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MEDICAL OPHTHALMOLOGY

Effect of 1-year lutein supplementation on macular pigment optical density and visual function

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Abstract
Background Although it is known that antioxidants including lutein can affect macular pigment optical density (MPOD) and visual function, we still have much to learn about their effect. Our aim was to assess the 1-year changes in MPOD and visual function in response to supplementation containing lutein.
Methods We prospectively measured the MPOD level of those who received a supplement containing 6 mg of lutein daily for 1 year. MPOD level was measured every 3 months by using autofluorescence spectrometry with the two-wavelength method. Other examinations, including contrast sensitivity and retinal sensitivity were also measured every 3 or 6 months. Stepwise regression analysis was performed to determine the factors that correlated with the changes observed in those examinations.
Results Forty-three eyes of 43 Japanese subjects, including five normal eyes, five fellow eyes with central serous chorioretinopathy (CSC), and 33 fellow eyes with age-related macular degeneration (AMD) were enrolled. The higher baseline MPOD level was correlated with the eye with a clear intraocular lens (IOL). Although no time-dependent changes in the MPOD level were obtained in any area, subjects without cardiovascular diseases showed higher increase in the MPOD level. We observed significant increases in the contrast sensitivity at 1 year (p=0.0124) and in the retinal sensitivity at 6 months (p<0.0001) and 1 year (p<0.0001). Stepwise regression analysis showed that nonsmokers had increased contrast sensitivity (p=0.0173), and the fellow eye of those with CSC had less of an increase in retinal sensitivity (p=0.0491).
Conclusions Daily supplementation with 6 mg of lutein did not affect the MPOD level for 1 year, suggesting that 6 mg of lutein may be insufficient to increase the MPOD level. However, supplementation seems to improve visual functions such as contrast sensitivity and retinal sensitivity.

Keywords Macular pigment · Fundus autofluorescence · Lutein · Contrast sensitivity · Microperimetry

Introduction

Macular pigment, which is comprised of three carotenoids, i.e., lutein, zeaxanthin, and meso-zeaxanthin [1–3], has light-absorbing properties in the 400- to 540-nm range, with maximum absorption at about 460 nm [3–5]. In addition, the macular pigment itself has an antioxidative effect [3, 6–9]. Thus, macular pigment may help retard some destructive processes in the retina and the retinal pigment epithelium, which can cause macular diseases such as age-related maculopathy, age-related macular degeneration (AMD), and possibly central serous chorioretinopathy (CSC) [10–15].

Several studies have investigated the relationship between dietary supplementation with lutein and zeaxanthin and macular pigment optical density (MPOD). It is controversial whether supplementation with these carote-

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noids and/or other antioxidants increases the MPOD level and consequently prevents the development of AMD [16–28]. The role of macular pigment and vitamins in visual function, such as visual acuity (VA) and contrast sensitivity, has also been discussed [28–36]. Some studies have reported that the supplemental antioxidants had a positive effect on visual function, but other studies did not.

In the current study, we investigated the MPOD level in response to supplementation with lutein and other antioxidants and minerals in 43 eyes of 43 Japanese subjects without abnormal fundus autofluorescence (FAF) at the fovea. We also estimated the effect of this supplementation on visual functions, including VA, contrast sensitivity, and retinal sensitivity. To the best of our knowledge, this is the first study to report a relationship between supplementation with carotenoids and time-dependent changes in the MPOD levels and visual function in a Japanese population.

Materials and methods

Study population

We conducted a prospective interventional study at Osaka University Hospital from January 2008 to October 2009. The institutional review board approved this study.

We calculated the power (number of eyes) needed for this study, the primary outcome of which was the changes in the MPOD level averaged along the area of an annulus with a retinal eccentricity of 0.5 degree. Considering the normal data that we previously reported, we found that 39 eyes were needed to detect a change in the MPOD optical density of 0.10 density units (DUs) [15]. Because we expected dropout during the follow-up period, we enrolled 43 consecutive Japanese subjects over 40 years old who had never taken supplementation previously. Written informed consent was obtained from all subjects enrolled.

Eyes with less than 0.05 of logMAR score and without apparent retinal disorders and abnormal FAF including the fovea were recruited. All subjects had undergone the detailed fundus examination, optical coherence tomography, and fundus autofluorescence (FAF), and if any macular disorders were suspected, fluorescein and indocyanine green angiography was performed and excluded the subjects with bilateral disease. When one eye had retinal disorders such as CSC and AMD and fellow eyes confirmed to have no apparent abnormalities including FAF examination at the fovea, we selected the fellow eye as the target of our study. Eyes with dry AMD were not included. If both eyes had no ocular disorders, we selected the right eye.

Subjects took daily supplements of 6 mg of lutein and other vitamins and minerals (Ocuvite plus Lutein, Bausch & Lomb Japan, Tokyo, Japan) for 1 year and were examined every 3 months. The ingredients in Ocuvite plus Lutein are shown in Table 1. All participants provided informed consent at the beginning of the supplementation according to the tenets of the Declaration of Helsinki.

Measurement of the MPOD level

We measured the MPOD level in all eyes using the modified Heidelberg Retina Angiograph (HRA, Heidelberg Engineering, Dossenheim, Germany) every 3 months (0, 3, 6, 9, and 12 months). Autofluorescence spectrometry with the two-wavelength method was the principle measurement of the MPOD [37–39]. Two masked orthoptists who used the same testing device and protocol performed all measurements. Before the study, the reliability of the measurements between the two orthoptists was confirmed as reported previously [15].

Before the measurements, sufficient pupil dilation was obtained with instillation of dilating drops containing 0.5% tropicamide and 2.5% phenylephrine. The subjects sat at a table and fixated on an external light source with the fellow eye. If the fellow eye did not have adequate VA for fixation, the subjects were asked to look straight as much as possible. The modified HRA was aligned with the subject's eye, and movies were taken with the 488- and 514-nm excitation wavelengths (scan size, 30 degrees); computed mean autofluorescence images were obtained at each wavelength, and the two images were subtracted to calculate the MPOD level expressed in DUs. In accordance with other studies using this method, we chose the mean MPOD level averaged along the area of an annulus with a retinal eccentricity of 0.5 degree (MPOD level on 0.5 degree) as a primary outcome. We also calculated the MPOD level averaged within the area of an annulus with a retinal eccentricity of 0.5 degree (MPOD level within 0.5 degree) and 1.0 degree (MPOD level within 1.0 degree). We measured the MPOD two or three times in each eye during

Table 1 Ingredients in Ocuvite plus Lutein

Lutein	6 mg
Beta-carotene (provitamin A)	1200 μg
Vitamin C	300 mg
Vitamin E	60 mg
Vitamin B_2	3 mg
Niacin	12 mg
Zinc	9 mg
Selenium	45 μg
Copper	0.6 mg
Manganese	1.5 mg

each visit and then selected the data with the best quality image [37].

Ophthalmic examinations

To determine the effect of supplementation on visual function, we obtained the best spectacle corrected VA (BCVA) levels using Landolt C charts that then were converted to the logarithm of the minimal angle of resolution (logMAR) score, the low-contrast VA measured using the CSV-1000 LanC10% (Vector Vision Co., Greenville, OH), the contrast sensitivity using the CSV-1000E (Vector Vision Co.), and the mean retinal sensitivity measured by the MP-1 Microperimeter (Nidek Technologies, Padova, Italy).

The BCVA was measured at the beginning and after 1 year of supplementation. Low-contrast VA testing was measured at 0, 3, 6, 9, and 12 months to identify minute changes in visual function [40]. The CSV-1000LanC10% is based on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart (The Lighthouse, New York). This chart displays five letters per line at 10% low contrast. The low-contrast VA was scored by the number of letters identified correctly with full spectacle correction.

Contrast sensitivity usually is measured at several different spatial frequencies. We tested the contrast sensitivity at 3, 6, 12, and 18 cycles per degree (cpd). The contrast level of the last correct response for each cpd was recorded as the contrast threshold in logarithmic value under full spectacle correction. We then calculated the area under the log contrast sensitivity function (AULCSF) as representative of the contrast sensitivity data according to the method of Applegate et al. [41]. The log contrast sensitivity versus log spatial frequency data were fitted to a third-order polynomial curve. The fitted function was integrated between the fixed limits of log spatial frequencies of 0.48 (corresponding to 3 cpd) and 1.26 (18 cpd), and the resulting value was defined as the AULCSF.

Microperimetry was performed at 0, 6, and 12 months [42, 43]. The retinal sensitivity threshold was measured using Goldmann III stimuli (circle with a white background) projected on a white background with background illumination of 1.27 cd/m^2 and stimulus presentation time of 200 ms. We tested a radial grid of five stimuli within the area of an annulus with a retinal eccentricity of 0.5 degree and that of 45 stimuli within the area of an annulus with a retinal eccentricity of 6.0 degrees.

Statistical analysis

The baseline data are expressed as the mean ± standard deviation (SD).

Stepwise regression analysis using the Akaike information criteria was performed to determine the covariates that affected the MPOD level of each area at baseline, i.e., gender, age, smoking, lens status, cardiovascular diseases (stroke, angina, and myocardial infarction), disease in the fellow eye, low-contrast VA, AULCSF, and retinal sensitivity within 0.5 degree [44]. We did not select the logMAR VA as a covariate because low-contrast VA is more sensitive than logMAR VA and they are moderately correlated with each other (r=−0.63, p<0.0001). Similarly, we did not select retinal sensitivity within 6.0 degrees as a covariate because the MPOD level was measured within 1.0 degree and the retinal sensitivity within 0.5 degree and 6.0 degrees are strongly correlated with each other (r=0.86, p<0.0001). Stepwise regression analysis was conducted to detect the covariates that correlated with the low-contrast VA, the AULCSF, and the retinal sensitivity within 0.5 and 6.0 degrees at baseline, including gender, age, smoking, lens status, cardiovascular diseases and disease in the fellow eye plus low-contrast VA at baseline when evaluating the AULCSF and the retinal sensitivity.

To estimate the differences compared with baseline at each time point (3, 6, 9, and 12 months) within the variables, we calculated the 95% CI and performed a paired t test and the significance level was adjusted by Bonferroni correction. That is, because we considered $p \leqq 0.05$ significant when comparing just one time point with baseline, $p \leqq 0.025$ and $p \leqq 0.0125$, respectively, were considered significant when comparing two and four time points with baseline. To determine the variables that affected the 1-year change in the MPOD level, stepwise regression analysis was performed, where gender, age, smoking, lens status, cardiovascular diseases, disease in the fellow eye, MPOD on the 0.5 degree, the low-contrast VA, the AULCSF, and the retinal sensitivity within 0.5 degree at baseline were included as covariates. Stepwise regression analysis was also conducted to detect the covariates that correlated with the changes in the low-contrast VA, the AULCSF, and the retinal sensitivity within 0.5 and 6.0 degrees, including gender, age, smoking, lens status, cardiovascular diseases, disease in the fellow eye, MPOD on the 0.5 degree at baseline, and the low-contrast VA at baseline plus the baseline value of the respective factors.

JMP software version 8.0 (SAS Institute Inc., Cary, NC) was used for statistical analysis.

Results

Baseline characteristics

A total of 43 eyes of 43 subjects (26 men, 17 women; mean age ± SD, 64.5±9.1 years) were included. Twenty-seven

subjects were smokers and 16 subjects were nonsmokers. Six subjects had had a past history of cardiovascular diseases (stroke, angina, and myocardial infarction). Three eyes had undergone cataract surgery with implantation of clear intraocular lens (IOL) before the study. Five eyes were those of healthy volunteers, five eyes were fellow eyes of those with CSC, and 33 eyes were fellow eyes of those with AMD (18 eyes were polypoidal choroidal vasculopathy, 12 eyes were exudative AMD, two eyes were age-related maculopathy and one eye was retinal angiomatous proliferation). None of the subjects had an unbalanced diet. The subjects had spherical equivalent between −3.88 diopter (D) and 4.63 D (mean ± SD was 0.11±1.88 D) and cylinder magnitude up to 3.50 D. Although 16 eyes had minimal retinal pigment epithelium damage within 6.0 degrees, foveal regions in those eyes were not affected.

Accurate MPOD levels were obtained from all subjects. The mean ± SD MPOD level measured by autofluorescence spectrometry was 0.480±0.136 DU (on 0.5 degree), 0.493±0.138 DU (within 0.5 degree), and 0.474±0.134 DU (within 1.0 degree). The mean±SD logMAR BCVA was −0.078±0.077 (the mean Snellen equivalent; 24/20), and the low-contrast VA was 77.7±6.3 letters. The mean±SD AULCSF was 1.36±0.14, and the retinal sensitivity was 14.8±3.2 dB (within 0.5 degree) and 15.3±2.4 dB (within 6.0 degrees).

Stepwise regression analysis showed that the higher baseline MPOD levels on 0.5 degree and within 0.5 degree were correlated with the eye with clear IOL (T=2.65, p=0.0114; and T=2.53, p=0.0152, respectively). The low-contrast VA and the retinal sensitivity within 0.5 degree and 6.0 degrees were correlated negatively with age (T=−4.07, p=0.0002; T=−2.37, p=0.0225; and T=−3.75, p=0.0006, respectively). The AULCSF showed no significant correlation with any covariates.

Time-dependent changes in MPOD

During follow-up, all subjects took daily supplementation containing 6 mg of lutein. No enrolled eyes developed any ocular disorders during the follow-up period.

The time-dependent changes in the MPOD level on 0.5 degree are shown in Fig. 1a. The MPOD levels were 0.480 DU (95% CI, 0.438, 0.521) at baseline, 0.480 DU (95% CI, 0.439, 0.521) at 3 months, 0.485 DU (95% CI, 0.443, 0.527) at 6 months, 0.484 DU (95% CI, 0.442, 0.527) at 9 months, and 0.488 DU (95% CI, 0.445, 0.532) at 12 months. The MPOD differences between the beginning of supplementation (baseline) and each follow-up time point (3, 6, 9, and 12 months) were calculated by paired t test; the respective p values were as p=0.9558, p=0.4386, p=0.5183, and p=0.2610. There were no significant changes in the MPOD level at any time point during the follow-up period when compared to a significance level of 0.0125 adjusted by Bonferroni correction. We also measured the mean MPOD level within 0.5 and 1.0 degree (Fig. 1b). There were also no significant time-dependent changes in the MPOD levels in those areas. Stepwise regression analysis showed that the 1-year increase in the MPOD levels on 0.5 degree and within 0.5 degree were correlated with subjects with no cardiovascular diseases (T=2.20, p=0.0338; and T=2.42, p=0.0201, respectively), and 1 year decrease in the MPOD level within 1.0 degree was correlated with phakic eye (T=−3.96, p=0.0003).

Time-dependent changes in visual function

The mean baseline logMAR was −0.078 (95% CI, -0.102, -0.055) (the Snellen equivalent; 24/20), which did not differ significantly from the mean logMAR at 12 months, -0.096 (95% CI, -0.122, -0.069) (the Snellen equivalent; 25/20) (p=0.1658, paired t-test).

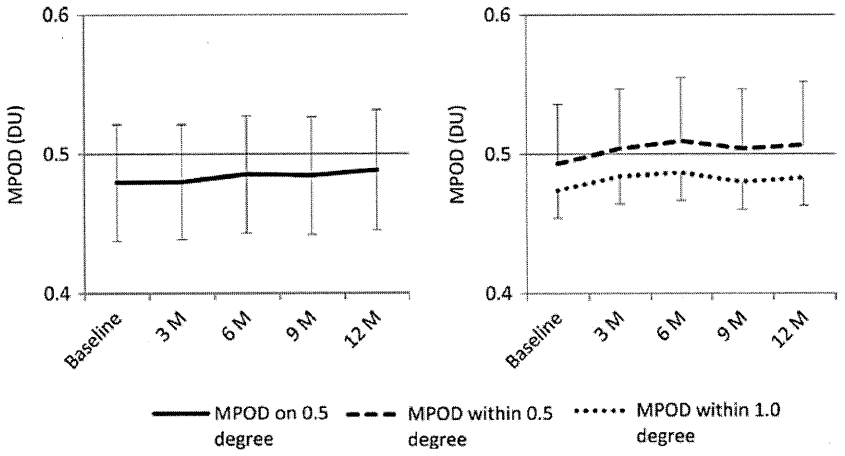

Fig. 1 Time-dependent changes in the mean MPOD levels on 0.5 degree (**a**) and within 0.5 and 1.0 degree (**b**). There were no significant differences between baseline and 3, 6, 9, and 12 months in those areas. *MPOD* macular pigment optical density; *DU* density unit; *M* months

The low-contrast VA and the AULCSF were measured every 3 months (Fig. 2). There were no significant differences between baseline and 3, 6, 9, and 12 months in the low-contrast VA (p=0.9051, p=0.6446, p=0.5598, and p=0.5556, respectively). Although there were also no significant differences between baseline and 3, 6, and 9 months in the AULCSF (p=0.3060, p=0.8850, and p=0.7151, respectively), the AULCSF was significantly (p=0.0124) higher at 12 months than at baseline (1.36, 95% CI, 1.32, 1.40 versus 1.41, 95% CI, 1.37, 1.45).

We also analyzed the differences between baseline and 6 and 12 months in the mean retinal sensitivity (Fig. 3). The retinal sensitivities within 0.5 degree were 16.2 decibels (dB) (95% CI, 15.3, 17.2) at 6 months and 17.0 dB at 12 months (95% CI, 16.0, 18.0), which were significantly higher than at baseline, 14.8 dB (95% CI, 13.9, 15.8) (p<0.0001, p<0.0001, respectively). Similarly, the retinal sensitivity within 6.0 degrees was 16.5 dB (95% CI, 15.8, 17.2) at 6 months and 17.2 dB (95% CI, 16.4, 18.0) at 12 months, and they were significantly higher than at baseline, 15.3 dB (95% CI, 14.6, 16.0) (p<0.0001, p<0.0001, respectively).

We performed stepwise regression analyses to determine the covariates that correlated with the 1-year changes in factors representative of visual function (Table 2). As a result, the increase in the low-contrast VA correlated with subjects with no cardiovascular diseases (T=2.14, p=0.0386) and the lower baseline low-contrast VA (T=−3.18, p=0.0029). The increase in the AULCSF correlated with the nonsmoking (T=2.49, p=0.0172), the phakic eye (T=2.16, p=0.0372) and the lower baseline AULCSF (T=−3.97, p=0.0003). The increase in the retinal sensitivity within 0.5 degree correlated with the phakic eye (T=2.42, p=0.0202) and the lower baseline retinal sensitivity within 0.5 degree (T=−2.92, p=0.0058), and the lower increase of the retinal sensitivity within 6.0 degrees correlated with the fellow eye of the eye with CSC (T=−2.03, p=0.0491)

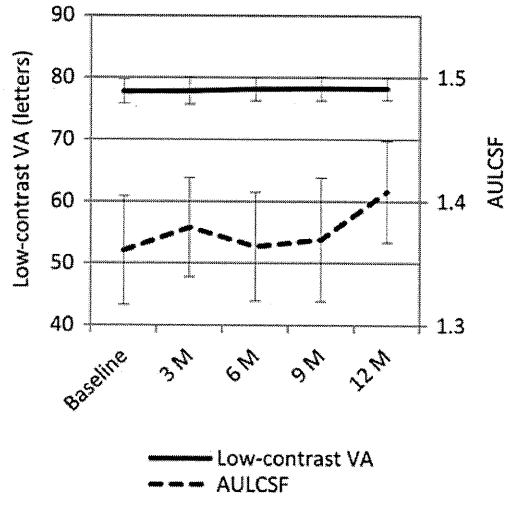

Fig. 2 Time-dependent changes in the low-contrast VA and the AULCSF. There were no significant differences between baseline and 3, 6, 9, and 12 months in the low-contrast VA. Although there were also no significant differences between baseline and 3, 6, and 9 months in the AULCSF, the AULCSF was significantly higher at 12 months than at baseline (p=0.0124). *VA* visual acuity; *AULCSF* area under the log contrast sensitivity function; *M* months

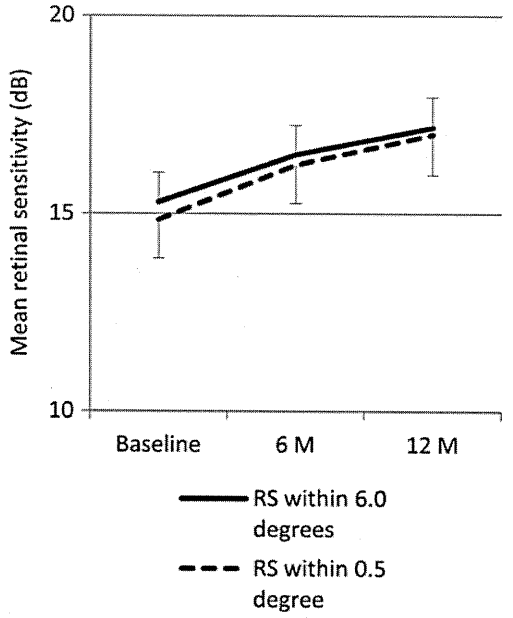

Fig. 3 Time-dependent changes in the retinal sensitivity. The retinal sensitivities within 0.5 degree at 6 months and 12 months were significantly higher than at baseline (p<0.0001, p<0.0001, respectively). Similarly, the retinal sensitivity within 6.0 degrees at 6 months and 12 months were significantly higher than at baseline (p<0.0001, p<0.0001, respectively). *RS* retinal sensitivity; *dB* decibels; *CI* confidence interval

Discussion

Supplementation with lutein may prevent development and/or progression of AMD because carotenoids help prevent antioxidative stress [3–9]. Whether lutein supplementation increases the MPOD level is now intensely discussed. Most studies have shown that lutein positively affects the MPOD level, but usually the increase in the MPOD level is not high [20–25]. However, a greater increase in the MPOD is likely to be correlated with higher doses of lutein [27, 28]. Previous studies in which a lutein dose under 10 mg was used reported no significant increase in the MPOD level, although the serum level of lutein increased [26].

In the current study, we evaluated the effect of supplementation with 6 mg of lutein, vitamins, and minerals on the MPOD level and the relationship with visual function in Japanese subjects. The 43 subjects who

Table 2 Selected covariates in the increased visual function

Visual function	Selected variable	T value	*p* value
Low-contrast VA	No cardiovascular disease	2.14	0.0386
	CSC in the fellow eye	−1.78	0.0822
	Baseline low-contrast VA	−3.18	0.0029
AULCSF	Non smoking	2.49	0.0172
	Phakic eye	2.16	0.0372
	Baseline AULCSF	−3.97	0.0003
Retinal sensitivity within 0.5 degrees	Phakic eye	2.42	0.0202
	Baseline retinal sensitivity within 0.5 degrees	−2.92	0.0058
Retinal sensitivity within 6.0 degrees	CSC in the fellow eye	−2.03	0.0491

VA visual acuity; *AULCSF* area under the log contrast sensitivity function; *CSC* central serous chorioretinopathy

took supplementation containing 6 mg of lutein were followed for 1 year and the MPOD level and visual function were measured every 3 or 6 months. We followed all subjects for 1 year, which satisfied the condition of the number needed for the primary outcome measure. As affected eyes with CSC and AMD had some foveal abnormalities when observed by fundus autofluorescence spectrometry and the measured MPOD levels were unstable, we did not include any affected eyes in the current study.

At baseline, we found that the eyes with clear IOL had higher MPOD levels. This agrees with our previous report that showed the MPOD level measured by autofluorescence spectrometry with two-wavelength autofluorescence method become higher after cataract surgery [45].

After 1 year of follow-up, the MPOD levels did not increase significantly, but it was stable throughout the study period and no covariates were significant for the changes in the MPOD levels. The LUtein Nutrition effects measured by Autofluorescence (LUNA) study in Germany, in which subjects with normal eyes or AMD took a supplement containing 12 mg of lutein, 1 mg of zeaxanthin, 120 mg of vitamin C, 17.6 mg of vitamin E, 10 mg of zinc, and 40 μg of selenium for 6 months, reported a significant increase in the MPOD level in the intervention group [24, 25]. Because the LUNA study used the same autofluorescence methods to measure the MPOD as we used in the current study, the different responses in MPOD seemed to be due to the different amounts of supplemental lutein. Although this difference may also be influenced by the racial difference, number of tested subjects and the amount of other antioxidants, 6 mg of lutein supplementation may be too low to increase the MPOD level. On the other hand, it is possible that the development of cataract might affect the measurement of MPOD since the decrease of the MPOD level within 1.0 degree correlated with the phakic eye. This theory is also supported by our previous report that showed a higher nuclear color grading score was correlated with a lower MPOD level measured by autofluorescence spectrometry with two-wavelength autofluorescence method [45]. Although we did not observe the apparent decrease of visual acuity during follow-up period, cataract might develop and mask the increase of MPOD induced by lutein supplementation. In addition, the 1-year increase in the MPOD level was correlated with subjects with no cardiovascular diseases. As previous reports showed that the cardiovascular risk factors are associated with AMD, subjects with cardiovascular diseases may have less response to lutein supplementation [46, 47].

The contribution of macular pigments to visual performance has been reported. Macular pigments can improve visual performance including contrast sensitivity by reducing chromatic aberration, blue haze, and the intensity of the rod signal, for example [28–36]. To identify the minute changes in visual contrast, we measured the low-contrast VA and contrast sensitivity [40]. The low-contrast VA was correlated with aging at baseline and did not change during the follow-up period; therefore, antioxidants may not affect the low-contrast VA. However, the AULCSF, which is a representative index for evaluating the contrast sensitivity, significantly increased at 12 months (p=0.0124). Supplementation containing lutein may have maintained the MPOD level and improved the contrast sensitivity. Interestingly, the increase in AULCSF was correlated with nonsmoking status, although the AULCSF was not correlated with smoking at baseline. Uz et al. reported that smoking reduced contrast sensitivity possibly because of the decreased serum level of the trace elements manganese and zinc [35]. Because the supplement we used in the current study contained manganese and zinc, they may have caused the contrast sensitivity to improve especially in nonsmokers. Contrary to our results, Bartlett and Eperjesi reported no correlation between contrast sensitivity and supplementation with 6 mg of lutein, vitamins, and minerals [29]. The relationship between antioxidant supplement and contrast sensitivity should be investigated further.

Retinal sensitivity was measured by microperimetry within 0.5 and 6.0 degrees. The baseline retinal sensitivity within 0.5 and 6.0 degrees was correlated with aging as reported previously [48, 49]. The retinal sensitivity significantly increased during the follow-up period. To the best of our knowledge, this is the first report to show a correlation between supplementation with antioxidants containing lutein and the retinal sensitivity. Because retinal sensitivity is measured by a white target on a white background by changing the light intensity of the target, there may be some mechanisms other than macular pigment playing roles in contrast sensitivity; one hypothesis is that antioxidants may improve the light threshold of the photoreceptors. Stepwise regression analysis showed that the fellow eyes with CSC had a lower increase of retinal sensitivity within 6.0 degrees. These results might be associated with lower MPOD in the fellow eyes of those with CSC, which have a high risk of developing CSC [15]. On the other hand, stepwise regression analysis revealed that the subjects with cardiovascular diseases showed lower increase in the low-contrast VA, and the subjects with clear IOL showed lower change of AULCSF and retinal sensitivity within 0.5 degree. The reasons for these results are hard to explain at the moment, possibly because the number of the subgroup is too small. Accordingly, further studies are needed on those points.

In conclusion, although there is a fear that the autofluorescence spectrometry with two-wavelength method may not be appropriate to detect MPOD augmentation in elderly eyes, daily supplementation with 6 mg of lutein, vitamins, and minerals did not affect the MPOD level measured by this method for 1 year. Supplementation of antioxidants containing 6 mg of lutein may be insufficient to increase the MPOD level, however, it may improve visual function such as contrast sensitivity and retinal sensitivity. So far, we cannot deny the possibility that the improved visual function was due to a learning effect, because our study had no placebo control group. Further studies may provide deeper insights into the role of antioxidant supplementation in maintaining the function of macula.

References

1. Handelman GJ, Dratz EA, Reay CC, van Kuijk JG (1988) Carotenoids in the human macula and whole retina. Invest Ophthalmol Vis Sci 29:850–855
2. Bone RA, Landrum JT, Tarsis SL (1985) Preliminary identification of the human macular pigment. Vision Res 25:1531–1535
3. Snodderly DM, Auran JD, Delori FC (1984) The macular pigment. II. Spatial distribution in primate retinas. Invest Ophthalmol Vis Sci 25:674–685
4. Snodderly DM, Brown PK, Delori FC, Auran JD (1984) The macular pigment. I. Absorbance spectra, localization, and discrimination from other yellow pigments in primate retinas. Invest Ophthalmol Vis Sci 25:660–673
5. Bone RA, Landrum JT, Cains A (1992) Optical density spectra of the macular pigment in vivo and in vitro. Vision Res 32:105–110
6. Beatty S, Koh H, Phil M, Henson D, Boulton M (2000) The role of oxidative stress in the pathogenesis of age-related macular degeneration. Surv Ophthalmol 45:115–134
7. Beatty S, Boulton M, Henson D, Koh HH, Murray IJ (1999) Macular pigment and age-related macular degeneration. Br J Ophthalmol 83:867–877
8. Landrum JT, Bone RA, Kilburn MD (1997) The macular pigment: a possible role in protection from age-related macular degeneration. Adv Pharmacol 38:537–556
9. Khachik F, Bernstein PS, Garland DL (1997) Identification of lutein and zeaxanthin oxidation products in human and monkey retinas. Invest Ophthalmol Vis Sci 38:1802–1811
10. LaRowe TL, Mares JA, Snodderly DM, Klein ML, Wooten BR, Chappell R (2008) Macular pigment density and age-related maculopathy in the carotenoids in Age-Related Eye Disease Study. An ancillary study of the women's health initiative. Ophthalmology 115(876–883):e1
11. Nolan JM, Stack J, O'Donovan O, Loane E, Beatty S (2007) Risk factors for age-related maculopathy are associated with a relative lack of macular pigment. Exp Eye Res 84:61–74
12. Obana A, Hiramitsu T, Gohto Y, Ohira A, Mizuno S, Hirano T, Bernstein PS, Fujii H, Iseki K, Tanito M, Hotta Y (2008) Macular carotenoid levels of normal subjects and age-related maculopathy patients in a Japanese population. Ophthalmology 115:147–157
13. Coleman H, Chew E (2007) Nutritional supplementation in age-related macular degeneration. Curr Opin Ophthalmol 18:220–223
14. Mares-Perlman JA, Fisher AI, Klein R, Palta M, Block G, Millen AE, Wright JD (2001) Lutein and zeaxanthin in the diet and serum and their relation to age-related maculopathy in the Third National Health and Nutrition Examination Survey. Am J Epidemiol 153:424–432
15. Sasamoto Y, Gomi F, Sawa M, Tsujikawa M, Hamasaki T (2010) Macular pigment optical density in central serous chorioretinopathy. Invest Ophthalmol Vis Sci 51:5219–5225
16. Christen WG, Ajani UA, Glynn RJ, Manson JE, Schaumberg DA, Chew EC, Buring JE, Hennekens CH (1999) Prospective cohort study of antioxidant vitamin supplement use and the risk of age-related maculopathy. Am J Epidemiol 149:476–484
17. Group A-REDSR (2001) A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. Arch Ophthalmol 119:1439–1452
18. Mares-Perlman JA, Klein R, Klein BE, Greger JL, Brady WE, Palta M, Ritter LL (1996) Association of zinc and antioxidant nutrients with age-related maculopathy. Arch Ophthalmol 114:991–997
19. Seddon JM, Ajani UA, Sperduto RD, Hiller R, Blair N, Burton TC, Farber MD, Gragoudas ES, Haller J, Miller DT et al (1994) Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. Eye Disease Case-Control Study Group. JAMA 272:1413–1420
20. Hammond BR Jr, Johnson EJ, Russell RM, Krinsky NI, Yeum KJ, Edwards RB, Snodderly DM (1997) Dietary modification of human macular pigment density. Invest Ophthalmol Vis Sci 38:1795–1801
21. Berendschot TT, Goldbohm RA, Klopping WA, van de Kraats J, van Norel J, van Norren D (2000) Influence of lutein supplementation on macular pigment, assessed with two objective techniques. Invest Ophthalmol Vis Sci 41:3322–3326
22. Bone RA, Landrum JT (2010) Dose-dependent response of serum lutein and macular pigment optical density to supplementation with lutein esters. Arch Biochem Biophys 504:50–55

23. Schalch W, Cohn W, Barker FM, Kopcke W, Mellerio J, Bird AC, Robson AG, Fitzke FF, van Kuijk FJ (2007) Xanthophyll accumulation in the human retina during supplementation with lutein or zeaxanthin - the LUXEA (LUtein Xanthophyll Eye Accumulation) study. Arch Biochem Biophys 458:128–135
24. Trieschmann M, Beatty S, Nolan JM, Hense HW, Heimes B, Austermann U, Fobker M, Pauleikhoff D (2007) Changes in macular pigment optical density and serum concentrations of its constituent carotenoids following supplemental lutein and zeaxanthin: the LUNA study. Exp Eye Res 84:718–728
25. Zeimer M, Hense HW, Heimes B, Austermann U, Fobker M, Pauleikhoff D (2009) The macular pigment: short- and intermediate-term changes of macular pigment optical density following supplementation with lutein and zeaxanthin and co-antioxidants: The LUNA Study. Ophthalmologe 106:29–36
26. Bone RA, Landrum JT, Guerra LH, Ruiz CA (2003) Lutein and zeaxanthin dietary supplements raise macular pigment density and serum concentrations of these carotenoids in humans. J Nutr 133:992–998
27. Landrum JT, Bone RA, Joa H, Kilburn MD, Moore LL, Sprague KE (1997) A one year study of the macular pigment: the effect of 140 days of a lutein supplement. Exp Eye Res 65:57–62
28. Richer S, Stiles W, Statkute L, Pulido J, Frankowski J, Rudy D, Pei K, Tsipursky M, Nyland J (2004) Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial). Optometry 75:216–230
29. Bartlett HE, Eperjesi F (2008) A randomised controlled trial investigating the effect of lutein and antioxidant dietary supplementation on visual function in healthy eyes. Clin Nutr 27:218–227
30. Hammond BR Jr, Wooten BR, Curran-Celentano J (2001) Carotenoids in the retina and lens: possible acute and chronic effects on human visual performance. Arch Biochem Biophys 385:41–46
31. Hammond BR Jr, Wooten BR, Snodderly DM (1998) Preservation of visual sensitivity of older subjects: association with macular pigment density. Invest Ophthalmol Vis Sci 39:397–406
32. Kvansakul J, Rodriguez-Carmona M, Edgar DF, Barker FM, Kopcke W, Schalch W, Barbur JL (2006) Supplementation with the carotenoids lutein or zeaxanthin improves human visual performance. Ophthalmic Physiol Opt 26:362–371
33. Rodriguez-Carmona M, Kvansakul J, Harlow JA, Kopcke W, Schalch W, Barbur JL (2006) The effects of supplementation with lutein and/or zeaxanthin on human macular pigment density and colour vision. Ophthalmic Physiol Opt 26:137–147
34. Stringham JM, Hammond BR (2008) Macular pigment and visual performance under glare conditions. Optom Vis Sci 85:82–88
35. Uz E, Sahin S, Hepsen IF, Var A, Sogut S, Akyol O (2003) The relationship between serum trace element changes and visual function in heavy smokers. Acta Ophthalmol Scand 81:161–164
36. Wooten BR, Hammond BR (2002) Macular pigment: influences on visual acuity and visibility. Prog Retin Eye Res 21:225–240
37. Delori FC (2004) Autofluorescence method to measure macular pigment optical densities fluorometry and autofluorescence imaging. Arch Biochem Biophys 430:156–162
38. Delori FC, Goger DG, Hammond BR, Snodderly DM, Burns SA (2001) Macular pigment density measured by autofluorescence spectrometry: comparison with reflectometry and heterochromatic flicker photometry. J Opt Soc Am A Opt Image Sci Vis 18:1212–1230
39. Trieschmann M, Heimes B, Hense HW, Pauleikhoff D (2006) Macular pigment optical density measurement in autofluorescence imaging: comparison of one- and two-wavelength methods. Graefes Arch Clin Exp Ophthalmol 244:1565–1574
40. Verdon W, Bullimore M, Maloney RK (1996) Visual performance after photorefractive keratectomy. A prospective study. Arch Ophthalmol 114:1465–1472
41. Applegate RA, Howland HC, Sharp RP, Cottingham AJ, Yee RW (1998) Corneal aberrations and visual performance after radial keratotomy. J Refract Surg 14:397–407
42. Midena E, Radin PP, Pilotto E, Ghirlando A, Convento E, Varano M (2004) Fixation pattern and macular sensitivity in eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration. A microperimetry study. Semin Ophthalmol 19:55–61
43. Sawa M, Gomi F, Toyoda A, Ikuno Y, Fujikado T, Tano Y (2006) A microperimeter that provides fixation pattern and retinal sensitivity measurement. Jpn J Ophthalmol 50:111–115
44. Akaike H (1974) A new look at the statistical model identification. IEEE Trans Autom Control 19:716–723
45. Sasamoto Y, Gomi F, Sawa M, Sakaguchi H, Tsujikawa M, Nishida K (2010) Effect of cataract in evaluation of macular pigment optical density using autofluorescence spectrometry. Invest Ophthalmol Vis Sci 52:927–932
46. Chakravarthy U, Wong TY, Fletcher A, Piault E, Evans C, Zlateva G, Buggage R, Pleil A, Mitchell P Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. BMC Ophthalmol 10:31
47. Tan JS, Mitchell P, Smith W, Wang JJ (2007) Cardiovascular risk factors and the long-term incidence of age-related macular degeneration: the Blue Mountains Eye Study. Ophthalmology 114:1143–1150
48. Lachenmayr BJ, Kojetinsky S, Ostermaier N, Angstwurm K, Vivell PM, Schaumberger M (1994) The different effects of aging on normal sensitivity in flicker and light-sense perimetry. Invest Ophthalmol Vis Sci 35:2741–2748
49. Midena E, Vujosevic S, Cavarzeran F (2010) Normal values for fundus perimetry with the microperimeter MP1. Ophthalmology 117:1571–1576, 1576 e

Intravitreal bevacizumab for exudative branching vascular networks in polypoidal choroidal vasculopathy

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ABSTRACT

Aims To assess the long-term efficacy of intravitreal bevacizumab for recurrent leakage owing to the residual branching vascular networks in polypoidal choroidal vasculopathy after photodynamic therapy.

Methods Forty-five eyes with exudative branching vascular networks were treated with intravitreal bevacizumab and followed for at least 24 months. Original polypoidal lesions had been treated successfully with previous photodynamic therapy in all eyes. The best-corrected visual acuity and retinal morphological changes were assessed retrospectively.

Results Exudative branching vascular networks were characterised as occult choroidal neovascularisation (38 eyes) or classic choroidal neovascularisation (7 eyes) on fluorescein angiography. Intravitreal bevacizumab maintained or improved vision in 38 eyes (84%) over 12 months and in 36 eyes (80%) over 24 months, although the mean visual acuity at 12 and 24 months did not differ significantly compared with baseline. Complete resolution of macular fluid was achieved continuously in 26 eyes (58%) during 24 months. Sixteen eyes (36%) responded once to treatment but became unresponsive to additional injections for recurrent exudation. Three eyes (7%) were refractory to treatment throughout follow-up. Cystoid macular oedema eventually developed in 10 eyes and was a poor prognostic sign for visual outcome.

Conclusion Intravitreal bevacizumab improved the retinal morphology and maintained vision over 1 year in most eyes with recurrent fluid owing to persistent abnormal vascular networks in polypoidal choroidal vasculopathy. The therapeutic response, however, may decrease during the second year.

Polypoidal choroidal vasculopathy (PCV), characterised by a complex of branching vascular networks terminating in polypoidal lesions,[1–5] accounts for 23–54% of neovascular age-related macular degeneration (AMD) in Asian populations.[6 7] Photodynamic therapy (PDT) maintains or improves vision by resolving the polypoidal lesions and accompanying fluid beneath the neurosensory retina.[8–10] However, the branching vascular networks usually remain even after PDT,[11–13] and may enlarge further over time, resulting in persistent exudation appearing as choroidal neovascularisation (CNV) secondary to AMD in some cases.[14] Therefore, stabilisation of the branching vascular networks may be crucial for long-term management of PCV.

Recent studies have reported the efficacy and safety of bevacizumab (Avastin, Genentech, South San Francisco, California) for stabilising neovascular activity and maintaining vision in patients with neovascular AMD.[15] Those results promoted us to consider the drug as the treatment of choice for CNV-like branching vascular networks of PCV after PDT.

The purpose of this retrospective study is to assess the long-term efficacy of intravitreal bevacizumab in the management of exudative branching vascular networks in eyes with PCV.

METHODS

This study was a retrospective, consecutive, interventional case series conducted at Osaka University Hospital. Patients who received intravitreal bevacizumab for the treatment of recurrent exudation associated with branching vascular networks between December 2006 and April 2008 and followed for at least 24 months were initially enrolled. All eyes had a previous history of successful PDT for PCV with resolution of polypoidal lesions. Recurrent exudation was determined by the presence of subretinal fluid (SRF) or macular oedema on optical coherence tomography (OCT) with CNV-like fluorescein leakage caused by branching vascular networks. Patients were excluded if they had SRF or macular oedema caused by recurrent polypoidal lesions, follow-up <24 months after intravitreal bevacizumab or clinically relevant media opacity.

All patients underwent a comprehensive ocular examination, including measurement of the best-corrected visual acuity (BCVA), intraocular pressure, binocular indirect ophthalmoscopy and contact lens slit-lamp biomicroscopy, colour fundus photography, OCT, fluorescein angiography (FA) and indocyanine green angiography (ICGA). The patients were examined after a detailed explanation of the study was provided, and they provided informed consent. This study was approved by the institutional review board committee of Osaka University Hospital.

ICGA analysis

ICGA was performed at baseline before intravitreal bevacizumab and 3–6 months and 12–24 months after intravitreal bevacizumab. A confocal scanning laser ophthalmoscope (Heidelberg Retina Angiograph 2 (HRA2), Heidelberg Engineering GmbH, Dossenheim, Germany) was used as previously described.[14] The planimetric size of the branching vascular networks was measured from the early-phase ICGA at baseline to the final visits using software included in the HRA2.[14] The individual readings of two investigators were averaged.

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A change in lesion size was recorded when the lesion increased or decreased more than 50% in the corresponding area.

OCT analysis

OCT images were obtained by Stratus OCT (Carl Zeiss Meditec, Dublin, California) or the Cirrus HD-OCT (Carl Zeiss Meditec). The central retinal thickness (CRT), defined as the distance between the internal limiting membrane and the inner surface of the retinal pigment epithelium (RPE), was measured manually at the fovea.[16] The SRF and intraretinal fluid were included in the CRT measurements, whereas sub-RPE fluid was not included. The fluid in the macula was identified as intraretinal fluid (macular oedema) and SRF, and a fluid-free macula was defined by the absence of macular oedema and SRF as determined by OCT.

Follow-up and reinjection protocols

Intravitreal bevacizumab (1.25 mg) was injected during an outpatient procedure under strict aseptic conditions. All patients were followed monthly for more than 24 months. The VA and OCT were examined at every visit. Re-treatment with intravitreal bevacizumab was considered if there was OCT evidence of macular fluid with at least one-line loss of VA, new macular haemorrhage or newly developed fibrinous changes. A treatment response on OCT was defined as complete if there was no macular fluid, partial if there was no macular fluid initially but the lesions become refractory to treatment after recurrence of exudation, or no response if there was not an absence of macular fluid. When recurrence was suspected, FA and ICGA were performed at the discretion of the physician.

Data collection and statistical analysis

The main outcome measures were the changes in exudative fluid and the BCVA during 24 months after the initial injection. The changes in the CRT and the size of the branching vascular networks before and after injection were also evaluated. Statistical analyses were performed with SAS software, version 9.1 (SAS Institute). P-values <0.05 were considered significant.

RESULTS

Forty-five eyes of 45 patients met the criteria for data analysis. The patient demographics are shown in table 1. Original polypoidal lesions had resolved in all eyes on ICGA with complete absence of fluid after previous PDT, but the branching vascular network remained in all eyes. The development of subsequent exudative changes associated with residual branching vascular networks without recurrent polypoidal lesions was seen 9.3±8.4 months (range 1–36) after the previous PDT (figure 1).

Table 1 Patient baseline characteristics

No eyes	45
No patients	45
Age (years) (mean±SD; range)	70.4±6.9 (53–83)
Gender (no/%)	
Men	35 (78)
Women	10 (22)
Eye (no/%)	
Right	20 (44)
Left	25 (56)
Interval between intravitreal bevacizumab and previous photodynamic therapy (mean±SD; range)	9.3±8.4 (1–36)
Optical coherence tomography characteristics	
Subretinal fluid (no/%)	43 (96)
Pigment epithelial detachment (no/%)	26 (58)
Macular oedema (no/%)	10 (22)
Leakage pattern on fluorescein angiography	
Classic choroidal neovascularisation	7 (16)
Occult choroidal neovascularisation	38 (84)
Baseline best-corrected visual acuity	
Landolt C acuity chart (mean; range)	0.35 (0.09–1.2)
Logarithm of the minimum angle of resolution (mean±SD)	0.45±0.30

Angiographic and OCT characteristics of exudative branching vascular networks

FA showed leakage mimicking occult CNV in 38 eyes (84%) (figure 1C,G) and classic CNV in seven eyes (16%) (figure 1K). Of the 38 eyes with occult CNV-like lesions, ICGA showed thin branching choroidal vessels that depicted relatively well-delineated plaque in the late phase. Of the seven eyes with classic CNV-like lesions, subretinal fibrinous exudation was seen in all eyes. The exudation associated with the branching vascular networks was characterised by OCT as SRF in 43 eyes (96%) and macular oedema in 10 eyes (22%). Apparent PED was seen in 24 eyes (53%), and the limited RPE elevation was detected in 14 eyes (31%).

Visual acuity, ICG angiography and OCT outcomes

The mean number of injections in the 45 eyes during the first 12 months was 2.9±1.8 (range 1–8) and 1.9±1.8 (range 0–6) during the second year.

The mean baseline BCVA was 0.45±0.30 (table 1). The mean BCVA values were 0.43±0.33, 0.43±0.30, 0.48±0.32 and 0.51±0.38 at 3, 6, 12 and 24 months, respectively (p=0.118, p=0.428, p=0.523 and p=0.206, respectively) (figure 2A). The BCVA at the 12-month follow-up visit improved by three or more lines in four eyes (9%), was unchanged within three lines in 34 eyes (76%) and worsened in seven eyes (16%). At 24 months, BCVA improved by three or more lines in six eyes (13%), was unchanged in 30 eyes (67%) and worsened in nine eyes (20%).

ICGA images showed persistent branching vascular networks in all 45 eyes during follow-up. The size of the branching vascular network increased in 20 eyes (44%), remained unchanged in 21 eyes (47%) and decreased in four eyes (9%) at the final ICGA examination compared with baseline. In six eyes, polypoidal lesions reappeared at the site connected to the branching vascular networks. The period between the initial intravitreal bevacizumab and detection of newly developed polypoidal lesions was 3 months in one eye, 6 months in one eye and 24 months in four eyes.

The mean baseline CRT measured on OCT was 222±71 μm (range 87–434). The CRT decreased an average of 31.0 μm from baseline by 3 months (p<0.001) and an average of 40.0 μm by 6 months (p<0.001) (figure 2B). Those initial decreases lessened over time after initial intravitreal bevacizumab, with an average reduction of 25.8 μm by 12 months (p=0.050) and 1.8 μm by 24 months (p=0.296). There tended to be a correlation between the CRT at 24 months and the BCVA at 24 months (r=0.292, p=0.051).

A fluid-free macula was achieved during the first 12 months in 42 eyes (93%). The mean number of injections required to achieve a fluid-free macula was 1.9±1.6 (range 1–9). Subsequently, 36 eyes developed recurrent macular fluid and received additional injections. Overall, 26 eyes (58%) were regarded on OCT as complete responders because intravitreal bevacizumab was effective throughout the 24 months of follow-up in completely resolving the exudation. One initial injection was effective to keep the macula dry for 24 months in two eyes.

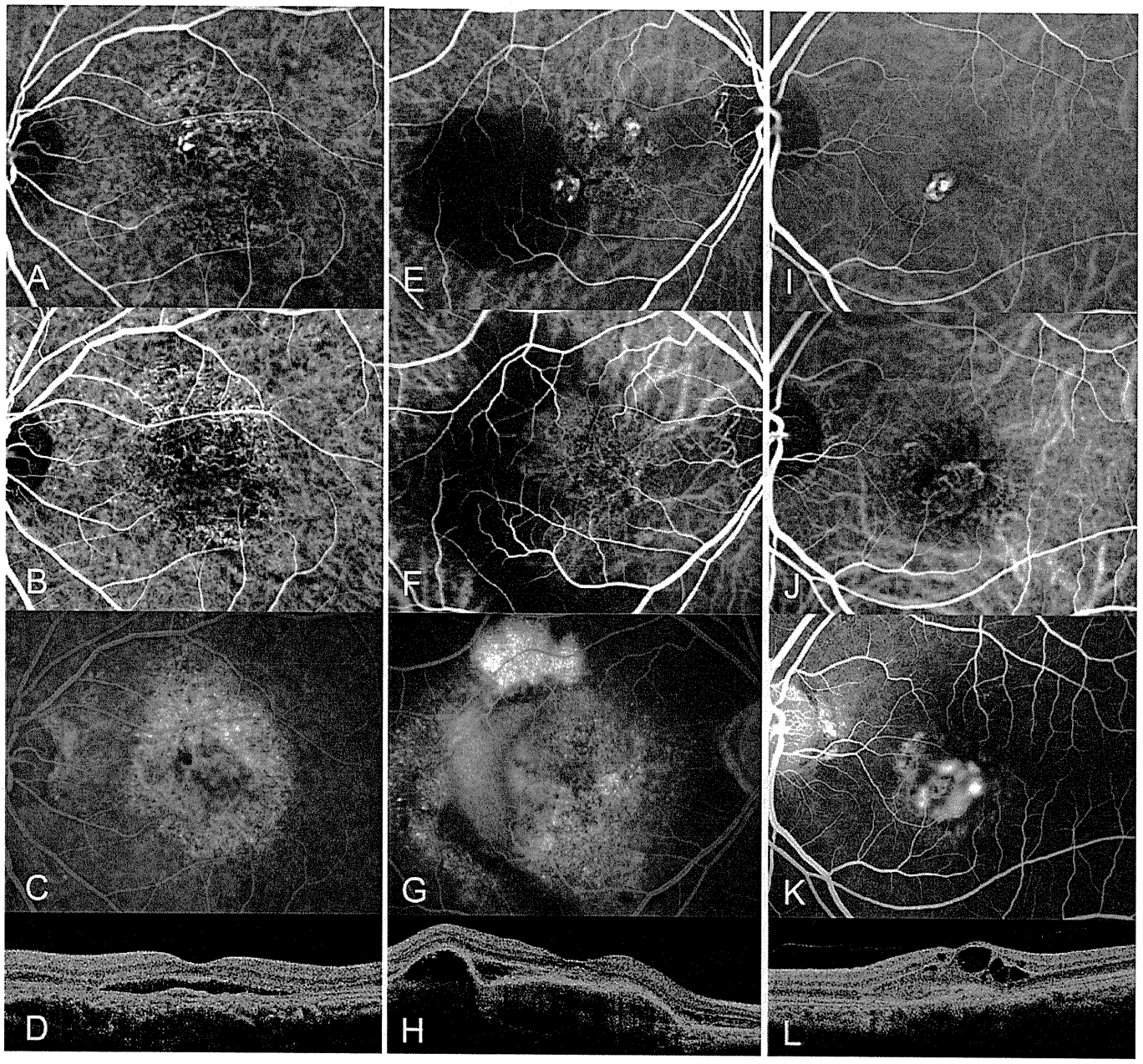

Figure 1 Exudation associated with branching vascular networks in eyes with polypoidal choroidal vasculopathy. The exudation patterns are characterised as occult choroidal neovascularisation (CNV) without apparent pigment epithelial detachment (PED) (A—D), occult CNV with fibrovascular PED (E—H) or classic CNV (I—L). (A) Indocyanine green angiography (ICGA) before previous photodynamic therapy (PDT) showing branching vascular networks terminating in small polypoidal lesions in a 64-year-old man. The polypoidal lesions resolved completely after PDT. However, the branching vascular networks remained (B) and subsequently developed exudative changes resembling occult CNV on fluorescein angiography (FA) 6 months after the previous PDT (C). (D) Optical coherence tomography (OCT) showing subretinal fluid (SRF) with limited retinal pigment epithelium elevation. (E) ICGA before previous PDT showing branching vascular networks terminating in polypoidal lesions with a serous PED in a 77-year-old man. The polypoidal lesions have resolved completely after PDT. However, the branching vascular networks have enlarged (F) and subsequently developed exudative changes resembling occult CNV with a fibrovascular PED on FA 3 months after previous PDT (G). (H) OCT showing a large PED with SRF. (I) ICGA before previous PDT showing small branching vascular networks terminating in polypoidal lesions in a 57-year-old woman. The polypoidal lesions have resolved completely after PDT. Without recurrence of the polypoidal lesion, the branching vascular networks show exudative changes at the macula (J) resembling classic CNV on FA 6 months after previous PDT (K). (L) The OCT shows fibrin accumulation and macular oedema.

Sixteen eyes (36%) were considered to be partial responders. Those eyes once had no macular fluid after injection during the first 12 months; however, they became unresponsive to treatment despite repeated injections for recurrent exudation (figure 3). Three eyes (7%) were considered non-responders because the macular fluid persisted during 24 months despite repeated injections. Eight of 16 eyes with partial responses and two of three eyes with no response eventually developed cystoid macular oedema (CMO), and six of these lost three lines or more at 24 months compared with baseline.

The differences between complete responders and partial or non-responders with respect to BCVA and OCT findings are shown in table 2. Although the baseline BCVA, the leakage pattern on FA, CRT and the lesion size did not differ significantly

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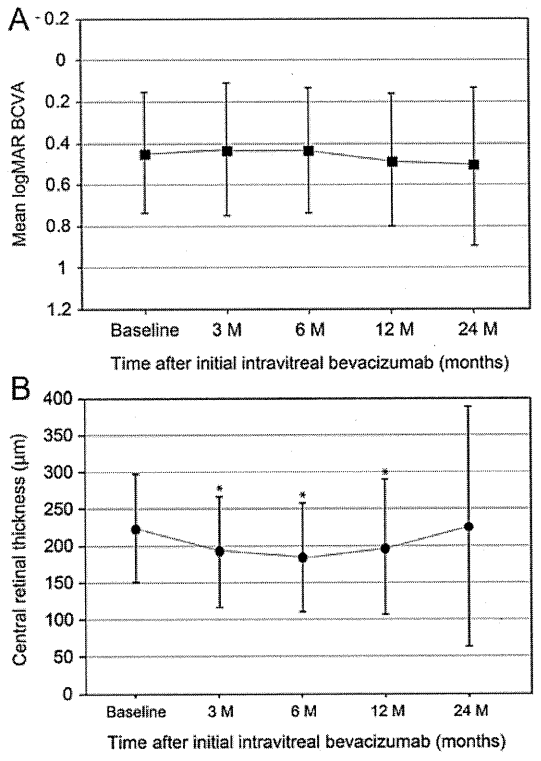

Figure 2 (A) Mean change in the best-corrected visual acuity (BCVA) (mean±SD) after intravitreal bevacizumab for exudative branching vascular networks through 24 months. The visual acuity is expressed as the logarithm of the minimum angle of resolution (logMAR). There are no statistical differences between the baseline and post-treatment BCVA values at any time point. (B) Mean change in the central retinal thickness (CRT) (mean±SD) after intravitreal bevacizumab for exudative branching vascular networks through 24 months. The mean CRT has decreased significantly at 3, 6 and 12 months after initial intravitreal bevacizumab (*$p<0.05$ compared with baseline). However, there are no statistical differences in CRT between baseline and 24 months. M, months.

between the groups, the mean BCVA in eyes with a complete response was significantly better than in eyes with a partial or no response at 24 months ($p=0.041$). However, there was no significant difference in the BCVA between eyes with a complete response and those with partial responses or no response at 24 months when the 10 eyes with CMO were excluded from the analysis (0.41±0.34 vs 0.34±0.30, $p=0.675$). The CRT also differed significantly between the groups at 24 months ($p=0.001$). The branching vascular networks were significantly larger in eyes with a partial response or no response compared with those who were complete responders at 24 months ($p=0.049$).

No adverse systemic and local complications related to intravitreal bevacizumab were observed during the study period. One eye developed an RPE tear.

DISCUSSION

In the current study, we focused on identifying the characteristics of the exudative features associated with branching vascular networks and assessed the potential efficacy of bevacizumab to treat those lesions. We found two angiographic patterns of exudative branching vascular networks at an average of 9.3±8.4 months (range 1–20) after previous PDT, that is, occult CNV-like lesions with or without fibrovascular PED (84%) and classic CNV-like leaky vascular lesions (16%).

In eyes with occult CNV-like leakage, the complex of abnormal vessels was clearly seen on early-phase ICGA, with hyperfluorescent plaques on late-stage ICGA. On OCT, the lesion was also identifiable as elevated RPE, indicating invasion of the networks beneath the RPE. Thus, PCV in this stage was clinically and angiographically indistinguishable from type 1 neovascularisation. Imamura and associates also indicated that it would be difficult to differenciate between PCV and CNV unless typical polypoidal lesion exists in the network vessels.[17] Serous and haemorrhagic PEDs associated with PCV before PDT seemed to be potentially predictive of the development and progression of occult CNV-like exudative vessels, because in those eyes, the rate of PED at the time of PDT was 63% and was higher than that reported previously in PCV (19–44%).[7 8 18] In eyes with classic CNV-like lesions, OCT showed subretinal fibrin formation, indicating extensive exudation. Both the occult and classic CNV-like lesions in our study did not seem to have the same characteristics as the original branching vascular networks of PCV, which had previously been considered as long-term stable abnormal choroidal vessels.[18 19] We speculate that pre-existing branching vascular networks acquired hyperpermeable properties mimicking CNV or the CNV newly emerged from residual branching vascular networks over time after PDT.

Intravitreal bevacizumab for exudative branching vascular networks maintained or improved vision in 38 eyes (84%) over 12 months, although the mean VA at 12 months did not differ significantly compared with baseline. The significant decrease in retinal thickness was achieved during the first year due to complete resolution of macular fluid in 42 (93%) eyes, indicating the potent effect of bevacizumab on antipermeability in most eyes over 12 months.

Improved or stabilised VA was continuously achieved in 36 eyes (80%) over 24 months. According to a previous study of patients with PCV treated only by PDT for 3 years, VA deteriorated three lines or more in 37%, owing to the enlargement of abnormal networks with neovascular changes and recurrent polyps.[20] In contrast to these reports, the current results using bevacizumab are encouraging because VA deterioration was seen in 20%, despite a mean follow-up period of 33 months after initial PDT.

Complete resolution of macular fluid was maintained throughout the study in 58% of eyes (complete responders). However, 36% of eyes that responded to treatment during the first 12 months showed less treatment effect, despite repeated injections for recurrent exudation (partial responders). Three eyes were considered non-responders on OCT, and the macular fluid increased further. As a result, the decrease in the mean retinal thickness during the first year lessened during the second year and became non-significant ($p=0.296$) at 24 months compared with baseline.

The loss of the therapeutic response to bevacizumab during 2 years may be explained by a potential change in the sensitivity to bevacizumab. In the current study, the vascular networks persisted on ICGA in all eyes after intravitreal bevacizumab and even enlarged in 20 eyes (44%) despite repeated injections. Continuous growth of the CNV despite repeated anti-vascular endothelial growth factor therapy also had been reported in eyes with AMD.[21] The persistence and expansion of the networks may lead to more mature and less vascular-endothelial-growth-factor-dependent vessels with increased treatment resistance. In addition, a tachyphylactic response, that is, a progressive decrease in the bioefficacy of bevacizumab, after repeated injections has been reported in AMD.[22] Those responses also

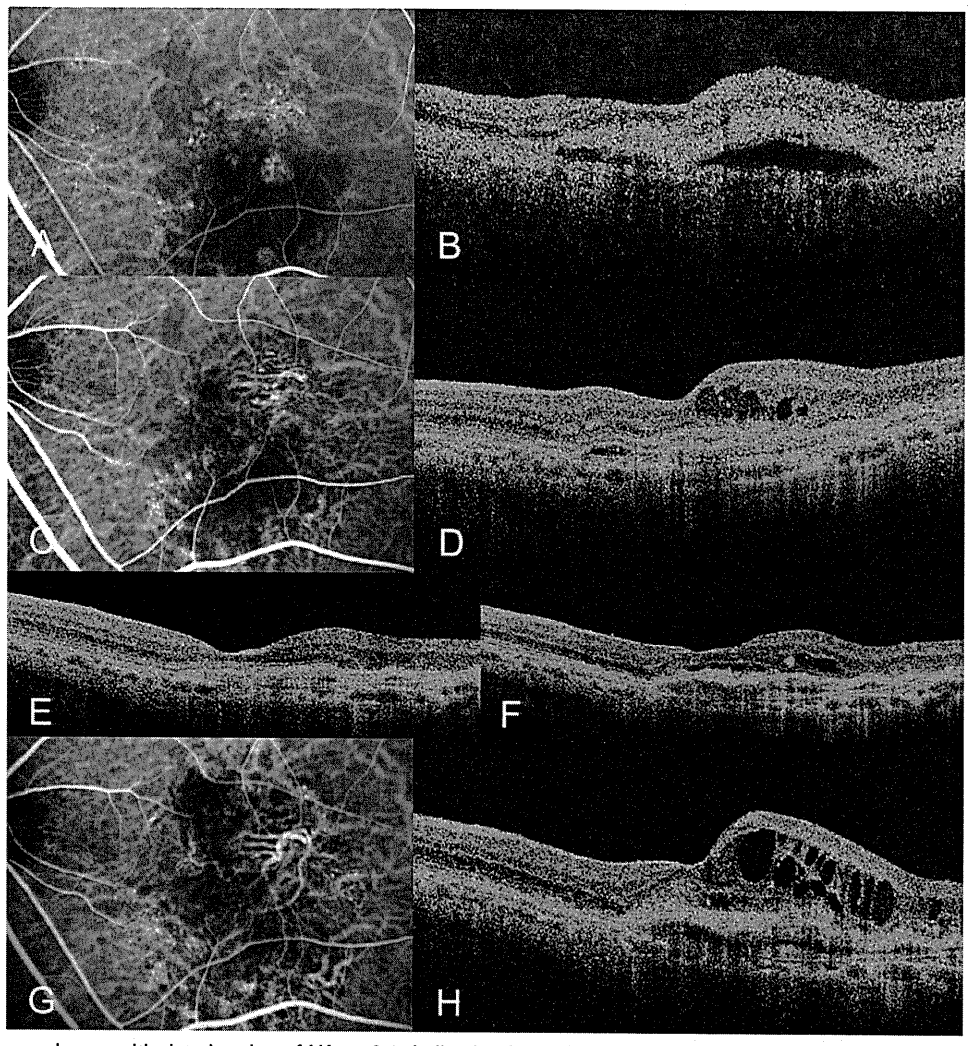

Figure 3 Indocyanine green angiography (ICGA) and optical coherence tomography (OCT) images before and after intravitreal bevacizumab in an 83-year-old man. (A) ICGA showing branching vascular networks terminating in polypoidal lesions with a serous pigment epithelial detachment (PED) before previous photodynamic therapy (PDT). (B) OCT image confirming the PED. The polypoidal lesions have resolved completely after PDT. However, the branching vascular networks remain with subsequently developing exudation 6 months after previous PDT (C). (D) OCT showing slight subretinal fluid (SRF), macular oedema and a fibrovascular PED. The visual acuity (VA) is 0.2. Intravitreal bevacizumab was administered. After intravitreal bevacizumab, the SRF and macular oedema have resolved on the OCT image (E). The VA is 0.3. However, OCT shows recurrent macular oedema 3 months after the first injection (F). The VA is 0.2. Additional intravitreal bevacizumab was administered, and the SRF and macular oedema resolved again. The macular oedema recurred once again and was successfully treated with repeated injections during the first year. Fifteen months after the initial injection, the branching vascular networks have increased in size (G). Despite repeated intravitreal bevacizumab for recurrent exudation, the SRF and macular oedema that had once responded to treatment during the first year persistently remained during the second year with deterioration of VA to 0.1, indicating loss of the treatment efficacy (H).

Table 2 Differences between complete responders and partial or non-responders in best-corrected visual acuity and optical coherence tomography findings

	Complete responders (n=26)	Partial or non-responders (n=19)	p Value
Age (years), mean±SD (range)	70.5±6.5 (57–83)	70.4±7.6 (53–83)	0.985
Patterns of leakage on fluorescein angiography at baseline			
Classic choroidal neovascularisation	5	1	
Occult choroidal neovascularisation	21	18	0.222
Baseline optical coherence tomography findings			
Pigment epithelial detachment (no/%)	15 (58)	11 (58)	0.770
Subretinal fluid (no/%)	25 (96)	18 (95)	1.000
Macular oedema (no/%)	5 (19)	5 (26)	0.720
Best-corrected visual acuity, logarithm of the minimum angle of resolution±SD			
Baseline	0.43±0.29	0.48±0.32	0.583
12 months	0.40±0.31	0.58±0.32	0.058
24 months	0.41±0.34	0.66±0.40	0.041
Logarithm of the minimum angle of resolution change between baseline and 24 months	0.02±0.37	−0.18±0.27	0.047
Central retinal thickness (μm), mean±SD			
Baseline	219±60 (87–337)	226±85 (128–434)	0.738
12 months	172±56 (80–347)	229±115 (128–664)	0.017
24 months	159±54 (76–288)	313±216 (113–834)	0.001
Change between baseline and 24 months	−61±81 (−215–118)	87±216 (−246–678)	0.003
Branching vascular network size (mm^2)			
Baseline	4.59±2.72 (1.18–9.98)	5.52±4.23 (0.88–16.86)	0.705
24 months	6.30±3.53 (1.14–15.90)	11.39±10.01 (2.85–45.23)	0.049

may be responsible for the loss of treatment efficacy in the current study eyes.

Fortunately, half of the eyes that were partial and non-responders maintained the VA through 24 months despite persistent macular fluid. However, 10 eyes eventually developed significant CMO with poor visual outcomes. The CMO has been reported to be associated with all forms of neovascular AMD, including classic CNV, occult CNV, PED and disciform scars,[23 24] or with PCV.[20] We speculated that the persistent exudative vascular networks beneath the RPE may cause RPE decompensation, resulting in severe damage to the neurosensory retina, as seen in progressed AMD.

The limitations of the current study were its retrospective nature and the absence of a control group. Because the individual responses vary among the patients, we did not re-treat patients at fixed intervals but did so with the criteria based on their responses under monthly monitoring. Some patients with a lower morphological response despite consecutive injections were not always re-treated unless VA declined, as reported in the treatment of AMD.[25] To confirm whether the current strategy is optimal for long-term follow-up, a prospective, randomised, comparative study should be considered comparing different injection strategies for exudative branching vascular networks in PCV.

In summary, the intravitreal bevacizumab to treat exudative branching vascular networks in patients with PCV improves the retinal morphology and maintains vision over 1 year. However, the network vessels persist, and the therapeutic response may be lost during the second year. The visual prognosis is poor in eyes with CMO. Further studies may elucidate the appropriate use of intravitreal bevacizumab or other treatment modalities for better management of branching vascular networks in PCV.

Competing interests None.

Patient consent Obtained.

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REFERENCES

1. **Yannuzzi LA,** Sorenson J, Spaide RF, *et al*. Idiopathic polypoidal choroidal vasculopathy (IPCV). *Retina* 1990;**10**:1–8.
2. **Spaide RF,** Yannuzzi LA, Slakter JS, *et al*. Indocyanine green videoangiography of idiopathic polypoidal choroidal vasculopathy. *Retina* 1995;**15**:100–10.
3. **Yannuzzi LA,** Ciardella A, Spaide RF, *et al*. The expanding clinical spectrum of idiopathic polypoidal choroidal vasculopathy. *Arch Ophthalmol* 1997;**115**:478–85.
4. **Yannuzzi LA,** Wong DWK, Storzolini BS, *et al*. Polypoidal choroidal vasculopathy and neovascularized age-related macular degeneration. *Arch Ophthalmol* 1999;**117**:1503–10.
5. **Ciardella AP,** Donsoff IM, Huang SJ, *et al*. Polypoidal choroidal vasculopathy. *Surv Ophthalmol* 2004;**49**:25–37.
6. **Sho K,** Takahashi K, Yamada H, *et al*. Polypoidal choroidal vasculopathy: incidence, demographic features, and clinical characteristics. *Arch Ophthalmol* 2003;**121**:1392–6.
7. **Maruko I,** Iida T, Saito M, *et al*. Clinical characteristics of exudative age-related macular degeneration in Japanese patients. *Am J Ophthalmol* 2007;**144**:15–22.
8. **Gomi F,** Ohji M, Sayanagi K, *et al*. 1-Year outcomes of photodynamic therapy in age-related macular degeneration and polypoidal choroidal vasculopathy in Japanese patients. *Ophthalmology* 2008;**115**:141–6.
9. **Chan WM,** Lam DS, Lai TY, *et al*. Photodynamic therapy with verteporfin for symptomatic polypoidal choroidal vasculopathy. *Ophthalmology* 2004;**111**:1576–84.
10. **Otani A,** Sasahara M, Yodoi Y, *et al*. Indocyanine green angiography: guided photodynamic therapy for polypoidal choroidal vasculopathy. *Am J Ophthalmol* 2007;**144**:7–14.
11. **Sayanagi K,** Gomi F, Sawa M, *et al*. Long-term follow-up of polypoidal choroidal vasculopathy after photodynamic therapy with verteporfin. *Graefes Arch Clin Exp Ophthalmol* 2007;**245**:1569–71.
12. **Akaza E,** Mori R, Yuzawa M. Long-term results of photodynamic therapy of polypoidal choroidal vasculopathy. *Retina* 2008;**28**:717–22.
13. **Yamashiro K,** Tsujikawa A, Nishida A, *et al*. Recurrence of polypoidal choroidal vasculopathy after photodynamic therapy. *Jpn J Ophthalmol* 2008;**52**:457–62.
14. **Wakabayashi T,** Gomi F, Sawa M, *et al*. Marked vascular changes of polypoidal choroidal vasculopathy after photodynamic therapy. *Br J Ophthalmol* 2008;**92**:936–40.
15. **Avery RL,** Pieramici DJ, Rabena MD, *et al*. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology* 2006;**113**:363–72.
16. **Kiernan DF,** Hariprasad SM, Chin EK, *et al*. Prospective comparison of Cirrus and Stratus optical coherence tomography for quantifying retinal thickness. *Am J Ophthalmol* 2009;**147**:267–75.
17. **Imamura Y,** Engelbert M, Iida T, *et al*. Polypoidal choroidal vasculopathy: a review. *Surv Ophthalmol* 2010;**55**:501–15.
18. **Gomi F,** Sawa M, Mitarai K, *et al*. Angiographic lesion of polypoidal choroidal vasculopathy on indocyanine green and fluorescein angiography. *Graefes Arch Clin Exp Ophthalmol* 2007;**245**:1421–7.
19. **Yuzawa M,** Mori R, Kawamura A. The origins of polypoidal choroidal vasculopathy. *Br J Ophthalmol* 2005;**89**:602–7.
20. **Akaza E,** Yuzawa M, Mori R. Three-year follow-up results of photodynamic therapy for polypoidal choroidal vasculopathy. *Jpn J Ophthalmol* 2011;**55**:39–44.
21. **Gragoudas ES,** Adamis AP, Cunningham ET Jr, *et al*; VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 2004;**351**:2805–16.
22. **Schaal S,** Kaplan HJ, Tezel TH. Is there tachyphylaxis to intravitreal anti-vascular endothelial growth factor pharmacotherapy in age-related macular degeneration? *Ophthalmology* 2008;**115**:2199–205.
23. **Soubrane G,** Coscas G, Larcheveque F. Macular degeneration related to age and cystoid macular edema. Apropos of 95 cases (100 eyes). *J Fr Ophtalmol* 1988;**11**:711–20.
24. **Ting TD,** Oh M, Cox TA, *et al*. Decreased visual acuity associated with cystoid macular edema in neovascular age-related macular degeneration. *Arch Ophthalmol* 2002;**120**:731–7.
25. **Bashshur ZF,** Haddad ZA, Schakal AR, *et al*. Intravitreal bevacizumab for treatment of neovascular age-related macular degeneration: the second year of a prospective study. *Am J Ophthalmol* 2009;**148**:59–65.