Intravitreal Ranibizumab and Bevacizumab Treatment for Pigment Epithelium Detachment with Exudative Age Related Macular Degeneration: Long-Term Visual and Anatomical Results

Eksudatif Yaşa Bağlı Makula Dejenerasyonu ile İlişkili Pigment Epitel Dekolmanlı Hastalarda İntravitreal Ranibizumab ve Bevacizumab Tedavinin Uzun Dönem Anatomik ve Fonksiyonel Sonuçları

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ABSTRACT

Purpose: To evaluate the effect of vascular endothelial growth factor (VEGF) inhibition on vascularized pigment epithelium detachment (vPED) associated with exudative age-related macular degeneration (AMD).

Material and Methods: The records of patients with exudative AMD associated with vPED who have been treated with anti-VEGFs were reviewed for outcome of measures to determine the effects of treatment on the lesion characteristics and vPED dimensions. Best corrected visual acuity (BCVA), central foveal thickness (CFT) and vPED height measurements in optical coherence tomography (OCT) were recorded for each eye. Fluorescein angiography (FA)was performed initially and as needed thereafter to determine the lesion characteristics and PED diameter.

Results: One hundred and six eyes of 96 patients were included in the study. All of the patients had received three loading doses of anti-VEGF followed by PRN (pro re nata) (as needed) dosing regimen. The mean follow-up time was 22.4±2.3months (20-35mo).The mean number of anti-VEGF injections was 8.5±2.3 (4-12). The best-corrected visual acuity (BCVA) did not vary significantly; the central foveal thickness (CFT), PED height, and PED diameters decreased significantly at the end of follow-up. Complete resolution of PED was noted only in 21.6% of eyes; persistence of PED was observed in 78.4% of eyes. The persistence or resolution of PED in response to treatment did not correlate with the final visual acuity. Twenty one out of 106 eyes (19.8%) developed retina pigment epithelium (RPE) tear.

Conclusions: This retrospective study showed that intravitreal anti-VEGF therapy for vPED preserved vision and reduced PED height and diameter; also demonstrated that the anatomical response of the PED may not correlate directly with the visual outcome.

Key Words: Age related macular degeneration, anti-VEGF treatment,choroidal neovascularization, pigment epithelial detachment.

ÖZ

Amaç: Eksudatif tip yaşa bağlı makula dejenerasyonu (eksudatif YBMD) ile ilişkili vaskularize pigment epitel dekolmanlı (vPED) hastalarda anti vasküler endotelyal büyüme faktörü (anti-VEGF) tedavisinin etkinliğini araştırmak.

Gereç ve Yöntem: Eksudatif YBMD ile ilişkili vPED'li ve anti-VEGF tedavi almış hastaların kayıtları retrospektif olarak incelendi. Tedavinin lezyon karakteristikleri ve PED boyutları üzerine etkileri irdelendi.Başlangıçta ve tedavi boyunca olan tüm vizitlerde en iyi düzeltilmiş görme keskinlikleri belirlendi ve santral foveal kalınlık (SFK) ve vPED yükseklikleri optik koherens tomografi kullanılarak kaydedildi.Fundus florosein anjiografi kayıtları başlangıçta ve takiplerde lezyon özelliklerini ve PED çapını belirlemek için kullanıldı.

Bulgular: Doksan altı hastanın 106 gözü çalışmaya dahil edildi. Tüm hastalara üç doz yükleme anti-VEGF tedavisi sonrasında gerektiğinde (pro renata-PRN) tedavi protokolü uygulandı. Ortalma takip süresi 22.4±2.3 ay (20-35 ay) iken ortalama tedavi sayısı 8.5±2.3 (4-12) idi. Son takipte en iyi görme keskinliği başlangıca göre anlamlı olarak değişmezken; SFK; vPED çapı ve yüksekliği anlamlı olarak azaldı.Ortalma gözlerin %21.6'sında vPED tamamen kaybolurken %78.4'sında varlığını sürdürdü. Vaskülarize PED boyutlarındaki değişim ile görme keskinlikleri arasında ilişki gözlenmedi. Tedavi süresince 106 gözün 21'inde (%19.8) retina pigment epitel yırtığı saptandı.

Sonuç: Eksudatif YBMD ile ilişkili vPED'li hastalarda anti-VEGF tedavi ile görme keskinliği korunurken vPED çap ve yüksekliği azalma göstermiştir ancak görme keskinliği ile vPED çapları arasında anlamlı ilişki saptanmamıştır.

Anahtar Kelimeler: Anti-VEGF tedavi, koroid neovaskülarizasyonu, pigment epitel dekolmanı,yaşa bağlı makula dejenerasyonu.

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INTRODUCTION

Retinal pigment epithelium detachment (PED) is the result of physical separation of the retinal pigment epithelium from the underlying Bruch's membrane. PED in the presence of age-related macular degeneration (AMD) can be classified into the following four subtypes according to clinical, angiographic, and optical coherence tomography (OCT) features:1-4drusenoid PED, serous PED, vascularized PED (vPED), and hemorrhagic PED. Each type has distinct characteristics and a different underlying pathogenesis. Drusenoid PED is produced by one or more large drusen or by the confluence of soft drusen. It typically represents an intermediate stage of AMD, and it is generally considered the PED subtype with a better short-term visual prognosis. Serous PED is characterized by the accumulation of sub-RPE fluid caused by two main mechanisms: exudation from choroidal neovascularization (CNV) and the presence of an hydrophobic lipoproteic barrier on Bruch membrane that blocks the fluid transport between RPE and choroid.[1-4] In vPED, growth of an occult CNV with secondary extravasation of fluid is thought to be responsible for the retinal pigment epithelium elevation.[1-4] This type of PED has original angiographic features and is considered to be a subtype of occult CNV. It is also referred to as "fibrovascular PED". Also vPED is characterized by the presence of a fibrovascular membrane and exudative accumulation of fluid that alter the proper apposition of the RPE layer to the Bruch membrane.

No proven treatment exists for all types of PEDs. It has been shown that most lesions associated with PED have limited response to anti-vascular endothelial growth factor (VEGF) treatment.[5-8]

The aim of this study was to evaluate the effect of anti-VEGF treatment on vPED associated with CNV secondary to AMD and to examine the correlations between the functional and anatomical outcomes.

MATERIALS AND METHODS

Patients and Study Design: This was a retrospective single-arm study. The records of patients with exudative AMD associated with vPED who have been treated with anti-VEGFs between 2007 and 2012 in our retina clinic were reviewed retrospectively to determine the effects of treatment on the lesion characteristics and PED dimensions. Eyes with other ophthalmic pathology affecting vision (e.g. visually significant cataract, optic nerve pathology, corneal opacity, vitreous hemorrhage), other retinal vascular diseases, history of vitrectomy or trabeculectomy, follow-up period of <20 months; lesions with serous or hemorrhagic PED, retinal angiomatous proliferation and large subretinal hemorrhage being >50% of the lesion were excluded from the study.

Visual acuity testing, ophthalmologic examination, lesion characteristics in fluorescein angiography (FA), central foveal thickness (CFT) and vPED dimensions measurements were recorded for each eye for each visit records. The study was approved by the local Ethics Committee. All applicable institutional and governmental regulations concerning the ethical use of data of human volunteers were followed during this research.

Study Procedures: The patients' demographics, best-corrected visual acuity (BCVA), ophthalmologic examination records, fluorescein angiography findings (e.g. lesion characteristics, total lesion sizes and PED diameter) and OCT findings (OCT Stratus, Carl Zeiss Meditec, Dublin, CA)were reviewed at initial and 3, 6,12, 20th month visits. Patients without FA records in all visits were excluded from the study. ETDRS chart was used for BCVA measurements and the logMAR scale was used for comparisons. The maximum PED height (μm) was determined using the retinal thickness analysis protocol and The built-in manual calipers in OCT for every visit9 and total area and PED diameter were measured as greatest linear diameter(GLD) in FA records (Topcon Imagenet i-base, Japan). PED diameter were measured as mm. Total lesion area were measured as mm^2. Also the rate of RPE tear development was determined.Treatment dosing regimen and number of anti-VEGF treatments for each eye were also recorded. All of the patients had received three loading doses of anti-VEGF followed by PRN (pro re nata) (as needed) dosing regimen. The criteria for additional treatment applied in our clinic were as follows: at least five-letter decrease in visual acuity with the presence of fluid on OCT; or any qualitative change in intra/subretinal fluid in OCT or an increase in central foveal thickness (CFT) or PED height or lesion dimensions (at least 10% increase) as determined by OCT; or presence of new hemorrhage associated with the lesion; or the presence of late leakage on fluorescein angiography.

Statistical Methods: Because the data of this study were taken from paired eyes of the same patient, the data set was treated as clustered. Thus, each patient was considered to be a cluster, and each eye to be one unit of this cluster. The key feature of clustered data is that outcomes from the same cluster are likely to be positively correlated. Proper analysis of clustered data requires taking this correlation into consideration. The ignorance of this correlation can bias the statistical inference. Therefore, repeated-measures analysis for clustered data was used in the evaluation of the time effect for each variable. For this purpose, the PROC GENMOD SAS procedure was used. The SAS Portable 9.1.3 software (SAS Institute Inc., North Carolina, USA) was used for statistical analysis. Descriptive statistics are given as means and standard deviations. Statistical level of significance was defined as $p<0.05$.

RESULTS

One hundred and six eyes of 96 patients fulfilled the inclusion criteria and were included in the study. All of the eyes had received three loading doses of anti-VEGF and PRN treatment thereafter. They received additional bevacizumab or ranibizumab treatment when the lesion was found to be active. Fourteen of ninety-six patients have been treated with only bevacizumab, eighteen of ninety-six patients have been treated with only ranibizumab, sixty-four of ninety-six patients have been treated with both anti-VEGF. Baseline characteristics before the treatment are summarized in table 1, where the mean BCVA was 0.74±0.42 logMAR, the CFT was 304±118 μm, the PED diameter was 2.8±1,8 mm, and the maximum PED height was 397.02±227.06 μm. Patients received a mean of 8.5±2.3 (min:4 max:12) anti-VEGF treatments during the follow-up. The mean follow-up time was 22.4±2.3months (20-35 mo).

Table 1: *Baseline characteristics of study patients.*

Parameter	Result (n=106 eyes of 96 patients)
Gender (famele/male)	40(41.6%)/56 (58.3%)
Age (years)	70.74±12.42
Best–corrected visual acuity (logMAR)	0.74±0.42
Central foveal thickness (μm)	304±118
Maximum PED height (μm)	397±227
Choroidal neovascularization size (mm^2)	12.05±9.70
PED diameter (optic disc diameter)	1.9±1.1

PED: pigment epithelium detachment. Data are given as n(%) or mean±standard deviation

The mean of the visit intervals was 1.25±0.2 months. In our study 21 out of 106 eyes (19.8%) developed a postinjection RPE tear. RPE tears occurred after ranibizumab in 11 of 21 eyes, and after bevacizumab injection in 10 of 21 eyes. The RPE tear was detected within a month after an anti-VEGF injection in all the patients.

Changes in Best-Corrected Visual Acuity: The changes in the BCVA are summarized in Table 2 and graphic. The results indicate that the BCVA increased significantly only at months 3 and 6 from baseline; but did not change significantly at months 12 or 20 from baseline.

Table 2: *The changes in the BCVA during the study (n=106 eyes of 96 patients.)*

	BCVA	p values			
Time of measurement	(logMAR)	Month 3	Month 6	Month 12	Month 20
Baseline	0.75±0.42	<0.001	0.023	>0.05	>0.05
Month 3	0.62±0.32		>0.05	0.001	<0.001
Month 6	0.64±0.37			0.018	<0.001
Month 12	0.72±0.39				0.025
Month 20	0.78±0.43				

BCVA: Best-corrected visual acuity. Data are given as mean±standard deviation.

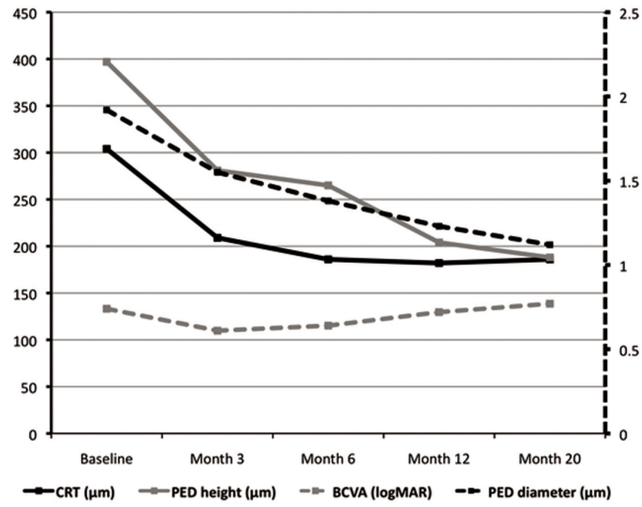

Figure 1: *The change in Central foveal thickness (CFT), pigment epithelium detachment (PED) diameter and maximum height, and best-corrected visual acuity (BCVA) during the study.*

Changes in Central Foveal Thickness: The changes in CFT are summarized in Table 3 and graphic. The results indicate that CFT decreased gradually during the follow up. Serial comparison between baseline and follow-up values demonstrated that the reduction in CFT was significant at all time points (p<0.05).

Changes in Maximum Pigment Epithelium Detachment Height and Diameter: The changes in the maximum PED height are summarized in Table 4 and graphic. Results from repeated- measures, serial comparison between baseline and follow-up values demonstrated that the reduction in maximum PED height was significant at all time points (p<0.05). However, complete PED resolution was observed only in 21.6% (23/106) of the eyes, a partial resolution defined as at least 10% decrease in PED height could be achieved in 50.94% (54/106) and PED height remained unchanged in 22.7% (24/106) of the eyes. Statistical analysis demonstrated that there is no correlation between change in BCVA and change in PED height at all time points (Spearman rho, r =0.13, P>0,05).

Changes in the PED sizes are also summarized in table 4 and graphic. The results indicate that the PED diameter decreased significantly at all time points. We found that there is no correlation between change in BCVA and change in PED diameter at all time points (Spearman rho, r =0.185, P>0,05).

Table 3: *The changes in the CFT during the study (n=106 eyes of 96 patients).*

		p values			
Time of measurement	CFT (μm)	Month 3	Month 6	Month 12	Month 20
Baseline	304.93±118.731	0.027	0.001	<0.001	0.001
Month 3	209.71±112.879		>0.05	>0.05	>0.05
Month 6	186.61±71.818			>0.05	>0.05
Month 12	182.72±111.354				>0.05
Month 20	186.57±129.472				

CFT: Central foveal thickness. Data are given as mean±standard deviation.

Table 4: The changes in the maximum PED height and PED diameter during the study (n=106 eyes of 96 patients).

		p values			
Time of measurement	**CFT (μm)**	**Month 3**	**Month 6**	**Month 12**	**Month 20**
Baseline	304.93±118.732	0.018	0.012	0.001	<0.001
Month 3	281.60±210.89		>0.05	0.022	0.02
Month 6	265.20±233.38			0.028	0.021
Month 12	204.72±198.53				>0.05
Month 20	188.21±206.42				
PED diameter (optic disc diameter)					
Baseline	1.93±1.13	0.032	0.025	0.001	<0.001
Month 3	1.56±1.08		>0.05	0.033	0.028
Month 6	1.39±1.04			>0.05	0.042
Month 12	1.24±1.00				>0.05
Month 20	1.12±0.95				

PED: pigment epithelium detachment. Data are given as mean±standard deviation.

DISCUSSION

In this retrospective, long-term follow-up study, we found that although anti-VEGF treatment resulted in significant decrease in PED height and diameter in patients with vPED, complete PED resolution could be obtained in a limited number of eyes. Furthermore, the decrease in PED height and diameter did not correlate with an increase in visual acuity.

The favorable outcomes of treatment of different neovascular AMD subtypes with anti-VEGFs shown by previous clinical trials (ANCHOR, MARINA, and CATT)[10-12] were not achieved peculiarly for vascularized PED, a difficult-to-manage subtype of neovascular AMD. Unfortunately, few data are available regarding the effects of anti-VEGF therapy for this kind of lesion. In addition, most published studies exclude eyes with vascularized PED, purely serous PED as well as PED associated with retinal angiomatous proliferation.[13-16] Lommatzschet al.,[15] reported that anti-VEGF agents are the most effective treatment for lesions associated with PEDs. In a prospective study on 57 eyes of 57 consecutive patients with different types of PED associated with exudative AMD, anti-VEGF therapy was reported to be effective for stabilizing vision in patients with fibrovascular and hemorhagic PED and even more effective in eyes with associated serous PED.[17]

In a retrospective study of 50 eyes with vPED treated with anti-VEGF therapy, only stabilization of visual acuity was achieved during a 12-month follow-up.[18] Ach et al.,[19] treated 28 eyes of 26 patients with vPED with intravitreal bevacizumab every 6 to 8 weeks and have reported that, the height of PED decreased in 54%, while the visual acuity remained stable which confirms our results. Parodi et al.,[20] performed a prospective study on 40 eyes with vascularized PED treated with 3 loading dose of intravitreal ranibizumab followed by PRN strategy. The mean BCVA significantly decreased at 12 and 24 months despite anti-VEGF injections, while the mean CFT and mean lesion area decreased significantly at 12 and 24 months. In a recent study byVeritti et al,visual results were again not parallel to the anatomical favorable response.[21] Also in another recent study Giansanti et al.,[22] demonstrated that no effect was seen on the change of VA according to PED height and there was a borderline trend that PED GLD affected response to treatment.This may be explained by the anatomical issues; since vascularized PEDs are type 1 membranes which lie under the retinal pigment epithelium layer, it can be speculated that intraretinal or subretinal fluid and lesions can effect the visual acuity more than sub-RPE fluid and lesions. The present study confirms the previous study results where the anatomical improvements as indicated with a decrease in PED height and PED diameter were not followed by functional improvement as indicated by only stabilization of VA. However at least the stabilization of vision could be achieved with a mean of 8.5 anti-VEGF injections in these eyes. Although PED height and size significantly decreased, complete PED resolution could be achieved only in 1/5 of the eyes. As abundantly demonstrated in the literature,[17,19,22-24] it seems that there is no correlation between BCVA and changes in PED size.

The main limitation of our study was its retrospective nature, however, relatively large number of eyes and a long- term follow-up adds value to the study.

In conclusion, intravitreal anti-VEGF therapy for vPED reduced PED height and diameter; but the functional results are less satisfactory than those for other CNV subtypes (classic, occult without PED) and the anatomical response of the PED may not correlate directly with the visual outcome.

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