Subfoveal Choroidal Thickness Changes Following Anti-
Vascular Endothelial Growth Factor Therapy in Myopic
Choroidal Neovascularization

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PURPOSE. To investigate subfoveal choroidal thickness (SFCT) changes following intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy and to identify clinical and choroidal parameters associated with visual outcome in eyes with myopic choroidal neovascularization (CNV).

METHODS. In 60 eyes of 54 patients who were treated with anti-VEGF injections for myopic CNV, SFCT was measured using enhanced depth imaging optical coherence tomography at baseline, at 1, 3, and 6 months after initial anti-VEGF therapy, and at the final visit. Subfoveal choroidal thickness was compared between visits in subgroups separated based on anatomic outcome, recurrence, or resolution. Univariate and multivariate regression analyses were performed to identify factors associated with final best-corrected visual acuity (BCVA).

RESULTS. At baseline, the mean SFCT was 47.6 ± 24.7 μm, significantly lower than that of the contralateral eyes (59.8 ± 34.4 μm, P = 0.022). The thickness significantly decreased to 45.2 ± 24.0 μm (P = 0.027) 1 month after the anti-VEGF therapy. In the recurrent cases, the SFCT significantly increased from 46.1 ± 25.5 μm at month 1 to 52.4 ± 25.8 μm at the time of recurrence (P = 0.020); however, no significant change in the SFCT was noted in the nonrecurrent cases. In the regression analyses, the baseline BCVA (P < 0.001) and central macular thickness (CMT; P = 0.005) significantly correlated with the final BCVA, whereas SFCT or its change was not significantly associated with final BCVA.

CONCLUSIONS. Subfoveal choroidal thickness significantly decreased following anti-VEGF therapy in myopic CNV, but showed a subsequent increase in recurrence. Subfoveal choroidal thickness may reflect disease activity and aid decision making regarding retreatment in myopic CNV for recurrent cases.

Keywords: antivascular endothelial growth factor, choroidal neovascularization, myopia, optical coherence tomography
patients were included in our analyses. The posterior border of the choroid ($n = 3$) showed that subfoveal choroidal thickness is greater in the eyes with myopic CNV than the contralateral eyes (bottom). Axial length is 30.85 and 30.09 mm and SFCT is 57 and 94 μm in the eyes with myopic CNV and the contralateral eye, respectively. (B) Box plots of subfoveal choroidal thickness in the eyes with myopic CNV and the contralateral eyes. Quantitative analyses show that there are significant differences in subfoveal choroidal thickness between the eyes with myopic CNV and the contralateral eyes.

METHODS

Subjects

This retrospective observational study included 71 eyes of 65 consecutive patients with myopic CNV who visited Seoul National University Bundang Hospital between January 2009 and December 2013. All patients received at least one intravitreal injection of an anti-VEGF agent, either bevacizumab (Avastin; Roche, Basel, Switzerland) or ranibizumab (Lucentis; Novartis, Basel, Switzerland) and had undergone follow-up examinations for at least 6 months. The institutional review board of Seoul National University Bundang Hospital approved our study, and the study adhered to the tenets of the Declaration of Helsinki.

Inclusion criteria for myopic CNV in this study were (1) high myopia (axial length > 26.0 mm and/or myopia > −6 diopters [D]) and (2) active subfoveal or juxtafoveal CNV with decreased VA attributable to the CNV. Exclusion criteria were (1) presence of other macular diseases, such as age-related macular degeneration, foveoschisis, macular hole, or epiretinal membrane ($n = 3$); (2) previous surgery (except cataract extraction), intravitreal injection, or PDT ($n = 3$); (3) age ≥ 75 years (for the possibility of age-related CNV etiology) ($n = 2$); and (4) poor image quality or poor demarcation of the posterior border of the choroid ($n = 3$). Finally, 60 eyes of 54 patients were included in our analyses.

Examinations

Before anti-VEGF therapy, all patients received complete ocular examinations, including Snellen best-corrected visual acuity (BCVA) assessment, slit-lamp biomicroscopy, intraocular pressure (IOP) and axial length measurement, color fundus photography, fluorescein angiography (FA), indocyanine green angiography (ICGA), and SD-OCT (Spectralis OCT; Heidelberg Engineering, Inc., Heidelberg, Germany). Fluorescein angiography and ICGA were obtained using the Heidelberg Retina Angiograph system (Heidelberg Engineering, Inc.) with a confocal scanning laser ophthalmoscope. The size of the CNV before treatment was measured on the FA/ICGA images with embedded software programs. Axial length was measured in all patients using the IOL Master 500 (Carl Zeiss Meditec, Inc., Jena, Germany). After treatment, fundus photography, BCVA assessment, and OCT examination were performed for each patient at monthly intervals up to 3 months after initial treatment and at 3-month intervals thereafter. It was recommended that patients come to the clinic earlier in cases of visual loss with or without metamorphopsia. Additional FA, ICGA, and SD-OCT were performed whenever physicians suspected recurrence of myopic CNV or in cases of visual loss or recurrent metamorphopsia.

Full-thickness choroidal images were obtained using EDI-OCT with eye-tracking and image-averaging systems as described by Spaide et al. Choroidal thickness was measured manually with calipers as the distance from the outer border of the retinal pigment epithelium to the inner surface of the sclera, as demonstrated in Figure 1, on the horizontal OCT line passing through the fovea. Subfoveal choroidal thickness was measured at the point of the thinnest inner retinal layers that both investigators (SJA and SJW) agreed on as a foveal point before actual measurement. During the measurement, magnified OCT images (225%) were used to determine choroidal borders and minimize potential errors caused by involuntary movement during manual measurement. Using the same method, the choroidal thicknesses were measured 1 mm from the fovea at the temporal, nasal, superior, and inferior points at baseline and at subsequent visits for supplemental analyses. Central macular thickness (CMT) was measured using a circular map analysis protocol, which measures the distance between the first signal from the vitreoretinal interface and the outer border of the retinal pigment epithelium. An average thickness is then calculated in a 1-mm-diameter circle centered on the fovea. Segmentation errors, if present, were corrected.
by manual segmentation before the CMT measurement. The OCT interpretations and measurements were performed by two independent and experienced investigators who were masked to the patients’ clinical information, including information on the disease activity, clinical characteristics, and therapy details. The average of the two measurements was calculated and used for our analyses.

Fundus photographs, FA, and ICGA were used to evaluate the location of CNV and presence of lacquer cracks and to grade myopic degeneration (scale: M0–M5) according to the methods described by Avila et al.1,2 Resolution of CNV was evaluated 1 month after treatment and defined as absence of intra-/subretinal fluid on OCT images and no fluorescein leakage. Recurrence of CNV was defined as the recurrence of intra-/subretinal fluid and fluorescein leakage.

### Treatment

Patients were treated with a single intravitreal injection of 1.25 mg bevacizumab (Avastin; Roche) or 0.5 mg ranibizumab (Lucentis; Novartis) at baseline after topical anesthesia. All injections were given under sterile conditions; after povidone-iodine. The anti-VEGF agent, either bevacizumab or ranibizumab was injected into the vitreous cavity using a 30-gauge needle, at a position 3.5 mm posterior to the corneal PM, 11:42 AM, and 11:56 AM at the baseline and 1-, 3-, and 6-month visits, respectively. In the eyes that showed recurrence, thickness at 1 month after anti-VEGF therapy was also compared with that at the time of CNV recurrence using the Wilcoxon signed rank test.

### Results

#### Demographic and Clinical Characteristics

Baseline demographic and clinical characteristics are presented in Table 1. There was no patient in whom cataract surgery was performed during follow-up period.

**TABLE 1.** Demographic and Clinical Characteristics of Included Patients

<table>
<thead>
<tr>
<th>Factors</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of eyes</td>
<td>60</td>
</tr>
<tr>
<td>Age, y</td>
<td>58.7 ± 10.1; range, 37–74</td>
</tr>
<tr>
<td>Sex, female (%)</td>
<td>44 (81.5)</td>
</tr>
<tr>
<td>Follow-up period, mo</td>
<td>21.3 ± 12.7; range, 6–60</td>
</tr>
<tr>
<td>Spherical refractive error, D</td>
<td>–12.3 ± 5.0; range, –24.5 to –6.0</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>29.7 ± 1.6; range, 26.9–33.0</td>
</tr>
<tr>
<td>Lens status, phakia:pseudophakia (%)</td>
<td>38:22 (63.3:36.7)</td>
</tr>
<tr>
<td>Central macular thickness, µm</td>
<td>0.83 ± 0.57; range, 0.23–6.5</td>
</tr>
<tr>
<td>Location of CNV, subfoveal:juxtafoveal (%)</td>
<td>47 ± 15 (78.3:21.7)</td>
</tr>
<tr>
<td>Lacquer crack (%)</td>
<td>50 (83.3)</td>
</tr>
<tr>
<td>Myopic degeneration grade, 1:2:3:4:5 (%)</td>
<td>57 (95.0)</td>
</tr>
<tr>
<td>Posterior staphyloma (%)</td>
<td>8 (13.3)</td>
</tr>
<tr>
<td>Dome-shaped macula (%)</td>
<td>46:14 (76.7:23.3)</td>
</tr>
<tr>
<td>Materials used for injection, bevacizumab:ranibizumab (%)</td>
<td>2.1 ± 1.5; range, 1–8</td>
</tr>
</tbody>
</table>

* There was no patient in whom cataract surgery was performed during follow-up period.

Statistical analyses were performed using SPSS 18.0 for Windows (SPSS, Inc., Chicago, IL, USA), and P values less than 0.05 were considered statistically significant. Continuous data are presented as means ± standard deviation.
the OCT images were obtained at 12:35 PM on average. The difference in the OCT image acquisition time between baseline and the 1-month visit was 2 hours and 9 minutes on average, and it ranged from 2 minutes to 5 hours and 3 minutes. The difference between the 1-month visit and the time of recurrence in the eyes with recurrent CNV was 2 hours and 2 minutes, and it ranged from 5 minutes to 5 hours and 1 minute. The maximum difference in the OCT acquisition time between baseline and the follow-up visits in each patient ranged from 32 minutes to 5 hours and 52 minutes, with a mean of 2 hours and 52 minutes.

**Choroidal Thicknesses in Eyes With Myopic CNV Before and 1 Month After Anti-VEGF Therapy**

Figure 1 shows the box plots of baseline SFCT in eyes with myopic CNV and contralateral eyes. There was good interobserver agreement on baseline and follow-up choroidal thickness measurements, with ICC ranging from 0.968 at 1-month measurement (95% confidence interval [CI], 0.943–0.982) to 0.983 at baseline measurement (95% CI, 0.971–0.991). The Bland-Altman plot showed that 3 of 60 points were located outside the 95% limits of agreement (Supplementary Fig. S1). Compared to the contralateral eye (59.8 ± 34.4 μm), eyes with myopic CNV showed significantly thinner baseline subfoveal choroid (P = 0.022 by Student’s t-test). However, there was no significant difference in axial length between the eyes (29.7 ± 1.6 mm in eyes with myopic CNV versus 29.5 ± 2.5 mm in the contralateral eyes, P = 0.763 by Student’s t-test).

Figure 2 shows OCT images in subgroups separated on the basis of anatomic outcome, resolution, and recurrence. One month after anti-VEGF injection, mean SFCT decreased from 47.6 ± 24.7 to 45.2 ± 24.0 μm (5.0% decrease compared to baseline), which was statistically significant (P = 0.027 by paired t-test), as shown in Supplementary Figure S2. In the 31 fellow eyes in which the OCT images were obtained before and 1 month after the anti-VEGF therapy, however, there was no significant difference in the SFCT before and after the therapy (51.0 ± 26.0 to 50.8 ± 26.2 μm, P = 0.641). In 23 (38.3%) eyes without CNV resolution 1 month after anti-VEGF therapy, SFCT did not differ significantly between before and after anti-VEGF injections (from 47.3 ± 26.4 at baseline to 46.7 ± 26.1 μm at 1 month after treatment, P = 0.460 by Wilcoxon signed rank test). However, in 37 (61.7%) eyes showing CNV resolution 1 month after treatment, a significant difference in SFCT between baseline and the 1-month visit (47.9 ± 25.9 to 44.2 ± 22.9 μm, P = 0.005 by Wilcoxon signed rank test) was observed (Fig. 3).

Twenty-seven eyes with myopic CNV (45%) experienced a mean of 1.48 CNV recurrences. In these eyes, SFCT increased from 46.1 ± 25.5 μm at 1 month after anti-VEGF therapy to 52.4 ± 25.8 μm (14% increase compared to 1-month thickness) at the time of recurrence (Fig. 4), which was statistically significant (P = 0.020 by Wilcoxon signed rank test). In 33 eyes without CNV recurrence, SFCT showed no significant change between 1 month (44.7 ± 22.4 μm) and 3 months (43.1 ± 20.5, P = 0.537) and also between 1 month and 6 months (46.0 ± 22.2, P = 0.343 by Wilcoxon signed rank test) after anti-VEGF treatment.

**Visual Improvement and Its Association With Choroidal Thickness Change**

Anti-VEGF therapy resulted in significant visual improvement from 0.83 ± 0.57 logMAR at baseline to 0.65 ± 0.55 logMAR at the final visit (P < 0.001, paired t-test) in eyes with myopic CNV. Final visual improvement (final BCVA better than baseline) was obtained in 37 (61.7%) patients, whereas 9 (15%) and 14 (23.3%) patients had the same or worse VA at the final visit, respectively. There was no significant
difference in baseline SFCT (48.2 ± 25.7 μm in eyes with final visual improvement versus 47.0 ± 21.6 μm in those without improvement) or 1-month SFCT change (difference of SFCT between baseline and month 1, 4.6 ± 7.0 vs. 1.2 ± 7.6 μm) between patients with and without final visual improvement (P = 0.965 and 0.266 by Mann-Whitney U test, respectively).

Table 2 presents the association between clinical/choroidal parameters and final BCVA and between the parameters and visual improvement. In univariate regression analyses, final BCVA significantly correlated with baseline BCVA (r = 0.713, P < 0.001) and CMT (r = 0.378, P = 0.003). Choroidal thickness parameters, such as baseline and final SFCT and 1-month SFCT change, showed no significant association with final BCVA or visual improvement (all P > 0.05). In multivariate stepwise regression analyses, a significant association was noted between baseline BCVA and final BCVA (regression coefficient [B] = 0.741, P < 0.001) and between baseline BCVA and visual improvement (B = −0.259, P = 0.042).

DISCUSSION

The present study showed that SFCT in eyes with myopic CNV decreased 1 month after anti-VEGF therapy, but increased at the time of recurrence. Our results suggest that choroidal thickness changes may be associated with the pathogenesis and disease activity of myopic CNV.

Maruko and associates\textsuperscript{16} reported that SFCT in PCV at baseline was thicker than in normal eyes. The authors suggest that choroidal thickening may be due to choroidal hyperpermeability, which can be noted in central serous chorioretinopathy. Based on their results, they hypothesize that the pathogenesis of PCV is related to choroidal hyperpermeability. In eyes with exudative age-related macular degeneration (ARMD), previous studies reported foveal choroidal thinning.\textsuperscript{24} Similar to CNV in exudative ARMD, our results showed that SFCT was thinner in eyes with myopic CNV than contralateral eyes, which is compatible with the finding reported by Ikuno et al.\textsuperscript{18} Although it remains unclear why choroidal thinning is associated with the development of myopic CNV, we hypothesize that the pathogenesis of CNV in myopic eyes might be different from that of PCV but similar to that of CNV in exudative ARMD.

However, this study also demonstrated that the SFCT in patients with myopic CNV decreased 1 month after anti-VEGF therapy. Furthermore, it remained thin for up to 6 months after treatment in nonrecurrent cases, whereas the thickness significantly increased at the time of CNV recurrence in recurrent cases. A similar course of choroidal thickness changes has been reported in cases with PCV following PDT and anti-VEGF injection\textsuperscript{15} and in those with idiopathic...
therapy. Furthermore, RPE atrophy can progress in eyes with CNV, may result in limited visual improvement following anti-VEGF therapy. Although the pathogenic mechanisms of CNV formation may differ between some types of CNV and myopic CNV, the CNV that developed may have common properties, as those with myopic CNV showed no association with baseline BCVA, rather than possible indicators of CNV activity, and that, compared to other types of CNV, this effect should be carefully considered for visual prognosis following anti-VEGF therapy.

Several limitations require careful consideration regarding the interpretation of our results. First, the retrospective design results in intrinsic drawbacks, namely, selection bias. Additionally, the 2.4-μm difference in the SFCT before and after anti-VEGF therapy might result from measurement error or aging. Furthermore, this small difference may not be sufficient to have a clinical impact or implication. However, the analyses of the four parafoveal choroidal thicknesses showed a similar trend of choroidal thinning. Therefore, we suggest that the SFCT decrease may be explained by true choroidal thinning rather than by measurement error. Margolis and Spaide reported a 1.56-μm decrease in choroidal thickness per year as a result of choroidal aging in nonmyopic eyes, and this suggests that choroidal aging may explain the choroidal change following anti-VEGF therapy. However, the eyes with very thin choroids in our study may be less likely to show changes of up to 2.4 μm in the SFCT for the 1-month period owing to choroidal aging alone.

Most importantly, diurnal variation may have affected our results, as it is well known that choroidal thickness shows diurnal variation. Tan et al. showed that the highest mean choroid thickness was obtained at 9:00 AM and that the mean choroid thickness then decreased progressively over subsequent time points to 5:00 PM, which has been confirmed in other studies. It was impossible to control the diurnal variation in every patient of our study because the patients visited our clinic at slightly different times during the day. Despite the limitation of diurnal variation, we evaluated the mean time of day at which OCT images were acquired to assess whether there was an overall effect of diurnal variation on mean choroidal thickness at baseline and each posttreatment visit. The thickness changes due to diurnal variation between 1 month (mean: 12:32 PM) and the time of recurrence (mean: 12:35 PM) in eyes with recurrence is expected to be insignificant, as the difference in the mean time between the visits was small. Furthermore, as choroidal thickness decreased progressively over the subsequent time points, the thickness at 1 month (mean time of day when OCT was performed: 12:28 PM) was expected to be greater than at baseline (mean: 12:42 PM) due to diurnal variation. However, this was not observed in our cases. Therefore, choroidal thickness changes 1 month after anti-VEGF therapy may be explained as a posttreatment change rather than diurnal variation.

We did not exclude patients with diabetes mellitus or hypertension in our study if they did not show any retinopathy. However, microvascular changes that result from hypertension or diabetes mellitus cannot be excluded, and these changes may have affected the baseline choroidal characteristics in our patients. For a more careful interpretation of our results, the choroidal response to anti-VEGF in patients with hypertension or diabetes mellitus should be investigated in future studies.

In conclusion, our study showed that SFCT decreased after anti-VEGF therapy and subsequently increased at the time of recurrence in eyes with myopic CNV. Choroidal thickness change following anti-VEGF therapy may reflect disease activity in myopic CNV. Thus, it may guide decisions related to retreatment for recurrent myopic CNV cases. Further prospective studies with a larger sample size are necessary to confirm our findings.

| TABLE 2. The Association Between Visual Outcome After Intravitreal Anti-Vascular Endothelial Growth Factor (VEGF) Therapy and Clinical/Choroidal Parameters at Baseline or 1 Month After Initial Injection |
|---------------------------|----------------|----------------|----------------|----------------|
|                          | Final BCVA | BCVA Change |                          |                 |
|                          |   r      |    P      |      r      |      P      |
| Age                      | 0.161   | 0.224    |    0.095   | 0.480    |
| Axial length             | 0.185   | 0.208    |    0.125   | 0.598    |
| CNV area                 | 0.439   | <0.001   |   -0.094   | 0.483    |
| Follow-up period         | -0.082  | 0.537    |   0.096    | 0.466    |
| Baseline BCVA            | 0.713   | <0.001   |   -0.404   | 0.001    |
| Baseline CMT             | 0.378   | 0.003    |    0.035   | 0.794    |
| Baseline subfoveal choroidal thickness | -0.052  | 0.819    |   -0.199   | 0.149    |
| Subfoveal choroidal thickness |         |          |          |          |
| change at month 1        | -0.035  | 0.813    |   -0.053   | 0.717    |

r, correlation coefficient. Boldface indicates statistical significance.
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References