Table 5 Relationship between mean blur rate and Heidelberg retina tomograph II parameters

	Disc MA		Disc MV		Disc MT	
	r	*P*	*r*	*P*	*r*	*P*
Disc area	0.0431	0.7971	0.3086	0.0594	−0.0922	0.5821
Cup area	**0.3637**	**0.0248**	0.0477	0.7760	**−0.5616**	**0.0002**
Rim area	**0.5588**	**0.0003**	**0.3300**	**0.0431**	**0.6534**	**<0.0001**
Cup/Disc area ratio	**−0.5437**	**0.0004**	−0.1979	0.2337	**−0.7116**	**<0.0001**
Rim/Disc area ratio	**0.5437**	**0.0004**	0.1979	0.2337	**0.7116**	**<0.0001**
Cup volume	**−0.3636**	**0.0248**	−0.0760	0.6504	**−0.4831**	**0.0021**
Rim volume	**0.3430**	**0.0350**	0.1134	0.4978	**0.4969**	**0.0015**
Mean cup depth	−0.1848	0.2667	−0.1542	0.3555	−0.1805	0.2782
Maximum cup depth	−0.1737	0.2970	**−0.3334**	**0.0408**	0.0381	0.8204
Height variation contour	**−0.4261**	**0.0076**	**−0.3365**	**0.0388**	**−0.3875**	**0.0162**
Cup shape measure	−0.3017	0.0657	−0.0224	0.8939	**−0.4747**	**0.0026**
Mean RNFL thickness	**0.4096**	**0.0106**	0.1852	0.2657	**0.4606**	**0.0036**
RNFL cross-sectional area	**0.4418**	**0.0055**	0.2518	0.1272	**0.4523**	**0.0044**
Horizontal cup/disc ratio	−0.2344	0.1567	−0.0984	0.5567	−0.2386	0.1491
Vertical cup/disc ratio	**−0.6208**	**<0.0001**	**−0.3226**	**0.0482**	**−0.6438**	**<0.0001**

Notes: Data are described in each column; r = correlation coefficient between mean deviation slope and each clinical parameter; *P* = statistical significanc; bold signifies statistically significant values.

Abbreviations: RNFL, retinal nerve fiber layer; disc MA, mean blur rate in all area of the optic disc; disc MA, mean blur rate in all area of the optic disc; disc MT, mean blur rate in tissue area of the optic disc.

association between HRT II parameters and the Humphrey field analyzer mean deviation.[23] Furthermore, we found that the generalized enlargement disc type was significantly more common than the other disc types in patients with severe high-tension glaucoma in our hospital-based study.[24] These data prompted us to focus on patients with the generalized enlargement disc type.

The disc MA was significantly associated with the degree of visual field damage in patients with glaucoma. Mean blur rate represented blood flow[36] and was strongly and positively correlated with the degree of visual field damage (r = 0.6010, *P* = 0.0001). Decreased blood flow has previously been demonstrated in patients with glaucoma using fluorescein angiography,[37–40] color Doppler flowmetry,[41] and scanning laser Doppler flowmetry.[42] In a rabbit model of vascular dysfunction using intravitreal administration of endothelin-1, the endothelin-1-induced decrease in mean blur rate in the optic disc led to cupping after 1 month.[43] In our human study, the mean blur rate showed a high correlation with the Humphrey field analyzer mean deviation, which suggests that LSFG-NAVI, like OCT and HRT II, is a suitable device for assessment of patients with glaucoma.

When we examined the associations between disc MV and disc MT with the other parameters, the disc MT showed stronger correlations than did the disc MV. When we separated the optic nerve head into the nerve fiber layer, lamina cribrosa, and prelaminar region, it was evident that the vasculature of the nerve fiber layer fed from the branch of the central retinal artery. The vasculature of the prelaminar region and lamina cribrosa fed from the post-ciliary artery.[44] These data suggest that the vessel mean is composed of the retinal central artery and vein, and the tissue mean is composed of the post-ciliary artery. On the other hand, for the HRT II disc parameters, only the rim area, maximum cup depth, height variant contour, and vertical cup/disc area ratio were associated with the disc MV, and this association was weak. Taken together, the stronger associations between the disc MT and the other cupping parameters from HRT II provide support for the important contribution of the post-ciliary artery to the pathogenesis of optic neuropathy in patients with glaucoma.

Here, the correlation between mean blur rate and average peripapillary retinal nerve fiber layer thickness (r = 0.7546) was stronger than that between mean blur rate and Humphrey field analyzer mean deviation (r = 0.6010) in patients with the generalized enlargement disc type of glaucoma. Generally, decreased retinal nerve fiber layer thickness is preceded by decreased Humphrey field analyzer mean deviation in the glaucoma disease process.[10] It would be interesting to study further whether the higher association between mean blur rate and average peripapillary retinal nerve fiber layer thickness indicates that blood flow also shows abnormalities, like the retinal nerve fiber layer thickness (ie, whether decreased

blood flow in the optic disc can be detected earlier than visual field loss) in the glaucoma disease process.

In conclusion, mean blur rate with LSFG-NAVI in patients with the generalized enlargement disc type of glaucoma provided valuable information, and the parameters studied correlated with retinal nerve fiber layer thickness, cupping parameters, and visual function.

Disclosure

This manuscript was presented and nominated as one of the top ten best presentations at the Japanese Glaucoma Society meeting in 2010. The abstract was published in the International Glaucoma Review meeting report (IGR December 12–13, 2010). The authors report no conflicts of interest in this work.

References

1. Weinreb RN, Khaw PT. Primary open-angle glaucoma. *Lancet*. 2004;363:1711–1720.
2. Quigley HA. Number of people with glaucoma worldwide. *Br J Ophthalmol*. 1996;80:389–393.
3. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. *Bull World Health Organ*. 2004;82:844–851.
4. Iwase A, Suzuki Y, Araie M, et al. The prevalence of primary open-angle glaucoma in Japanese: the Tajimi Study. *Ophthalmology*. 2004;111:1641–1648.
5. Cedrone C, Mancino R, Cerulli A, et al. Epidemiology of primary glaucoma: prevalence, incidence, and blinding effects. *Prog Brain Res*. 2008;173:3–14.
6. Pekmezci M, Vo B, Lim AK, et al. The characteristics of glaucoma in Japanese Americans. *Arch Ophthalmol*. 2009;127:167–171.
7. Harwerth RS, Carter-Dawson L, Smith EL, et al. Neural losses correlated with visual losses in clinical perimetry. *Invest Ophthalmol Vis Sci*. 2004;45:3152–3160.
8. Kerrigan-Baumrind LA, Quigley HA, Pease ME, et al. Number of ganglion cells in glaucoma eyes compared with threshold visual field tests in the same persons. *Invest Ophthalmol Vis Sci*. 2000;41:741–748.
9. Quigley HA, Dunkelberger GR, Green WR. Retinal ganglion cell atrophy correlated with automated perimetry in human eyes with glaucoma. *Am J Ophthalmol*. 1989;107:453–464.
10. Sommer A, Katz J, Quigley HA, et al. Clinically detectable nerve fiber atrophy precedes the onset of glaucomatous field loss. *Arch Ophthalmol*. 1991;109:77–83.
11. Quigley HA, Katz J, Derick RJ, et al. An evaluation of optic disc and nerve fiber layer examinations in monitoring progression of early glaucoma damage. *Ophthalmology*. 1992;99:19–28.
12. Zeyen TG, Caprioli J. Progression of disc and field damage in early glaucoma. *Arch Ophthalmol*. 1993;111:62–65.
13. Mardin CY, Junemann AG. The diagnostic value of optic nerve imaging in early glaucoma. *Curr Opin Ophthalmol*. 2001;12:100–104.
14. Badala F, Nouri-Mahdavi K, Raoof DA, et al. Optic disk and nerve fiber layer imaging to detect glaucoma. *Am J Ophthalmol*. 2007;144:724–732.
15. Naithani P, Sihota R, Sony P, et al. Evaluation of optical coherence tomography and Heidelberg retinal tomography parameters in detecting early and moderate glaucoma. *Invest Ophthalmol Vis Sci*. 2007;48:3138–3145.
16. Brusini P. Monitoring glaucoma progression. *Prog Brain Res*. 2008;173:59–73.
17. Saarela V, Airaksinen PJ. Heidelberg retina tomograph parameters of the optic disc in eyes with progressive retinal nerve fibre layer defects. *Acta Ophthalmol*. 2008;86:603–608.
18. Kalaboukhova L, Fridhammar V, Lindblom B. Glaucoma follow-up by the Heidelberg retina tomograph – new graphical analysis of optic disc topography changes. *Graefes Arch Clin Exp Ophthalmol*. 2006;244:654–662.
19. Downs JC, Roberts MD, Burgoyne CF. Mechanical environment of the optic nerve head in glaucoma. *Optom Vis Sci*. 2008;85:425–435.
20. Nicolela MT, Drance SM. Various glaucomatous optic nerve appearances: clinical correlations. *Ophthalmology*. 1996;103:640–649.
21. Nicolela MT, McCormick TA, Drance SM, et al. Visual field and optic disc progression in patients with different types of optic disc damage: a longitudinal prospective study. *Ophthalmology*. 2003;110:2178–2184.
22. Omodaka K, Nakazawa T, Yokoyama Y, et al. Correlation between peripapillary macular fiber layer thickness and visual acuity in patients with open-angle glaucoma. *Clin Ophthalmol*. 2010;4:629–635.
23. Omodaka K, Nakazawa T, Otomo T, et al. Correlation between morphology of optic disc determined by Heidelberg Retina Tomograph II and visual function in eyes with open-angle glaucoma. *Clin Ophthalmol*. 2010;4:765–772.
24. Nakazawa T, Fuse N, Omodaka K, et al. Different types of optic disc shape in patients with advanced open-angle glaucoma. *Jpn J Ophthalmol*. 2010;54:291–295.
25. Caprioli J, Coleman AL. Blood pressure, perfusion pressure, and glaucoma. *Am J Ophthalmol*. 2010;149:704–712.
26. Melamed S, Levkovitch-Verbin H. Laser scanning tomography and angiography of the optic nerve head for the diagnosis and follow-up of glaucoma. *Curr Opin Ophthalmol*. 1997;8:7–12.
27. Yaoeda K, Shirakashi M, Funaki S, et al. Measurement of microcirculation in the optic nerve head by laser speckle flowgraphy and scanning laser Doppler flowmetry. *Am J Ophthalmol*. 2000;129:734–739.
28. Yamazaki Y, Hayamizu F. Comparison of flow velocity of ophthalmic artery between primary open angle glaucoma and normal tension glaucoma. *Br J Ophthalmol*. 1995;79:732–734.
29. Yamazaki Y, Drance SM. The relationship between progression of visual field defects and retrobulbar circulation in patients with glaucoma. *Am J Ophthalmol*. 1997;124:287–295.
30. Sugiyama T, Araie M, Riva CE, et al. Use of laser speckle flowgraphy in ocular blood flow research. *Acta Ophthalmol*. 2010;88:723–729.
31. Nagahara M, Tamaki Y, Tomidokoro A, et al. In vivo measurement of blood velocity in human major retinal vessels using the laser speckle method. *Invest Ophthalmol Vis Sci*. 2011;52(1):87–92.
32. Tamaki Y, Araie M, Kawamoto E, et al. Noncontact, two-dimensional measurement of retinal microcirculation using laser speckle phenomenon. *Invest Ophthalmol Vis Sci*. 1994;35:3825–3834.
33. Tamaki Y, Araie M, Kawamoto E, et al. Non-contact, two-dimensional measurement of tissue circulation in choroid and optic nerve head using laser speckle phenomenon. *Exp Eye Res*. 1995;60:373–383.
34. Tamaki Y, Kawamoto E, Araie M, et al. An application of laser speckle phenomenon for noninvasive two-dimensional evaluation of microcirculation in ocular fundus – a preliminary report. *Jpn J Ophthalmol*. 1993;37:178–186.
35. Yaoeda K, Shirakashi M, Funaki S, et al. Measurement of microcirculation in optic nerve head by laser speckle flowgraphy in normal volunteers. *Am J Ophthalmol*. 2000;130:606–610.
36. Konishi N, Tokimoto Y, Kohra K, et al. New laser speckle flowgraphy system using CCD camera. *Optical Review*. 2002;9: 163–169.
37. Plange N, Kaup M, Huber K, et al. Fluorescein filling defects of the optic nerve head in normal tension glaucoma, primary open-angle glaucoma, ocular hypertension and healthy controls. *Ophthalmic Physiol Opt*. 2006;26:26–32.
38. Plange N, Kaup M, Weber A, et al. Fluorescein filling defects and quantitative morphologic analysis of the optic nerve head in glaucoma. *Arch Ophthalmol*. 2004;122:195–201.

39. Sihota R, Saxena R, Taneja N, et al. Topography and fluorescein angiography of the optic nerve head in primary open-angle and chronic primary angle closure glaucoma. *Optom Vis Sci*. 2006;83:520–526.
40. Talusan ED, Schwartz B, Wilcox LM Jr. Fluorescein angiography of the optic disc. A longitudinal follow-up study. *Arch Ophthalmol*. 1980;98:1579–1587.
41. Quaranta L, Harris A, Donato F, et al. Color Doppler imaging of ophthalmic artery blood flow velocity: a study of repeatability and agreement. *Ophthalmology*. 1997;104:653–658.
42. Michelson G, Schmauss B, Langhans MJ, et al. Principle, validity, and reliability of scanning laser Doppler flowmetry. *J Glaucoma*. 1996;5:99–105.
43. Sugiyama T, Mashima Y, Yoshioka Y, et al. Effect of unoprostone on topographic and blood flow changes in the ischemic optic nerve head of rabbits. *Arch Ophthalmol*. 2009;127:454–459.
44. Hayreh SS. The 1994 Von Sallman Lecture. The optic nerve head circulation in health and disease. *Exp Eye Res*. 1995;61:259–272.

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CASE REPORT

Over 10 years follow-up of Coats' disease in adulthood

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Abstract: Coats' disease diagnosed in adulthood is rare; therefore, the treatment options and longer clinical course are not well established. We report on two cases of adult onset Coats' disease, which have been observed for more than 10 years after conventional treatment. In the first case, a 76-year-old man with 9 years of diabetic retinopathy noticed a visual field defect in his left eye. Yellowish subretinal exudation with serous retinal detachment in his superior peripheral retina, and telangiectatic vessels with fluorescein leakage, numerous microaneurysms, and areas of capillary nonperfusion observed in a fluorescein angiography indicated adult Coats' disease, and retinal photocoagulation was applied. Within 1 year, subretinal exudation was regressed and visual acuity was improved from 20/50 to 20/20, and was maintained for the next 11 years. In the second case, a 71-year-old man presented with decreased vision in his right eye. The fundus of his right eye showed multiple telangiectasic vessels and subretinal exudates extended to the fovea, which is diagnosed as adult Coats' disease. Despite retinal photocoagulation, an increase of exudation and an enlargement of retinal detachment was observed within 1 month, and subsequently, additional treatment of cryotherapy was performed. Two months after these therapies, the exudation was regressed without retinal detachment, and visual acuity was improved to 20/200 which was maintained for the next 10 years. Even with adult Coats' disease, conventional therapies of retinal photocoagulation and cryotherapy are effective and are the initial choice for improving or maintaining visual function.

Keywords: adult onset, Coats' disease, treatment, follow-up

Introduction

Coats' disease was first described by George Coats in 1908,[1] and is characterized by the formation of telangiectatic and aneurismal changes of the retinal vessels and is associated with a large amount of yellowish intraretinal and subretinal exudates.[2] It is predominantly unilateral occurring mostly in young males under the age of 5 years, and can cause severe visual loss resulting from exudative retinal detachment.[3]

Less commonly, Coats' disease presents in adulthood. The mean age at the time of diagnosis is approximately 50 years, and it progresses at a slower rate, but with similar features.[4] Although various methods have been employed to treat Coats' disease, including diathermy, retinal photocoagulation, cryotherapy, and vitreous surgery to elucidate the abnormal vessels, thereby minimizing exudation, the prognosis of visual function remains unsatisfactory.[5] However, only a few cases of the clinical course of adult Coats' disease after treatment have been reported.

In this article, we report the long-term follow-up of two cases of rapidly progressive Coats' diseases diagnosed over the age of 60 years with more massive and/or extensive

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lipid exudates close to the macular area. In these cases successful treatment with conventional therapy of retinal photocoagulation and/or cryoretinopexy improved Coats' disease and allowed the patients to keep their visual function for more than 10 years.

Case 1

A 76-year-old man noticed a visual field defect and decreased vision of 20/50 in his left eye. He had a history of diabetic retinopathy diagnosed 9 years before (at age of 67) and focal retinal photocoagulation had been applied and observed every year without any visual disturbance. At the initial visit (Figure 1A), fundus examination revealed thick subretinal exudates extended to and threatening the fovea, and fluorescein angiography (FA) showed telangiectatic vessels with fluorescein leakage, numerous microaneurysms, and areas of capillary nonperfusion. An optical coherence tomography (OCT) indicated an exudative retinal detachment, which is a hallmark of advanced Coats' disease.[6] He was diagnosed as having Coats' disease at age 76. Laser photocoagulation was applied to the vascular lesion, and then subretinal exudates were gradually regressed. At 1 year after the treatment, visual acuity improved to 20/20, and abnormal retinal vessels and subretinal exudates were significantly regressed. FA indicated marked reduction of fluorescein leakage from abnormal retinal vessels compared to the previous status, and OCT presented a disappearance of exudative retinal detachment (Figure 1B).

At a follow-up 11 years after the treatment for Coats' disease, subretinal exudation was minimized with retinal atrophy and visual acuity in his left eye remained at 20/20 (Figure 1C).

Case 2

A 71-year-old man was referred to our hospital due to visual impairment in his right eye despite successful cataract surgery. He noticed visual disturbance 3 years before the surgery. At his initial visit, the best-corrected visual acuity of his right eye was 12/20 and the fundus examination and FA revealed severe lipid exudation and multiple telangiectatic vessels found on the overall retina with exudative retinal detachment (Figure 2A). A clinical diagnosis of Coats' disease was made and laser photocoagulation was applied to all telangiectatic vessels. However, it was difficult to inhibit aggravation of the disease condition, and visual acuity worsened to 8/200. Thus, additional treatment of cryotherapy

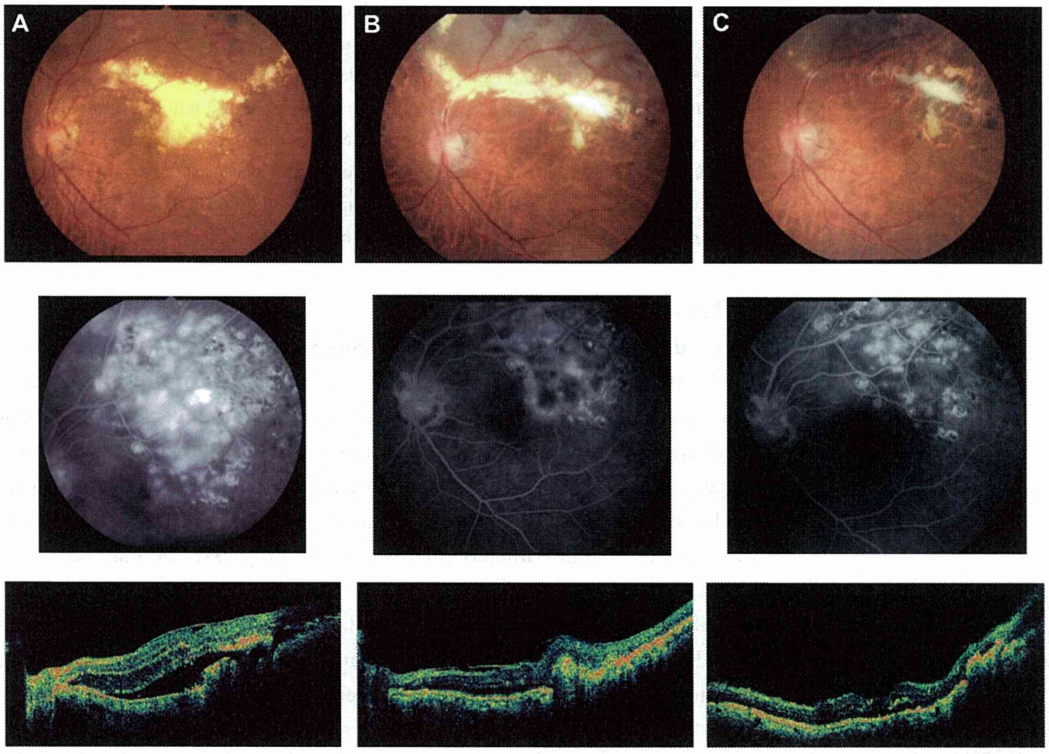

Figure 1 Color fundus photograph (upper panel), corresponding fluorescein angiography (middle), and optical coherence tomography (lower) of the left eye in patient #1 with adult Coats' disease: (**A**) at the initial visit; (**B**) 1 year after treatment of retinal photocoagulation; (**C**) 11 years after treatment.

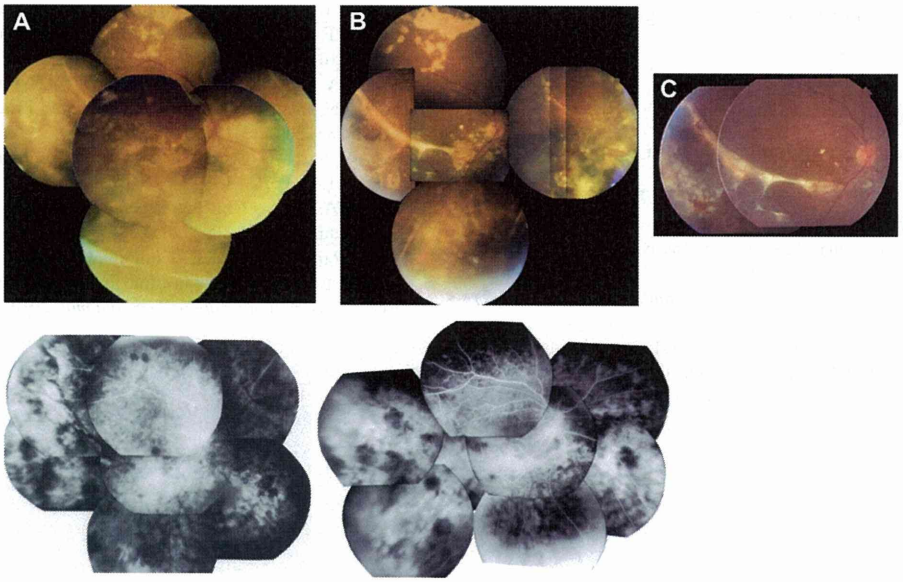

Figure 2 Color fundus photograph (upper panel), corresponding fluorescein angiography (lower) of the right eye in patient #2 with adult Coats' disease. (**A**) At the initial visit; (**B**) 3 months after treatment of retinal photocoagulation and cryotherapy; (**C**) 10 years after treatment (FA image not available).

was performed 1 month after the photocoagulation. Three months after that, lipid exudation was settled with the disappearance of exudative detachment, and visual acuity improved to 20/200 (Figure 2B). At a follow-up 10 years after the treatment, subretinal exudation was diminished and the right VA remained at 20/200 (Figure 2C).

Comments

According to several studies,[2–7] the progression of Coats' disease is relatively slow in older children or adults, and it shows indolent clinical features. The adult cases are often asymptomatic and the extent of exudation and retinal detachment tends to be mild and limited; however, the involvement of the macula as a result of subretinal exudates or exudative retinal detachment can produce poor visual acuity. Although diabetes mellitus was associated with case #1, clinical features and clinical course were typical Coats' disease. Visual prognosis in the long timespan of the follow-up (more than 10 years) showed poor results including visual acuity change from 20/40 to 4/200 over 15 years, and 20/30 to 20/70 over 11 years.[4]

Although clinical treatments for adult onset Coats' disease are not well established due to the low number of cases, ablation of abnormal retinal vessels either by laser photocoagulation or by cryotherapy are adopted in clinical situations. In this case report, intensive therapy of photocoagulation and cryoretinopexy to vascular lesions was effective enough to reduce or remove the exudative changes, and more importantly, have suppressed the worsening or recurrence of exudation for more than 10 years. Thus, these therapies were able to either improve or stabilize vision in both cases. Laser photocoagulation in the early stages, either alone, or in combination with cryotherapy, has proven to be effective especially in cases of the young. In case #1, prompt photocoagulation after decreased vision, similar to treatment in Coats' disease of the young, resulted in a good visual prognosis for a long time, which indicated that prompt treatment and careful follow-up in adult-onset Coats' disease are crucial for the preservation of visual function. Even in case #2, although conventional therapies were effective for inhibition of worsening visual function, final visual acuity of 20/200 was not satisfactory, and earlier treatment before vision deteriorates might lead to better visual prognosis. In addition, more powerful treatment options such as recently successful treatments using a combination therapy of photodynamic therapy (PDT) and intravitreal bevacizumab injection (IVB) for severe adult Coats' disease have been reported for a better visual prognosis.[8] Unfortunately, both PDT and IVB were not available in 1997, but in the future, such a treatment option may help patients similar to those in case #2.

In conclusion, we have presented two cases of rapidly progressive adult onset Coats' disease with exudative retinal detachment and massive and/or extensive lipid exudates. For these cases, conventional therapies were confirmed as effective and useful treatments to maintain visual function

not only for the short term but also for longer clinical courses of more than 10 years.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Coats G. Forms of retinal disease with massive exudation. *R Lond Ophthal Hosp Rev*. 1908;17(3):440–525.
2. Rubin MP, Mukai S. Coats' disease. *Int Ophthalmol Clin*. 2008;48(2):149–158.
3. Shields JA, Shields CL, Honavar SG, Dermici H. Clinical variations and complications of Coats disease in 150 cases: the 2000 Sanford Gifford Memorial Lecture. *Am J Ophthalmol*. 2001;131(5):561–571.
4. Smithen LM, Brown GC, Brucker AJ, Yannuzzi LA, Klais CM, Spaide RF. Coats' disease diagnosed in adulthood. *Ophthalmology*. 2005;112(6):1072–1078.
5. Shields JA, Shields CL, Honavar SG, Dermici H, Cater J. Classification and management of Coats disease: the 2000 Proctor Lecture. *Am J Ophthalmol*. 2001;131(5):572–583.
6. Jones JH, Kroll AJ, Lou PL, Ryan EA. Coats' disease. *Int Ophthalmol Clin*. 2001;41(4):189–198.
7. Shields JA, Shields CL. Review: coats disease: the 2001 LuEsther T. Mertz lecture. *Retina*. 2002;22(1):80–91.
8. Kim J, Park KH, Woo SJ. Combined photodynamic therapy and intravitreal bevacizumab injection for the treatment of adult Coats' disease: a case report. *Korean J Ophthalmol*. 2010;24(6):374–376.

4. Bottoni F, De Angelis S, Luccarelli S, Cigada M, Staurenghi G. The dynamic healing process of idiopathic macular holes after surgical repair: a spectral-domain optical coherence tomography study. Invest Ophthalmol Vis Sci 2011;52(7): 4439–4446.
5. Oh J. Outer foveolar defect after surgery for macular hole: gone or hidden? Am J Ophthalmol 2011;151(1):183–184.
6. Kawano H, Uemura A, Sakamoto T. Incidence of outer foveal defect after macular hole surgery. Am J Ophthalmol 2011;151(2): 318–322.

REPLY

WE APPRECIATE THE INSIGHTFUL COMMENTS OF DR OH concerning our article, in which we describe the correlation between the recovery of foveal microstructure and visual function after macular hole (MH) closure.[1] We reported that the presence of photoreceptor inner/outer segment (IS/OS) junction was correlated with good visual recovery after MH surgery.[2] Using spectral-domain optical coherence tomography (OCT), we found that the restoration of external limiting membrane (ELM) is closely associated with that of the IS/OS junction.[1]

Dr Oh provided additional points of view concerning our observations. He pointed out that change in foveal contour such as thickening or widening of the foveal center, which was observed on the serial OCT images in our Figure 3, may be the result of the regeneration or rearrangement of retinal layers. In reply to this comment, we re-examined the postoperative OCT images in our study and investigated the relationship between central foveal thickness (CFT) and length of IS/OS junction or ELM defect. There was a significant negative relationship between postoperative CFT and postoperative IS/OS junction defect ($r = -0.37$, $P = .0173$; $r = -0.40$, $P = .0099$; $r = -0.53$, $P = .0006$; at 1, 3, and 6 months, respectively). The correlation between postoperative CFT and ELM defect was significant only at 1 month ($r = -0.38$, $P = .0138$). These data suggest that IS/OS junction or ELM restoration is accompanied by foveal thickening. The reason for the absence of correlation between CFT and ELM defect at 3 and 6 months may be because ELM defect was 0 μm in most eyes at these times. There was no significant correlation between postoperative CFT and visual acuity ($P > .05$ for all), which was consistent with the previous report.[3] The visual outcome may not be dependent on CFT, but rather on the IS/OS junction or ELM restoration.

In traumatic MH, we reported a bridge formation of the tissue, which mimicked foveal detachment, in the process of spontaneous MH closure.[4] In our study, we observed foveal detachment in 28% of eyes at 1 month, 12% at 3 months, and 7% at 6 months. There was no significant difference of IS/OS junction or ELM defect between eyes with and without foveal detachment at each observation point ($P > .05$ for all).

We agree with Dr Oh's comment that changes in foveal contour also were influenced by the factor that the serial images may not have been obtained exactly in the same location. Bottoni and associates analyzed changes of the outer retina after MH repair using Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) with the AutoRescan function, which automatically guides the OCT instrument to scan the same location.[5] However, there may be a slight variation of the position in their serial images, as also pointed by the authors. We also agree with the comment that "3 or 6 months seems too short of a time for the outer foveolar defect to be healed completely." It has been reported that outer foveolar defect was observed in one third of the eyes at 12 months.[6] In our study, we found incomplete restoration of IS/OS junction in 70% at 6 months. Thus, further studies to evaluate the recovery of foveal microstructure for a longer period are needed.

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Conflict of Interest Disclosures: See the original article[1] for any disclosures of the authors.

REFERENCES

1. Ooka E, Mitamura Y, Baba T, Kitahashi M, Oshitari T, Yamamoto S, et al. Foveal microstructure on spectral-domain optical coherence tomographic images and visual function after macular hole surgery. Am J Ophthalmol 2011;152(2): 283–290.
2. Baba T, Yamamoto S, Arai M, et al. Correlation of visual recovery and presence of photoreceptor inner/outer segment junction in optical coherence images after successful macular hole repair. Retina 2008;28(3):453–458.
3. Sano M, Shimoda Y, Hashimoto H, Kishi S. Restored photoreceptor outer segment and visual recovery after macular hole closure. Am J Ophthalmol 2009;147(2):313–318.
4. Mitamura Y, Saito W, Ishida M, Yamamoto S, Takeuchi S. Spontaneous closure of traumatic macular hole. Retina 2001; 21(4):385–389.
5. Bottoni F, De Angelis S, Luccarelli S, Cigada M, Staurenghi G. The dynamic healing process of idiopathic macular holes after surgical repair: a spectral domain optical coherence tomography study. Invest Ophthalmol Vis Sci 2011;52(7): 4439–4446.
6. Kawano H, Uemura A, Sakamoto T. Incidence of outer foveal defect after macular hole surgery. Am J Ophthalmol 2011;151(2):318–322.

Miami to Japan Eye-Care Rescue Mission: Vision Van Helps with Relief Efforts

EDITOR:

THE DEVASTATING EARTHQUAKE OF MARCH 11—THE BIGgest disaster of modern Japan—hit the northeastern part of the island nation; the subsequent tsunami struck and destroyed almost all coastal villages and cities, leaving

more than 20 000 either dead or missing.[1] The destruction was so severe that communication infrastructures and transportation systems were disabled, leading to challenges for rescue and recovery as well as lack of supplies and gasoline. Thousands of survivors were homeless and without immediate medical care.

As reported in Haiti, a quick rescue response is critical.[2] However, in this case, eye care needs were considered minor given the magnitude of this disaster. Yet, many survivors lost their eyeglasses or medicines. A complete eye examination requires basic ophthalmic instruments, so a visit by an ophthalmologist with minimal instrumentation may not be effective. Thus, we sought to deliver urgent eye care with a mobile vision care facility.

The media in the United States had reported the use of Bascom Palmer Eye Institute's Vision Van in New Orleans after Hurricane Katrina in 2005 to aid in the treatment of visual casualties.[3] This van is equipped with modern specialized eye instrumentation necessary for examinations. Arrangements were made to borrow the van, and the initial challenge of transporting the van was overcome through the offer from Volga-Dnepr Airlines for the use of the Anotov An-124—the world's largest cargo airplane. This international assistance made it possible to transport the Vision Van from Miami to Sendai Airport, where it began rotating between Iwate and Miyagi prefectures, visiting evacuation centers in coastal cities on a weekly rotation. Volunteer ophthalmologists simply go to the care site and provide eye care to the evacuees in these remote areas. Additionally, care for chronic eye disorders such as diabetic retinopathy, glaucoma, and age-related macular degeneration is necessary to preserve vision and prevent further vision loss. During the first 12 clinic days of the Vision Van's rotation, 567 patients were seen, averaging 47 patients per day. Overall, the primary eye-related trouble for evacuees has been the loss of eyeglasses and treatment for pre-existing conditions.

The international collaboration involved in this ambitious endeavor was successful. Mobile vans are useful in such situations, and we would like to propose to world leaders that emergent medical systems be prepared as a precaution. Initially, the *Mission Vision Van* seemed impossible, but became *Mission Possible* through the efforts of many, and for that, we are most grateful.

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REFERENCES

1. National Police Agency of Japan. Damage situation and police countermeasures associated with 2011 Tohoku district—off the Pacific Ocean earthquake. Available at: http://www.npa.go.jp/archive/keibi/biki/index.htm. Accessed July 25, 2011.
2. Ginzburg E, O'Neill WW, Goldschmidt-Clermont PJ, de Marchena E, Pust D, Green BA. Rapid medical relief—Project Medishare and the Haitian earthquake. N Engl J Med 2010; 362(10):e31.
3. Bascom Palmer's Vision Van offered services to battered Louisiana. Ocular Surgery News. October 15, 2005. Available at: http://www.osnsupersite.com/view.aspx?rid=12678. Accessed July 25, 2011.

Pre-seasonal Treatment With Topical Olopatadine Suppresses the Clinical Symptoms of Seasonal Allergic Conjunctivitis

MASAHIKO SHIMURA, KANAKO YASUDA, AKIKO MIYAZAWA, TETSURO OTANI, AND TORU NAKAZAWA

• PURPOSE: To evaluate the effectiveness of pre-seasonal treatment with topical olopatadine on the reduction of clinical symptoms of seasonal allergic conjunctivitis (SAC).

• DESIGN: Prospective interventional case series.

• METHODS: Eleven patients with SAC received topical olopatadine in one eye at least two weeks before the onset of allergy symptoms, and the other eye served as the control. After the onset of allergic conjunctivitis, both eyes were treated with topical olopatadine. Visual analogue scale (VAS), which evaluated the subjective symptoms of ocular allergy, and the tear levels of histamine and substance P were measured up to six weeks.

• RESULTS: At the onset of allergy symptoms, the VAS score in the pretreatment eyes was statistically significantly lower than that in the control eyes. The VAS score in the control eyes decreased with time but did not decrease to the level seen in the pretreatment eyes until four weeks later. The tear level of substance P at the onset of allergy symptoms was significantly suppressed in the pretreatment eyes, while the level of histamine was not suppressed. Alteration of the VAS scores in the pretreatment eyes significantly correlated with the level of substance P, but not of histamine.

• CONCULSIONS: To suppress clinical symptoms in patients with SAC, pre-seasonal treatment with topical olopatadine is effective. The effectiveness of treatment correlates with the tear level of substance P. (Am J Ophthalmol 2011;151:697–702. © 2011 by Elsevier Inc. All rights reserved.)

SEASONAL ALLERGIC CONJUNCTIVITIS (SAC) IS THE most prevalent ocular allergy, affecting approximately 25% of the US population.[1] SAC is usually an acute or subacute condition characterized by self-limited signs and symptoms that become persistent with repeated allergen exposure during pollen season. The hallmark signs and symptoms are itching, redness, and lid swelling, along with tearing, mucous discharge, and burning.

The allergic response in conjunctivitis is typically elicited by ocular exposure to allergens that causes cross-linkage of membrane-bound IgE, which triggers mast cell degranulation, releasing a cascade of allergic and inflammatory mediators.[2] Histamine is the major mediator contributing to the development of the early-phase signs and symptoms of seasonal allergic conjunctivitis.[3,4] Two types of histamine receptors, H_1 and H_2, have been identified in the human conjunctiva. The activation of H_1 receptors induces itching, whereas activation of vascular endothelial cells through the actions of both H_1 and H_2 receptors induces hyperemia attributable to vasodilation and eyelid swelling and chemosis attributable to the transduction of fluid.[5] Several different drugs target mast cells and histamine receptors in order to reduce this allergic response in patients with SAC.

A bidirectional regulation of neuronal stimulation and allergic response has been theorized to occur during allergic inflammation. Neuromediators represent the key factor in this process, working on either immune or structural cells and exerting neuroimmunomodulatory functions in maintaining homeostasis and an inflammatory tissue remodeling system.[6] Substance P is the representative neuromediator involved in allergic inflammation[7] and contributes to the severity of ocular allergy symptoms.[8] However, little is known about the regulation of substance P secretion by anti-allergic ophthalmic drugs in patients with SAC.

Although pre-seasonal administration of multiple-action drugs, which combine antihistamine effects, mast cell stabilization, and anti-inflammatory actions, is believed to suppress the ocular allergy signs and symptoms of itching, redness, chemosis, tearing, and lid swelling, the efficacy of this treatment option has not been investigated. Olopatadine hydrochloride 0.1% ophthalmic solution is one of these multiple-action drugs and has recently become the primary medication choice for prevention and treatment of allergic conjunctivitis.[9]

In this prospective study, we investigated whether pre-seasonal administration of the multiple-action drug olopatadine suppressed ocular allergy symptoms at the onset of SAC; and the concentrations of the chemical mediator "histamine" and the neuromediator "substance P" in tears,

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with and without pre-seasonal treatment, were measured to assess their correlation with the severity of disease.

METHODS

• PATIENT ELIGIBILITY: Patients who had a history of seasonal allergic conjunctivitis to cedar pollen in both eyes, with a serum level of IgE specific to cedar pollen of greater than 4 IU/mL (class 3), and had itching and signs of ocular allergy every year during cedar pollen season were recruited for this study. The following patients were excluded from the study: those who 1) had any ocular disease other than allergic conjunctivitis; 2) used systemic or topical concomitant medications including corticosteroids, nosteroidal anti-inflammatory drugs, anticholinergics, and immunosuppressives; 3) suffered from severe ocular allergic diseases such as those associated with giant papilla formation; or 4) needed to wear contact lenses during the treatment period. Written informed consent was obtained from all patients.

• OUTCOME MEASURES: To evaluate the severity of subjective symptoms including conjunctival itching, injection, discharge, lacrimation, and foreign body sensation, a visual analogue scale (VAS; 0 = none to 10 = most severe) was adopted.[10] Tears were collected from both eyes of each patient using a glass capillary with a filament (GDC-1, Narishige Scientific Instrument Lab, Tokyo, Japan) placed at the inferior tear meniscus for 30 to 60 seconds. A total volume of 20 to 50 μL was easily collected with this unique technique (video available at AJO.com). After the collection of samples, both sides of the glass capillary were sealed with clay and immediately transferred on ice to the laboratory. The specimens were stored at −80°C.

The levels of histamine and substance P in the tears were determined using commercially available competitive enzyme-linked immunosorbent assay kits from Oxford Biomedical Research, Inc (Oxford, Michigan, USA) and Assay Designs, Inc (Ann Arbor, Michigan, USA), respectively. Total protein was quantified with the BCA Protein Assay Reagent from PIERCE Biotechnology, Inc (Rockford, Illinois, USA). Tear samples were prepared by appropriate dilutions for measurement of substance P, histamine, and total protein. Each assay was performed according to the manufacturer's direction.

• STUDY DESIGN: This study was conducted from January 2009 to April 2009. Initial examination of each eligible patient was completed by the middle of February 2009 because the beginning of cedar pollen season in this area of Sendai city in Japan, is usually at the end of February every year. At the beginning of the study, it was confirmed that the patients did not have symptoms of allergic conjunctivitis in either eye (VAS = 0 in both eyes). Subsequently one eye received topical administration of olopatadine hydrochloride 0.1% ophthalmic solution (Patanol; Alcon Laboratories, Fort Worth, Texas, USA) four times per day, and the other eye served as the control. To perform precise case-control study, the other eye should received Patanol without olopatadine hydrochloride; however, such an ophthalmic solution is not commercially available. Also, Patanol contains benzalkonium chloride (BAC) as preservative and administration of only BAC to preclinical SAC patients was not permitted by the Institutional Review Board (IRB), NTT East Japan Tohoku Hospital. Also in clinical phase, patients with SAC either receive or do not receive pre-seasonal administration of anti-allergic eye drugs; thus the IRB had recommended the other control eye without any eye drops until the onset of allergy symptoms.

At the onset of allergy symptoms, olopatadine was administered to both eyes. Ocular examination including VAS scoring and tear collection from both eyes was performed at the initial examination, at the onset of allergy symptoms, and at two, four, and six weeks after the onset of allergy symptoms. Alterations in the levels of the chemical mediators were assessed using the ratio of chemical mediators to total protein.

• STATISTICS: Obtained data do not always follow a metric scale, so statistical analyses were done with the Wilcoxon signed rank test (pretreatment and posttreatment data in the same eye) and with the Mann-Whitney U test (data for treated and control groups) as appropriate using a statistical program (SPSS Science, Chicago, Illinois, USA). To investigate the correlation between levels of chemical mediators and VAS, the Pearson correlation coefficient (r) and a P value were calculated. Since the number of samples was 11, an r^2 value of more than 0.3 ($|r| > 0.6$) was considered statistically significant and defined as a strong correlation. All of the data are presented as means ± standard deviations.

RESULTS

ELEVEN PATIENTS (MEAN AGE 40.3 ± 12.6 YEARS) WITH seasonal allergic conjunctivitis in both eyes participated in this study. Seven patients were male and four were female. The average level of serum IgE specific for cedar pollen was 23.8 ± 26.8 IU/mL.

No ocular or systemic side effects of the study drug were observed in any participants.

• INITIAL EXAMINATION PRIOR TO THE ONSET OF CEDAR POLLEN SEASON: At the beginning of this study, the VAS score of both eyes in all patients was confirmed to be 0. The total protein (TP) level in tears from the treated eyes was 7.83 ± 5.09 mg/mL, which was not significantly different from the level in the control eyes of 8.57 ± 6.47

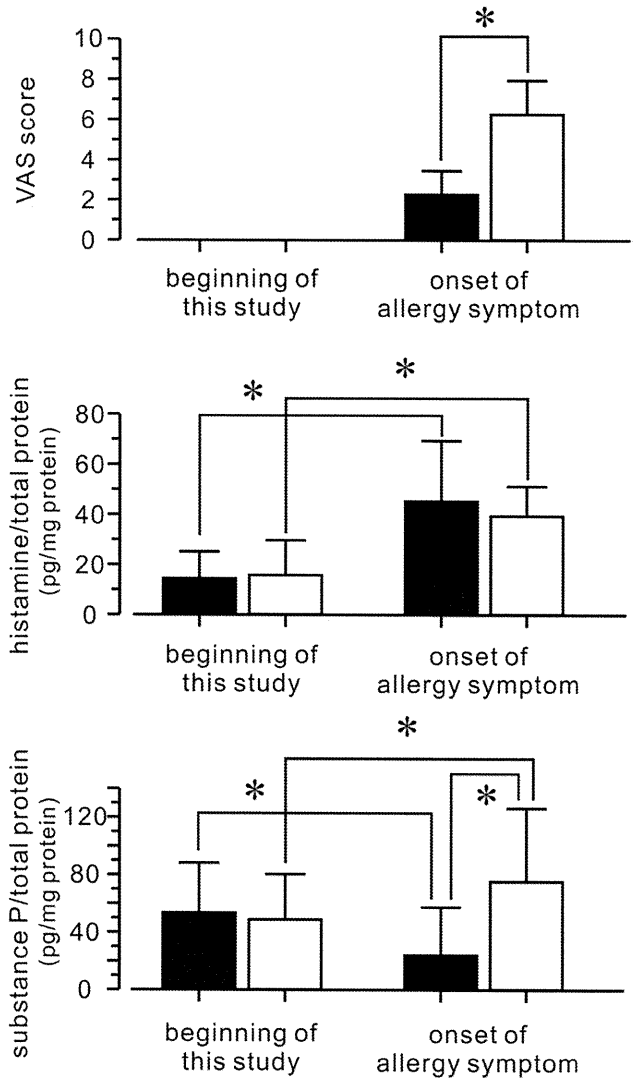

FIGURE 1. Visual analogue scale (VAS) and tear levels of cytokines before and at the onset of allergy in patients with seasonal allergic conjunctivitis with and without pretreatment of topical olopatadine. Comparison of (Top) VAS, (Middle) histamine/total protein ratio in tears, and (Bottom) substance P/total protein ratio in tears between the eyes with pre-seasonal topical olopatadine treatment (black bar) and the control eyes (white bar) at the beginning of this study and at the onset of allergy symptoms. Asterisks indicate a statistically significant difference ($P < .05$).

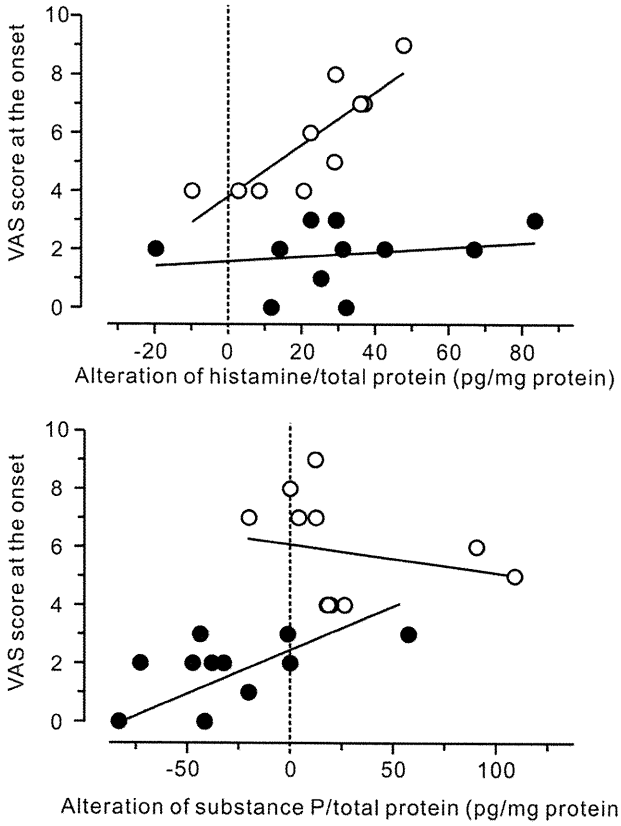

FIGURE 2. The relationships between subjective symptom and induction of cytokines in patients with seasonal allergic conjunctivitis with and without pretreatment of topical olopatadine. (Top) The relationships between the visual analogue scale (VAS) score at the onset of allergy symptoms and the alteration of the histamine/total protein ratio. There is no statistically significant correlation in the eyes with pre-seasonal treatment ($r^2 = 0.081$, $P = .409$), while there is a significant correlation in the control eyes ($r^2 = 0.711$, $P = .001$). (Bottom) The relationships between the VAS score at the onset of allergy symptoms and the alteration of the substance P/total protein ratio. There is a statistically significant correlation in the eyes with pre-seasonal treatment ($r^2 = 0.379$, $P = .039$), while there is no significant correlation in the control eyes ($r^2 = 0.094$, $P = .371$). Filled circles indicate the eyes with pre-seasonal treatment and open circles indicate the control eyes.

mg/mL. The histamine level in tears from the treated eyes was 1.04 ± 1.09 ng/mL, and the level in the control eyes was 1.23 ± 1.40 ng/mL. The substance P level in tears from the treated eyes was 3.60 ± 2.33 ng/mL, and the level from the control eyes was 3.79 ± 2.53 ng/mL.

The level of TP varied according to the day of tear collection even in the same patient. The ratios of histamine/TP and substance P/TP were calculated and adopted for this comparative study. The histamine/TP level in tears was not significantly different between the treated eyes (14.4 ± 10.6 pg/mg protein) and the control eyes (15.8 ± 13.9 pg/mg protein). The substance P/TP level in tears was also not significantly different between the treated eyes (53.5 ± 34.8 pg/mg protein) and the control eyes (49.0 ± 31.4 pg/mg protein).

• EFFECTIVENESS OF PRE-SEASONAL THERAPY AT THE ONSET OF ALLERGY SYMPTOMS: Although cedar pollen season began on February 26, clinical allergy symptoms were not seen in any of the patients until after March 7. The average duration of pre-seasonal therapy was 27.9 ± 13.5 days.

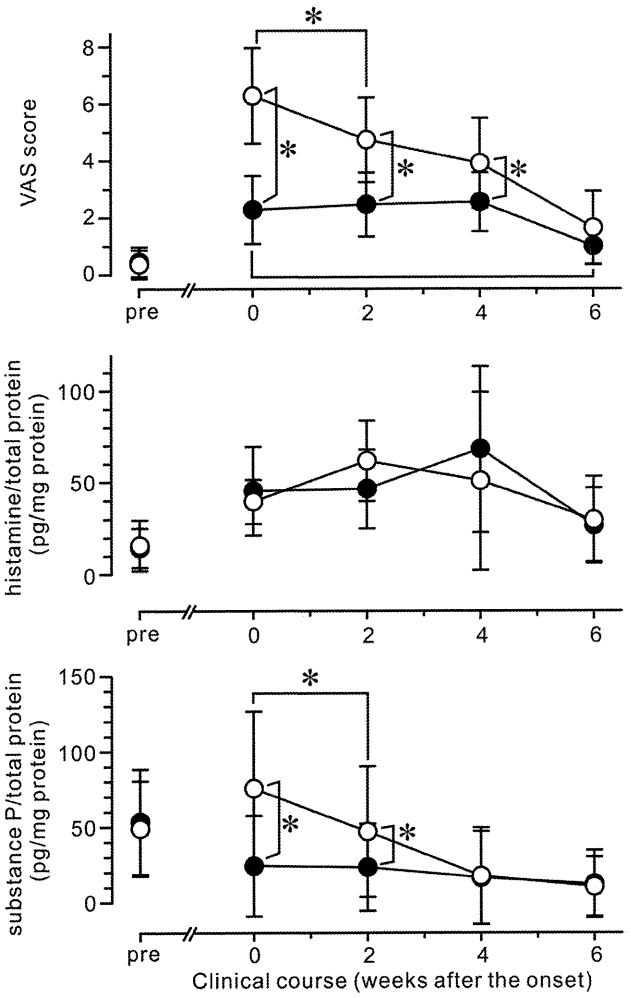

FIGURE 3. The alterations of subjective symptom and tear levels of cytokines in patients with allergic conjunctivitis with and without pretreatment of topical olopatadine. (Top) The alteration of the visual analogue scale (VAS) after the onset of allergy symptoms in eyes with pre-seasonal treatment (filled circle) and in control eyes (open circle). There is a statistically significant difference between the eyes at the week 0 (the onset of symptoms), week 2, and week 4 points. (Middle) The alteration of the histamine/total protein ratio after the onset of allergy symptoms in eyes with pre-seasonal treatment (filled circle) and in control eyes (open circle). There is no statistically significant difference between the two groups of eyes at any time point. (Bottom) The alteration of the substance P/total protein ratio after the onset of allergy symptoms in eyes with pre-seasonal treatment (filled circle) and in control eyes (open circle). There is a statistically significant difference between the eyes at the week 0 (the onset of symptoms) and week 2 points. Note that topical administration of olopatadine was performed in both eyes after the onset of symptoms (week 0). Asterisks indicate a statistically significant difference ($P < .05$).

At the onset of allergy symptoms (week 0), the VAS score in the treated eyes averaged 2.27 ± 1.19, which is significantly lower than the VAS score in the control eyes of 6.27 ± 1.68 ($P = .0001$) (Figure 1, Top) The histamine/TP level in tears was significantly elevated to 45.31 ± 24.11 pg/mg protein in the treated eyes ($P = .0067$) and to 39.46 ± 11.87 pg/mg protein in the control eyes ($P = .0076$). However, there was no significant difference in the histamine/TP level in tears from the treated eyes and the control eyes ($P = .5767$) (Figure 1, Middle). While substance P/TP level in tears was significantly decreased to 24.16 ± 33.32 pg/mg protein in the treated eyes ($P = .0469$), it was significantly increased to 75.49 ± 51.26 pg/mg protein in the control eyes ($P = .0367$). There was also a significant difference in the substance P/TP level in tears from the treated eyes and the control eyes ($P = .0138$) (Figure 1, Bottom).

• CONTRIBUTION OF CHEMICAL MEDIATORS TO ALLERGY SYMPTOMS: The relationship between the VAS score at the onset of allergy symptoms and the alteration of histamine/TP, which is defined as subtraction of the ratio at the onset of symptoms from the ratio at the beginning of this study, is depicted in Figure 2 (Top). Although there is no significant correlation ($r^2 = 0.081$, $P = .409$) in the treated eyes, there is a significant correlation ($r^2 = 0.711$, $P = .001$) in the control eyes. The relationship between the VAS score and the alteration of substance P/TP is depicted in Figure 2 (Bottom). In contrast, although there is a significant correlation in the treated eyes ($r^2 = 0.379$, $P = .039$), there is no significant correlation in the control eyes ($r^2 = 0.094$, $P = .371$).

• CLINICAL COURSE AFTER THE ONSET OF ALLERGY SYMPTOMS: After the onset of ocular allergy symptoms, olopatadine was administered to both eyes. The VAS score in the control eyes decreased with time but was statistically significantly higher than in the pretreated eyes for the first four weeks. At six weeks, there was no statistically significant difference in the VAS scores between the two groups of eyes (Figure 3, Top). The tear histamine/TP levels in both groups of eyes were not altered during the clinical course (Figure 3, Middle). Interestingly, the tear substance P/TP levels in the untreated eyes decreased with time but were statistically significantly higher than the levels in the pretreated eyes for up to two weeks. After four weeks, there was no statistically significant difference in tear histamine/TP levels between the two groups of eyes (Figure 3, Bottom).

DISCUSSION

IN THIS PROSPECTIVE STUDY, PRE-SEASONAL TREATMENT with olopatadine ophthalmic solution before the onset of pollen season was found to suppress the clinical symptoms of conjunctival itching, injection, discharge, lacrimation, and foreign body sensation. Interestingly, the clinical symptom under the pretreatment with olopatadine was

correlated with substance P, but not with histamine level in tears.

According to a previous study, conjunctival allergen challenge causes symptoms similar to those of SAC and increases the concentration of histamine in tears.[11] Even in this study, tear histamine levels were increased at the onset of allergy symptoms both with and without pretreatment. Although clinical allergy symptoms were significantly suppressed only with pretreatment, there was no significant difference in tear histamine levels between the pretreatment and control groups despite the fact that olopatadine inhibits IgE-mediated histamine release.[12] One possible explanation for this discrepancy is that olopatadine ophthalmic solution exerts an antagonistic action on the histamine H_1 receptor, suppressing the clinical allergy symptoms, while the antagonistic action may induce histamine secretion from mast cells through a feedback system. To confirm this hypothesis, further studies with mast cell stabilizers other than multiple-action agents such as olopatadine should be performed.

In contrast, the substance P level in tears was markedly suppressed by pretreatment with olopatadine ophthalmic solution at the onset of allergy symptoms. Substance P is a classic sensory neuropeptide and takes part in the pathogenesis of allergic response, contributing to tissue damage and/or chronicity.[13,14] During inflammatory allergic states, substance P synthesis is activated in unmyelinated sensory neurons, and subsequently, substance P enhances lymphocyte proliferation, immunoglobulin production, and cytokine secretion from lymphocytes, monocytes, macrophages, and mast cells. Substance P also induces release of inflammatory mediators such as cytokines, oxygen radicals, and arachidonic acid derivatives. Histamine potentiates tissue injury, thereby amplifying the inflammatory response.[15] Therefore, the induction of substance P and allergic inflammation are bidirectionally regulated.[6] Although the reason why olopatadine suppressed the level of substance P in tears at the onset of allergy symptoms remains unknown, it is possible that subclinical allergic inflammation may have occurred before the clinical onset of ocular allergy symptoms. Cedar pollen season began more than one week before the onset of allergy symptoms, and olopatadine may have prevented the subclinical inflammation-dependent induction of substance P.

The VAS score at the onset of symptoms in the control eyes correlated with tear histamine levels but not with tear substance P. Although substance P as a chemical mediator plays an important role in inflammation caused by an increase in vascular permeability and vasodilation,[16] ocular allergy symptoms are mainly induced by histamine H_1 activity, which supports previous results.[17]

In contrast, in the eyes that received pre-seasonal treatment with olopatadine, the VAS score at the onset was correlated with the tear substance P levels but not with the histamine levels. It has been reported that the inhibitory effect of olopatadine on H_1 activity is not affected even in the presence of high levels of histamine because of noncompetitive antagonism;[18] therefore, pretreatment with olopatadine suppressed H_1 activity, leading to a reduction of clinical symptoms. The remaining clinical symptoms were likely dependent upon substance P in a concentration-dependent manner.[10]

The tear levels of substance P obtained after pre-seasonal administration of topical olopatadine are a good index for evaluation of treatment.

In this study, another interesting result is that even without pre-seasonal treatment, within four weeks, topical administration of olopatadine after the onset of allergy symptoms suppressed the symptoms to the same extent as in the eyes with pre-seasonal treatment. Olopatadine inhibits mast cell degranulation in addition to antagonizing H_1 receptor activity.[12] Mast cell stabilizers exert their effects by inhibiting the antigen-induced degranulation process of the mast cells, preventing the exocytosis of preformed mediators that eventually lead to SAC. They have no effect on already synthesized and released inflammatory mediators.[19] Therefore it took about four weeks to suppress the clinical allergy symptoms.

In addition, in this study, we showed (probably for the first time) video images of tear collection with a glass capillary with a filament. In previous studies, to our knowledge, tears have been commonly collected in cellulose sponges, in capillary tubes, or by aspiration, but these methods have the technical difficulty of not a large enough volume of tears collected without stimulation.[20] In our method, as seen in the video images (available at AJO.com), glass capillaries were placed at the edge of the lower eyelid, easily collecting the tear samples without reflex lacrimation and therefore allowing the precise results obtained in this investigation.

We are aware of the limitations of this small case-series study. In this study, the control eye received no placebo eye drops until the onset of allergy symptoms; thus the possibility of "placebo effect" influencing VAS score is not excluded. However, pretreatment of topical olopatadine affects tear levels of cytokines, which is closely related with allergy symptom in patients with SAC.

To confirm the conclusion in this study, further studies with placebo control study, multicenter larger case series, and/or animal models should be performed in the future.

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(M.S.); collection (M.S., K.Y., A.M., T.O., T.N.), management (T.N.), and interpretation of the data (M.A., K.Y., T.N.); and preparation (M.S., K.Y., A.M., T.O.) and approval of the manuscript (M.S., K.Y., A.M., T.O., T.N.). This prospective study was conducted in accordance with the institutional guidelines of NTT East Japan Tohoku Hospital Clinical Research Ethics Committee and was approved by the Institutional Review Board (IRB) (nttthk #142008) before performing this study. The procedures conformed to the tenets of the World Medical Association's Declaration of Helsinki. Informed consent was obtained from each of the patients after they were provided information on the procedures to be used. The authors thank Dr Norio Sugimoto in Theranostic Instruments Research Laboratories for technical support of statistical analyses and useful comments.

REFERENCES

1. Abelson MB, George MB, Garofolo C. Differential diagnosis of ocular allergic disorders. Ann Allergy 1993;70(2):95–107.
2. Ono SJ, Abelson MB. Allergic conjunctivitis: Update on pathophysiology and prospects for future treatment. J Allergy Clin Immunol 2005;115(1):118–122.
3. Abelson MB, Allansmith MR. Histamine in the eye. In: Silverstein A, O'Connor G, eds. Immunology and Immunopathology of the Eye. New York: Masson Publishing; 1979: 362–364.
4. Yamaji M, Takada M, Fujiwara R, et al. Role of substance P in experimental allergic conjunctivitis in guinea pigs. Meth Find Exp Clin Pharmacol 1997;19(9):637–643.
5. Leonardi A. Role of histamine in allergic conjunctivitis. Acta Ophthalmol Scand Suppl 2000;(230):18–21.
6. Micera A, Lambiase A, Bonini S. The role of neuromediators in ocular allergy. Curr Opin Allergy Clin Immunol 2008; 8(5): 466–471.
7. Foreman JC. Substance P and calcitonin gene-related peptide: Effects on mast cells and in human skin. Int Arch Allergy Appl Immunol 1987;82(3–4):366–371.
8. Fujishima H, Takeyama M, Takeuchi T, Saito I, Tsubota K. Elevated levels of substance P in tears of patients with allergic conjunctivitis and vernal keratoconjunctivitis. Clin Exp Allergy 1997;27(4):372–378.
9. Lambiase A, Micera A, Bonini S. Multiple action agents and the eye: do they really stabilize mast cells? Curr Opin Allergy Clin Immunol 2009;9(5):454–465.
10. Fujishima H, Fukagawa K, Takano Y, et al. Comparison of efficacy of bromfenac sodium 0.1% ophthalmic solution and fluorometholone 0.02% ophthalmic suspension for the treatment of allergic conjunctivitis. J Ocular Pharmacol Ther 2009;25(3):265–269.
11. Bacon AS, Ahluwalia P, Irani AM, et al. Tear and conjunctival changes during the allergen-induced ealry- and late-phase responses. J Allergy Clin Immunol 2000;106(5):948–954.
12. Abelson MB. A review of olopatadine for the treatment of ocular allergy. Expert Opin Pharmacother 2004;5(9):1979–1994.
13. Taylor AW. Ocular immunosuppressive microenvironment. Chem Immunol Allergy 2007;92:71–85.
14. Scott JR, Muangman P, Gibran NS. Making sense of hypertrophic scar: a role for nerves. Wound Repair Regen 2007; 15(Suppl 1):S27–S31.
15. Lembeck F, Holzer P. Substance P as neurogenic mediator of antidromic vasodilation and neurogenic plasma extravasation. Naunyn-Schmied Arch Pharmacol 1979;310(2):175–183.
16. O'Connor TM, O'Connell J, O'Brien DI, Goode T, Bredin CP, Shanahan F. The role of substance P in inflammatory disease. J Cell Physiol 2004;201(2):167–180.
17. Minami K, Kamei C. A chronic model for evaluating the itching associated with allergic conjunctivitis in rats. Int Immunopharmacol 2004;4(1):101–108.
18. Matsumoto Y, Funahashi J, Mori K, Hayashi K, Yano H. The noncompetitive antagonism of histamine H_1 receptors expressed in Chinese hamster ovary cells by olopatadine hydrochloride: potency and molecular mechanism. Pharmacology 2008;81(3):266–274.
19. Bieoly L. Ocular allergy treatment. Immunol Allergy Clin North Am 2008;28(1):189–224.
20. Tuft SJ, Dart JKG. The measurement of IgG in tear fluid: a comparison of collection by sponge or capillary. Acta Ophthalmol 1989;67(3):301–305.

Biosketch

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Biosketch

Kanako Yasuda, MD, PhD, has been the Senior Medical Doctor in the Department of Ophthalmology, NTT East Japan Tohoku Hospital, Sendai, Miyagi, Japan, since 2004. Dr. Yasuda graduated from Tohoku University Graduate School of Medicine in 2004 and is a cataract surgeon and clinical advisor in vitreoretinal disease who specializes in ocular physiology and pharmacology. Improvement of tear sampling technique is her recent concern.

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

KEIICHIRO IWAO, MASARU INATANI, AND HIDENOBU TANIHARA, ON BEHALF OF THE JAPANESE STEROID-INDUCED GLAUCOMA MULTICENTER STUDY GROUP

• 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.

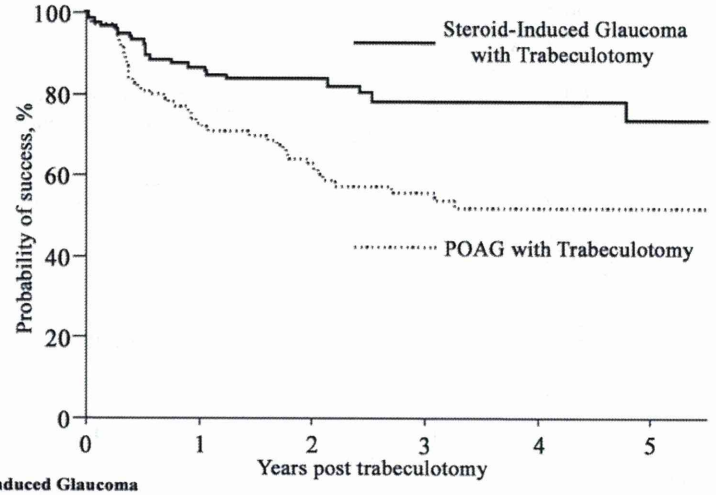
glaucoma, we retrospectively reviewed clinical charts at 17 clinical centers in Japan.

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