Short-term Effect of Intravitreal Bevacizumab Therapy on Choroidal Structures in Eyes with Neovascular Age-related Macular Degeneration

Serdar Bilici[1], *Neriman Selçuk*[2]

ABSTRACT

Purpose: To evaluate the choroidal structural changes in neovascular age-related macular degeneration (nAMD) patients treated with intravitreal bevacizumab injection over a 3-month period

Materials and Methods: Medical records of 28 eyes with treatment-naïve nAMD were retrospectively analyzed before and after 3 monthly intravitreal injections of bevacizumab. Central macular thickness and subfoveal choroidal thickness were measured from enhanced depth imaging optical coherence tomography (EDI-OCT) scans. The ImageJ software was used to binarize OCT scans and measure the total choroid area (TCA), luminal area (LA), and stromal area (SA). The choroidal vascularity index (CVI) was calculated as the ratio of LA to TCA.

Results: After treatment, there were decreases in means of CMT (from 425.3 ± 136.0 to 341.6 ± 107.1 µm, p<0,001), SFCT (from 186.3 ± 67.6 to 172.7 ± 64.4 µm, p=0,02), and CVI (from 66.8 ± 6.7% to 64.3 ± 4.7%, p<0,01). No significant changes were observed in TCA (0.247 ± 0.09 vs 0.242 ± 0.08 mm2, p=0.15), LA (0.163 ± 0.05 vs 0.156 ± 0.05 mm2, p=0.052), and SA (0.083 ± 0.03 vs 0.086 ± 0.03 mm2, p=0.27).

Conclusion: Significant decline in SFCT and CVI after treatment demonstrates that bevacizumab affects choroidal vascular structures besides retinal layers in eyes with nAMD.

Keywords: Age-related macular degeneration, Anti-VEGF, Bevacizumab, Choroidal vascularity index, Optical coherence tomography.

INTRODUCTION

Age-related macular degeneration (AMD), which is the leading cause of visual disability among patients over 60 years, is a progressive degenerative disease of the macula.[1] Intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents that inhibit angiogenesis by inhibiting all isoforms of VEGF-A has been recommended as first-line therapy for neovascular AMD (nAMD) to suppress exudation induced by choroidal neovascularization (CNV).[2-5]

Subfoveal choroidal thickness (SFCT) changes have been evaluated to demonstrate the effect of anti-VEGF agents on choroidal structures, but the results are controversial.[6-13] However, SFCT is affected by numerous factors and also cannot provide detailed information about the vascular and stromal structure of the choroid.[14,15] Recently a more stable biomarker, choroidal vascularity index (CVI), that provides information on the relative change between the stromal and luminal vascular components of the choroid has been developed based on the binarization of enhanced depth imaging optical coherence tomography (EDI-OCT) images.[16] There are a few studies that found significantly decreased CT and CVI after treatment with aflibercept in nAMD eyes, however, to our knowledge there is no previous study about the effect of bevacizumab on CVI in eyes with treatment-naive nAMD.[17-19] The purpose of this study was to demonstrate the changes in the choroidal

1- Asst. Prof. Dr., Zonguldak Bulent Ecevit University, Department of Ophthalmology, Zonguldak, Türkiye

2- Dr., Zonguldak Bulent Ecevit University, Department of Ophthalmology, Zonguldak, Türkiye

Received: 20.12.2022
Accepted: 27.03.2022

J Ret-Vit 2023; 32:252-256

DOİ:10.37845/ret.vit.2023.32.42

Correspondence Adress:
Serdar Bilici
Zonguldak Bulent Ecevit University, Department of Ophthalmology, Zonguldak, Türkiye

Phone: +90 555 634 2989

E-mail: drserdarbilici@gmail.com

structure after 3 consecutive bevacizumab injections in eyes with treatment-naive nAMD.

MATERIALS AND METHODS

This retrospective study was conducted with 28 eyes of 28 treatment-naive nAMD patients who were examined at the Department of Ophthalmology of Zonguldak Bulent Ecevit University Hospital between September 2021 and June 2022. The study was approved by the Ethics Committee of Zonguldak Bulent Ecevit University (2022/06-11) and adhered to the tenets of the declaration of Helsinki. Informed consent was obtained from every patient before starting the treatment.

All patients underwent a detailed ophthalmic examination including best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, fundoscopy, fluorescein angiography, and spectral domain OCT imaging (Spectralis®, Heidelberg, Germany). All OCT images were obtained between 10:00 a.m. and 12:00 p.m. to minimize the effect of diurnal variations in the choroidal structures. The eyes with polypoidal choroidal vasculopathy, on the basis of protruded orange-red elevated lesions and/or those with polypoidal vasculopathy findings in OCT, history of any other retinal diseases like vascular occlusions, diabetic retinopathy, central serous retinopathy, previous intraocular intervention, IV injections, or laser photocoagulation, a spherical equivalent of –6 diopters or less, and presence of glaucoma were excluded.

All patients were treated with three consecutive monthly 1.25-mg intravitreal injections of bevacizumab. 1 month after the last injection, ophthalmic evaluation including BCVA testing, slit-lamp biomicroscopy, fundoscopy, and EDI-OCT imaging was repeated. CMT was measured manually as the distance from the internal limiting membrane to the retina pigment epithelium. SFCT was measured vertically from the outer surface of the retinal pigment epithelium to the choroidal-scleral interface.

Binarization of EDI-OCT images was performed with Image-J software (Version 1.50a; National Institutes of Health, Bethesda, MD, USA). 1500 µm wide area with the margins of 750-µm nasal and 750-µm temporal from the fovea was selected. Borders of the choroidal area were set manually with the Image-J ROI Manager. The image was adjusted by the Niblack auto-local threshold. Total choroidal area (TCA), luminal area (LA), and stromal area (SA) were measured (Fig. 1). CVI was formulated as the ratio between LA and TCA.[20] All measurements were made at baseline and 3rd month.

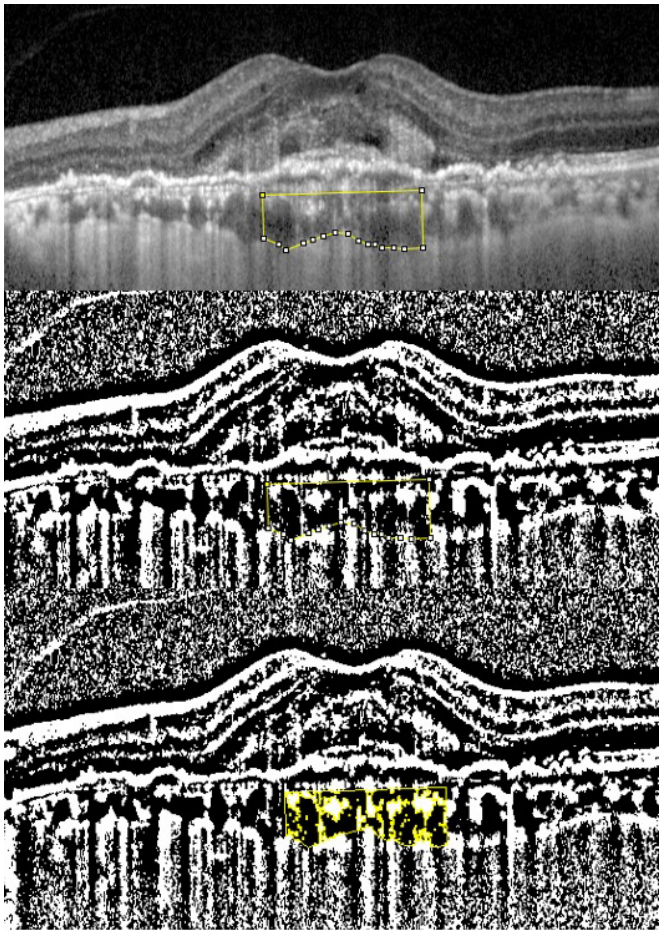

Figure 1: *Binarization of EDI-OCT images and calculation of stromal and luminal area with ImageJ software.*

Statistical Analysis

The analysis of the data was done using IBM SPSS 22.0 (SPSS Inc., Chicago, IL, USA) software. Descriptive statistics were defined as mean ±standard deviation for variables with normal distribution, median (min-max) for variables with non-normal distribution, and the number of cases (%) for nominal variables. To evaluate the differences in BCVA, CMT, SFCT, CVI, TCA, LA, and SA before and after bevacizumab injections, paired t-tests were performed. A p-value of <0.05 was considered statistically significant.

In the power analysis made with the G-power program (version 3.1.9.7), 90% power was calculated with a sample size of 28, 0.5 effect size, and a 5% margin of error.

RESULTS

Baseline Characteristics

A total of 28 eyes of 28 treatment-naive nAMD patients were enrolled in the study. Of the patients, 18 (64.3%) were males and 10 (35.7%) were females and the mean age was 76.5 ± 5.8 years. (Table 1)

Table 1: *Demographic and baseline clinical characteristics of patients*

Characteristic	Value
No. eyes	28
Age (years, mean ± SD)	76,5 ± 5,8
Gender (m/f)	18 / 10
BCVA (logMAR ± SD)	0,96 ± 0,51
Intraocular Pressure (mmHg± SD)	13,3 ± 4

SD standard deviation, BCVA best-corrected visual acuity, logMAR logarithm of the minimum angle of resolution

Changes in Visual Acuity

After the 3-month treatment period 12 (42.8%) eyes had improved, 10 (35.7%) eyes had stable, and 6 (21.4%) eyes had declined BCVA. The means of BCVA at the first and the last visit were 1.0 ± 0.5 and 0.9 ± 0.5 LogMAR, respectively. Although there was a slight improvement in the mean BCVA, this improvement didn't reach the level of statistical significance in the short term (p=0.18).

Changes in Central Macular Thickness

The mean CMT for all eyes decreased significantly from 425.3 ± 136.0 µm at baseline to 341.6 ± 107.1 µm at the final visit after bevacizumab therapy (p<0.001). (Table 2)

Changes in Subfoveal Choroid Thickness

The mean SFCT before and after bevacizumab therapy were 186.3 ± 67.6 and 172.7 ± 64.4, respectively. The decline in SFCT at the last visit was statistically significant (p=0.02). (Table 2)

Changes in Choroidal Vascularity Index

After treatment, there was a significant decrease in the mean CVI which was 66.8 ± 6.7 at baseline and 64.3 ± 4.7 at the final visit (p<0.01). There were no significant differences between initial and final visit means of the TCA (0.247 ± 0.09 vs 0.242 ± 0.08 mm^2, p=0.15), LA (0.163 ± 0.05 vs 0.156 ± 0.05 mm^2, p=0.052), and SA (0.083 ± 0.03 vs 0.086 ± 0.03 mm^2, p=0.27), respectively. Although there was a slight decline in LA, that couldn't reach the level of significance statistically. (Table 2)

DISCUSSION

In the present study, we evaluated choroidal structural changes in eyes with treatment-naive nAMD at baseline and after 3 consecutive intravitreal bevacizumab injections. There were significant decreases in CMT, SCFT, and CVI at the final visit. In addition, the binarization analyses of the choroid showed a reduction of TCA, and LA, however, these changes couldn't reach the level of significance statistically. Since CVI represents the proportion of LA and TCA, its decrease reflects a higher reduction in the vascular component rather than the stromal one.

Choroid has a key role in the pathogenesis of AMD and SFCT has been evaluated in several studies in these patients.[6-13, 21,22] It has been shown that eyes with nAMD have a thicker choroid compared with fellow eyes before anti-VEGF treatment.[21] Several previous studies have demonstrated a decrease in SFCT after both ranibizumab and aflibercept therapy.[6-10] Kim et al reported that the reduced SFCT after the anti-VEGF treatment was progressively increased by treatment cessation and it decreased again with further anti-VEGF administrations.[22] However, some studies reported no significant changes in SFCT after intravitreal injections of bevacizumab and ranibizumab.[11-13] The present study also documented a significant decline in SFCT in the short-term treatment with bevacizumab.

There is a limited number of studies about CVI changes in eyes with nAMD after anti-VEGF therapy.[17-19] Pellegrini et al reported that SCFT and CVI significantly decreased

Table 2: *Changes in optical coherence tomography parameters in eyes with nAMD after bevacizumab therapy*

Parameters	Baseline	3rd month	p
CMT (µm)	425.3 ± 136.0	341.6 ± 107.1	<0.001
SFCT (µm)	186.3 ± 67.6	172.7 ± 64.4	0.02
CVI (%)	66.8 ± 6.7	64.3 ± 4.7	<0.01
TCA (mm^2)	0.247 ± 0.09	0.242 ± 0.08	0.15
LA (mm^2)	0.163 ± 0.05	0.156 ± 0.05	0.052
SA (mm^2)	0.083 ± 0.03	0.086 ± 0.03	0.274

nAMD: neovascular age-related macular degeneration; SFCT: subfoveal choroidal thickness; CMT: central macular thickness; TCA: total choroidal area, LA luminal area, SA stromal area, CVI choroidal vascularity index

after 3 consecutive aflibercept treatments in nAMD eyes.[17] Temel et al also revealed a significant decrease in SFCT, LA, and CVI particularly in the 3rd month, and that significance was kept in the 12th month.[18] Alis et al reported that there was no significant decrease in CVI in 12-month follow-up with aflibercept injections, however, they also reported that while the number of injections increasing there is a decrease in CVI.[19] These studies include only aflibercept among anti-VEGF agents. To the best of our knowledge, this is the first study about the effect of bevacizumab on CVI. The present study demonstrated a significant decrease in CVI which leads us that bevacizumab also affects choroidal vascular structures as aflibercept in eyes with nAMD.

VEGF-A stimulates angiogenesis and promotes microvascular permeability and vasodilatation.[23] A decrease in VEGF levels with anti-VEGF therapy leads to a decline in choriocapillaris endothelial cell fenestrations and may result in decreased SFCT by reducing choroidal vascular permeability and/or vasoconstriction.[10,24] Bevacizumab is a humanized recombinant monoclonal antibody that inhibits angiogenesis by inhibiting all isoforms of VEGF-A.[3] The reduction in CVI by bevacizumab therapy in this study also supports this hypothesis. It's also claimed that the suppression of the CNV activity and leakage with anti-VEGF treatment may also lead to choroidal changes in eyes with nAMD.[17,18]

The most important limitation of the present study was its retrospective design which hindered us from assessing potential confounders such as axial length, systemic blood pressure, and smoking which may affect choroidal parameters.[14, 15] In addition, the lack of a control group, fewer participants, and a short follow-up period are other limitations.

CONCLUSION

The present study showed that intravitreal bevacizumab therapy leads to a decrease in SFCT, and CVI of treatment-naive nAMD patients. Bevacizumab, as an anti-VEGF agent, affects not only retinal layers but also choroidal structures in eyes with nAMD.

REFERENCES

1. Friedman DS, O'Colmain BJ, Muñoz B, et al. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 2004;122:564-72.
2. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–31.
3. CATT Research Group; Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011;364:1897-908.
4. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology 2012;119:2537–48.
5. Nguyen CL, Oh LJ, Wong E, et al. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration: a meta-analysis of randomized controlled trials. BMC Ophthalmol 2018;18:130. doi: 10.1186/s12886-018-0785-3.
6. Yamazaki T, Koizumi H, Yamagishi T, et al. Subfoveal choroidal thickness after ranibizumab therapy for neovascular age-related macular degeneration: 12-month results. Ophthalmology 2012;119:1621-7.
7. Gharbiya M, Cruciani F, Mariotti C, et al. Choroidal thickness changes after intravitreal antivascular endothelial growth factor therapy for age-related macular degeneration: Ranibizumab versus Aflibercept. J Ocul Pharmacol Ther 2015;31:357-62.
8. Koizumi H, Kano M, Yamamoto A, et al. Short-term changes in choroidal thickness after aflibercept therapy for neovascular age-related macular degeneration. Am J Ophthalmol 2015;159:627-33.
9. Yun C, Oh J, Ahn J, et al. Comparison of intravitreal aflibercept and ranibizumab injections on subfoveal and peripapillary choroidal thickness in eyes with neovascular age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 2016;254:1693-702.
10. Koizumi H, Kano M, Yamamoto A, et al. Subfoveal choroidal thickness during aflibercept therapy for neovascular age-related macular degeneration: twelve-month results. Ophthalmology 2016;123:617-24.
11. Ellabban AA, Tsujikawa A, Ogino K, et al. Choroidal thickness after intravitreal ranibizumab injections for choroidal neovascularization. Clin Ophthalmol 2012;6:837-44.
12. Kim H, Lee K, Lee CS, et al. Subfoveal choroidal thickness in idiopathic choroidal neovascularization and treatment outcomes after intravitreal bevacizumab therapy. Retina 2015;35:481-6.
13. Minnella AM, Federici M, Falsini B, et al. Choroidal thickness changes after intravitreal ranibizumab for exudative age-related macular degeneration. BioDrugs 2016;30:353-9.
14. Gupta P, Jing T, Marziliano P, et al. Distribution and determinants of choroidal thickness and volume using automated segmentation software in a population-based study. Am J Ophthalmol 2015;159:293-301.e3.
15. Sansom LT, Suter CA, McKibbin M. The association between systolic blood pressure, ocular perfusion pressure and subfoveal choroidal thickness in normal individuals. Acta Ophthalmol 2016;94:e157-e158.

16. Iovino C, Pellegrini M, Bernabei F, et al. Choroidal Vascularity Index: An In-Depth Analysis of This Novel Optical Coherence Tomography Parameter. J Clin Med. 2020;9:595.
17. Pellegrini M, Bernabei F, Mercanti A, et al. Short-term choroidal vascular changes after aflibercept therapy for neovascular age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2021;259:911-8.
18. Temel E, Örnek K, Aşıkgarip N. Choroidal structural changes determined by the binarization method after intravitreal aflibercept treatment in neovascular age-related macular degeneration. Int J Ophthalmol 2021;14:1213-7.
19. Alis A, Guler Alis M. Long-term effect of intravitreal aflibercept treatment on choroidal vascularity index in neovascular age-related macular degeneration. Photodiagnosis Photodyn Ther 2021;36:102582.
20. Vupparaboina KK, Nizampatnam S, Chhablani J, et al. Automated estimation of choroidal thickness distribution and volume based on OCT images of posterior visual section. Comput Med Imaging Graph 2015;46:315-27.
21. Koh LHL, Agrawal R, Khandelwal N, et al. Choroidal vascular changes in age-related macular degeneration. Acta Ophthalmol 2017;95:e597-e601.
22. Kim YK, Park SJ, Woo SJ, et al. Choroidal thickness change after intravitreal anti-vascular endothelial growth factor treatment in retinal angiomatous proliferation and its recurrence. Retina 2016;36:1516-26.
23. Tilton RG, Chang KC, LeJeune WS, et al. Role for nitric oxide in the hyperpermeability and hemodynamic changes induced by intravenous VEGF. Invest Ophthalmol Vis Sci 1999;40:689-96.
24. Peters S, Heiduschka P, Julien S, et al. Ultrastructural findings in the primate eye after intravitreal injection of bevacizumab. Am J Ophthalmol 2007;143:995-1002.