

Subfoveal choroidal thickness changes after intravitreal bevacizumab therapy for neovascular age-related macular degeneration

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Dear Sir,

I am Dr. Cihan Ünlü, from the Department of Ophthalmology, Ümraniye Training and Research Hospital, Istanbul, Turkey. I write to present our study findings on subfoveal choroidal thickness (SFCT) changes after intravitreal bevacizumab (IVB) therapy for neovascular age-related macular degeneration (AMD).

AMD is the leading cause of severe visual loss in adults older than 60y [1]. Visual loss in late stages of AMD may be the result of one of the two processes: geographic atrophy (GA) or choroidal neovascularization (CNV). Many types of therapies have been used in an attempt to inhibit exudation by CNV. IVB has been increasingly used as "off-label" for CNV in neovascular AMD. The efficacy and safety of IVB treatments have been reported for neovascular AMD in many studies [2,3].

Choroidal circulation seems to play a significant role in the pathophysiology of neovascular AMD. Choroidal ischemia findings were noted in indocyanine green angiography in eyes with neovascular AMD [4]. However, currently we have little knowledge about the choroids of patients with AMD and the effect of anti-vascular endothelial growth factor (VEGF) treatments on the choroid of patients with AMD. Enhanced depth imaging optical coherence tomography (EDI-OCT) has enabled clinicians to investigate the choroid in normal and disease states since it was introduced by Spaide *et al* in 2008 [5-9].

This study followed the tenets of the Declaration of Helsinki and was approved by the ethics committee at Istanbul Ümraniye Education and Research Hospital. A retrospective chart review was performed on 44 eyes of 36 patients with diagnosis of neovascular AMD. To be included in this study, all patients were required to undergo a comprehensive ophthalmological examination. Typical neovascular AMD was characterised by exudative changes due to CNV revealed by FA and optical coherence tomography (OCT). All eyes were examined with the RTVue-100 OCT device (Optovue Inc., Fremont, CA, USA). SFCT was defined as the vertical distance from the base of the hyperreflective retinal pigment epithelium to the choroid-sclera junction under the center of the fovea (Figure 1). Baseline and final SFCT measurements were obtained for IVB and control groups. The charts of the patients with systemic or eye diseases which might affect choroidal thickness were excluded from this study. Patients who were included in this study had at least 3mo of follow-up.

We administered an intravitreal injection of 0.05 mL (1.25 mg) of bevacizumab (Avastin®) to 44 eyes with neovascular AMD. Those 44 eyes were grouped as IVB group and 26 untreated fellow eyes were grouped as control group. The eyes were treated with an as-needed regimen with IVB. The control group included the patients with early AMD or fibrous scar secondary to CNV in the fellow eye. The eyes in the control group did not receive IVB therapy and were observed without any intervention.

The primary outcomes were the changes in the SFCT in the affected eyes treated with IVB and those in the untreated fellow eyes. The secondary outcomes were the changes in the BCVA and CMT in both groups.

The study included 70 eyes of 36 patients [19 males (53%) and 17 females (47%)]. The mean age of the patients was 71.8±7.7y (range, 56 to 90y). The mean follow-up time was 22.1±13.8mo (range, 3 to 45mo). There were 44 affected eyes with neovascular AMD in the IVB group and 26 untreated fellow eyes in the control group. The mean number of IVB injections which were administered during the follow up period was 4.3±3.2 (range, 1 to 17).

The mean SFCT at baseline was 215.8±46.9 µm in IVB group. At the final visit, after a mean follow up period of

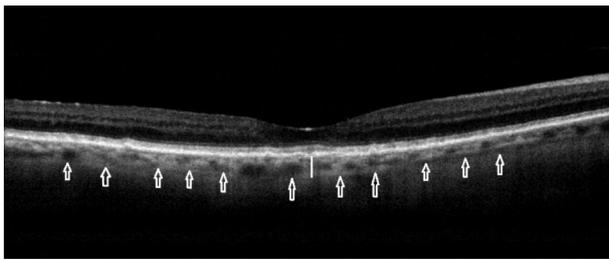


Figure 1 SFCT measurement by using enhanced depth imaging spectral-domain optical coherence tomography
Arrows indicate the inner surface of the sclera. Line indicates the SFCT.

22mo and a mean of 4 injections, the mean SFCT was $205.5 \pm 51.9 \mu\text{m}$. Compared with baseline, the mean SFCT in IVB group significantly decreased at final visit ($P=0.012$). The mean SFCT at baseline and final visits were $207.2 \pm 42.1 \mu\text{m}$ and $205.9 \pm 39.5 \mu\text{m}$ respectively in control group. In contrast to the IVB group, there was no significant decrease in the mean SFCT for the control group ($P=0.938$). The mean central macular thickness at baseline was $321.6 \pm 69.1 \mu\text{m}$ in the IVB group and reduced to $302.4 \pm 71.1 \mu\text{m}$ at final visit. The decrease was not significant ($P=0.115$). In the control group, the mean CMT at baseline and final visits were $261.0 \pm 20.4 \mu\text{m}$ and $288.4 \pm 38.4 \mu\text{m}$, respectively. The mean best corrected visual acuities of the IVB group were 0.29 ± 0.28 (logMAR units, 0.79 ± 0.55) at baseline and 0.26 ± 0.28 (logMAR units, 0.87 ± 0.56) at final visits. The change in logMAR visual acuity was not significant ($P=0.371$). The mean best corrected visual acuities of the control group were 0.51 ± 0.34 (logMAR units, 0.51 ± 0.61) at baseline and 0.53 ± 0.34 (logMAR units, 0.48 ± 0.57) at final visits. The change in logMAR visual acuity was not significant ($P=0.741$). Analysis of the relationship between the number of IVB injections and final-baseline SFCT differences in eyes with neovascular AMD demonstrated no correlation ($r=-0.088$, $P=0.568$).

Analysis of the relationship between final logMAR BCVA and final SFCT in IVB group demonstrated a significant negative correlation ($r=-0.357$, $P=0.016$, $P<0.05$). Final BCVA was positively correlated with final SFCT.

The morphologic changes in the choroid is of particular interest in neovascular AMD. Doppler flow and histologic studies have already disclosed that choroidal blood flow decreases with increased age^[10]. The abnormalities of the choroidal circulation have been postulated to contribute the development and progression of AMD^[11]. Compared with normal eyes, eyes with AMD have been shown to have decreased blood volume and abnormal flow^[12]. Decreased blood flow may be due to narrowing of the choriocapillaries lumen, loss of cellularity and thinning of the choroid or a combination of these^[11]. Recently, Spaide^[7] found decreased choroidal thickness in elderly patients with the use of

EDI-OCT. Manjunath *et al*^[13] demonstrated that most AMD patients had thinner choroids than age-adjusted normal volunteers and eyes with wet AMD had a thinner average choroidal thickness than eyes with dry AMD, possibly suggesting a role for choroidal thinning in the pathogenesis or progression of AMD.

The emergence of EDI-OCT allowed for more accurate evaluation of the choroidal cross-sectional structure and its thickness. The choroidal thickness in healthy individuals has been assessed in many studies by using OCT^[6,8,14]. However, only a few studies have examined the thickness of the choroid in AMD^[9,13,15]. Wood *et al*^[15] reported no significant change in choroidal thickness in early AMD. Whereas, Chung *et al*^[9] found that SFCT of eyes with exudative AMD and eyes with early AMD were significantly lower than age-matched normal subjects, $171 \mu\text{m}$ and $177 \mu\text{m}$ respectively. The changes in choroidal thickness during anti-VEGF therapy for neovascular AMD have been reported in only a few studies^[16,17]. In their prospective study, Yamazaki *et al*^[16] reported that SFCT decreased in eyes with neovascular AMD treated with intravitreal injection of ranibizumab. In contrast, Rahman *et al*^[17] suggested that no gross reduction appeared in SFCT in neovascular AMD patients after multiple intravitreal injections of anti-VEGF agents. In the current study, SFCT was measured before and after IVB therapy in eyes with neovascular AMD and compared the results with that of untreated fellow eyes. In eyes with neovascular AMD, the mean SFCT decreased from $216 \mu\text{m}$ to $205 \mu\text{m}$ over a mean of 22mo of follow up. In contrast, the mean SFCT decreased only from $207 \mu\text{m}$ to $206 \mu\text{m}$ in untreated fellow eyes. Our finding supports the study of Yamazaki *et al*^[16] in which the mean SFCT in eyes with neovascular AMD treated with intravitreal ranibizumab decreased from $244 \mu\text{m}$ at baseline to $226 \mu\text{m}$ at 3mo. The mean SFCT did not change through the following nine months and was $226 \mu\text{m}$ at 12mo. In our study, the rate of decrease in SFCT was found to be $6 \mu\text{m}/\text{y}$. This rate was greater than that of reported in normal eyes ($1.56 \mu\text{m}/\text{y}$)^[6]. Our results might indicate the possible effect of IVB on the choroidal structure in eyes with neovascular AMD.

In rabbits, bevacizumab penetrated full-thickness of retina to reach choroid in 24h after intravitreal injection^[18]. In the present study, decreased choroidal thickness in the IVB group might be related to the vasoconstrictive effects of the penetrating bevacizumab on the choroid. A similar effect was shown in eyes with central serous retinopathy treated with IVB^[19]. In their study, Yamazaki *et al*^[16] indicated the possibility that intravitreal ranibizumab influenced the choroidal structure under the neovascular membrane in neovascular AMD. However further studies are necessary for a better explanation to reduction in choroidal thickness after IVB injection.

In the present study, we found no correlation between the number of IVB injections and the SFCT. In addition, no correlation was found between the number of IVB injections and the difference of final and baseline SFCTs. However, we found a significant positive correlation between final SFCT and final best corrected visual acuity ($r=0.357$, $P=0.017$). Thus, visual acuity was better in eyes with thicker SFCT. Similar to our results, in their study with patients with typical exudative AMD. Kang *et al* [20] found that the patients who responded to 3 monthly intravitreal ranibizumab injections had significantly thicker subfoveal choroid at baseline and during 6-month follow-up and the responders showed significantly better visual outcome than the nonresponders. In contrast, Manjunath *et al* [13] found no correlations between choroidal thickness and the number of intravitreal anti-VEGF injections, duration of time since first diagnosis, and visual acuity.

In conclusion, SFCT seemed to decrease after IVB injections in eyes with neovascular AMD compared with untreated fellow eyes. Final visual acuity correlated significantly with SFCT. Further studies are necessary to understand the role of choroid in the pathophysiology of AMD.

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