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The Impact of Intravitreal Ranibizumab Treatment on Outer Retinal Layer Thickness in Neovascular Age-related Macular Degeneration

Neovasküler Yaşa Bağlı Maküla Dejenerasyonunda Intravitreal Ranibizumab Tedavisinin Dış Retinal Tabaka Kalınlığı Üzerine Etkisi

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ABSTRACT

Background: In this study, it was aimed to evaluate outer retinal layer thickness (ORLT) via spectral-domain optical coherence tomography (SD-OCT) in age-related macular degeneration (AMD) patients treated with intravitreal ranibizumab injection.

Materials and Methods: Patients with unilateral neovascular AMD who received intravitreal ranibizumab injection with a follow-up period of at least 24 months were retrospectively identified. The fellow eyes with dry AMD served as a control group. Data on best corrected visual acuity (BCVA) and OCT findings on ORLT were recorded at baseline, at 12- and 24-month follow-ups.

Results: Sixty-four eyes of 32 patients were included. The mean number of injections was 10.7 over a 24-month period. In the injection group, ORLT was 81.6±4.7 μm before the treatment, and decreased to 80.9±4.8 μm and 78.8±4.8 μm at 12- and 24-month follow-ups, respectively. In the control group, the same parameters were 81.9±4.4 μm, 81.6±4.4 μm and 80.8±4.3 μm, respectively. In both groups, a significant decline was noted in ORLT from baseline to 12- and 24-month follow-ups and from 12- to 24-month follow-ups ($p<0.001$, all values). While the injection and control groups were similar in terms of baseline ORLT, at the 24-month follow-up, ORLT was significantly lower in the injection group ($p=0.043$). The changes in BCVA were not significant from baseline to 12- and 24-month follow-ups in both groups ($p>0.05$, all values). A significant positive correlation was noted between the decrease in ORLT and the number of injections ($p<0.05$, all values).

Conclusion: ORLT was found to be decreased significantly in the natural course of AMD regardless of the subtype, whereas the decrease in ORLT was aggravated by ranibizumab injection in neovascular AMD eyes.

Keywords: Age-related macular degeneration, neovascular, OCT, outer retinal layer thickness, ranibizumab

ÖZ

Amaç: İntravitreal ranibizumab enjeksiyonu ile tedavi edilen yaşa bağlı maküla dejenerasyonu (YBMD) hastalarında dış retinal tabaka kalınlığının (DRTK) spektral-domain optik koherens tomografi (SD-OKT) ile değerlendirilmesi.

Gereç ve Yöntemler: Tek taraflı neovasküler YBMD nedeniyle intravitreal ranibizumab tedavisi almış en az 24 aylık takibi olan hastalar retrospektif olarak incelendi. Kuru tip YBMD olan diğer gözler kontrol grubu olarak kabul edildi. Başvuru anındaki, 12. aydaki ve 24. aydaki en iyi düzeltilmiş görme keskinlikleri (EİDGK) ve SD-OKT'deki DRTK değerleri kaydedildi.

Bulgular: Otuz iki hastanın 64 gözü dahil edildi. Yirmi dört aylık sürede ortalama enjeksiyon sayısı 10,7 idi. Enjeksiyon grubunda DRTK, tedaviden önce 81,6±4,7 μm iken, 12. ve 24. aylarda sırasıyla 80,9±4,8 μm'ye ve 78,8±4,8 μm'ye düştü. Aynı parametreler kontrol grubunda sırasıyla, 81,9±4,4 μm, 81,6±4,4 μm ve 80.8±4.3 μm idi. Her iki grupta da hem başlangıçtan 12. ve 24. ay kontrollere hem de 12. ay kontrolden 24. ay kontrole DRTK'de anlamlı düşüş vardı ($p<0,001$, tüm değerler). Başlangıçta DRTK açısından enjeksiyon ve kontrol grupları benzer olsa da 24 ayın sonunda DRTK enjeksiyon grubunda anlamlı derecede düşüktü ($p=0,043$). Her iki grupta da başlangıç, 12 ve 24. aylardaki EİDGK değişiklikleri anlamlı değildi ($p>0,05$, tüm değerler). DRTK azalma ve toplam enjeksiyon sayısı arasında pozitif anlamlı korelasyon izlendi ($p<0,05$, tüm değerler).

Sonuç: YBMD'nin alt tipinden bağımsız olarak hastalığın doğal seyrinde DRTK anlamlı olarak azalmaktadır. Bununla birlikte neovasküler YBMD'li gözlere uygulanan ranibizumab enjeksiyonu bu azalmayı şiddetlendirmektedir.

Anahtar Kelimeler: Dış retinal tabaka kalınlığı, neovasküler, OKT, yaşa bağlı maküla dejenerasyonu, ranibizumab

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Introduction

Neovascular age-related macular degeneration (AMD) is a progressive disease and a leading cause of permanent vision loss in the older age (1,2,3). The safety and efficacy of anti-vascular endothelial growth factor (VEGF) drugs in the management of neovascular AMD have consistently been reported worldwide, whereas because of limited information about anti-VEGF ocular pharmacokinetics, no standard practice exists regarding the administration schedules in clinical practice (4,5,6,7,8). Ranibizumab inactivates all VEGF-A isoforms, enabling anatomic and functional healing in choroidal neovascularization (CNV) in patients with neovascular AMD (5,6).

The introduction of spectral-domain optical coherence tomography (SD-OCT) to the practice of ophthalmology has provided high-resolution retinal images that help to collect detailed data on the quantitative assessment of each retinal layer for the investigation of diseases affecting specific retinal layers (9). The outer retinal layer, involving photoreceptors, retinal pigment epithelium (RPE), and Bruch's membrane, is considered likely to undergo degenerative changes related to the aging process. AMD-related changes are also characterized by an increase in thickness of the Bruch's membrane initially, progressing to a loss of RPE and photoreceptors in dry AMD, and the development of CNV in neovascular AMD (10,11).

Non-etheless, VEGF is a mediator with vital importance for retinal photoreceptors, Müller cells, and RPE as well as for the integrity of choriocapillaris (12,13). Inner retinal layers with a peripapillary nerve and retinal ganglion cell layer rather than outer retinal layer have become more extensively addressed by the segmentation studies in AMD patients with limited data on SD-OCT-based automatic segmentation analysis of outer retinal layer in relation to visual function in neovascular AMD patients (8,14,15,16,17). Hence, whether the VEGF suppression has potential age independent hazards on the outer retina remains an enigma.

This study was therefore designed to quantitatively evaluate outer retinal layer thickness (ORLT) via SD-OCT in neovascular AMD patients treated with intravitreal ranibizumab in comparison to fellow (untreated) eyes with dry AMD.

Material and Methods

Study Population

The examination records of patients with neovascular AMD who received intravitreal ranibizumab injection treatment at a tertiary-care ophthalmology clinic between January 2014 and December 2017 were retrospectively reviewed. Patients with neovascular AMD in one eye and dry AMD in the fellow eye were included in the study. They were treated with intravitreal ranibizumab with pro re nata (PRN) basis following three loading doses for subfoveal CNV and those with CNV lesions with borders not extending beyond the inner circle (r: 0.5-1.5 mm) of the ETDRS grid on OCT images. Fellow (untreated) eyes with dry AMD served as a control group. The exclusion criteria of the study included having inability to clearly detect retinal layers in OCT because of opacity, development of CNV in the control eye within 24 months, prior history of ocular surgery (except uncomplicated cataract surgery at least six months ago), comorbid diabetic retinopathy, retinal vein occlusion, ocular inflammation, glaucoma or optic nerve diseases and follow-up of less than 24 months.

This study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Ankara Training and Research Hospital (no. E-19-168). Patients gave written informed consent before the study procedures.

Assessments

All patients underwent complete ophthalmologic examination including measurement of best-corrected visual acuity (BCVA) by using Snellen chart and SD-OCT imaging at baseline and monthly visits as well as fundus fluorescein angiography before the first injection. BCVA was recorded as Snellen fractions and converted to equivalent a logarithm of the minimal angle of resolution (logMAR) values. Retreatment was given after three loading doses every four weeks on an as-required basis depending on predefined OCT (presence of subretinal and/or intraretinal fluid in monthly OCT imaging) and clinical criteria (hemorrhage in fundus examination). Data on patient demographics (age, gender), number of injections, ophthalmic examination findings, including BCVA (logMAR) and OCT findings on ORLT, were recorded both at baseline and at 12- and 24-month follow-ups and compared between neovascular AMD (injection group) and dry AMD (control group) eyes. The correlation of decrease in ORLT and the number of injections were also analyzed.

OCT Measurements

ORLT was measured with SD-OCT (Spectralis SD-OCT, Heidelberg, Germany) by two experienced examiners (BSG, MK). The technique for automated retinal segmentation of the SD-OCT device was performed to identify each retinal layer and quantify ORLT, from the external limiting membrane to the Bruch's membrane. Of the nine ETDRS macular areas (which include a central 0.5 mm circle, and

inner and outer rings measuring 0.5-1.5 mm and 1.5-3.0 mm in diameter, respectively), only measurements from outer ring were acquired, where disease pathology was usually least severe, and retinal layers were most easily distinguishable. An average of ORLT values obtained from superior, inferior, nasal, and temporal quadrants of the outer ring as automatically divided by the segmentation application of the SD-OCT device was evaluated (Figure 1).

Statistical Analysis

Statistical analysis was made using SPSS version 15.0. Data were expressed as mean ± standard deviation, minimum-maximum and percent (%) where appropriate. The normal distribution of the variables was tested using visual (histogram and probability plots) and analytical (Shapiro-Wilk tests) methods. The data showed an abnormal distribution; therefore, nonparametric tests were used for the analysis. The Mann-Whitney U test (for values between two independent groups) and the Friedman test (for values among three dependent groups) were used to analyze numerical variables. If there was a significant difference among three or more independent groups, the Bonferroni correction was applied in post-hoc binary comparisons. Correlation analysis was performed using the Spearman correlation analysis. We considered $p<0.05$ as statistically significant.

Results

Sixty-four eyes of 32 patients were included in the study. The mean age of patients at the initiation of treatment

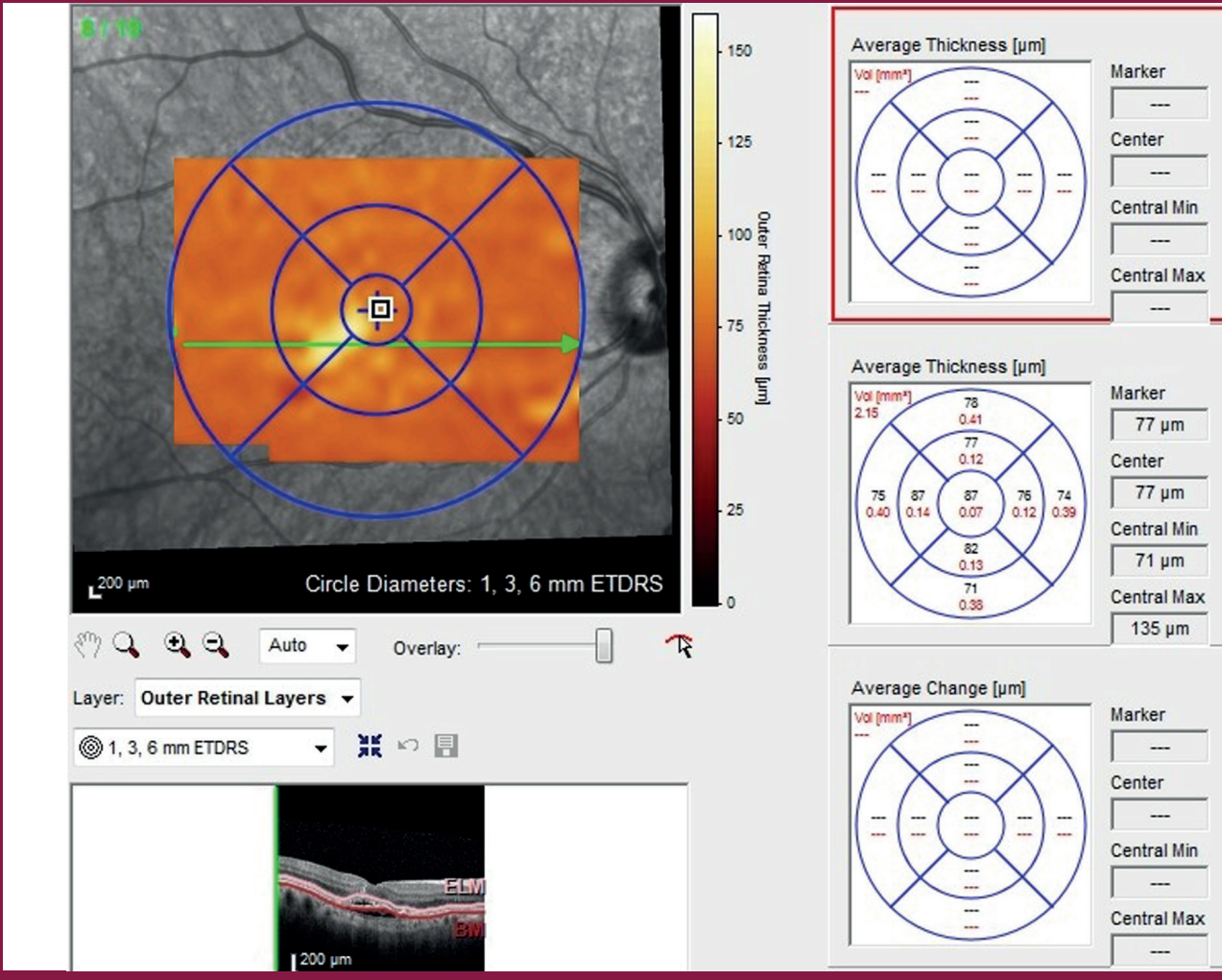

Figure 1. Representation of automated retinal layer segmentation and thickness measurements obtained by spectral-domain optical coherence tomography, regarding average ORLT values obtained from superior, inferior, nasal and temporal quadrants of outer ring as automatically divided by the segmentation application of the SD-OCT device
ORL: Outer retinal layer, SD-OCT: Spectral-domain optical coherence tomography

was 68.4±2.1 years (range: 57 to 78). There were 14 males (43.7%) and 18 females (56.3%). The mean number of injections was 10.7±3.5 (range: 7 to 17) over a 24 month period. In the injection group, the mean ORLT was measured as 81.6±4.7 µm (range: 75 to 93) before the treatment, and decreased to 80.9±4.8 µm (range: 75 to 92) and 78.8±4.8 µm (range: 72 to 90) at 12 and 24-month follow-up respectively. In the dry AMD (control) group, the same parameters were 81.9±4.4 µm (range: 75 to 93), 81.6±4.4 µm (range: 75 to 92), and 80.8±4.3 µm (range: 74 to 91), respectively. In both injection and control groups, a significant decline was noted in ORLT from baseline to 12 and 24 months follow-up and from 12 to 24 months follow-up (p<0.001, all values) (Table 1). While the injection and control groups were similar in terms of baseline ORLT, at the 24-month of follow up, ORLT was significantly lower in the injection group (p=0.043) (Table 1).

Considering BCVA, in the injection group, the mean BCVA was found to be improved at each annual follow-up compared to that of baseline, but not significantly (p>0.05). Also, the changes in BCVA were not statistically significant in the control group from baseline to 12- and 24-months follow-up (p>0.05) (Table 1).

A significant positive correlation was noted between the decrease in ORLT and the number of injections from baseline to 12- month (Figure 2a) and 24-month follow-up (Figure 2b) and from 12-month to 24-month follow-up (Figure 2c), (r=0.472, p=0.006; r=0.632, p<0.001; r=0.376, p=0.034, respectively) in the injection group.

Discussion

VEGF has been considered as an important mediator for the development of CNV in animal studies (18). Intravitreal

Table 1. ORL thickness and BCVA in injection and control eyes

		Baseline	12th month	24th month	p[a]
		mean ± SD (min-max)	mean ± SD (min-max)	mean ± SD (min-max)	
ORL (µ)	Injection	81.6±4.7 (75-93)	80.9±4.8 (75-94)	78.8±4.8 (72-92)[0,12]	<0.001**
	Control	81.9±4.4 (76-92)	81.6±4.4 (75-91)	80.8±4.3 (74-91)[0,12]	<0.001**
	p[b]	0.691	0.462	0.043	
GK (LogMAR)	Injection	0.61±0.32 (0.1-1.0)	0.59±0.35 (0-1.0)	0.58±0.38 (0-1.0)	0.308
	Control	0.16±0.13 (0-0.5)	0.17±0.13 (0-0.5)	0.17±0.13 (0-0.5)	0.577
	p[b]	<0.001**	<0.001**	<0.001**	

SD: Standard deviation, [a]: Friedman test, [b]: Mann-Whitney U test, 0: There was a significant difference in post-hoc binary comparison with "baseline", 12: There was a significant difference in post-hoc binary comparison with "12th month" ORL: Outer retinal layer, BCVA: Best corrected visual acuity, LogMAR: Logarithm of the minimal angle of resolution

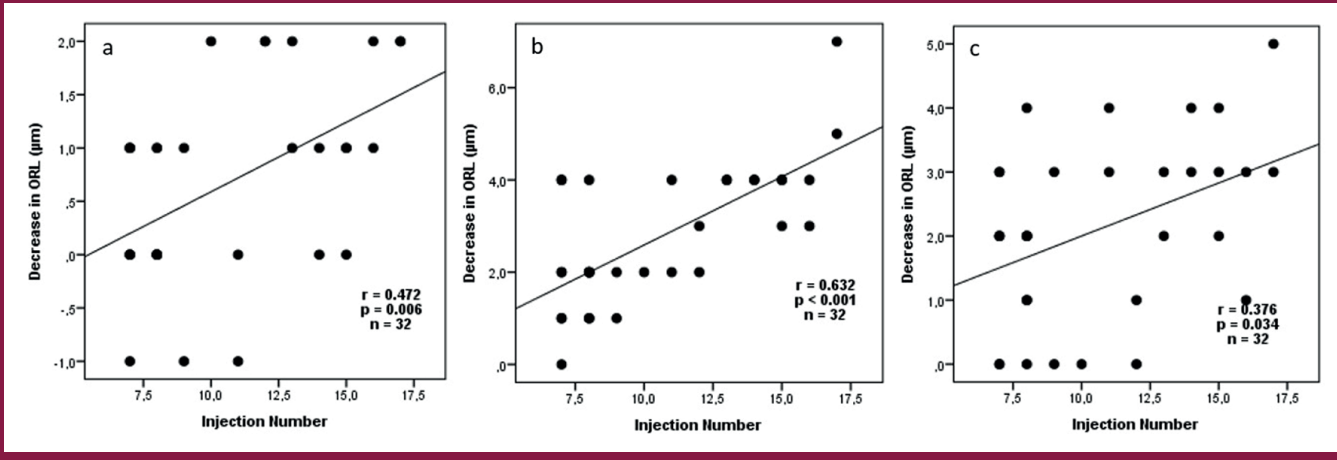

Figure 2. Scattered diagrams showing a positive correlation between decrease in ORLT and the number of injections from baseline to 12-month follow-up (r=0.472, p=0.006) (a), baseline to 24-month follow-up (r=0.632, p<0.001) (b), and from 12-month to 24-month follow-up (r=0.376, p=0.034) (c)
ORLT: Outer retinal layer thickness

usage of anti-VEGF drugs increases vision by reducing leakage from CNV, but repeated injections are required to maintain the effect. When the treatment regimen is applied steadily at regular intervals, the best visual acuity is achieved, while the risk of unnecessary injections into the dry lesion arises. In the PRN regimen, injection is made during monthly controls depending on whether there is any fluid present in OCT (19). In any kind of treatment regimens, anti-VEGF therapy should be continued for a long time related to the natural course of the disease. Continuous inhibition of VEGF with anti-VEGF therapy can reduce the VEGF level, which is also necessary for ocular homeostasis thereby causes RPE and choriocapillaris atrophy (20,21).

In the SEVEN-UP study that reports seven-year results of intravitreal ranibizumab injection in the treatment of CNV secondary to AMD, 98% of the eyes developed macular atrophy (22). In the two-year results of the Comparison of Age-Related Macular Degeneration Treatment Trials (CATT) study comparing ranibizumab and another anti-VEGF drug, i.e., bevacizumab, it was reported that more geographic atrophy was observed in patients receiving monthly treatment for both agents compared to the PRN group. It was also reported that VEGF was important to keep normal functioning of the retina and the integrity of the choriocapillaris via RPE, and its blockage might cause the development and progression of geographic atrophy (23). Five-year results of the CATT study showed that there was no statistical difference between monthly treatment and PRN treatment regimens in terms of the risk of developing geographic atrophy (24). According to clinical studies, since there is an increase in the frequency of geographic atrophy in eyes treated with anti-VEGF therapy, whether this condition develops in association with the anti-VEGF therapy or results from the natural course of the disease is controversial.

Of experimental studies to demonstrate the retinal toxicity of anti-VEGF therapy are quite controversial either. In an animal study with mice, systemic administration of the adenoviral vector expressing VEGFR1 was shown to cause photoreceptor degeneration, and it was emphasized that VEGF must have been vital for photoreceptors and Müller cells (12). However, various publications show that VEGF suppression does not negatively affect photoreceptors (13,25).

So, is it possible to show clinically the effects of anti-VEGF medications on retina and RPE? The segmentation feature in the new generation OCTs could be used to assess the progression of specific retinal disorder by quantitatively measuring the thickness of the retinal layers.

OCT-segmentation studies enable to report thickness changes in inner retinal layers associated with the treatment of neovascular AMD with ranibizumab (14,15,16,17). Moreover, in an OCT segmentation study that investigated the impact of aging on the outer retinal layer and choroid, it was shown that the RPE and photoreceptor layers and the choroidal thickness decreased with increasing age (26). Another study reported that patients with dry AMD in one eye had more thinning in the RPE-photoreceptor layer thickness in the healthy eye compared to the normal population of the same age group (27).

In a study evaluating the effect of intravitreal ranibizumab treatment of neovascular AMD on all retinal layers, it was reported that there was a significant thinning in the inner retina layers after one year of treatment, and a significant decrease in total outer retinal layer and RPE thickness was restricted to occur for the first three months (14). However, the lack of a control group in the relevant study cannot exclude the effect of the natural course of the disease in this thinning. The current study revealed a significant decrease in ORLT in neovascular AMD patients treated with ranibizumab when compared to both pretreatment levels and corresponding outer retinal layer values in fellow eyes with dry AMD. Notably, a decrease was noted in ORLT along with an increase in the number of ranibizumab injections in eyes with neovascular AMD. In the presence of CNV, the evaluation of the outer retinal layers using the OCT segmentation method is difficult because the lesion often has complex configuration. In the current study, measurements from the outer ring were acquired enabling data on the outer retinal layer from quadrants outside the CNV lesion, where disease pathology was usually least severe and retinal layers were most easily distinguishable, increasing the reliability of measurements. Hence, our findings suggest a decrease in ORLT in both injection (neovascular AMD) and control (dry AMD) eyes during follow-up, whereas there is an association of intravitreal ranibizumab injection with further reduction in ORLT in eyes with AMD as compared to outer retinal layer changes in the fellow (untreated) eyes with dry AMD.

Our findings revealed no significant change in BCVA at the end of the two-year ranibizumab injection treatment. The reason for this insignificant increase in visual acuity may be due to the regimen applied. In the HORIZON study, it was reported that the increase in vision which was achieved with monthly ranibizumab injections for two years decelerated upon lowering the injection frequency (6). Another reason for the insignificant increase in visual acuity may be due to the fact that all of the lesions included in this study were located subfoveally. However, besides the poorer visual acuity at baseline in eyes with neovascular AMD versus dry AMD, no significant change was noted in

visual acuity under ranibizumab therapy in neovascular AMD eyes in our cohort, despite the correlation of frequency of injections with a decrease in ORLT. Nonetheless, our findings support the likelihood of considering additional morphologic characteristics of CNV lesions on OCT to improve the observed correlations of retinal changes with visual function (28).

The major strength of the current study is the inclusion of fellow eyes as for the control group to recognize the direct effects of ranibizumab injection on ORLT and the use of OCT data from the areas outside of the CNV lesion in measuring ORLT improved the reliability of measurements. However, certain limitations of this study should be considered. First, the relatively low sample size might prevent us from achieving statistical significance concerning the visual acuity changes and limit the generalizability of our results. Second, the changes in total retinal thickness were not evaluated in the study. Therefore, it is not possible to assess whether the resolution of edema may be more responsible for the thinning rather that "drug induced atrophy".

In conclusion, in the current study, ORLT was found to be decreased significantly in the natural course of AMD regardless of the subtype, whereas the decrease in ORLT was aggravated by ranibizumab injection in neovascular AMD eyes.

Study Limitations

The relatively low sample size might prevent us from achieving statistical significance concerning the visual acuity changes and limit the generalizability of our results. And also, the changes in total retinal thickness were not evaluated in the study. Therefore, it is not possible to assess whether the resolution of edema may be more responsible for the thinning rather that drug induced atrophy.

Conclusion

In the current study ORLT was found to be decreased significantly in the natural course of AMD regardless of the subtype, whereas the decrease in ORLT was aggravated by ranibizumab injection in neovascular AMD eyes.

Ethics

Ethics Committee Approval: Ethics committee approval was received from Ankara Training and Research Hospital (no: E-19-168).

Informed Consent: Patients gave written informed consent before the study procedures.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Ş.G., M.K., Concept: B.Ş.G., Design: B.Ş.G., Data Collection or Processing: M.K., Analysis or Interpretation: B.Ş.G., Literature Search: B.Ş.G., Writing: B.Ş.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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