

Outer Plexiform Layer Elevations as a Marker for Prior Ocular Attacks in Patients With Behcet's Disease

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Submitted: March 16, 2018

Accepted: May 5, 2018

Citation: Kido A, Uji A, Morooka S, et al. Outer plexiform layer elevations as a marker for prior ocular attacks in patients with Behcet's disease. *Invest Ophthalmol Vis Sci.* 2018;59:2828-2832. <https://doi.org/10.1167/iovs.18-24348>

PURPOSE. Patients with Behcet's disease frequently have abnormal focal outer plexiform layer (OPL) bumps, which compress the inner nuclear layer. This study investigates the clinical relevance of these OPL elevations in Behcet's disease patients.

METHODS. Thirty-one consecutive patients (59 eyes) with Behcet's disease in remission and with available optical coherence tomography (OCT) images were included. The number of OPL bumps was counted using spectral-domain OCT images. The relationships between the number of bumps and visual acuity (VA), retinal thickness, choroidal thickness, disease duration, number of prior ocular attacks, and photoreceptor layer status (including external limiting membrane [ELM] and ellipsoid zone [EZ] continuity) were examined.

RESULTS. Eyes with more severe EZ or ELM disruptions had lower VA, more ocular attacks, and thinner retinas. Additionally, EZ line and ELM line status were significantly correlated with the number of OPL elevations. Eyes with OPL elevations had poorer VA, longer disease duration, more ocular attacks, and thinner retinas than those without OPL elevations. Additionally, the number of OPL elevations was strongly correlated with the number of ocular attacks in eyes with a preserved photoreceptor layer ($R = 0.720$, $P < 0.0001$).

CONCLUSIONS. The number of OPL elevations was associated with the number of prior ocular attacks in eyes with preserved photoreceptor layers. Therefore, OPL elevations may be a marker of prior posterior ocular attacks, which is important when determining how best to manage Behcet's uveitis.

Keywords: Behcet's disease, optical coherence tomography, retina

Behcet's disease is a chronic, autoimmune, systemic inflammatory disorder. The ocular manifestation of Behcet's disease is characterized by repeated uveitis with retinal and choroidal inflammation, often referred to as an ocular attack.¹⁻³ Posterior inflammation during ocular attacks often leads to irreversible, severe vision loss, which has been shown to be a major contributor to lowering quality of life in Behcet's disease patients.³⁻⁶ Good visual prognosis generally depends on controlling or preventing ocular attacks. Therefore, close patient monitoring and treatment with anti-inflammatory agents, including infliximab (anti-tumor necrosis factor- α [TNF- α] antibody), are important for managing patients with Behcet's disease.⁷

Recent advancements in optical coherence tomography (OCT) technology are remarkable. With its high axial resolution, OCT imaging is now an indispensable tool for visualizing retinal and ocular microstructures, including the photoreceptor layers,⁸⁻¹⁰ which were previously indiscernible with other imaging modalities. Photoreceptor layer integrity is associated with (VA) visual acuity in patients with several types of retinal disorders,¹¹⁻¹³ including Behcet's disease.¹⁴ Therefore, photoreceptor layer disruption may play a large role in the serious visual disturbances that occur after ocular attacks.¹⁴ OCT imaging can likely provide useful information to help determine whether treatment or observation is needed to prevent severe visual impairment.

We often observe small, focal inner retinal disruptions in the eyes of Behcet's disease patients, which we have named, "outer plexiform layer (OPL) elevations." To the best of our knowledge, these OPL elevations have not been previously reported. This study investigated the morphologic features of OPL elevations. The relationships between OCT findings and subject and ocular characteristics, including prior ocular attacks, were also examined to determine if OCT findings could be helpful in managing Behcet's uveitis.

METHODS

The protocol for this retrospective, observational, consecutive case study was reviewed and approved by the institutional review board (IRB) at Kyoto University Graduate School of Medicine (Kyoto, Japan). Because this study only retrospectively evaluated existing patient data, the IRB assigned the study an exempt status, waiving the requirement of informed consent. All study conduct adhered to the tenets of the Declaration of Helsinki.

Study Subjects

This study included patients with Behcet's disease who were in remission and had visited Kyoto University Hospital between February 2013 and October 2015. All subjects had both



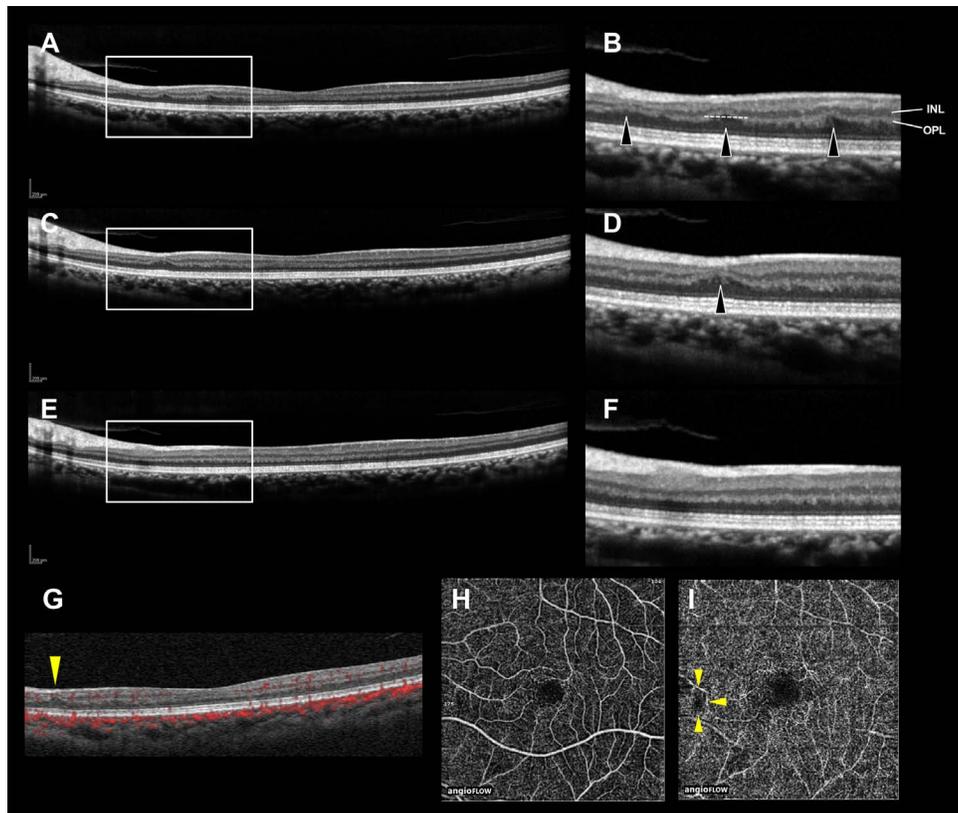


FIGURE 1. OPL elevation detected in the three consecutive OCT scans of Behcet's disease. (A) Horizontal OCT B-scan centered on the fovea of the patient with Behcet's disease. OPL elevations were detected in the nasal side of the scan. (B) Magnified view of the area outlined in A. Three OPL elevations characterized by the elevation of the inner border line of the OPL above the additional line drawn by connecting the outer border line of the intact part of INL adjacent to bumps of OPL were visible (*arrowheads*). (C) OCT B-scan next to scan in A at a distance of 240 μm . (D) Magnified view of the area outlined in (Bottom, left). OPL elevation was not detected in this scan. (E) OCT B-scan next to scan in C at a distance of 240 μm . (F) Magnified view of the area outlined in (Bottom, left). OPL elevation was not detected in this scan. (G) OCT angiography (OCTA) B-scan image (RTVue XR Avanti with AngioVue; Optovue, Inc., Fremont, CA, USA) of the area observed in the SD-OCT image in C. Angiographic overlay (*red pixels*) reveals a flow signal. Note that a flow signal was not detected beneath the OPL elevation (*yellow arrowhead*). (H) Enface OCTA image of the SCP. (I) Enface OCTA image of the DCP. A signal defect (*yellow arrowheads*) was observed at the location corresponding to the OPL elevation detected in (G).

spectral-domain (SD) and swept-source (SS) OCT images available that were of sufficient quality. Eyes with signs of active ocular inflammation, including vitreous opacity, iritis, macular edema, or retinal vasculitis, for the past 3 months were excluded. Eyes with senile cataract that resulted in poor image quality or that had been previously operated on (except for cataract surgery) were also excluded.

All patients had undergone standard-of-care comprehensive ophthalmologic examinations. These included best-corrected VA (BCVA) assessment (Landolt C chart), slit-lamp biomicroscopy, color fundus photography, and OCT imaging. Signs and symptoms of Behcet's uveitis were noted and ocular attack was defined as the exacerbation of uveoretinitis (e.g., vitreous opacity and retinal vasculitis).

Optical Coherence Tomography

Macular microstructures were assessed using SD-OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany). Macular scans included 30°, horizontal, and vertical line scans through the foveal center and a 13-line horizontal raster scan, which covered a 30° × 10° macular area.

We noticed that eyes of Behcet's disease patients often had abnormal focal OPL bumps on OCT images, which elevated and compressed the inner nuclear layer (INL). Because this structural change may indicate focal inner retinal thinning with concomitant OPL deformation, we named this abnormality an

“OPL elevation.” The OPL bumps were identified by manually drawing a reference line across the line scan where the INL should have been (using intact INL as a guide). Any place where the actual INL line was elevated above the reference INL line was defined as an OPL bump (Fig. 1).

Photoreceptor layer integrity was assessed as complete, discontinuous, or absent, as was previously described,^{12,15} using both horizontal and vertical scans that passed through the fovea (Fig. 2). In brief, eyes in which the ellipsoid zone (EZ) was detected as a complete line in the fovea were classified as EZ (+), while eyes in which the EZ was detected as a discontinuous line in the fovea were classified as EZ (\pm); when the EZ could not be detected in the fovea, eyes were classified as EZ (–). Each eye also was classified based on the status of the external limiting membrane (ELM) beneath the fovea, with the same criteria described for the EZ, that is, ELM (+), ELM (\pm), and ELM (–). Two experienced examiners (A.K. and A.U.) classified the status of the EZ and the ELM for each eye, and counted the number of OPL elevations. In cases of disagreement, the results were discussed until consensus was reached. The κ coefficient was calculated as a measure of agreement between the observers for photoreceptor layer statuses. Intraclass correlation coefficient (ICC) was used to evaluate measurement reproducibility of the number of OPL elevations.

Average foveal thickness in the evaluation area (within 1-mm of the fovea) was automatically measured using the OCT system's built-in software. Central choroidal thickness, defined

TABLE 1. Baseline Demographic and Ocular Characteristics of Subjects With Behcet's Disease

Age, y	47.3 ± 10.8
Sex	
Men	29 (49.2%)
Women	30 (50.8%)
LogMAR VA	-0.010 ± 0.338
Disease duration, y	9.07 ± 5.60
Number of prior posterior ocular attacks	1.32 ± 2.53
Use of infliximab	30 (50.8%)
Status of the ELM line	
Complete	39 (66.1%)
Discontinuous	14 (23.7%)
Absent	6 (10.2%)
Status of EZ line	
Complete	46 (78.0%)
Discontinuous	7 (11.8%)
Absent	6 (10.2%)
Retinal thickness, μm	214 ± 36
Choroidal thickness, μm	231 ± 83
Number OPL elevations	0.66 ± 1.10

Data are presented as mean ± standard deviation or as *n* (%) as applicable. logMAR, logarithm of the minimal angle of resolution.

as the vertical distance between the inferior retinal pigment epithelium margin and the choriocleral border,¹⁶ was measured using SS-OCT (DRI OCT-1; Topcon, Tokyo, Japan) horizontal scans that passed through the fovea.

Statistical Analyses

Data are presented as mean ± standard deviation, where applicable. All BCVA measurements were converted to the logarithm of the minimum angle of resolution (logMAR) before performing data analyses. Subject (age, sex, disease duration) and ocular (logMAR VA, retinal thickness, choroidal thickness, and number of ocular attacks) parameters were assessed in each of the three photoreceptor status groups. Relationships between status group and each parameter were examined using a 1-way analysis of variance with post-hoc comparisons using the Scheffe procedure. Student's *t*-tests were used to compare continuous variables between eyes with and without OPL elevations. Bivariate correlations were analyzed using Pearson's correlation coefficients. All analyses were performed using StatView (version 5.0; SAS Institute, Cary, NC, USA). Statistical significance was defined as *P* < 0.05.

RESULTS

Fifty-nine eyes of 31 consecutive Behcet's disease patients were included in this study. Subject characteristics are summarized in Table 1. Briefly, subjects were 47.3 ± 10.8

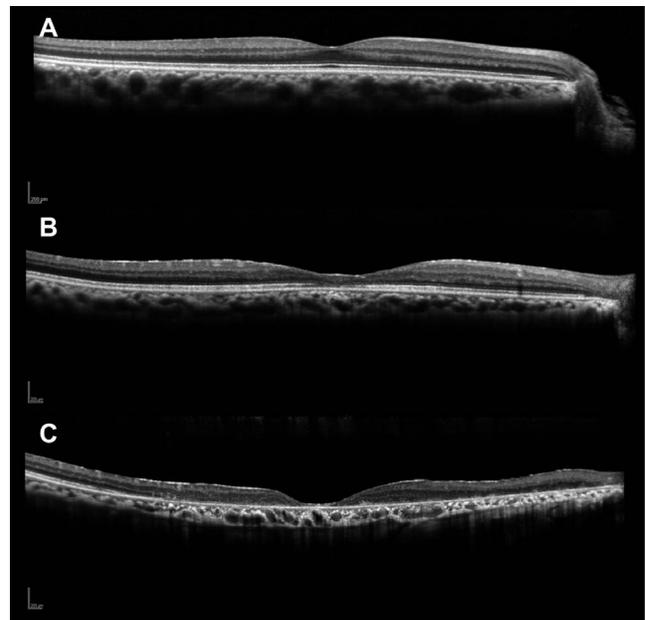


FIGURE 2. The evaluation of the integrity of the photoreceptor layers in Behcet's disease. (A) OCT B-scan centered on the fovea of the patient with Behcet's disease have an intact EZ and ELM within a 1-mm area centered at the fovea. (B) OCT shows a discontinuous EZ and ELM. (C) OCT shows absent EZ and ELM.

years old (range, 28–69 years), 29 subjects (49.2%) were male, and disease duration was 9.07 ± 5.60 years.

Associations Between Photoreceptor Layer Status and Ocular Characteristics

The κ coefficient was 0.771 for the EZ and 0.871 for the ELM, indicating good interobserver agreement. Both EZ and ELM status were significantly associated with BCVA (both *P* < 0.0001; Table 2). Additionally, logMAR VA was significantly worse in both the EZ and ELM absent groups than in either of the corresponding discontinuous (both *P* < 0.0001) or complete groups (both *P* < 0.0001; Fig. 2). Furthermore, eyes with absent EZ and ELM layers had a significantly larger number of ocular attacks (*P* = 0.0185 and *P* = 0.0041, respectively), and a smaller retinal thickness (both *P* < 0.0001).

OPL Elevations in OCT Images

Three eyes, in which only the horizontal and the vertical line scans were available, were excluded from further analyses, resulting in a final total of 56 eyes. The OPL elevations were

TABLE 2. Associations Between Photoreceptor Layer Status and Clinical Characteristics in Patients With Behcet's Disease

Photoreceptor Layer Status	Eyes, <i>N</i>	LogMAR VA		Disease Duration, y		Number of Ocular Attacks		Retinal Thickness, μm		Number of OPL Elevations	
		Mean	<i>P</i>	Mean	<i>P</i>	Mean	<i>P</i>	Mean	<i>P</i>	Mean	<i>P</i>
EZ(+)	46	-0.107 ± 0.143		8.28 ± 5.62		0.96 ± 2.40		224 ± 15.1		0.46 ± 0.90	
EZ(±)	7	-0.033 ± 0.120		11.0 ± 5.63		1.43 ± 1.62		212 ± 49.2		1.00 ± 1.00	
EZ(-)	6	0.757 ± 0.579	<0.0001	12.8 ± 3.55	0.1067	4.00 ± 3.35	0.0185	130 ± 49.9	<0.0001	3.00 ± 2.00	0.0001
ELM line(+)	39	-0.096 ± 0.154		9.17 ± 5.75		0.67 ± 1.68		227 ± 16.7		0.33 ± 0.70	
ELM line(±)	14	-0.101 ± 0.105		7.18 ± 5.30		2.00 ± 3.31		211 ± 31.4		1.07 ± 1.14	
ELM line(-)	6	0.757 ± 0.579	<0.0001	12.8 ± 3.55	0.1144	4.00 ± 3.35	0.0041	130 ± 49.9	<0.0001	3.00 ± 2.00	<0.0001

TABLE 3. Subject and Ocular Characteristics in Eyes With and Without OPL Elevations on OCT Images

Characteristic	Eyes Without OPL Elevations	Eyes With OPL Elevations	P
n (eyes)	36	20	-
Sex, male/female	16/20	10/10	-
Age, y	45.5 ± 9.6	49.9 ± 11.2	0.1298
LogMAR VA	-0.137 ± 0.074	0.091 ± 0.426	0.0027
Number of prior ocular attacks	0.2 ± 0.5	3.1 ± 3.5	< 0.0001
Disease duration, y	7.75 ± 5.80	11.15 ± 4.96	0.0313
Retinal thickness, μm	225 ± 12	208 ± 39	0.0167
Choroidal thickness, μm	226 ± 87	238 ± 84	0.6783

approximately 200 to 400 μm wide and approximately 10 to 20 μm high in single B-scan images. Additionally, a single OPL elevation was found in no more than three consecutive scans (Fig. 1). These 56 eyes were divided into two groups based on the presence/absence of OPL elevations. The 20 eyes with OPL elevations had a larger number of ocular attacks (with: 3.1 ± 3.5 attacks, without: 0.2 ± 0.5 attacks; $P < 0.0001$) and a longer disease duration (with: 11.15 ± 4.96 years, without: 7.75 ± 5.80 years, $P = 0.0313$) than the 36 eyes without OPL elevations (Table 3). Moreover, eyes with OPL elevations had thinner retinas (with: 208 ± 39 μm, without: 225 ± 12 μm; $P = 0.0167$) and poorer BCVA (with: 0.091 ± 0.426, without: -0.137 ± 0.074; $P = 0.0027$) than those without OPL elevations. Choroidal thickness was not significantly different between groups.

Associations Between the Number of OPL Elevations and Ocular Characteristics in Eyes With Preserved Photoreceptor Layers

ICC for the number of OPL elevations showed good agreement of 0.992. The number of OPL elevations was significantly different among the three EZ line groups and the three ELM line groups, indicating an association between inner retinal and outer retinal layer damage in eyes with Behcet's disease (Table 2). When only eyes with complete or discontinuous EZ and ELM lines were examined (53 eyes), the number of OPL elevations was strongly correlated with the number of ocular attacks ($R = 0.720$, $P < 0.0001$; Table 4). A modest correlation was also found between the number of OPL elevations and subject age ($R = 0.306$, $P = 0.0509$), but BCVA was not significantly correlated with the number of OPL elevations.

DISCUSSION

The study investigated whether OCT can provide information, other than irreparable photoreceptor layer damage, related to the history of past ocular attacks. We specifically examined inner retinal morphology near retinal vessels and found that focal INL collapse is accompanied by focal OPL elevations. These anatomical changes were frequently detectable on OCT images obtained from subjects with Behcet's disease. Although the number of OPL elevations was not significantly correlated with BCVA, it was strongly correlated with the number of past ocular attacks in eyes with preserved photoreceptor layers.

Photoreceptor layer integrity has been shown to be significantly associated with visual function in various retinal disorders, including diabetic macular edema,^{8,12,15} branch retinal vein

TABLE 4. Associations Between the Number of OPL Elevations and Various Subject and Ocular Characteristics in Behcet's Disease Patients With a Preserved Photoreceptor Layer

	Regression Coefficient	P
Age	0.306	0.0509
LogMAR VA	0.176	0.2728
Disease duration	0.214	0.1802
Number of prior ocular attacks	0.720	<0.0001
Retinal thickness	-0.320	0.0410
Choroidal thickness	-0.005	0.9757

logMAR, logarithm of the minimal angle of resolution.

occlusion,¹³ and epi-retinal membrane.^{17,18} This association has also been found following retinal surgery.^{19,20} The EZ line integrity (evaluated with SD-OCT) has also been shown to be correlated with BCVA in patients with Behcet's disease.¹⁴ In agreement, the current study found that both EZ line status and ELM line status were strongly correlated with BCVA and retinal thickness. Moreover, eyes with more photoreceptor disruption had a larger number of prior ocular attacks than eyes with intact photoreceptor layers. This finding suggests that SD-OCT photoreceptor layer evaluations may be helpful in better understanding and predicting serious visual disturbances following Behcet ocular attacks. Unfortunately, the association between the number of prior ocular attacks and photoreceptor layer preservation cannot be made in eyes with preserved photoreceptor layers and without active inflammatory findings.

The OPL elevations observed here are similar to the wavy boundary of a normal Henle fiber layer. Fortunately, OPL elevations differ from Henle fiber layer waves in that OPL elevations are wider and the INL above an OPL elevation is thinned. In the current study, OPL elevations were detected in 35.7% of included eyes, indicating that OPL elevations are not rare in eyes of Behcet's disease patients. Unfortunately, the clinical relevance and origin of this novel finding remain unknown. However, we speculate that previous inflammatory episodes may have caused focal inner retinal damage, resulting in focal inner retinal layer disarrangement. This theory is supported by the correlation between retinal thickness and the number of past ocular attacks (thinner retina associated with a higher number of attacks). Choroidal thickness was not significantly correlated with the number of prior attacks. Furthermore, Oray et al.²¹ showed that the presence of localized retinal nerve fiber layer (RNFL) defects indicated posterior pole involvement and put Behcet's disease patients at a higher risk factor for a poor visual outcome. They speculated that these localized RNFL defects may have been caused by microvascular ischemia at the optic nerve head and/or posterior pole. Oray et al.²¹ did not examine other retinal layers, but we presume that microvascular ischemia also played a role in OPL elevation development. However, OPL elevations had a multifocal distribution, but RNFL defects involved a band-shaped area. Therefore, the two OCT anomalies may have different pathological mechanisms.

OCT angiography (OCTA) precisely visualizes the three-dimensional retinal microvasculature by detecting moving blood.^{22,23} Khairallah et al.²⁴ documented perifoveal microvascular changes in Behcet's uveitis using OCTA, which was better at visualizing the retinal microvasculature than fluorescein angiography. Interestingly, they found that the deep capillary plexus (DCP) had more severe changes than the superficial capillary plexus (SCP). Given that the DCP is located in both sides of the INL,²⁵ focal changes in the DCP (e.g., non-perfusion) may be related to the focal OPL elevations and INL thinning observed here. In fact, for one patient in this study, no flow signal was observed beneath the OPL elevation in the

OCTA B-scan image as well as the enface OCTA image of DCP (Figs. 1G, 1H, 1D). Further OCTA studies are needed to better understand the association between OPL elevations and microvascular changes in eyes with Behcet's uveitis.

The presence of OPL elevations was significantly correlated with BCVA when all patients were included in analysis (Table 3). However, this correlation was not significant when only eyes with preserved photoreceptor layers were examined (Table 4). This suggests that BCVA is likely more affected by photoreceptor layer status than by OPL elevation presence/absence. Moreover, a greater number of OPL elevations were associated with a greater number of past ocular attacks, even in eyes with a preserved photoreceptor layer. This finding suggests that both photoreceptor layer status and the number of OPL elevations can provide information on prior ocular attacks. Additionally, this information may be useful in determining TNF- α antibody therapy initiation/adjustment in eyes with Behcet's uveitis to avoid irreversible degenerative photoreceptor changes. Perhaps monitoring OPL elevation development over time would be useful for managing Behcet's uveitis.

Our study had several limitations. First, our sample size was small and our study may have been underpowered to detect very small differences between study groups. Second, the retina was not evaluated outside the macular scan area. Scans with larger areas may have a higher sensitivity for detecting OPL elevations. Third, we only investigated eyes with Behcet's disease and OPL elevations may be present in eyes with other ocular disease, particularly uveitis. Follow-up studies that include eyes with other retinal and ocular diseases are needed. Despite these limitations, our study did demonstrate a clinically relevant OPL elevation in patients with Behcet's disease.

In conclusion, we identified OPL elevations, a novel OCT finding, in patients with Behcet's disease. The number of OPL elevations was associated with the number of prior ocular attacks, even in eyes with preserved photoreceptor layers. Therefore, OPL elevations may be a useful marker of prior posterior ocular attacks, which can influence how Behcet's uveitis is managed.

Acknowledgments

Disclosure: **A. Kido**, None; **A. Uji**, Novartis (F), Senju (F), Nidek (F), Canon (F); **S. Morooka**, None; **Y. Kuroda**, None; **S. Arichika**, None; **T. Akagi**, Pfizer (F), Bayer (F), Santen (F), Senju (F), Alcon (F), Otsuka (F), Kowa (F), Canon (F); **A. Tsujikawa**, Pfizer (F), Bayer (F), Novartis (F), Santen (F), Senju (F), Alcon (F), Nidek (F), AMO Japan (F), Kowa (F), Sanwa Kagaku (F)

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