Association between Choroidal Morphology and Anti-Vascular Endothelial Growth Factor Treatment Outcome in Myopic Choroidal Neovascularization

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PURPOSE. To investigate associations between outcome of anti-vascular endothelial growth factor (VEGF) therapy and choroidal morphology in eyes with myopic choroidal neovascularization (CNV).

METHODS. Fifty-two eyes of 46 patients with myopic CNV received a single intravitreal anti-VEGF injection, followed by as-needed injections. Baseline choroidal thickness was measured at the fovea and 1.5 and 3 mm nasal, temporal, superior, and inferior to the fovea using enhanced depth imaging optical coherence tomography. Measurements were compared between eyes with and without CNV resolution after a single injection and between those with and without CNV recurrence within 1 year of initial injection. Associations between treatment outcomes and morphologic or clinical factors were assessed using regression analyses.

RESULTS. Patients received 1.8 ± 1.3 intravitreal injections during follow-up. Eyes with CNV resolution after a single anti-VEGF injection had a significantly thicker inferior choroid than those without resolution (67.3 ± 32.9 vs. 44.5 ± 17.6 μm; P = 0.002). The subfoveal choroid was thinner in eyes with recurring CNV than in those without recurrence (35.7 ± 23.7 vs. 52.0 ± 20.8 μm; P = 0.029). Adjusted odds ratios were 9.1 for CNV resolution with an inferior choroidal thickness >49 μm and 5.6 for recurrence within 1 year with a subfoveal choroidal thickness ≤47.5 μm.

CONCLUSIONS. A thinner subfoveal/inferior choroid at baseline may indicate poor anatomic outcome after intravitreal anti-VEGF treatment in eyes with myopic CNV. (Invest Ophthal Vis Sci. 2013;54:2115–2122) DOI:10.1167/iovs.12-11542

M yopia is a major cause of visual impairment in many countries. Pathologic myopia is characterized by progressive anteroposterior elongation of the sclera and is associated with diverse secondary ocular changes. Choroidal neovascularization (CNV) caused by pathologic myopia, that is, myopic CNV, is a serious, vision-threatening condition in these patients. Although the incidence of myopic CNV has not been extensively investigated, a hospital-based study reported an occurrence rate of 5% to 10% in highly myopic patients.1 Among secondary causes of CNV, myopia is the most common, accounting for 62% of all CNV cases in patients less than 50 years of age.1

High-resolution cross-sectional images obtained with spectral-domain optical coherence tomography (SD-OCT) can be used to detect morphologic changes in the choroid and sclera in myopic eyes.2–4 Ikuno et al.4 identified several morphologic abnormalities of the choroid and suggested that some were risk factors for myopic CNV. Enhanced depth imaging SD-OCT (EDI-OCT) shows even more details of choroidal changes in myopic eyes. Fujiwara et al.2 showed a thinned choroid in myopic eyes and determined the association between age-related choroidal thinning and the degree of myopia. Choroidal thickness measurements obtained using high-penetration OCT (HP-OCT) show good agreement with those obtained using EDI-OCT,5 and Maruko et al.6 showed unique choroidal and scleral characteristics in eyes with pathologic myopia using HP-OCT. The findings of these studies suggest that pronounced mechanical stretching, and the associated choroidal thinning, play a role in the development of myopic CNV.4,6

Although studies have presented evidence of a pathogenic association between choroidal morphologic characteristics and myopic CNV,4,6 little is known about the effect of these characteristics on the outcome of intravitreal anti-vascular endothelial growth factor (VEGF) therapy, the most common treatment for myopic CNV.7–11 Here, we evaluate associations of baseline choroidal morphologic parameters with treatment outcome, CNV resolution, and CNV recurrence within 1 year of intravitreal anti-VEGF therapy in eyes with myopic CNV. Because anatomic outcomes may be associated with visual outcome, associations between choroidal morphologic factors and final visual acuity were also examined.

METHODS

Subjects

This retrospective study included 62 eyes from 56 consecutive patients who visited Seoul National University Bundang Hospital between January 2009 and June 2012 with high myopia (axial length >26.5 mm)4,6,9,12,13 and/or refractive error <--dipeters [D]11 and newly developed myopic CNV. All patients had received intravitreal anti-VEGF injections and had undergone follow-up examinations for at least 3 months. Approval to conduct this study was obtained from the

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Institutional Review Board (IRB) of Seoul National University Bundang Hospital, and the study adhered to the tenets of the Declaration of Helsinki.

Myopic CNV was defined as the presence of dye leakage associated with myopic changes on a fluorescein angiogram (FA). Thorough fundus examination and SD-OCT images (Spectralis; Heidelberg Engineering, Heidelberg, Germany) confirmed that no other macular disease was present, particularly age-related macular degeneration, foveoschisis, macular hole, or epiretinal membrane. Additionally, patients who were treated with photodynamic therapy (PDT) or other intravitreal injections were excluded from analyses (n = 3). Patients older than 75 years (n = 2) were also excluded because the etiology of CNV in these patients may not have been exclusively myopic. We also excluded patients in whom the retinal pigment epithelium (RPE), choroid, and sclera were indistinguishable (n = 3). Thus, 54 eyes from 48 patients were ultimately included in our analyses.

Examinations

Before treatment, a complete ophthalmic evaluation was performed for each patient, including best-corrected visual acuity (BCVA) assessment, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement, fundus photography, FA, indocyanine green angiography (ICGA), and SD-OCT. Trained examiners, masked to patients' information, measured BCVA in the examination room using a Snellen chart at 6 m. Fundus photographs, FA, and ICGA were used to evaluate CNV location and to grade myopic degeneration (scale: M0–M5) and lacquer cracks (scale: 0–2), according to the methods described by Avila et al.14 and Ikuno et al.,15 respectively. Late-phase ICGA images, obtained using the Heidelberg Retina Angiograph 2 (HRA2; Heidelberg Engineering), were used for evaluation of lacquer cracks.

Full-thickness choroidal images were obtained using EDI-OCT with eye-tracking and image-averaging systems, as described by Spaide et al.1 The OCT images obtained before anti-VEGF therapy were used for baseline analyses. The device was operated by a single experienced technician, who positioned the OCT camera close enough to the eye to obtain an inverted image. The eye-tracking and image-averaging capabilities of the device enabled better visualization of the choroid and increased the signal-to-noise ratio. Choroidal thickness was measured manually with calipers as the distance from the outer border of the RPE to the inner surface of the sclera (Fig. 1). These measurements were obtained at the fovea and 1.5 and 3 mm superior, inferior, nasal, and temporal to the fovea. All measurements were obtained on horizontal and vertical OCT scans that passed through the fovea.10 OCT interpretations and measurements were performed by two independent, experienced investigators (SJA, KEK) who were masked to patient information. The average of the investigators' measurements was calculated and used in analyses. When needed, a retina specialist (SJW) was consulted. If a convex elevation of the macula was observed on OCT images, a dome-shaped macula was diagnosed.10

During the follow-up period, patients were seen monthly. At each visit, BCVA was measured and OCT was performed in the treated eye. In patients with symptoms or signs of CNV aggravation, FA was also performed. Treatment outcome, assessed as resolved or not resolved, was evaluated 1 month after the initial anti-VEGF injection using OCT and FA. Resolution was defined as absence of intra-/subretinal fluid, as identified on OCT images, and no fluorescein leakage. Recurrence of CNV was defined, also on an anatomic basis, as the recurrence of intra-/subretinal fluid, as detected on OCT images, and fluorescein leakage.

Treatment

Patients were treated with a single 0.05 mL intravitreal injection of an anti-VEGF agent (1.25 mg bevacizumab [Avastin; Genentech, San Francisco, CA] or 0.50 mg ranibizumab [Lucentis; Novartis, Basel, Switzerland]) at baseline. Patients were re-treated with the drug that was used in the initial injection on an as-needed basis. Retreatment was administered for recurrent or aggravated intra-/subretinal fluid on OCT. All intravitreal injections were administered under topical anesthesia using a 30-gauge needle inserted 3.5 to 4.0 mm posterior to the limbus. Injections were administered in an outpatient setting using strict aseptic techniques.

Statistical Analysis

Descriptive statistics were obtained for data pertaining to demographic, axial length, CNV location, lacquer crack grade, BCVA at baseline, presence/absence of posterior staphyloma, and presence/absence of a dome-shaped macula. For descriptive statistics of choroidal thickness data, a box plot was used to display the distribution. Relationships between various choroidal morphologic parameters were investigated using linear regression analyses. The intraclass correlation coefficient (ICC) was used to examine interobserver agreement in choroidal thickness measurements. Pearson's correlation coefficients were also calculated.

Clinical and morphologic factors associated with anatomic outcome were evaluated using Student's t-test or the Mann-Whitney U test, depending on normality, as determined by results of the Shapiro-Wilk test. These methods were used to compare continuous variables between eyes with and without CNV resolution after a single intravitreal anti-VEGF injection. The same tests were also used to compare clinical and morphologic parameters between eyes with and without recurrence of intra-/subretinal fluid within 12 months of the initial injection.

Predictive factors for CNV resolution after a single injection and for 1-year recurrence were identified using logistic regressions. Predictability of clinical and morphologic parameters for anatomic outcome was evaluated by receiver operating characteristic (ROC) curve analysis, and sensitivity and specificity were determined using cutoff values. Clinical factors (initial BCVA, age, axial length, and central...
macular thickness \([\text{CMT}]\) and choroidal morphologic parameters were used to calculate the area under the ROC curve (AUC) for resolution or recurrence within 1 year. Cutoff values for stratifying patients with myopic CNV into groups with thicker and thinner choroid were determined to maximize sensitivity for the prediction of resolution and 1-year recurrence without significant loss of specificity (around 80%). The cutoff values were used to calculate the odds ratios (ORs) for CNV resolution and CNV recurrence.

**RESULTS**

**Demographic and Clinical Characteristics**

Demographic data from 54 eyes (48 patients) are summarized in Table 1. The mean patient age was 58.2 ± 10.1 years, and the mean follow-up period was 15.9 ± 12.4 months (range, 3–42 months). Mean spherical refractive error was −12.4 ± 4.7 D, and mean axial length was 29.6 ± 1.5 mm. Lacquer cracks were present in 48 of 54 (88.9%) eyes with myopic CNV. Foveal and extrafoveal CNVs were present in 42 (77.8%) and 12 (22.2%) eyes, respectively. The location of CNV was within the lacquer crack or adjacent to it in 32 (59.3%) and 11 (20.4%) eyes, respectively. The CNV appeared independent of the lacquer crack in 11 (20.4%) eyes.

**Choroidal Thickness**

Figure 2 shows the descriptive statistics, represented by box plots, of baseline choroidal thickness in each region examined. The nasal choroid was the thinnest area, whereas the superior choroid was the thickest area. The subfoveal choroid was thinner than the superior, inferior, and temporal choroid. Subfoveal choroidal thickness was inversely correlated with axial length \((r = -0.285, \ P = 0.079)\), but this correlation was only marginally significant. However, the thickness was strongly correlated with choroidal thickness in other regions.
Among the 39 eyes that underwent follow-up examinations for more than 1 year, 19 (48.7%) needed retreatment within the year because of intra/subretinal fluid recurrence. Table 3 and Figure 4 show comparisons of clinical and baseline morphologic characteristics between patients with and without recurrence within 1 year. Subfoveal choroidal thickness was significantly different between eyes with (35.7 ± 23.7 μm) and without (52.0 ± 20.8 μm) recurrence (P = 0.029, Student’s t-test). Additionally, foveal CNV was more frequently noted in eyes with recurrence within 1 year (89.5% vs. 60%, P = 0.039). Logistic regression analyses revealed that baseline subfoveal choroidal thickness was the only predictive factor for CNV recurrence within 1 year (OR = 0.932 per 1 μm increment; 95% CI, 0.880–0.987; P = 0.016). This result indicates that recurrence was less likely to occur in eyes with a thicker subfoveal choroid.

**Predictability of Clinical and Choroidal Parameters for Anatomic Outcome**

Inferior choroidal thickness was the strongest predictive morphologic parameter for CNV resolution after a single anti-VEGF injection (AUC, 0.78 and 0.66 at 1 and 1.5 mm inferior to the fovea, respectively). Clinical parameters such as initial BCVA, age, axial length, spherical equivalent, and CMT showed smaller AUC values (0.66, 0.54, 0.47, 0.51, and 0.50, respectively). However, for predicting recurrence within 1 year, subfoveal choroidal thickness was the most useful parameter (AUC, 0.79). After separation of eyes into two groups based on inferior choroidal thickness 3 mm from the fovea (cutoff value, 49 μm), analyses revealed a 77.8% sensitivity and 85.3% specificity for complete CNV resolution after a single anti-VEGF injection. A cutoff value of 47.5 μm for subfoveal choroidal thickness resulted in a 66.7% sensitivity and 80.0% specificity for predicting recurrence of CNV within 1 year.
Figure 3. Comparison of choroidal thickness with and without resolution of myopic choroidal neovascularization after a single intravitreal injection of an anti-vascular endothelial growth factor agent. Choroidal thickness was measured 3 and 1.5 mm from the fovea in each anatomic direction. Error bars indicate the upper bound of 95% confidence intervals. The asterisk indicates a statistically significant difference (P = 0.002 by Student’s t-test).

Table 3. Comparison of Clinical and Morphologic Factors between Eyes with and without Recurrence within 1 Year after the Initial Anti-VEGF Injection

<table>
<thead>
<tr>
<th>Clinical/Morphologic Factors</th>
<th>Nonrecurrence, n = 20</th>
<th>Recurrence, n = 19</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>58.3 ± 10.4</td>
<td>58.9 ± 10.0</td>
<td>0.845*</td>
</tr>
<tr>
<td>Baseline BCVA</td>
<td>0.68 ± 0.43</td>
<td>0.83 ± 0.57</td>
<td>0.377*</td>
</tr>
<tr>
<td>Baseline CMT</td>
<td>327 ± 90</td>
<td>386 ± 176</td>
<td>0.219*</td>
</tr>
<tr>
<td>Spherical equivalent, D</td>
<td>−11.5 ± 5.2</td>
<td>−14.5 ± 4.2</td>
<td>0.101*</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>29.5 ± 1.7</td>
<td>29.7 ± 1.4</td>
<td>0.691*</td>
</tr>
<tr>
<td>Materials used for treatment, bevacizumab (%)</td>
<td>14 (70.0)</td>
<td>15 (78.9)</td>
<td>0.394</td>
</tr>
<tr>
<td>CNV location, foveal (%)</td>
<td>12 (60.0)</td>
<td>17 (89.5)</td>
<td>0.039</td>
</tr>
<tr>
<td>Lacquer crack grade, 0:1:2</td>
<td>2:1:2:1</td>
<td>2:1:2:1</td>
<td>0.895</td>
</tr>
<tr>
<td>Myopic degeneration grade, 1:2:3:4:5</td>
<td>0.5:8:7:0</td>
<td>1:3:8:7:0</td>
<td>0.876</td>
</tr>
<tr>
<td>Posterior staphyloma (%)</td>
<td>19 (95)</td>
<td>18 (94.7)</td>
<td>0.744</td>
</tr>
<tr>
<td>Dome-shaped macula (%)</td>
<td>3 (15.0)</td>
<td>3 (15.8)</td>
<td>0.644</td>
</tr>
<tr>
<td>Choroidal thickness, µm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subfovea</td>
<td>52.0 ± 20.8</td>
<td>35.7 ± 23.7</td>
<td>0.029*</td>
</tr>
<tr>
<td>3 mm superior</td>
<td>63.3 ± 38.7</td>
<td>61.3 ± 48.3</td>
<td>0.897*</td>
</tr>
<tr>
<td>3 mm inferior</td>
<td>54.9 ± 28.4</td>
<td>58.2 ± 32.1</td>
<td>0.747*</td>
</tr>
<tr>
<td>3 mm nasal</td>
<td>39.6 ± 23.9</td>
<td>31.8 ± 24.6</td>
<td>0.392*</td>
</tr>
<tr>
<td>3 mm temporal</td>
<td>72.2 ± 41.5</td>
<td>63.2 ± 41.8</td>
<td>0.410†</td>
</tr>
<tr>
<td>1.5 mm superior</td>
<td>56.3 ± 20.8</td>
<td>64.2 ± 39.5</td>
<td>0.884†</td>
</tr>
<tr>
<td>1.5 mm inferior</td>
<td>40.5 ± 21.0</td>
<td>47.5 ± 21.2</td>
<td>0.302*</td>
</tr>
<tr>
<td>1.5 mm nasal</td>
<td>47.4 ± 25.4</td>
<td>55.6 ± 36.1</td>
<td>0.428*</td>
</tr>
<tr>
<td>1.5 mm temporal</td>
<td>53.9 ± 27.4</td>
<td>55.7 ± 32.9</td>
<td>0.855*</td>
</tr>
</tbody>
</table>

Statistical analyses were performed using Student’s t-test or the Mann-Whitney U test for continuous variables depending on normality, as determined by results of the Shapiro-Wilk test, and \( \chi^2 \) or Fisher’s exact test for dichotomous or interval variables.

* Student’s t-test.
† Mann-Whitney U test.
In eyes that had an inferior choroidal thickness (3 mm from the fovea) >49 μm, the OR (adjusted for age, sex, and potential confounders including subfoveal choroidal thickness) for complete CNV resolution after the initial injection was 9.1 (95% CI, 2.1–38.8, P = 0.003). In those with subfoveal choroidal thickness ≤47.5 μm, the adjusted OR for recurrence within 1 year was 5.6 (95% CI, 1.4–23.3, P = 0.017).

Visual Outcomes and Associated Factors

Intravitreal injections of an anti-VEGF agent resulted in a significant visual improvement from 0.78 ± 0.52 at baseline to 0.65 ± 0.51 logMAR (P = 0.015, paired t-test). Table 4 presents the association between choroidal thickness in several regions and visual outcome. Baseline BCVA and CMT were significantly associated with final BCVA, but no choroidal thickness parameters were associated with final BCVA or change in BCVA from baseline. Among clinical factors, the only predictive factor of final BCVA was baseline BCVA, as identified by multiple regression analysis (r = 0.71, P < 0.001).

DISCUSSION

Our study investigated the association between outcome of intravitreal anti-VEGF injections and choroidal morphology. By measuring baseline choroidal thickness at multiple posterior pole locations using EDI-OCT images, we found that choroidal thinning 3 mm inferior to the fovea was associated with incomplete resolution of myopic CNV after a single anti-VEGF injection. Additionally, subfoveal choroidal thinning was associated with 1-year recurrence of myopic CNV. According to ROC analyses, the subfoveal and inferior choroidal thickness likely predicts treatment outcome, resolution, and 1-year recurrence of CNV. Use of thickness cutoff values facilitates prediction of treatment outcomes after intravitreal anti-VEGF therapy in clinical practice. We showed highly significant OR values (9.1 for resolution and 5.6 for recurrence within 1 year) when eyes were divided into two groups according to inferior and subfoveal choroidal thickness.

In addition to axial length elongation in pathologic myopia, morphologic parameters of the choroid are believed to be associated with the development of myopic CNV. For example, Ikuno et al. compared choroidal morphology of eyes with myopic CNV to that of healthy fellow eyes and showed...
significant thinning of the subfoveal and inferior choroid in the eyes with myopic CNV. They also found that inferior choroidal thickness was an ocular risk factor for the development of myopic CNV. It remains unknown why choroidal thinning is associated with development of myopic CNV. McLeod et al. showed choroidal dropout adjacent to active CNV in eyes treated with anti-VEGF drugs. Although recent studies have suggested that efficacy of bevacizumab and ranibizumab is similar in terms of visual gain, the use of two different drugs may add a source of bias. We found that there were no significant differences in visual or anatomic outcomes between eyes treated with bevacizumab and those treated with ranibizumab (see Supplementary Material and Supplementary Table S1, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.12-11542/-/DCSupplemental). As there were no significant differences in baseline choroidal thickness at any point measured between bevacizumab- and ranibizumab-treated eyes, the use of different anti-VEGF drugs likely did not confound our results. Second, because a dome-shaped macula generally has a thicker subfoveal choroid, the nine eyes with a dome-shaped macula in our study may have influenced the association between subfoveal choroidal thickness and treatment outcome. In addition, the location and size of myopic CNV, in relation to our measuring points, may have affected our measurements; but these factors could not be controlled in our study. The interval between CNV development and examination may have influenced our study outcomes. We included patients who had at least 3 months of follow-up, but five patients were followed for less than 6 months. This short follow-up duration may have been insufficient to allow adequate determination of anatomic outcome in these patients. Additionally, we measured Snellen visual acuity, which has well-documented limitations, including inconsistent progression in letter size and unequal legibility of letters. Furthermore, this was a retrospective study with a small sample size, and larger, prospective studies are needed. Moreover, choroidal thickness can be affected by age, spherical equivalent, refactive error, axial length, and diurnal variation. Factors affecting choroidal thickness must also be considered in interpretation of our choroidal thickness data. In particular, diurnal variation may have affected our results. Using Spectralis OCT, Tan et al. showed that subjects with a thin choroid (≤300 μm) had a smaller diurnal variation in subfoveal thickness (11.8 μm) than the average in normal, healthy subjects (31.6 μm), indicating that the amplitude of diurnal variation may depend on choroidal thickness. Because our patients with myopic CNV had a very thin choroid (mean subfoveal thickness = 46.7 μm), we expected diurnal variation in our patients to be less than 11.8 μm; and the difference in subfoveal choroidal thickness between recurrent and noncurrent cases was 17 μm, greater than the expected diurnal variation. Additionally, OCT images were acquired in each group of patients, on average, at almost same time of day (12:18 PM with resolution versus 11:56 AM without resolution;
12:06 PM with 1-year recurrence versus 11:57 AM without 1-year recurrence). As choroidal thickness peaks in the morning and progressively decreases during the day,24 patients who have CNV resolution are expected to have a thinner choroid due to diurnal variation; however, our results showed the opposite. Patients with recurrent CNV are also expected to have a thinner subfoveal choroid due to diurnal variation, but the slight time difference in OCT acquisition (9 minutes) between patients with and without recurrence likely did not affect our results meaningfully. Finally, because choroidal thickness measurements can vary with different OCT devices,25 our choroidal thickness cutoff values may be applicable only to Spectralis OCT measurements.

In conclusion, inferior and subfoveal choroidal thinning at baseline were associated with incomplete resolution and recurrence after intravitreal anti-VEGF therapy in eyes with myopic CNV. This association also supports the hypothesis of a pathogenic association between choroidal thinning and myopic CNV, as previously suggested by others.4,6

References


