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Transient Choroidal Thinning after Intravitreal Bevacizumab Injection for Myopic Choroidal Neovascularization

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Abstract

Purpose: To evaluate the choroidal thickness changes in the eyes with myopic choroidal neovascularization (mCNV) after intravitreal injection of bevacizumab (IVB).

Methods: Ten highly myopic eyes with mCNV treated with IVB were included. All patients underwent a single, horizontal B-scan image centered on the fovea, before, and 1 month and 3 month after IVB using Heidelberg optical coherence tomography (OCT). Choroidal thickness (CT) defined as the distance from the retinal pigment epithelium to the chorio-scleral interface in OCT image at the fovea, 2mm nasally and 2mm temporally was measured.

Results: Foveal mean CT was 52.8 microns before IVB, and it significantly decreased to 37.5 microns 1 month after (P<0.05). Similarly, the 2mm temporal mean CT was 80.5 microns before IVB, and it significantly decreased to 69.5 microns 1 month after (P<0.05). On 3 months after IVB, mean CT at the fovea improved to 48.9 microns (P=0.67); however, the mean temporal CT remained thin as 67.0 microns (P=0.07 vs. baseline). The mean nasal CT remained at the similar throughout the follow-up (P=0.90 and 0.56) The change in CT on 1 month after IVB was significantly correlated with age and preoperative CT (P=0.01 and 0.04, respectively).

Conclusions: Subfoveal and temporal choroidal thinning is transiently observed. IVB may affect the choroidal circulation in such myopic eyes as with thin choroid.

Myopic choroidal neovascularization (mCNV) is a leading cause of severe visual loss and blindness in highly myopic eyes [1]. The subsequent chorioretinal atrophy is thought to be the main cause of poor long-term visual acuity [2]. A histopathologic study reported occlusion and disappearance of large choroidal vessels and choriocapillaries along with replacement of the normal choroidal structure with fibrous tissue [3], resulting in chorioretinal atrophy; however, the precise mechanism is unknown.

Several treatments for mCNV including thermal laser photocoagulation, photodynamic therapy, triamcinolone acetonide, and surgical excision have been reported. However, none has achieved a beneficial long-term effect [4-6]. Intravitreal bevacizumab (IVB) (Avastin, Genentech, South San Francisco, CA) recently has been used widely and has achieved favorable visual outcomes [7-13]. A superior beneficial effect over that of other treatments also has been reported [14]. The incidence of systematic and ocular side effects is reportedly low [15,16].

Several investigators have reported the absence of retinal toxicity by electrophysiologic and histologic evaluation, and tissue cultures showed that there were no effects on ganglion cells at an IVB concentration of 2.5 mg/ml and no increase in the rate of retinal pigment epithelial (RPE) cell apoptosis after 48 hours at a concentration of 0.8 mg/ml [17-21]. However, we found marginal crack formation at retinal pigment epithelium (RPE) and choroid level [22], which worsens the visual outcome after IVB for mCNV [23]. This finding suggested that IVB has a negative impact on the choroidal structures.

The choroidal vessels are highly dependent on vascular endothelial growth factor (VEGF) in vitro [24] and *in vivo* [25]. For instance, the more VEGF receptor expression was revealed in the choriocapillary endothelial cells facing the RPE that secrets VEGF more to the basal side than the apical side [24]. The absence of VEGF from the RPE resulted in failure of choroidal vessels and choriocapillaries to form in knockout mice [25]. These findings suggested the close paracrine trophic loop between the RPE and choroidal vessels; the choriocapillaries especially are highly dependent on VEGF. This led us to hypothesize that blocking VEGF with an anti-VEGF reagent has a potent impact on choroidal vascular systems especially in permeability and size.

The choroid is relatively inaccessible tissue in terms of imaging examination because fluorescein angiography (FA) does not effectively visualize the tissue because the RPE blocks the signal. Indocyanine green angiography is also a modality used to study the choroidal vascular status; however, the vascular status is difficult to quantitate because of its choroidal thickness containing multiple vascular layers. Recent advances in optical coherence tomography (OCT) have enabled measurement of the choroidal thickness by measuring the hyperreflective line from the RPE and chorioscleral interface in vivo [26,27]. The choroidal thickness varies a great deal among individuals; however, the myopic choroidal thickness of about 100μm [26,28], is about one third of that in eyes without myopia, i.e., generally 250 to 350μm [27,29]. Therefore, it is necessary to determine the effect of blocking VEGF in highly myopic eyes, which are normally atrophic with poor vascular systems.

In the current study, we compared the transient choroidal thickness before and after IVB using spectral-domain (SD) OCT and evaluated the effect of bevacizumab on the choroid. The correlation between the

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choroidal thickness changes at 1 and 3 months and factors including age, axial length, and preoperative thickness also were analyzed.

Patients and Methods

Patients

Consecutive eyes treated with IVB for mCNV at the Department of Ophthalmology, Osaka University Medical School, were enrolled in this study if they had high myopia, defined as a spherical equivalent refractive error greater than -6D or an axial length of 26.5 mm or longer; no posterior abnormality other than mCNV that can affect the choroidal thickness measurement; no whitish chorioretinal atrophy seen on fundus examination and/or FA; and the ability to provide written informed consent. FA was used to confirm the presence of mCNV. The research adhered to the tenets of the Declaration of Helsinki and all participants provided written, informed consent. The off-label usage of bevacizumab for mCNV and this retrospective study were approved by IRB of Osaka University Hospital.

SD-OCT Examination

All patients underwent SD-OCT (Spectralis Heidelberg Retina Angiograph +OCT; Spectralis; Vista, Heidelberg, Germany) through a dilated pupil by a trained technician. One horizontal B-scan image centered on the fovea (1,536 A-scans, scan angle 30 degrees, scan length 9 mm) was obtained from all patients before and 1 and 3 months after IVB. The scans were obtained using the automated averaging system (ART=33) that amplifies the signals and reduces noise in the images. The choroidal thickness was measured at the fovea, 1 and 2 mm nasally, and 1 and 2 mm temporally by manually using the scale supplied with the software. The choroidal thickness was defined as the distance from the RPE line to the hyperreflective line behind the large vessel layers of the choroid, presumed to be the chorioscleral interface [26]. This clear chorioscleral interface was visible in all eyes because they had a thinned choroid. If the choroid was tilted, the distance was measured to the RPE line. Two independent investigators measured the choroidal thickness in all patients. We recorded the average value of the two measurements.

Because the choroidal thickness varies among patients, it was expressed as the change in the choroidal thickness, defined as the pretreatment thickness minus the posttreatment thickness.

Statistics

Statistical analysis was performed using JMP statistical software package (version 7.0, SAS Institute Inc, Cary, NC). A comparison to determine a significant difference in the choroidal thickness between before and after IVB was analyzed using the paired *t*-test. The correlation between the change in the choroidal thickness at 1 and 3 months and the factors analyzed was determined using Spearman'srank test. *P* values <0.05 were considered significant.

Result

Patient demographic data

A total of 10 eyes Patient Demographic data of 10 patients (7 women, 3 men) were enrolled. Eight eyes were phakic and two were pseudophakic. The mean patient age was 59.4 ± 13.9 years (27-74 years); the mean spherical equivalent refractive error wa;s -11.1 ± 4.0 diopters (-6 to -19 diopters) excluding pseudophakic eyes; and the mean axial length was 29.0 ± 1.4 mm (26.57-31.75 mm). mCNV was newly developed in nine eyes and recurred in one eye that had been treated with IVB 6 months previously.

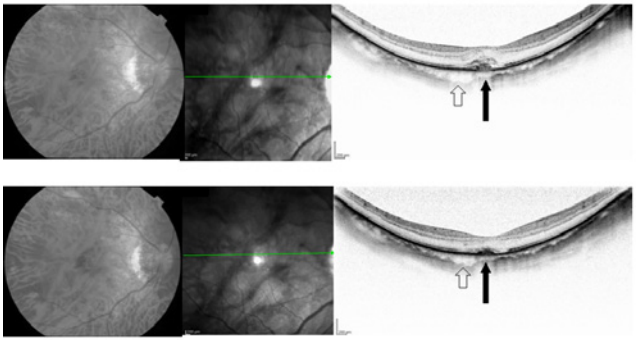

Figure 1: Fundus photograph and optical coherence tomography (OCT) appearance of case 7 before and 1 month after intravitreal bevacizumab (IVB) injection for myopic choroidal neovascularization (mCNV). The registration of both panels is identical. (Top) The fundus photographshows a typical myopic fundus and small mCNV at the fovea. The OCT image shows a typical small mCNV subfoveally with minimal subretinal fluid around the CNV (solid arrow). The subfoveal choroidal thickness is 88 microns. (Bottom) There is no marked change in the fundus photograph; however, the mCNV has shrunk and the subretinal fluid has resolved 1 month after IVB. The choroid has thinned to 62 microns at the fovea (solid arrow). The temporal choroidal vessels adjacent to the fovea are markedly smaller (open arrows).

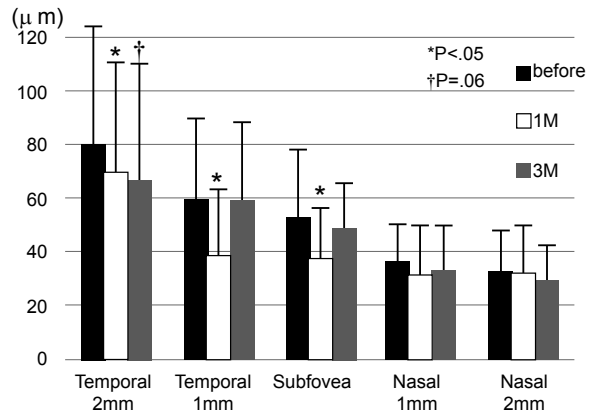

Figure 2: The mean choroidal thickness is measured by spectral-domain optical coherence tomography at the fovea, 2 and 1mm temporally, and 2 and 1mm nasally before (closed) and 1 (open) and 3 months (gray) after intravitreal bevacizumab (IVB) injection for myopic choroidal neovascularization. The mean choroidal thickness has decreased significantly at the fovea, and 1 and 2 mm temporally 1 month after IVB. However, the significance is lost 3 months after IVB; this decrease is still of borderline significance 2mm temporally. Bar=standard deviation. **P*<0.05, †*P*=0.06.

Representative case

Case 7 was that of a 69-year-oldwoman who visited the Myopia Clinic of Osaka University Hospital with visual loss in the right eye. The VA was 20/63 and FA confirmed the presence of mCNV. The patient had no history of treatment of mCNV. OCT showed choroidal thinning due to myopic chorioretinal atrophy and CNV at the fovea (Figure 1). The subfoveal choroidal thickness was 88μm. One month after IVB, the CNV was inactive; however, the choroid was thinner (Figure 1). The VA improved to 20/20however,the choroidal thickness decreased to 62μm.

Mean baseline choroidal thickness

The mean baseline subfoveal choroidal thickness of all patients was 52.8 ± 25.5μm (80.5 ± 43.4μm 2mm temporally, 59.3 ± 30.9μm

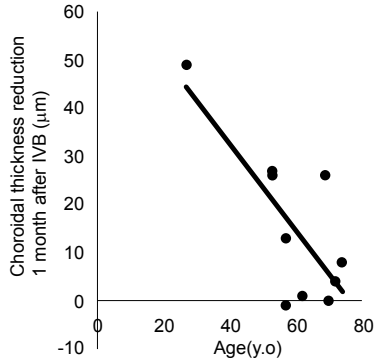

Figure 3: The relationship between subfoveal choroidal thickness reduction 1 month after intravitreal bevacizumab from baseline and age. There is a significantly negative correlation (*P*=0.01).

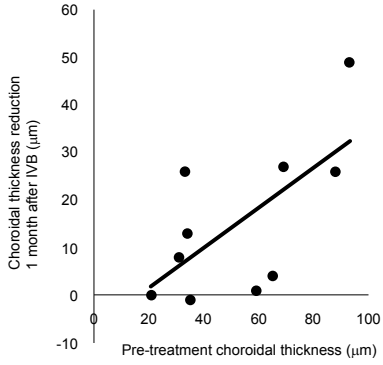

Figure 4: The relationship between choroidal thickness reduction 1 month after IVB from baseline and preoperative choroidal thickness age. There is a significantly positive correlation (*P*=0.04).

1mm temporally, 36.5 ± 13.8μm 1mm nasally, and 32.8 ± 17.0μm 2mm nasally). There were no significant differencesbetween1 and 2 mm temporally compared to the fovea (*P*=0.50 and *P*=0.07,respectively); however, the nasal choroid was significantly (*P*=0.02 at 1mm and *P*=0.04 at 2mm) thinner than the fovea.

Mean choroidal thickness changes after treatment

The choroidal thickness changes at the five points are shown in Figure 2. The subfoveal choroidal thickness was 52.8μm before IVB and significantly (*P*<0.05) decreased to 38.0μm 1 month after IVB. Similarly, the mean 2-mm temporal choroidal thickness was 80.5μm before IVB and significantly (*P*<0.05) decreased to 69.5μm 1 month after IVB. Three months after IVB, the mean subfoveal choroidal thickness increased to 48.9μm (*P*=0.67 compared to before treatment), and the change was no longer significant. The mean 2-mm temporal choroidal thickness remained 67.0μm and was of borderline significance (*P*=0.07). The mean 2-mm nasal choroidal thickness remained similar throughout the follow-up period (*P*=0.90 and *P*=0.56). The mean 1-mm temporal choroidal thickness decreased significantly 1 month after treatment; however, it returned to the baseline level 3 months later. There was no significant change 1mm nasally throughout the follow-up period.

Factors associated with choroidal thickness

The changes in choroidal thickness 1 month after IVB were correlated significantly with age (Figure 3) and preoperative thickness (Figure 4) (*P*=0.01 and *P*=0.04, respectively); however, there was no correlation with the axial length (*P*=0.96). The change in the choroidal thickness at 3 months was correlated significantly only with the preoperative choroidal thickness (*P*=0.01) and was not correlated with age or axial length (*P*=0.07 and *P*=0.94, respectively).

Discussion

The choroid is generally thinner in highly myopic eyes because of global expansion posteriorly. In eyes that do not have myopia, we and other investigators have reported the mean subfoveal choroidal thicknessesto be 354μm and 287μm, respectively [27,29]. We reported that the mean subfoveal choroidal thickness in highly myopic eyes measured by SD-OCT was 100.5μm, which was correlated with age and posterior staphyloma [26]. Fujiwara et al. reported that the mean subfoveal choroidal thickness was 93.2μm and it was correlated negatively with age, refractive error, and a history of mCNV [28].

Choroidal thinning accompanied by choroidal circulatory disturbances has been reported as a risk factor for development of CNV. The mean subfoveal choroidal thickness was reported to be 108.1μm, but for those with a history of mCNV, the mean thickness was 64.8μm, which was significantly thinner [28]. Based on our recent data, choroidal thinning was significantly more prominent in eyes with mCNV [30]. These observations indicate that the choroid is thinner in eyes with mCNV, and thus, the effect on changes in the choroidal structures after treatment must be studied.

The choroid was significantly thinner in the temporal and macular regions 1 month after IVB; the mechanism of this thinning is not totally understood. VEGF is expressed robustly during the embryonic stage; however, VEGF also plays a critical role in maintaining the survival and fenestration in vascular tissue in adults [31]. The RPE secretes VEGF for the choroidal vessels [32,33], and the VEGF receptorsare abundant in the endothelial cells of the choriocapillaris [24,34], and some large choroidal vessels [24]. This also agrees with the loss of RPE leading to choroidal vascular loss [35]. IVB penetrates the retina and RPE, spreads in the choroids, and accumulates in the choroidal vessel wall [36]. These observations led us to hypothesize that bevacizumab blocks VEGF, which is essential for choroidal vascular physiologic activity, and leads to reduced permeability and consequent choroidal thinning. In fact, fenestration of the choriocapillaris endothelium rapidly decreased 2 weeks after IVB was administered in monkey eyes, although the fenestration recovered to almost 80% of the baseline level 2 weeks after injection [37].

A second question is whether bevacizumab causes permanent damage or has only a transient effect on choroidal vessels. The half-life of bevacizumab is about 4 days in the rabbit vitreous [38]. Based on this assumption, there supposedly is no longer an effective dose present in tissue 1 month after injection. In addition, the concentration should be about 1pg/ml of bevacizumab 3 months later. We found a significant reduction in the choroidal thickness 1 month after treatment at the fovea and temporally. At 3 months, the significance in the change was lost at the fovea and 1mm temporally; however, it was maintained 2 mm temporally. This finding is important because IVB injections into myopic eyes might cause permanent damage (i.e.,choroidal vascular cell apoptosis),because VEGF plays a critical role in the survival of the choroidal vasculature [31].

The results also raise the question about why only the temporal choroid becomes thinner but not the nasal choroid. Univariate analysis showed that the baseline choroidal thinning was correlated significantly

with the baseline choroidal thickness. As shown in the previous and the current study, the nasal choroid is significantly thinner than the temporal choroid [26,27,29]. Thus, the effect of bevacizumab on the choroidal thickness is more prominent temporally and in the fovea than nasally. Further investigation with the larger number of the eyes may provide the significant change even in the nasal choroid.

Previous studies of bevacizumab have reported a low incidence of systematic and ocular side effects, no retinal toxicity on electrophysiology and histologic evaluations, and no effects on the ganglion cells and RPE apoptosis [17-20]. However, clinically significant effects have been reported, such as the appearance of marginal cracks, which appears as hypofluorescence around the CNV after IVB for mCNV [22] and an increased number of lacquer cracks [23]. Therefore,we hypothesized that anti-VEGF therapy must affect the choroidal structures though we don't know whether these structural changes promote the reaction to IVB or not. However, this requires further investigation.

In summary, we studied the choroidal thickness in eyes with mCNV before and after IVB using SD-OCT. Subfoveal and temporal choroidal thinning occurred transiently. Our results suggested that IVB affects the choroidal circulation in eyes with mCNV.

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