell et al. (2010) recommended that if continued monthly injections are not feasible after initiation, a flexible regimen may be adopted with monthly monitoring of lesion activity. The results from the extension phase with PRN regimen in EXTEND-I study are consistent with these clinical recommendations on ranibizumab treatment.

Regarding safety, the comparison between the multiple-injection phase and the extension phase is difficult as there were substantial differences between these two phases with regard to the duration, the number of patients and the number of injections. Although the mean duration of observation in the extension phase was longer than 12 months (1.45 and 1.36 years in the 0.3 and 0.5 mg dose groups, respectively), the incidence rate of ocular AEs appears to be lower than those during the 12-month multiple-injection phase (Tano & Ohji 2010). As the incidence

Table 7. Serious adverse events (SAEs) observed during the extension phase.

	Group A Ranibizumab 0.3 mg $N = 3$	Group A Ranibizumab 0.5 mg $N = 6$	Group B Ranibizumab 0.3 mg $N = 28$	Group B Ranibizumab 0.5 mg $N = 33$
Total, *n* (%)	1 (33.3)	1 (16.7)	4 (14.3)	7 (21.2)
Ocular SAE of study eye	1 (33.3)	0 (0.0)	2 (7.1)	0 (0.0)
Glaucomatocylitic crisis	0 (0.0)	0 (0.0)	1 (3.6)*	0 (0.0)
Macular degeneration	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
Retinal detachment	0 (0.0)	0 (0.0)	1 (3.6)†	0 (0.0)
Vitreous haemorrhage	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)
Ocular SAE of fellow eye	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)
Visual acuity reduced	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)
Nonocular SAE	0 (0.0)	1 (16.7)	2 (7.1)	6 (18.2)
Abscess neck	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0) *
Cerebral infarction	0 (0.0)	0 (0.0)	1 (3.6)*	1 (3.0)*
Colon cancer	0 (0.0)	0 (0.0)	1 (3.6)†	0 (0.0)
Colon polyp	0 (0.0)	1 (16.7)*	0 (0.0)	0 (0.0)
Depression	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)†
Emphysema	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)
Enterocele	0 (0.0)	0 (0.0)	1 (3.6)*	0 (0.0)
Gastric cancer	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)†
Gastric polyps	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)*
Small cell lung cancer stage unspecified	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)†
Spondylitic myelopathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)*
SAEs causing discontinuation from study drug/study	0 (0.0)	0 (0.0)	2 (7.1)	2 (6.1)
Ocular SAE of study eye	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)
Ocular SAE of fellow eye	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nonocular SAE	0 (0.0)	0 (0.0)	1 (3.6)	2 (6.1)

Both of gastric cancer and small cell lung cancer stage unspecified occurred in same patient of the 0.5 mg dose group.
N = number of enrolled patients; n = number of patients.
* SAE resolved by the last visit of the study.
† SAE led to discontinuation.

rate of conjunctival haemorrhage, conjunctival hyperaemia and eye pain in the study eye appears to be lower in the extension phase than those in the multiple-injection phase, these AEs are likely to be related to the intravitreal injection of ranibizumab and subconjunctival anaesthesia. Because the estimated number of ranibizumab injections per year was reduced by about one-third because of the PRN regimen in comparison with monthly regimen, there appears to be a relationship between the lower incidence of ocular AEs and reduction of number of injections. On the other hand, the incidence rate of nonocular AEs appears to be similar to those in the multiple-injection phase.

In conclusion, given the efficacy and safety profile observed in the extension phase, an individualized flexible interval regimen (PRN regimen) of ranibizumab, guided by monthly monitoring of BCVA score and other ophthalmic examinations, appears sufficiently effective and feasible in sustaining BCVA gained by consecutive monthly treatment and helps reducing the number of injections and treatment burden. Ranibizumab administered over the extension phase in Japanese patients with subfoveal CNV secondary to AMD was safe and well tolerated.

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References

Bressler NM (2004): Age-related macular degeneration is the leading cause of blindness. JAMA **291**: 1900–1901.

Brown DM, Kaiser PK, Michels M et al. (2006): Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med **355**: 1432–1444.

Brown DM, Michels M, Kaiser PK et al. (2009): Ranibizumab versus Verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. Ophthalmology **116**: 57–65.

Ferrara N, Damico L, Shams N et al. (2006): Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. Retina **26**: 859–870.

Ferrara N, Mass RD, Campa C & Kim R (2007): Targeting VEGF-A to treat cancer and age-related macular degeneration. Annu Rev Med **58**: 491–504.

Holz FG, Korobelnik JF, Lanzetta P et al. (2010): The effects of a flexible visual acuity-driven ranibizumab treatment regimen in age-related macular degeneration: outcomes of a drug and disease model. Invest Ophthalmol Vis Sci **511**: 405–412.

Kawasaki R, Wang JJ, Ji GJ et al. (2008): Prevalence and risk factors for age-related macular degeneration in an adult Japanese population: the Funagata study. Ophthalmology **115**: 1376–1381.

Mitchell P, Korobelnik JF, Lanzetta P et al. (2010): Ranibizumab (Lucentis) in neovascular age-related macular degeneration: evidence from clinical trials. Br J Ophthalmol **94**: 2–13.

Oshima Y, Ishibashi T, Murata T et al. (2001): Prevalence of age related maculopathy in a representative Japanese population: the Hisayama study. Br J Ophthalmol **85**: 1153–1157.

Regillo CD, Brown DM, Abraham P et al. (2008): Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol **145**: 239–248.

Rosenfeld PJ, Brown DM, Heier JS et al. (2006): Ranibizumab for neovascular age-related macular degeneration. N Engl J Med **355**: 1419–1431.

Tano Y & Ohji M (2010): EXTEND-I: safety and efficacy of ranibizumab in Japanese patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration. Acta Ophthalmol **88**: 309–316.

Waisbourd M, Loewenstein A, Goldstein M & Leibovitch I (2007): Targeting vascular endothelial growth factor: a promising strategy for treating age-related macular degeneration. Drugs Aging **24**: 643–662.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Number (%) of patients with nonocular adverse events by preferred term in Part B (Enrolled patients).

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Comparison of Retinal Nerve Fiber Layer Thickness Measurements Using Time Domain and Spectral Domain Optical Coherence Tomography, and Visual Field Sensitivity

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Purpose: To investigate the relationship between the peripapillary retinal nerve fiber layer (RNFL) thickness, as measured by Stratus time domain optical coherence tomography (OCT) (Stratus OCT) and Cirrus spectral domain OCT (Cirrus HD-OCT), and the severity indices of the visual field (VF) defects in glaucoma patients.

Methods: This was a prospective, cross-sectional study. Correlations between the individual VF sensitivity at 52 test points and the Stratus OCT and Cirrus HD-OCT, which determined peripapillary RNFL thicknesses from 6 sectors, were calculated in 54 eyes with open-angle glaucoma and 22 normal control eyes. The association between the RNFL thickness and VF sensitivity was evaluated using a second-order regression model.

Results: A significant correlation was found for the RNFL thicknesses determined by the 2 OCT devices ($r = 0.51$ to 0.95; $P < 0.001$). VF sensitivities at each test point were also significantly correlated with the sectoral RNFL thicknesses. The inferotemporal RNFL sector exhibited the highest coefficient of determination, whereas the superotemporal test point had the highest VF sensitivity (Stratus, 0.70; Cirrus, 0.62).

Conclusions: The structure-function relationship was comparable between Cirrus HD-OCT and Stratus OCT RNFL measurements.

Key Words: peripapillary retinal nerve fiber layer thickness, optical coherence tomography, severity indices of the visual field

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After the introduction of optical coherence tomography (OCT) in clinical practice in 1995, it became possible to carry out routine measurements of retinal thickness. The first commercially available model, OCT 1 (Carl Zeiss Meditec; Humphrey Division, Dublin, CA) had an axial resolution of about 15 μm and a scan velocity of 100 axial scans per second. In 2002, the OCT 3000 model (Stratus OCT; Carl Zeiss Meditec) was introduced. This device used time domain technology, which initially had an axial resolution of 10 μm and a scan velocity of 400 axial scans per second. Recently, the Cirrus HD-OCT (Carl Zeiss Meditec) has become commercially available, with a spectra domain platform that has an axial resolution of 5 μm and a scan velocity of 27,000 axial scans per second. Although the Stratus OCT and Cirrus HD-OCT have a similar retinal nerve fiber layer (RNFL) measurement locations, they use different technologies. The Stratus OCT measures the RNFL thickness along a 3.46-mm-diameter circle around the optic disc in the fast RNFL mode, whereas the Cirrus HD-OCT resample data along a circle with a 1.73-mm radius around the optic disc.

Glaucoma is a progressive optic neuropathy in which there is loss of retinal ganglion cells that leads to visual field abnormalities. To diagnose and manage glaucomatous optic neuropathy, it is of critical importance to be able to detect the relationship between structural and functional damage. Sensory tests and various imaging techniques have been used to measure this relationship,[1–3] with significant correlations between perimetric tests and optic disc parameters found for the area of the neuroretinal rim or RNFL thickness. The perimetric mean defect of the whole visual field along with the mean RNFL thickness, as measured by Stratus OCT and Cirrus HD-OCT, have been used to determine the quantitative structure-function association.[4] However, local correspondence may be of greater importance in being able to judge the progression of glaucoma.

The purpose of this study was to investigate and compare the local structure-function associations obtained when using the Cirrus HD-OCT and the Stratus OCT devices.

PATIENTS AND METHODS

A total of 54 glaucoma patients and 22 normal participants were enrolled in the study and followed up during the period from October 2008 through January 2009 at Kagawa University Hospital. Among these patients, 34 had primary open-angle glaucoma and 20 had normal-tension glaucoma. All eligible participants received a detailed explanation of the study and signed an informed consent form in accordance with the principles embodied in the Declaration of Helsinki. All the participants underwent a complete ophthalmic examination that included visual acuity testing with refraction, intraocular pressure, and dilated fundus examination with stereoscopic biomicroscopy of the optic nerve head using slit lamp and indirect ophthalmoscopy. To be included in the study, all participants had to have a best corrected visual acuity of 20/40 or better, a spherical error within a range between 4.0 and −6.0 diopters, and a cylinder within ±2.0 diopters. Exclusion criteria included history of any kind of retinal pathology, retinal laser procedure, retinal surgery, or neurologic disease. One eye in each participant was randomly chosen for inclusion in the study. The glaucomatous eyes were defined as the eyes exhibiting structural

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glaucomatous changes (vertical cup-disc asymmetry between fellow eyes of more than equal to 0.2, a cup-disc ratio of more than equal to 0.6, and a neuroretinal rim narrowing, notches, localized pallor, or RNFL defects with glaucomatous visual field (VF) loss in the corresponding hemifield). The glaucomatous VF defects were defined as those with consecutive, repeated abnormal standard automated perimetry (SAP) results (≥ 2 contiguous points with a sensitivity loss of $P < 0.05$ in the superior or inferior arcuate areas, a 10-dB difference across the nasal horizontal midline at greater than 2 adjacent locations, or an abnormal glaucoma hemifield test result). The eyes with preperimetric glaucomatous optic neuropathy were excluded from this study.

Stratus OCT Retinal Nerve Fiber Layer Measurement

The fast RNFL 3.4 scan protocol was used to measure the peripapillary RNFL (software version 4.0.1). The RNFL thickness was determined at 256 circumpapillary points on a circle with a default diameter of 3.4 mm around the center of the optic disc. We excluded all poor-quality scans, which were defined as those with a single strength of < 6; the presence of overt misalignment of the surface detection algorithm on $\geq 15\%$ of consecutive A-scans or 20% of cumulative A-scans; or overdecentration of the measurement circle location, as subjectively assessed.

Cirrus HD-OCT Retinal Nerve Fiber Layer Measurement

The Cirrus HD-OCT uses spectral domain technology of an optic disc cube obtained from a 3-dimensional data set composed of 200 A-scans from each of 200 B-scans that cover a 6-mm^2 area centered on the optic disc. After creating an RNFL thickness map from the cube data set, the software automatically determined the center of the disc and then extracted a circumpapillary circle (1.73-mm radius) from this data set. The same signal strength cutoff value and exclusion criteria used for the Stratus OCT were also used for these measurements.

All images were acquired during a single visit by 1 well-trained technician. Right-hand orientation was used for documentation of the clock hour measurements in both the Cirrus HD-OCT and Stratus OCT.

TABLE 1. Clinical Characteristics of the Study Population

	Glaucoma	Normal	*P*
Age (y)	61.7 ± 11.8	63.1 ± 9.0	0.62
Sex (male/female)	19/35	14/8	0.19
Diagnosis			
POAG	33		
NTG	21		
Refraction (D)	−1.51 ± 2.47	−1.18 ± 2.25	0.59
Visual field MD (dB)	−7.7 ± 7.5	−1.4 ± 1.6	< 0.01

MD indicates mean deviation; NTG, normal-tension glaucoma; POAG, primary open-angle glaucoma.

Visual Field Examination

Standard visual field testing was done using static automated white-on-white threshold perimetry (Humphrey Field Analyzer II; Carl Zeiss Meditec). A visual field was defined as reliable when fixation losses, false-positive errors, and false-negative errors were less than 20%.

Statistical Analysis

The relationship between the 2 OCT measurements was assessed by Pearson correlation analysis. The structure-function relationships from the 6 measured regions were adapted from the map earlier created by Garway-Heath et al (Fig. 1).[5] The relationship between RNFL thickness and visual field mean deviation (MD) was evaluated using a second-order regression analysis, as it has been shown that the second-order regression analysis yields a stronger structure-function association than the first-order and other nonlinear regression analyses.[6,7] Comparisons of the strength of the structure-function association were evaluated by paired *t* tests on the log-transformed absolute value of the studentized residuals from the 2 second-order regression models. A Bland-Altman plot was graphed to assess the agreement between 2 instruments. All statistical values are presented as mean ± standard deviation (SD). In all statistical analyses, *P* values < 0.05 were considered statistically significant (Fig. 1).

RESULTS

The demographic characteristics are detailed in Table 1. As the normal control participants were selected

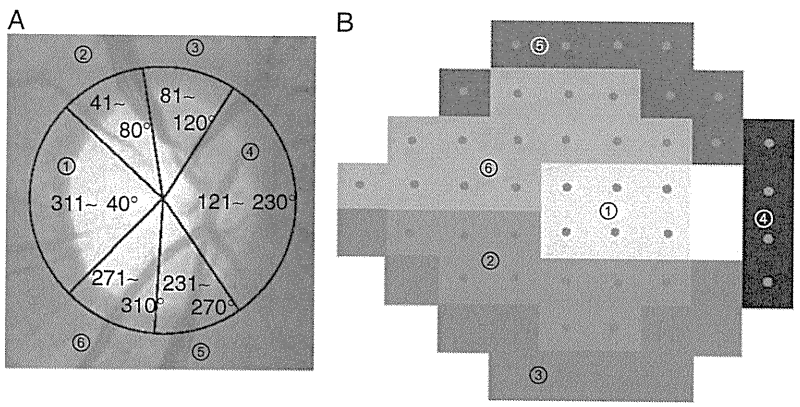

FIGURE 1. A topographic map generated using the methodology of Garway-Heath et al.[5] Areas of the peripapillary retinal nerve fiber layer are divided into 6 sectors (A), and the corresponding visual field regions are observed in standard automated perimetry (B).

TABLE 2. Correlation of RNFLT Measurement on Average and in Each of 6 Sectors as Determined by Stratus and Cirrus OCT

	RNFLT by Stratus (μm)	RNFLT by Cirrus (μm)	Correlation of Determination (R)	*P*
Average	74.3 ± 17.9	72.5 ± 13.6	0.91	< 0.001
Temporal, 311 degrees-40 degrees	62.6 ± 17.7	60.3 ± 12.5	0.83	< 0.001
Superotemporal, 41 degrees-80 degrees	86.5 ± 33.4	87.1 ± 28.7	0.88	< 0.001
Superonasal, 81 degrees-120 degrees	90.1 ± 30.8	85.8 ± 24.4	0.80	< 0.001
Nasal, 121 degrees-230 degrees	62.7 ± 14.4	65.5 ± 9.5	0.51	< 0.001
Inferonasal, 231 degrees-270 degrees	87.0 ± 25.1	77.1 ± 20.0	0.85	< 0.001
Inferotemporal, 271 degrees-310 degrees	92.8 ± 38.1	86.9 ± 33.6	0.95	< 0.001

OCT indicates optical coherent tomography; RNFL, retinal nerve fiber layer.

with age-matching and refractive error-matching, there was no significant difference in the mean age between the normal control participants (63.1 ± 9.0 y; range, 49 to 74) and those with glaucoma (61.7 ± 11.8; range, 35 to 85). The mean deviation (MD) in SAP ranged from −28.73 to −0.78 dB with a mean of −7.7 ± 7.5 dB in patients with glaucoma. Many glaucomatous eyes had early to moderate diseases based on the standard visual field severity grading,[8] of the 54 patient's eyes, 28 (52%) were classified as early, 13 (24%) were classified as moderate, and 13 (24%) were classified as severe.

The average RNFL thickness, as measured by Stratus OCT, was 74.3 ± 17.9 μm, whereas the average RNFL, as measured by Cirrus HD-OCT, was 72.5 ± 13.6 μm. Only the inferonasal Cirrus HD-OCT RNFL thickness measurement (77.1 ± 20.0 μm) was thinner than those measured by the Stratus OCT (88.0 ± 25.1 μm) ($P < 0.05$, unpaired t test). The Pearson correlation coefficient for mean RNFL thickness in each sector between the 2 instruments was 0.51 to 0.95 (Table 2), with the weakest correlation found in the nasal sector ($r = 0.51$; $P < 0.001$). Figure 2 shows the Bland-Altman plots for the agreement between Cirrus HD-OCT and Stratus OCT for the average RNFL thickness. For thinner RNFL thicknesses, Stratus measurements tend to be thinner than Cirrus, whereas for thicker RNFL thicknesses, Stratus measurements tend to be thicker than Cirrus.

The 52 VF test points were clustered into regional groups of VFs that corresponded to the RNFL sections. Coefficients of determination between these 6 VF sensitivity (VFS) clusters and the corresponding 6 sectors are listed in Table 3. Except for the nasal sector, there were significant correlations between the VFS at individual test points and in several of the RNFL sectors. The highest calculated coefficient of determination was for the superotemporal RNFL sector. There were no significant differences noted in the strength of the structure-function association between the Cirrus HD-OCT and Stratus OCT.

DISCUSSION

The results of this study show that Cirrus RNFL measurements correlate well with those from Stratus OCT, with comparable strength of the structure-function association between Cirrus HD-OCT and Stratus OCT. However, although we noted a correlation of the RNFL thickness measurements between Stratus OCT and those from Cirrus OCT, other studies have earlier reported systematic differences in the measurement values between Cirrus HD-OCT and Stratus OCT.[9–11] Although our results showed a high correlation between the Cirrus HD-OCT and Stratus OCT thickness measurements, the RNFL thickness measured by the Cirrus HD-OCT was only thinner than that measured

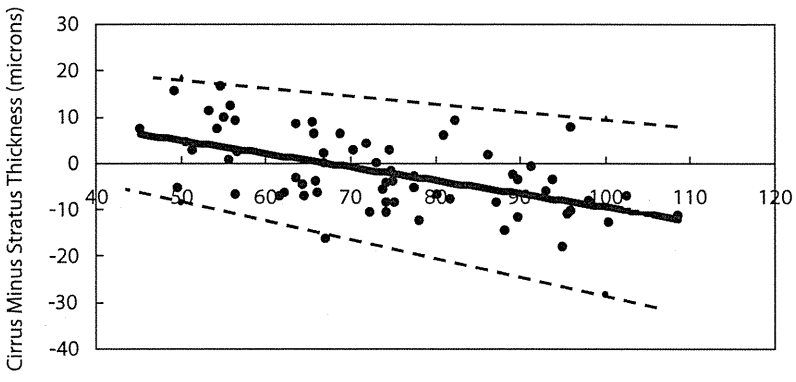

FIGURE 2. Bland-Altman plot of the agreement of mean retinal nerve fiber layer (RNFL) thickness between Cirrus OCT and Stratus OCT. The difference (Cirrus OCT RNFL thickness—Stratus OCT RNFL thickness) between both measurements is plotted against the average of both measurements ($r = 0.55$, $P < 0.01$). The dotted lines of equality are plotted the 95% limits of agreement. OCT indicates optical coherence tomography.

TABLE 3. Comparison of Structure-function Relationship using Stratus or Cirrus OCT by Garway-Heath et al

Sector in RNFL	Correlation of Determination (R)		P
	Stratus OCT	Cirrus OCT	
Temporal, 311 degrees-40 degrees	0.39	0.32	0.31
Superotemporal, 41 degrees-80 degrees	0.70	0.62	0.07
Superonasal, 81 degrees-120 degrees	0.54	0.57	0.63
Nasal, 121 degrees-270 degrees	0.03	−0.06	0.48
Inferonasal, 231 degrees-270 degrees	0.46	0.37	0.17
Inferotemporal, 271 degrees-310 degrees	0.53	0.51	0.65

OCT indicates optical coherent tomography; RNFL, retinal nerve fiber layer.

by Stratus OCT in the inferonasal sector. Although a good agreement was found for all parameters, Bland-Altman plots showed that for thinner RNFL thicknesses, Stratus measurements tend to be thinner than Cirrus, whereas for thicker RNFL thicknesses, Stratus measurements tend to be thicker than Cirrus. We suggest that the RNFL thickness measured by the Stratus OCT can not be transferred to Cirrus HD-OCT thickness measurements because of this discrepancy.

In this study, glaucoma was defined on the basis of structure and VF loss. We wanted to investigate the local structure-function associations. To facilitate this procedure, we included patients with glaucomatous optic neuropathy with VF loss and normal participants with a perfectly normal RNFL without VF loss. The patients with preperimetric glaucoma were excluded from this study. Therefore, we could not find any superiority Cirrus HD-OCT than Stratus OCT in finding RNFL defects.

In our study, 1 examiner scanned each patient on the same 2 instruments during a single day. As eye position relative to the scanning circle can affect the RNFL profile, it is important to keep the scan circle within a consistent location to make serial assessments using the Stratus OCT.[12] As the Cirrus HD-OCT uses a different data-acquisition process that has a considerably higher scan speed, it can be used to obtain 3-dimensional data sets. The Cirrus HD-OCT uses this data set to locate the center of the optic disc and then draws a circle with a 1.73-mm radius. The Cirrus HD-OCT has a theoretical advantage over Stratus OCT in terms of scan registration. The scan registration process carried out by the Cirrus algorithms is fully automated, reducing the likelihood of operator error. We assumed that there was good eye fixation during the RNFL measurements using the Stratus OCT device in all of our participants. However, as we excluded participants with scans that had signal strengths less than 6, we cannot definitively draw any generalized conclusions that apply to all participants, including those with poor signal strengths.

Kanamori et al[13] reported finding significant correlations between the VFS at individual test points and in several of the RNFL sectors when using the Stratus OCT for measurements. Leung et al[4] recently reported that there was no significant difference in the strength of the structure-function association between Cirrus HD-OCT and Stratus OCT (average RNFL thickness and visual field MD). With the exception of the nasal sector, we found that the strength of the structure-function association was similar between Cirrus HD-OCT and Stratus OCT in our study. Both instruments measure RNFL thickness at a diameter of 3.46 mm. Glaucomatous structural changes of the RNFL usually occur first in the inferotemporal and superotemporal areas, with corresponding functional VF losses occurring first in the so-called Bjerrum areas of the upper and lower hemifields. Therefore, VFS might be more closely related to the inferotemporal and superotemporal RNFL thickness as opposed to the temporal and nasal RNFL thickness. However, it is very difficult to estimate the structure-function relationship at the nasal area adjacent to the optic disc owing to the paucity of test points on SAP at the temporal regions adjacent to the blind spot.

In conclusion, a significant association with the VFS was noted for both Cirrus HD-OCT and Stratus OCT when used to measure sectoral RNFL thickness. Further longitudinal studies will be needed to determine the applicability of using the structure-function association to describe glaucoma progression.

REFERENCES

1. Garway-Heath DF, Holder GE, Fitzke FW, et al. Relationship between electrophysiological, psychophysical, and anatomical measurements in glaucoma. *Invest Ophthalmol Vis Sci.* 2002; 43:2213–2220.
2. Bowd C, Zangwill LM, Weinreb RN. Association between scanning laser polarimetry measurements using variable corneal polarization compensation and visual field sensitivity in glaucomatous eyes. *Arch Ophthalmol.* 2003;121: 961–966.
3. Reus NJ, Lemij HG. The relationship between standard automated perimetry and GDx VCC measurements. *Invest Ophthalmol Vis Sci.* 2004;45:840–845.
4. Leung CK, Cheung CY, Weinreb RN, et al. Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography. *Ophthalmology.* 2009;116:1257–1263.
5. Garway-Heath DF, Poinoosawmy D, Fitzke FW, et al. Mapping the visual field to the optic disc in normal tension glaucoma eyes. *Ophthalmology.* 2000;107: 1809–1815.
6. Schlottmann PG, De Cilla S, Greenfield DS, et al. Relationship between visual field sensitivity and retinal nerve fiber layer thickness as measured by scanning laser polarimetry. *Invest Ophthalmol Vis Sci.* 2004;45:1823–1829.
7. Leung CK, Chong KK, Chan WM, et al. Comparative study of retinal nerve fiber layer measurement by StratusOCT and GDx VCC, II: structure/function regression analysis in glaucoma. *Invest Ophthalmol Vis Sci.* 2005;46:3702–3711.
8. Hodapp E, Parrish RK II, Anderson DR. *Clinical Decision in Glaucoma.* St. Louis, MO: Mosby; 1993:5261.
9. Vizzeri G, Weinreb RN, Gonzalez-Garcia AO, et al. Agreement between spectral-domain and time-domain OCT for measuring RNFL thickness. *Br J Ophthalmol.* 2009;93: 775–781.

10. Sung KR, Kim DY, Park SB, et al. Comparison of retinal nerve fiber layer thickness measured by cirrus HD and stratus optical coherence tomography. *Ophthalmology*. 2009;116:1264–1270.
11. Knight OJ, Chang RT, Feuer WJ, et al. Comparison of retinal nerve fiber layer measurements using time domain and spectral domain optical coherent tomography. *Ophthalmology*. 2009;116:1271–1277.
12. Gabriele ML, Ishikawa H, Wollstein G, et al. Optical coherence tomography scan circle location and mean retinal nerve fiber layer measurement variability. *Invest Ophthalmol Vis Sci*. 2008;49:2315–2321.
13. Kanamori A, Naka M, Nagai-Kusuhara A, et al. Regional relationship between retinal nerve fiber layer thickness and corresponding visual field sensitivity in glaucomatous eyes. *Arch Ophthalmol*. 2008;126:1500–1506.

Success Rates of Trabeculotomy for Steroid-Induced Glaucoma: A Comparative, Multicenter, Retrospective Cohort Study

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• PURPOSE: To evaluate the surgical outcomes of trabeculotomy for steroid-induced glaucoma.
• DESIGN: Multicenter, retrospective cohort study.
• METHODS: At 17 Japanese clinical centers, 121 steroid-induced glaucoma patients who underwent trabeculotomy between 1997 and 2006 were reviewed. Surgical failure was defined by the need for additional glaucoma surgery, deterioration of visual acuity to no light perception, or intraocular pressure ≥21 mm Hg (criterion A) and ≥18 mm Hg (criterion B). Surgical outcomes were compared with those of 108 primary open-angle glaucoma (POAG) patients who underwent trabeculotomy and 42 steroid-induced glaucoma patients who underwent trabeculectomy. Prognostic factors for failure were evaluated using the Cox proportional hazards model.
• RESULTS: The probabilities of success at 3 years for trabeculotomy for steroid-induced glaucoma vs trabeculotomy for POAG was 78.1% vs 55.8% for criterion A ($P = .0008$) and 56.4% vs 30.6% for criterion B ($P < .0001$), respectively. At 3 years, the success of trabeculotomy for steroid-induced glaucoma was comparable to trabeculectomy for steroid-induced glaucoma for criterion A (83.8%; $P = .3636$), but lower for criterion B (71.6%; $P = .0352$). Prognostic factors for failure of trabeculotomy for steroid-induced glaucoma were previous vitrectomy (relative risk [RR] = 5.340; $P = .0452$ on criterion A, RR = 3.898; $P = .0360$ for criterion B) and corticosteroid administration other than ocular instillation (RR = 2.752; $P = .0352$ for criterion B).
• CONCLUSIONS: Trabeculotomy is effective for controlling intraocular pressure <21 mm Hg in steroid-induced glaucoma eyes. (Am J Ophthalmol 2011;151: 1047–1056. © 2011 by Elsevier Inc. All rights reserved.)

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STEROID-INDUCED GLAUCOMA IS A FORM OF OPEN-angle glaucoma associated with various modalities of corticosteroid administration such as oral, intravenous, inhaled, ocular instilled, intravitreal, and periocular.[1–6] Some histologic studies have reported the accumulation of extracellular matrices including basement membrane–like material,[7–9] fine fibrillar-like material,[8] or proteoglycans[9] in the trabecular meshwork of steroid-induced glaucoma patients. These observations suggest that such accumulation could lead to an increased resistance to aqueous outflow in the trabecular meshwork of steroid-induced glaucoma patients.

Surgical procedures for intraocular pressure (IOP) reduction in eyes with steroid-induced glaucoma include trabeculectomy,[2,10,11] trabeculotomy,[4,12] viscocanalostomy,[13] and laser trabeculoplasty.[14–18] Although several case series have shown that these surgeries are effective for IOP reduction, surgical outcomes for steroid-induced glaucoma are not fully understood due to lack of large case-control studies aiming to investigate the success rates of trabeculotomy in steroid-induced glaucoma eyes. It has previously been reported that trabeculotomy more effectively reduces IOP in adult Japanese patients with exfoliative glaucoma than primary open-angle glaucoma (POAG).[19] This IOP-lowering effect in eyes with exfoliative glaucoma is thought to be attributable to the relief of abnormally increased outflow resistance that was induced by the accumulation of exfoliative material within the trabecular meshwork.

For the same reason, trabeculotomy has been the surgical procedure of choice for adult patients with steroid-induced glaucoma among Japanese surgeons.[20] We previously showed that trabeculotomy helped to reduce IOPs to 21 mm Hg or less in 14 Japanese patients with steroid-induced glaucoma.[12] However, large-scale, comparative clinical data remain elusive on, for example, whether trabeculotomy is more effective for steroid-induced glaucoma than POAG, whether trabeculotomy for steroid-induced glaucoma offers better IOP management than other surgeries such as trabeculectomy with mitomycin C (MMC), or which characteristics of patients with steroid-induced glaucoma exhibit better prognosis after trabeculotomy. To evaluate the surgical outcomes of trabeculotomy for steroid-induced

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TABLE 1. Patients With Steroid-Induced Glaucoma and Primary Open-Angle Glaucoma who Underwent Trabeculotomy

	SIG-LOT, n (%) (n = 121)	SIG-LET, n (%) (n = 42)	*P* Value	POAG-LOT, n (%) (n = 108)	*P* Value
Female	62 (51.2)	26 (61.9)	.232[a]	38 (35.2)	.014[a]
Right eye	62 (51.2)	22 (52.4)	.899[a]	50 (46.3)	.455[a]
Age (years), mean ± SD	38.4 ± 17.6	42.3 ± 17.9	.153[b]	45.2 ± 15.0	.001[b]
Preoperative IOP (mm Hg), mean ± SD	38.1 ± 10.0	35.6 ± 8.3	.169[b]	28.9 ± 8.4	<.001[b]
Combined sinusotomy	20 (16.5)	—	—	33 (30.6)	.012[a]
Previous cataract surgery	17 (14.0)	4 (9.5)	.626[c]	5 (4.6)	.029[c]
Previous vitrectomy	6 (5.0)	0 (0.0)	.320[c]	0 (0.0)	.054[c]
Diabetic mellitus	13 (10.7)	6 (14.3)	.736[c]	10 (9.3)	.709[a]
Hypertension	18 (14.9)	8 (19.0)	.695[c]	15 (13.9)	.832[a]
Cause of corticosteroid use					
Atopic dermatitis	21 (17.4)	4 (9.5)	.335[c]		
Uveitis	25 (20.7)	11 (26.2)	.457[a]		
Collagen disease	37 (30.6)	17 (40.5)	.240[a]		
Route of administration					
Ocular instillation only	17 (14.0)	12 (28.6)	.591[a]		
Posterior sub-Tenon's injection of TA	13 (10.7)	1 (2.4)	.178[c]		
Intravitreal injection of TA	10 (8.3)	0 (0.0)	.121[c]		
Oral administration	72 (59.5)	26 (61.9)	.784[a]		
Intravenous administration	3 (2.5)	2 (4.8)	.826[c]		
Corticosteroid administration for more than 3 months after surgery	68 (56.2)	25 (59.5)	.708[a]		

IOP = intraocular pressure; POAG-LOT = primary open-angle glaucoma patients who underwent trabeculotomy; SD = standard deviation; SIG-LET = steroid-induced glaucoma patients who underwent trabeculectomy with mitomycin C; SIG-LOT = steroid-induced glaucoma patients who underwent trabeculotomy; TA = triamcinolone acetonide.

[a]*P* values are based on the χ^2 for independence test.

[b]*P* values are based on Mann-Whitney *U* test.

[c]*P* values are based on the χ^2 for independence test with Yates' correction.

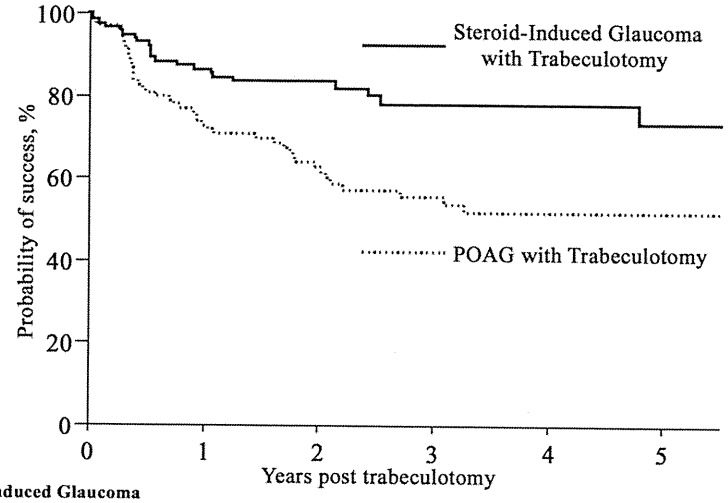
glaucoma, we retrospectively reviewed clinical charts at 17 clinical centers in Japan.

METHODS

• PATIENT SELECTION AND SURGICAL PROCEDURES: We retrospectively reviewed the medical records of patients with steroid-induced glaucoma who underwent trabeculotomy or trabeculectomy with MMC and those with POAG who underwent trabeculotomy between January 1, 1997, and December 31, 2006, at the following 17 clinical centers in Japan: Kumamoto University Hospital (Kumamoto), Niigata University Medical and Dental Hospital (Niigata), University of Tokyo Hospital (Tokyo), Kanazawa University Hospital (Kanazawa), Gifu University Hospital (Gifu), Kagawa University Hospital (Miki), University of Yamanashi Hospital (Chuo), Tohoku University Hospital (Sendai), Ryukyu University Hospital (Nishihara), Kyoto Prefectural University Hospital (Kyoto), Kagoshima University Medical and Dental Hospital (Kagoshima), Kyoto University Hospital (Kyoto), Nagoya City University Hospital (Nagoya), Saga University Hospital (Saga), Kobe University Hospital (Kobe), Hiroshima University Hospital (Hiroshima), and NTT West Kyushu Hospital (Kumamoto).

Eyes that presented with an IOP ≥22 mm Hg while on ocular hypotensive medications before surgery were included in this study. Steroid-induced glaucoma eyes were defined as open-angle eyes with an IOP elevation ≥22 mm Hg after the administration of corticosteroid. If both eyes underwent glaucoma surgeries, the eye that was treated first was investigated. Exclusion criteria were as follows: eyes with a history of previous glaucoma surgery, eyes that had undergone intraocular surgery up to 3 months before trabeculotomy or trabeculectomy, steroid-induced glaucoma eyes in the active phase of uveitis, eyes associated with IOP ≥22 mm Hg before corticosteroid administration in the medical records, and eyes that underwent combined glaucoma and cataract surgeries.

The technique of trabeculotomy performed in this study has been described previously.[19] In brief, after conjunctival incision, a 4 × 4-mm square or triangular scleral flap at four-fifths thickness was created at the corneal limbus. After identification of the Schlemm's canal, its outer wall was cut with a razor blade and excised with fine scissors. U-shaped probes were then inserted into both ends of the opened canal and rotated 90 degrees against the trabecular



Steroid-Induced Glaucoma											
No. at risk	121	121	100	89	77	63	42	32	26	22	20
Failure	0	8	7	3	0	2	1	0	0	0	1
Censored	0	13	4	9	14	19	9	6	4	2	5
POAG											
No. at risk	108	108	84	72	67	47	38	32	26	25	18
Failure	0	20	8	3	6	4	1	2	0	0	0
Censored	0	4	4	2	14	5	5	4	1	7	3

FIGURE 1. Criterion A–based Kaplan-Meier survival curves of surgical outcomes in patients with steroid-induced glaucoma (solid line) vs primary open-angle glaucoma (POAG; dotted line) that underwent trabeculotomy. The steroid-induced glaucoma eyes had a significantly higher cumulative probability of success than the POAG eyes ($P = .0008$).

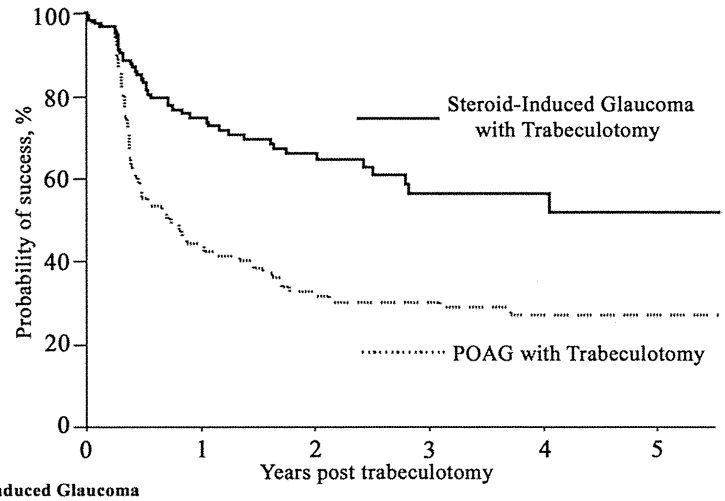
meshwork. Rotation of these probes achieved 120-degree opening of the trabecular meshwork. The scleral flap was closed with 1 to 7 10-0 nylon sutures until the wound became watertight.

During trabeculotomy, some cases were combined with a sinusotomy, based upon the procedure of Mizoguchi and associates,[21] which made 1 or 2 sites of 1-mm-diameter sclerotomy with a punch through the scleral flap before closure with 10-0 nylon sutures. Trabeculectomy was performed according to a modification of the technique developed by Cairns.[22] Conjunctiva incisions included limbal-based and fornix-based procedures. After the creation of a scleral flap, sponges soaked with MMC (0.4 mg/mL) were applied to the posterior surface of the conjunctiva, Tenon's capsule, the adjacent episcleral tissue, and the scleral flap for 2 to 5 minutes, followed by irrigation with balanced salt solution. A trabecular block was excised to create a fistula in the anterior chamber, and peripheral iridectomy was then performed. The scleral flap was closed with 10-0 nylon sutures while the conjunctival flap was sutured with 10-0 nylon or 7-0 silk. All patients were required to sign informed consent forms before surgery.

• MAIN OUTCOME MEASURE: The main outcome measure was the probability of success in the Kaplan-Meier survival-curve analysis. Before data analysis, surgical failure was defined by the following IOP levels, with or without ocular hypotensive medications, which were verified at the next visit: criterion A, IOP ≥21 mm Hg; criterion B, IOP ≥18 mm Hg. IOP data that were examined using a Goldmann applanation tonometer were collected from patients' medical records. IOPs that corresponded to criteria A and B up to 3 months after surgery were not considered a surgical failure because of the occurrence of postoperative IOP fluctuations after trabeculotomy.[19] If additional glaucoma surgery was performed, or visual acuity deteriorated to an absence of light perception, the eye was regarded as a surgical failure for both criteria.

We compared the surgical outcomes between the steroid-induced glaucoma with trabeculotomy group and the POAG with trabeculotomy group, and between the steroid-induced glaucoma with trabeculotomy group and the steroid-induced glaucoma with trabeculectomy group. To determine potential risk factors for surgical failure of steroid-induced glaucoma after trabeculotomy, the following variables were assessed: gender, age, pseudophakia, previous vitrectomy, route of corticosteroid administration (ocular instillation, intravitreal injection, posterior sub-Tenon's injection, or systemic administration), duration of corticosteroid administration after glaucoma surgery, reason for corticosteroid use (collagen disease, atopic dermatitis, or uveitis), sinusotomy, previous cataract surgery, and baseline IOP. These factors were analyzed statistically in the steroid-induced glaucoma with trabeculotomy group with criteria A and B. Data on postoperative complications were also collected from the medical records.

• STATISTICAL ANALYSIS: Data analysis was performed using the JMP version 8 statistical package program (SAS



Steroid-Induced Glaucoma											
No. at risk	121	121	89	76	64	48	33	22	16	13	10
Failure	0	19	9	5	3	2	3	0	0	1	0
Censored	0	13	4	7	13	13	8	6	3	2	2
POAG											
No. at risk	108	108	57	45	37	28	24	22	17	16	12
Failure	0	47	11	6	5	2	0	1	1	0	0
Censored	0	4	1	2	4	2	2	4	0	4	3

FIGURE 2. Criterion B–based Kaplan-Meier survival curves of surgical outcomes in patients with steroid-induced glaucoma (solid line) vs primary open-angle glaucoma (POAG; dotted line) that underwent trabeculotomy. The steroid-induced glaucoma eyes had a significantly higher cumulative probability of success than the POAG eyes ($P < .0001$).

TABLE 2. Cox Proportional Hazards Model Determining Likelihood of Surgical Outcomes for Patients With Steroid-Induced Glaucoma and Primary Open-Angle Glaucoma who Underwent Trabeculotomy

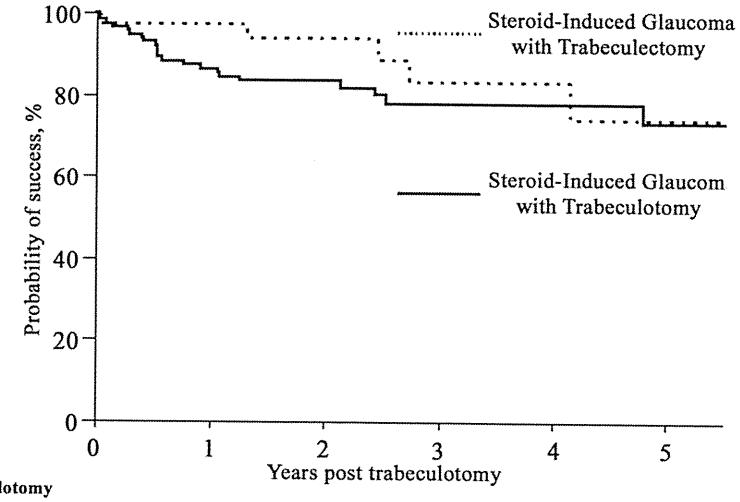
	Criterion A			Criterion B		
Variable	RR	95% CI	*P* Value	RR	95% CI	*P* Value
Steroid-induced glaucoma	0.409	0.223–0.735	.0027	0.451	0.286–0.706	.0005
Age (per year)	0.999	0.982–1.015	.8917	1.007	0.995–1.019	.2408
Preoperative IOP (per mm Hg)	1.004	0.977–1.029	.7557	0.993	0.972–1.013	.5115
Female	0.761	0.451–1.260	.2911	0.695	0.468–1.021	.0639
Previous cataract surgery	2.105	0.823–4.681	.1132	1.627	0.784–3.084	.1804
Combined sinusotomy	1.054	0.575–1.847	.8600	0.839	0.526–1.300	.4399

CI = confidence interval; IOP = intraocular pressure; RR = relative risk.

Institute, Cary, North Carolina, USA). Comparisons of the outcomes between the steroid-induced glaucoma with trabeculotomy group and the POAG with trabeculotomy group, as well as between the steroid-induced glaucoma with trabeculotomy group and the steroid-induced glaucoma with trabeculectomy group, were analyzed by the Kaplan-Meier survival curve and the log-rank test. To assess prognostic factors of steroid-induced glaucoma with trabeculotomy in univariate analysis, Kaplan-Meier survival-curve analysis and the log-rank test were used. To confirm the effects of prognostic factors and to identify the relative risk (RR) of surgical failure, multivariate prognostic factor analysis was performed with the Cox proportional hazards model. Multivariate factors were selected from variants with a probability (P) value of less than .15 shown by univariate analysis. A P value less than .05 was considered statistically significant.

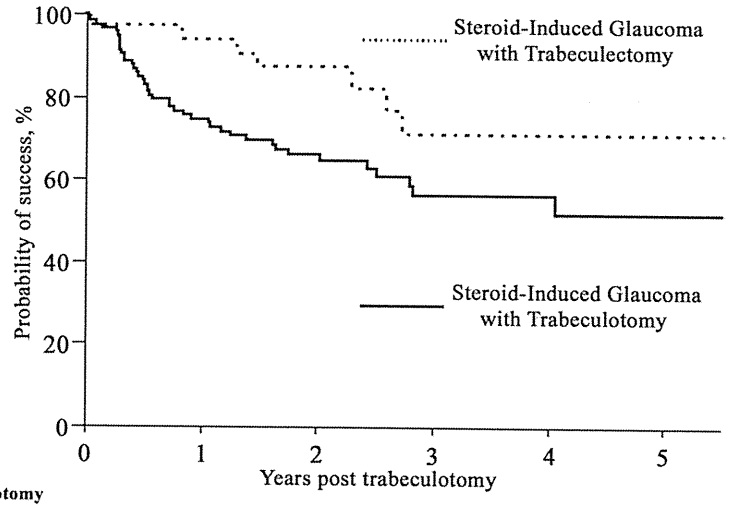
RESULTS

• PATIENT CHARACTERISTICS: In total, 163 patients (163 eyes) with steroid-induced glaucoma and 108 patients (108 eyes) with POAG satisfied the study criteria. All eligible patients were Japanese. Of the 163 eyes with steroid-induced glaucoma, 121 were included in the steroid-induced glaucoma with trabeculotomy group and 42 were included in the steroid-induced glaucoma with trabeculectomy group. Table 1 lists the characteristics of the enrolled patients.



Trabeculotomy											
No. at risk	121	121	100	89	77	63	42	32	26	22	20
Failure	0	8	7	3	0	2	1	0	0	0	1
Censored	0	13	4	9	14	19	9	6	4	2	5
Trabeculectomy											
No. at risk	42	42	32	31	28	23	17	14	11	10	8
Failure	0	1	0	1	0	1	1	0	0	1	0
Censored	0	9	1	2	5	5	3	3	1	1	2

FIGURE 3. Criterion A–based Kaplan-Meier survival curves of surgical outcomes in eyes with trabeculotomy (solid line) vs trabeculectomy (dotted line) for steroid-induced glaucoma. There was no significant difference in the cumulative probability of success between the eyes with trabeculotomy and trabeculectomy ($P = .3636$).



Trabeculotomy											
No. at risk	121	121	89	76	64	48	33	22	16	13	10
Failure	0	19	9	5	3	2	3	0	0	1	0
Censored	0	13	4	7	13	13	8	6	3	2	2
Trabeculectomy											
No. at risk	42	42	32	30	26	21	15	11	9	8	7
Failure	0	1	1	2	0	1	2	0	0	0	0
Censored	0	9	1	2	5	5	2	2	1	1	1

FIGURE 4. Criterion B–based Kaplan-Meier survival curves of surgical outcomes in eyes with trabeculotomy (solid line) vs trabeculectomy (dotted line) for steroid-induced glaucoma. The trabeculectomy group showed a significantly higher cumulative probability of success than the trabeculotomy group ($P = .0352$).

The steroid-induced glaucoma with trabeculotomy group was significantly younger ($P = .001$) and had a higher preoperative IOP ($P < .001$), a higher number of female patients ($P = .014$), a higher number of previous cataract surgeries ($P = .029$), and a lower number of combined sinusotomies ($P = .012$) than the POAG with

TABLE 3. Influence of Prognostic Factors on Survival Time of Steroid-Induced Glaucoma Patients who Underwent Trabeculotomy

Variable	Number of Patients	Criterion A 80% Survival Time (Days)	Criterion A *P* Value[a]	Criterion B 80% Survival Time (Days)	Criterion B *P* Value[a]
Gender			.1779		.0422
Female	62	>3850		305	
Male	59	385		146	
Age (years)			.9040		.2458
<30	51	852		206	
≥30	70	916		181	
Preoperative IOP (mm Hg)			.7443		.4387
<40	79	181		181	
≥40	42	840		200	
Diabetes mellitus			.1936		.0848
Yes	13	146		96	
No	108	816		291	
Hypertension			.9394		.9915
Yes	18	>2148		291	
No	103	852		195	
Combined sinusotomy			.2416		.9270
Yes	20	146		120	
No	101	916		260	
Previous cataract surgery			.0055		.1829
Yes	17	49		49	
No	104	1732		272	
Previous vitrectomy			<0.0001		.0050
Yes	6	10		10	
No	115	1742		260	
Cause of corticosteroid use					
Collagen disease			.3397		.9248
Yes	37	750		195	
No	84	1732		200	
Atopic dermatitis			.9929		.2449
Yes	21	278		162	
No	100	852		195	
Uveitis			.4674		.7942
Yes	25	>2519		177	
No	96	840		200	
Route of steroid administration					
Ocular instillation only			.6968		.1204
Yes	17	1732		1286	
No	104	852		181	
Posterior sub-Tenon's injection of TA			.9546		.3239
Yes	13	>1339		>1339	
No	108	916		200	
Intravitreal injection of TA			.1843		.4379
Yes	10	49		49	
No	111	916		206	
Oral administration			.7412		.6920
Yes	72	840		181	
No	49	1732		272	
Intravenous administration			.4050		.1883
Yes	3	>1580		>1580	
No	118	852		195	

Continued on next page

TABLE 3. Influence of Prognostic Factors on Survival Time of Steroid-Induced Glaucoma Patients who Underwent Trabeculotomy *(Continued)*

Variable	Number of Patients	Criterion A 80% Survival Time (Days)	Criterion A *P* Value[a]	Criterion B 80% Survival Time (Days)	Criterion B *P* Value[a]
Postoperative corticosteroid administration			.1987		.7335
>3 months	68	<3850		195	
≤3 months	53	372		200	

IOP = intraocular pressure; TA = triamcinolone acetonide.
[a]The *P* values are based on the log-rank test.

trabeculotomy group. However, there were no significant differences in patient characteristics between the steroid-induced glaucoma with trabeculotomy group and the steroid-induced glaucoma with trabeculectomy group.

• STEROID-INDUCED GLAUCOMA VS POAG: The mean follow-up periods were 38.4 ± 28.7 months in the steroid-induced glaucoma with trabeculotomy group and 49.8 ± 37.2 months in the POAG with trabeculotomy group (P = 0.010). Kaplan-Meier survival-curve analyses of the steroid-induced glaucoma with trabeculotomy group and the POAG with trabeculotomy group for criteria A and B are presented in Figures 1 and 2, respectively. The steroid-induced glaucoma with trabeculotomy group had a significantly higher cumulative probability of success for criteria A (P = .0008) and B (P < .0001). For criterion A, the probabilities of success 1, 2, 3, and 5 years after trabeculotomy in the steroid-induced glaucoma with trabeculotomy group and the POAG with trabeculotomy group were as follows: 86.5% vs 73.2%, 83.5% vs 63.0%, 78.1% vs 55.8%, and 73.5% vs 52.2%, respectively. For criterion B, the probabilities of success 1, 2, 3, and 5 years after trabeculotomy in the steroid-induced glaucoma with trabeculotomy group and the POAG with trabeculotomy group were as follows: 74.6% vs 44.7%, 66.1% vs 33.0%, 56.4% vs 30.6%, and 51.7% vs 27.5%, respectively. The number of eyes classified as surgical failures in the steroid-induced glaucoma with trabeculotomy group and the POAG with trabeculotomy group were 22/121 (18.2%) vs 45/108 (41.7%) for criterion A and 42/121 (34.7%) vs 73/108 (67.6%) for criterion B, respectively.

Since there were significant differences between the preoperative data of the steroid-induced glaucoma with trabeculotomy group and the POAG with trabeculotomy group, a Cox proportional hazards model including age, preoperative IOP, gender, previous cataract surgery, and combined sinusotomy was performed (Table 2). The multivariate model suggested that trabeculotomy in steroid-induced glaucoma eyes was independently associated with a better prognosis when compared with the same procedure in POAG eyes, even after adjusting for confounding factors (criterion A, RR = 0.409, P = .0027; criterion B, RR = 0.451, P = .0005).

• TRABECULOTOMY VS TRABECULECTOMY: The mean follow-up period in the steroid-induced glaucoma with trabeculectomy group was 37.1 ± 31.8 months (38.4 ± 28.7 months in the steroid-induced glaucoma with trabeculotomy group, P = .808). The Kaplan-Meier survival-curve analysis between the steroid-induced glaucoma with trabeculotomy group and the steroid-induced glaucoma with trabeculectomy group for criteria A and B are presented in Figures 3 and 4, respectively. No significant difference was found between the 2 groups for criterion A (P = .3636). The probabilities of success 1, 2, 3, and 5 years after surgery in the steroid-induced glaucoma with trabeculectomy group for criterion A were 97.6%, 94.3%, 83.8%, and 74.5%, respectively. The number of eyes classified as surgical failures in the steroid-induced glaucoma with trabeculectomy group was 5 (11.9%) for criterion A. However, the steroid-induced glaucoma with trabeculectomy group showed a significantly higher cumulative probability of success for criterion B (P = .0352). The probabilities of success 1, 2, 3, and 5 years after surgery in the steroid-induced glaucoma with trabeculectomy group for criterion B were 94.5%, 87.7%, 71.6%, and 71.6%, respectively. The number of eyes classified as surgical failures in the steroid-induced glaucoma with trabeculectomy group was 7 (16.7%) for criterion B.

• PROGNOSTIC FACTORS FOR FAILURE OF TRABECULOTOMY FOR STEROID-INDUCED GLAUCOMA EYES: The potential prognostic factors influencing survival time are listed in Table 3. Univariate analysis showed previous cataract surgery (P = .0055) and previous vitrectomy (P < .0001) to be significant prognostic factors for criterion A, and male gender (P = .0422) and previous vitrectomy (P = .0050) for criterion B. Diabetes mellitus (P = .0848) and ocular instillation of corticosteroid (P = .1204) were the factors with a P value of less than .15 for criterion B. The Cox proportional hazards model including these variables revealed that prognostic factors for surgical failure were

TABLE 4. Cox Proportional Hazards Model on Criteria A and B, Determining Likelihood of Surgical Outcomes for All 121 Patients With Steroid-Induced Glaucoma who Underwent Trabeculotomy

	Criterion A			Criterion B		
Variable	RR	95% CI	*P* Value	RR	95% CI	*P* Value
Previous cataract surgery	1.614	0.255–5.688	.5488		—	
Previous vitrectomy	5.340	1.037–38.655	.0452	3.898	1.108–10.688	.0360
Male		—		1.783	0.938–3.414	.0774
Diabetes mellitus		—		1.871	0.754–4.018	.1632
Corticosteroid administration other than ocular instillation		—		2.752	1.065–9.426	.0352

CI = confidence interval; IOP = intraocular pressure; RR = relative risk.

previous vitrectomy (RR = 5.340, P = .0452 for criterion A; RR = 3.898, P = .0360 for criterion B) and corticosteroid administration other than ocular instillation (RR = 2.752, P = .0352 for criterion B) (Table 4).

• POSTOPERATIVE COMPLICATIONS: In the steroid-induced glaucoma with trabeculectomy group, choroidal detachment occurred in 2 eyes (4.8%), flat anterior chamber requiring anterior chamber reformation occurred in 1 eye (2.4%), and hypotony maculopathy occurred in 7 eyes (16.7%). None of these complications occurred in either the steroid-induced glaucoma with trabeculotomy group or the POAG with trabeculotomy group. The progression of postoperative cataracts was observed in 9 eyes (7.4%) of the steroid-induced glaucoma with trabeculotomy group, 1 eye (0.9%) of the POAG with trabeculotomy group, and 4 eyes (9.5%) of the steroid-induced glaucoma with trabeculectomy group. No eyes encountered postoperative infectious blebitis or endophthalmitis.

DISCUSSION

THIS STUDY COMPARED THE SUCCESS RATES OF TRABECULotomy for steroid-induced glaucomatous eyes with those for trabeculectomy for steroid-induced glaucoma eyes, and for trabeculotomy for POAG eyes. Trabeculotomy showed a significantly higher cumulative probability of success in steroid-induced glaucoma patients than POAG patients for both criterion A (P = .0008) and criterion B (P < .0001). The probability of success in steroid-induced glaucoma eyes treated with trabeculotomy was comparable to that in steroid-induced glaucoma eyes treated with MMC trabeculectomy for criterion A (P = .3636), but was significantly lower for criterion B (P = .0352). Significant prognostic factors for surgical failure of trabeculotomy in steroid-induced glaucoma patients were previous vitrectomy for criteria A (RR = 5.340, P = .0452) and B (RR = 3.898, P = .0360), and corticosteroid treatment other than ocular instillation for criterion B (RR = 2.752, P = .0352).

Several studies have demonstrated surgical results for steroid-induced glaucoma patients.[10,11,13–15,17,23–27] For example, Sihota and associates[10] reported that 9 eyes with steroid-induced glaucoma that required trabeculectomy with MMC showed normal IOP levels after surgery. Several reports[11,23–27] demonstrated that filtering surgery was successful for IOP management in steroid-induced glaucomatous eyes after intravitreal injection of triamcinolone acetonide. Krishnan and associates[13] found that all of 3 eyes with triamcinolone-induced IOP elevation were successfully treated with viscocanalostomy. For laser trabeculoplasty, Ricci and associates[14] and Viola and associates[15] reported that argon laser trabeculoplasty was effective in all cases in their studies, and selective laser trabeculoplasty was shown to lower IOP in 5 of 7 eyes.[17] However, these reports on surgical treatment for steroid-induced glaucoma included only a small number of cases and lacked control groups and details of long-term prognosis. Our previous study lacked control groups but showed that trabeculotomy reduced IOPs to 21 mm Hg or less in 14 eyes with steroid-induced glaucoma.[12] To our knowledge, our present multicenter study reports on the largest number of steroid-induced glaucoma patients.

Trabeculotomy showed a better prognosis in steroid-induced glaucoma eyes than POAG eyes in the present study. The accumulation of extracellular matrices in trabecular meshwork has been believed to cause increased outflow resistance of the aqueous humor in steroid-induced glaucoma patients. This is because histochemical data demonstrate abnormally accumulated extracellular matrices such as type IV collagen, heparin sulfate, proteoglycan, and fibronectin in the trabecular meshwork of steroid-induced glaucoma patients.[9] Because the main target of trabeculotomy for IOP reduction is the relief of outflow resistance in the trabecular meshwork, the consistency between the surgical target and the pathologic lesion might explain the effectiveness of surgery for steroid-induced glaucoma eyes.

The surgical success of trabeculotomy for steroid-induced glaucoma was comparable to the success of MMC trabeculectomy for steroid-induced glaucoma for criterion

A. Trabeculectomy has a potential risk of late-onset infection of the filtering bleb.[28–31] A previous multicenter case-control study suggested that the use of systemic corticosteroid and juvenile-onset glaucoma should be included among the risk factors for late-onset infection after filtering surgery.[32] Moreover, younger patients are more susceptible to steroid-induced IOP elevation.[4,33,34] Trabeculotomy might be more beneficial for younger patients with steroid-induced glaucoma, from the viewpoint of late-onset infection, than trabeculectomy because of the nonfiltering surgery.

Trabeculectomy had a significantly higher probability of success than trabeculotomy using criterion B in the present study. Thus, many steroid-induced glaucoma eyes treated with trabeculotomy had postoperative IOPs of 18 to 20 mm Hg, which might be too high to prevent progressive visual field changes for glaucomatous eyes with advanced progressive visual field defects. The Advanced Glaucoma Intervention Study[35] found that visual field loss in eyes with advanced open-angle glaucoma progresses further if postoperative IOP of 18 mm Hg or higher is more frequent. These findings imply that trabeculectomy rather than trabeculotomy is more favorable for controlling IOP in steroid-induced glaucoma eyes with advanced visual field loss.

Even when other types of glaucoma are included, the prognostic factors for the surgical failure of trabeculotomy have not been sufficiently identified. Our previous report indicated that higher preoperative IOP results in poorer prognosis in eyes with POAG or exfoliative glaucoma.[19] Higher preoperative IOP might reflect the severity of glaucoma, resulting in a poorer response to reduce IOP. The present study showed that higher preoperative IOP was not a prognostic factor for surgical failure of trabeculotomy for steroid-induced glaucoma, while corticosteroid administration other than ocular instillation was shown to be a prognostic factor in criterion B. These data might reflect the fact that the severity of steroid-induced glaucoma depends on the route of corticosteroid administration rather than the preoperative IOP levels. In addition, previous vitrectomy was a prognostic factor for surgical failure for both criteria. Although we have no conclusive explanation, it is conceivable that vitrectomy causes the elevation of inflammatory factors or growth factors in the aqueous humor. Vitrectomized eyes might lead to recurrent fibrosis in the outflow pathway of the trabecular meshwork that was created by the trabeculotomy.

This study had some limitations caused by the retrospective design. First, the selection bias of the type of surgery performed for steroid-induced glaucoma eyes might have affected the surgical result. In fact, all 6 vitrectomized eyes were treated with trabeculotomy. Because of conjunctival scarring after vitrectomy, trabeculotomy rather than trabeculectomy might have been the surgery of choice for vitrectomized eyes. Second, as higher IOP is a prognostic factor for failure of trabeculotomy for POAG eyes,[19] POAG patients with higher IOP might have been treated with trabeculectomy rather than trabeculotomy; this might have increased the cumulative probability of success in POAG with trabeculotomy.

In conclusion, this study demonstrates that trabeculotomy might be more effective for steroid-induced glaucoma eyes than POAG eyes. Moreover, the surgical success in steroid-induced glaucoma eyes is comparable to the outcome of trabeculectomy unless more substantial IOP reduction is necessary, in which case trabeculectomy would be a better option. IOP reduction of steroid-induced glaucoma patients with previous vitrectomy or with corticosteroid administration other than ocular instillation might be more resistant to trabeculotomy. Trabeculotomy should be considered as an option for the surgical management of steroid-induced glaucoma, although future prospective studies are necessary to validate our findings.

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REFERENCES

1. Lewis JM, Priddy T, Judd J, et al. Intraocular pressure response to topical dexamethasone as a predictor for the development of primary open-angle glaucoma. Am J Ophthalmol 1988;106(5):607–612.
2. Jonas JB, Kreissig I, Degenring R. Secondary chronic open-angle glaucoma after intravitreal triamcinolone acetonide. Arch Ophthalmol 2003;121(5):729–730.
3. Smithen LM, Ober MD, Maranan L, Spaide RF. Intravitreal triamcinolone acetonide and intraocular pressure. Am J Ophthalmol 2004;138(5):740–743.
4. Iwao K, Inatani M, Kawaji T, Koga T, Mawatari Y, Tanihara H. Frequency and risk factors for intraocular pressure elevation after posterior sub-Tenon capsule triamcinolone acetonide injection. J Glaucoma 2007;16(2):251–256.
5. Opatowsky I, Feldman RM, Gross R, Feldman ST. Intraocular pressure elevation associated with inhalation and nasal corticosteroids. Ophthalmology 1995;102(2):177–179.
6. Becker B, Mills D. Corticosteroids and intraocular pressure. Arch Ophthalmol 1963;70(4):500–507.
7. Rohen JW, Linner E, Witmer R. Electron microscopic studies on the trabecular meshwork in two cases of corticosteroid-glaucoma. Exp Eye Res 1973;17(1):19–31.
8. Johnson D, Gottanka J, Flugel C, Hoffmann F, Futa R, Lutjen-Drecoll E. Ultrastructural changes in the trabecular meshwork of human eyes treated with corticosteroids. Arch Ophthalmol 1997;115(3):375–383.
9. Tawara A, Tou N, Kubota T, Harada Y, Yokota K. Immunohistochemical evaluation of the extracellular matrix in trabecular meshwork in steroid-induced glaucoma. Graefes Arch Clin Exp Ophthalmol 2008;246(7):1021–1028.
10. Sihota R, Konkal VL, Dada T, Agarwal HC, Singh R. Prospective, long-term evaluation of steroid-induced glaucoma. Eye (Lond) 2008;22(1):26–30.
11. Jonas JB, Degenring RF, Kamppeter BA. Outcome of eyes undergoing trabeculectomy after intravitreal injections of triamcinolone acetonide. J Glaucoma 2004;13(3):261.
12. Honjo M, Tanihara H, Inatani M, Honda Y. External trabeculotomy for the treatment of steroid-induced glaucoma. J Glaucoma 2000;9(6):483–485.
13. Krishnan R, Kumar N, Wishart PK. Viscocanalostomy for refractory glaucoma secondary to intravitreal triamcinolone acetonide injection. Arch Ophthalmol 2007;125(9):1284–1286.
14. Ricci F, Missiroli F, Parravano M. Argon laser trabeculoplasty in triamcinolone acetonide induced ocular hypertension refractory to maximal medical treatment. Eur J Ophthalmol 2006;16(5):756–757.
15. Viola F, Morescalchi F, Staurenghi G. Argon laser trabeculoplasty for intractable glaucoma following intravitreal triamcinolone. Arch Ophthalmol 2006;124(1):133–134.
16. Pizzimenti JJ, Nickerson MM, Pizzimenti CE, Kasten-Aker AG. Selective laser trabeculoplasty for intraocular pressure elevation after intravitreal triamcinolone acetonide injection. Optom Vis Sci 2006;83(7):421–425.
17. Rubin B, Taglienti A, Rothman RF, Marcus CH, Serle JB. The effect of selective laser trabeculoplasty on intraocular pressure in patients with intravitreal steroid-induced elevated intraocular pressure. J Glaucoma 2008;17(4):287–292.
18. Baser E, Seymenoglu R. Selective laser trabeculoplasty for the treatment of intraocular pressure elevation after intravitreal triamcinolone injection. Can J Ophthalmol 2009;44(3):e21.
19. Tanihara H, Negi A, Akimoto M, et al. Surgical effects of trabeculotomy ab externo on adult eyes with primary open angle glaucoma and pseudoexfoliation syndrome. Arch Ophthalmol 1993;111(12):1653–1661.
20. Sugimoto-Takeuchi R, Kuwayama Y, Shiga S, Takagi T. Trabeculotomy for steroid glaucoma. Atarashii Ganka (Journal of the Eye) 1992;9(7):1181–1183.
21. Mizoguchi T, Nagata M, Matsumura M, Kuroda S, Terauchi H, Tanihara H. Surgical effects of combined trabeculotomy and sinusotomy compared to trabeculotomy alone. Acta Ophthalmol Scand 2000;78(2):191–195.
22. Cairns JE. Trabeculectomy. Preliminary report of a new method. Am J Ophthalmol 1968;66(4):673–679.
23. Park HY, Yi K, Kim HK. Intraocular pressure elevation after intravitreal triamcinolone acetonide injection. Korean J Ophthalmol 2005;19(2):122–127.
24. Quiram PA, Gonzales CR, Schwartz SD. Severe steroid-induced glaucoma following intravitreal injection of triamcinolone acetonide. Am J Ophthalmol 2006;141(3):580–582.
25. Kubota T, Okabe H, Hisatomi T, Yamakiri K, Sakamoto T, Tawara A. Ultrastructure of the trabecular meshwork in secondary glaucoma eyes after intravitreal triamcinolone acetonide. J Glaucoma 2006;15(2):117–119.
26. Kaushik S, Gupta V, Gupta A, Dogra MR, Singh R. Intractable glaucoma following intravitreal triamcinolone in central retinal vein occlusion. Am J Ophthalmol 2004;137(4):758–760.
27. Singh IP, Ahmad SI, Yeh D, et al. Early rapid rise in intraocular pressure after intravitreal triamcinolone acetonide injection. Am J Ophthalmol 2004;138(2):286–287.
28. Lobue TD, Deutsch TA, Stein RM. Moraxella nonliquefaciens endophthalmitis after trabeculectomy. Am J Ophthalmol 1985;99(3):343–345.
29. Freedman J, Gupta M, Bunke A. Endophthalmitis after trabeculectomy. Arch Ophthalmol 1978;96(6):1017–1018.
30. Higginbotham EJ, Stevens RK, Musch DC, et al. Bleb-related endophthalmitis after trabeculectomy with mitomycin C. Ophthalmology 1996;103(4):650–656.
31. Wolner B, Liebmann JM, Sassani JW, Ritch R, Speaker M, Marmor M. Late bleb-related endophthalmitis after trabeculectomy with adjunctive 5-fluorouracil. Ophthalmology 1991;98(7):1053–1060.
32. Jampel HD, Quigley HA, Kerrigan-Baumrind LA, Melia BM, Friedman D, Barron Y. Risk factors for late-onset infection following glaucoma filtration surgery. Arch Ophthalmol 2001;119(7):1001–1008.
33. Inatani M, Iwao K, Kawaji T, et al. Intraocular pressure elevation after injection of triamcinolone acetonide: a multicenter retrospective case-control study. Am J Ophthalmol 2008;145(4):676–681.
34. Ohji M, Kinoshita S, Ohmi E, Kuwayama Y. Marked intraocular pressure response to instillation of corticosteroids in children. Am J Ophthalmol 1991;112(4):450–454.
35. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. Am J Ophthalmol 2000;130(4):429-440.