Response of Pigment Epithelial Detachment to Three-Loading-Dose of Intravitreal Anti-Vascular Endothelial Growth Factor in Neovascular Age-Related Macular Degeneration

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Abstract

Aim: Response of pigment epithelial detachment (PED) to three loading dose of intravitreal bevacizumab (IVB) treatment in neovascular age-related macular degeneration (nAMD) cases.

Methods: Optical coherence tomography (OCT) findings (PED height (µm), diameter(µm) and area (mm²), central macular thickness (CMT), central choroidal thickness (CCT), intraretinal fluid (IRF), subretinal fluid (SRF), and morphological features of macular neovascularization (MNV) in optical coherence tomography angiography (OCTA) before and after three loading doses of IVB were examined and compared.

Results: Forty-two eyes of 42 naive nAMD patients with PED were included. Fifteen patients had serous and 27 patients had fibrovascular PED. After three loading doses, best corrected visual acuity (BCVA) (in Snellen chart) increased from 0.22±0.19 to 0.29±0.22 (p<0.001). The mean PED height, width and area decreased (323.46±189.80 µm,274.79±199.80 µm, p=0.007; 1639.87±1037.44 µm, 1599.01±993.88 µm, p=0.138; 2.90±2.76 mm², 2.24±2.38 mm², p=0.038 respectively). CMT decreased from 500.34±286.62 µm to 366.14±238.10 µm, CCT decreased from 251.55±74.44 µm to 197.09±50.36 (p<0.001 for both). IRF or SRF were significantly regressed (p=0.008 and p=0.032). Branching decreased from 23.8% of patients to 11.9% (p=0.044), loops completely regressed (p<0.001), hypointense halo decreased from 7.1% of patients to 4.6% (p=0.323), open circuit pattern decreased from 23.8% to 4.6% (p<0.001). Seafan and medusa NV were present in 2.3% and 4.6% of patients, however did not differ. The pruned tree NV increased from 11.9% to 33.3% (p<0.001). Closed circuit pattern increased from 33.3% to 38% (p=0.083).

Conclusions: After three loading doses of IVB, PED height and area were significantly reduced and also 21.4% of PED completely regressed and 52.3% of PED decreased. MNV with PED, particularly brancing, loops had regressed, and most of the pruned tree NVs were increased and some of the open circuit pattern were converted to closed circuit pattern. In conclusion, 3 loading doses IVB decreased the size a half of PEDs and changed feature of MNVs with PED.

Keywords: *Pigment epithelial detachment, neovascular age-related macular degeneration, optical coherence tomography, optical coherence tomography angiography*

1. Introduction

Pigment epithelial detachment (PED) is the separation of the retinal pigment epithelium (RPE) from Bruch's membrane. It is often seen with choroidal diseases like neovascular age-related macular degeneration (nAMD) (most common), central serous chorioretinopathy, choroidal tumors.[1] The pathogenesis of PED within nAMD is thought to be vascular endothelial growth factor (VEGF)-associated fluid from the choroidal neovascular membrane (CNV) between Bruch's membrane and the RPE.[2]

The most current treatment of nAMD is intravitreal anti-VEGF agents. Bevacizumab (Avastin, Genentech, South San Francisco, CA, USA), one of an anti-VEGF agent, a recombinant full-length human-

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ized monoclonal antibodies against all isoforms of VEGF was originally developed to treat systemic cancers (lungt, gastrointestinal tract).[3,4] It has been effective in treating AMD and in a variety of types of choroidal vascular abnormalities treatments.[5,6]
Optical coherence tomography (OCT) is of particular importance in evaluating the effects of anti-VEGF treatments. It is suitable for identifying intra- and subretinal edema as well as identifying PED and its changes over time after treatment. However, analysis and measurement of the dimensions of a PED is still not possible in an objective, observer-independent manner.

Optical coherence tomography angiography (OCTA) is a new, noninvasive imaging modality that demonstrates the morphology of macular neovascularization (MNV) in nAMD. OCTA can produce fast, reproducible, high-resolution and three-dimensional images of MNV. Since fluorescein has no masking effect in angiography (FA), it can show the neovascular network more clearly and can provide qualitative and quantitative information about MNV.[7,8]

PED can be found in 63% to 80% of eyes with nAMD.[9,10] The presence of PED in nAMD often indicates poor visual prognosis, persistent fluid, and complications such as RPE rupture.[11,12] Nowadays, anti-VEGFs are administered at various intervals and in different regimens. Intravitreal bevacizumab (IVB) monotherapy for ten eyes with refractory PED in AMD found limited effect, because all PEDs remain the same, although leakage from CNV resolved.[13] In a study, the 12-month follow-up of groups with PED treated with ranibizumab and aflibercept were compared, and they reported that maximum visual acuity improvement, PED height and radius reduction were observed in the first 3 months in both groups.[14] Although it is off-label for nAMD, IVB is used quite frequently in our country and in the world due to cost effectiveness. To our knowledge, the number of studies investigating the effect of three loading doses of IVB on PED with nAMD is quite limited. Therefore, we wanted to examine the response of three loading doses of IVB in patients with PED in nAMD using OCT and OCTA.

2. Materials and methods

This retrospective study was conducted in Department of Ophthalmology of Bursa Yuksek Ihtisas Training and Research Hospital and evaluated, naive nAMD patients with PED initially treated with three loading doses IVB therapy. Forty two eyes of 42 patients were included in the present study. Ethics committee approval (number: 2011-KAEK-25 2023/08-06) was obtained from Bursa Yuksek Ihtisas Training and Research Hospital Local Ethics Committee. The study adhered to the tenets of the Declaration of Helsinki.
Patients with previous treatment except loading doses of IVB (other anti-VEGF treatments, photodynamic therapy, laser photocoagulation), nAMD patients without PED, PEDs of different origins (central serous choroidopathy etc.), patients with concurrent diabetic retinopathy and uncontrolled hypertension were excluded from the study.

Demographic characteristics, best-corrected visual acuity (BCVA) with a Snellen chart, intraocular pressure, spherical equivalent, slit lamp examination and funduscopy, fluorescein angiography (FA), OCT and OCTA data were recorded.

2.1. Optical Coherence Tomography and Optical Coherence Tomography Angiography

Spectral domain OCT (SD-OCT) and OCTA were performed using the same device (RTVue XR AVANTI, Optovue, Inc., Fremont, CA, USA) (wavelength= 840 nm, 70,000 A-scans/s and 5µm axial resolution). Motion correction technology system (Optovue, INC.) minimizes defects caused by saccadic or involuntary movement. Central macular 6×6 mm scans were taken with OCTA which volume contains 304 B-scans has equally spaced on the X-axis and Y-axis. OCTA images with a quality score of 6 and above were evaluated by a clinician (A.S.I).

PEDs are structural splitting within the inner aspect of Bruch's membrane separating the retinal pigment epithelium (RPE) from the remaining Bruch's membrane. PED height was measured between the inner border of Bruch's membrane and the external border of the RPE and PED width was assessed by measuring maximum distance horizontal diameter by manually. PED area was calculated with ImageJ software (National Institutes of Health Bethesda, Maryland, USA). Central macular thickness (CMT) was taken central-1mm macular thickness and central choroidal thickness (CCT) was assessed measuring subfoveal region and the perpendicular distance from the outer layer of the retina pigment epithelium (RPE) to the inner surface of the sclera by using the software bundled manually. IRF, including fluid intraretinal area between the inner limiting membrane (ILM) and the elipsoid zone, SRF, subretinal fluid extending from the elipsoid zone and RPE layer.

The morphological features of each MNV were evaluated with OCTA by performing 6×6mm scan over the macular region. The morphological appearance of CNVs was evaluated qualitatively, similar to previous studies [15-18] : 1. Presence of small vessels (branching), 2. Internal anastomoses between small vessels (loops), 3. Peripheral integration between tiny branching vessels (peripheral arcade) 4. The hypointense area is considered the zone of choriocapillaris alteration (hypointense halo). 5. Vessels branching from the center in all directions (medusa) 6. More than 90% of the membrane spreading from one side of the lesion (sea fan) 7. A network of vessels with densely interconnected anastomosis but no visible main body (glomeruli) 8. Long dilated fibrous straight vessels with membranes (pruned vascular tree pattern) 9. Presence of an anastomotic vessel limiting the outer border of the vascular lesion in more than 50% of the entire CNV margin (closed-circuit pattern) 10. Includes anatomic vessels for less than 50% (open circuit pattern). Small MNVs could not be placed in a clear pattern category.

2.2. Statistical analysis

Statistical analyses were performed using the SPSS software version 22 (IBM Corp., Armonk, NY, USA). Variables were examined using the Shapiro-Wilk's test to determine distribution. Continuous data are presented as the mean ± standard deviation. Categorical characteristics are presented as numbers (%). OCT and OCTA findings after three loading doses were compared with a paired samples T-test. $p<0.05$ was considered statistically significant.

3. Results

3.1. Demographic Characteristics of Patients

Forty two eyes of 42 patients were included in the study. The mean age of the patients was 71.08±7.41 (58-82) years. Half of the participants were female. 28.5 % of patients had vascular disease (hypertension, diabetes, cardiac diseas etc.). The mean spherical equivalent was 0.26±0.77 (-4-(+4)) diopter. The initial mean best-corrected visual acuity (BCVA) was 0.22±0.19 (0.001-0.7) in Snellen. 64.2% of PEDs were fibrovascular type. The baseline characteristics of the patients before the injection were given in Table 1.

3.2. Changes in Best Corrected Visual Acuity (BCVA) and Findings of Spectral Domain Optical Coherence Tomography (SD-OCT)

Changes in BCVA and SD-OCT findings after three loading doses were given in Table 2. BCVA (in Snellen chart) increased from 0.22±0.19 to 0.29±0.22 ($p<0.001$). The mean PED height, width and area decreased (323.46±189.80 µm,274.79±199.80 µm, $p=0.007$; 1639.87±1037.44 µm, 1599.01±993.88 µm, $p=0.138$; 2.90±2.76 mm^2, 2.24±2.38 mm^2, $p=0.038$ respectively). CMT decreased from

Table 1

Demographic Characteristics and Baseline Values

	n= 42 eyes with PED
Age (years)	71.08±7.41 (58-82)
Gender (F/M)	21/21
Vascular disease (yes/no) (n) (%)	12 (28.5%)
Laterality (R/L)	21/21
Intraocular pressure (mmHg)	15.07±3.89 (8-22)
Lens condition (phakic/pseudophakic)	23/19
Spherical equivalent (diopter)	0.26±0.77 (-4-(+4))
Initial BCVA (Snellen)	0.22±0.19 (0.001-0.7)
Serous/Fibrovascular PED	15(35.7%) /27(64.3%)

BCVA, best corrected visual acuity; PED, pigment epithelial detachment; Mean±SD, n (%)

Table 2

Changes in Best Corrected Visual Acuity (BCVA) and Spectral Domain Optical Coherence Tomography (OCT) Findings After Three Loading Doses

	Pre-injections	Post-injections	p-value
BCVA (Snellen)	0.22±0.19	0.29±0.22	0.001
CMT (µm)	500.34±286.62	366.14±238.10	<0.001
CCT (µm)	251.55±74.44	197.09±50.36	<0.001
IRF (yes/no) (%)	4 (9.5%)	1 (2.3%)	0.008
SRS (yes/no) (%)	17 (40.7%)	9 (21.4%)	0.032
IRS+SRS (yes/no) (%)	13 (30.9%)	10 (23.8%)	0.631
PED			
-height (µm)	323.46±189.80	274.79±199.80	0.007
-width (µm)	1639.87±1037.44	1599.01±993.88	0.138
-area mm2	2.90±2.76	2.24±2.38	0.038

BCVA, best corrected visual acuity; CMT, central macular thickness; CCT, central choroidal thickness; IRF, intraretinal fluid; SRF, subretinal fluid; PED, pigment epithelial detachment. Paired Samples T-test, Mean±SD, p <0.05

Table 3

Changes in Morphological Features of Macular Neovascularization (MNV) in Optical Coherence Tomography Angiography (OCTA) After Three Loading Doses

n (%)	Pre-injections	Post-injections	p-value
Branching	10 (23.8%)	5 (11.9%)	0.044
Loops	5 (11.9%)	0	<0.001
Hypointense halo	3 (7.1%)	2(4.6)	0.323
Peripheral arcade	2(4.6%)	0	0.044
Seafan	1 (2.3%)	1 (2.3%)	1
Medusa	2 (4.6%)	2 (4.6%)	1
Glomeruli	2 (4.6%)	1 (2.3%)	0.423
Prunedvascular tree	5(11.9%)	12 (33.3%)	<0.001
Open circuit pattern	10 (23.8%)	2 (4.6%)	<0.001
Closed circuit pattern	14 (33.3%)	18 (38%)	0.083

n, (%) , p <0.05

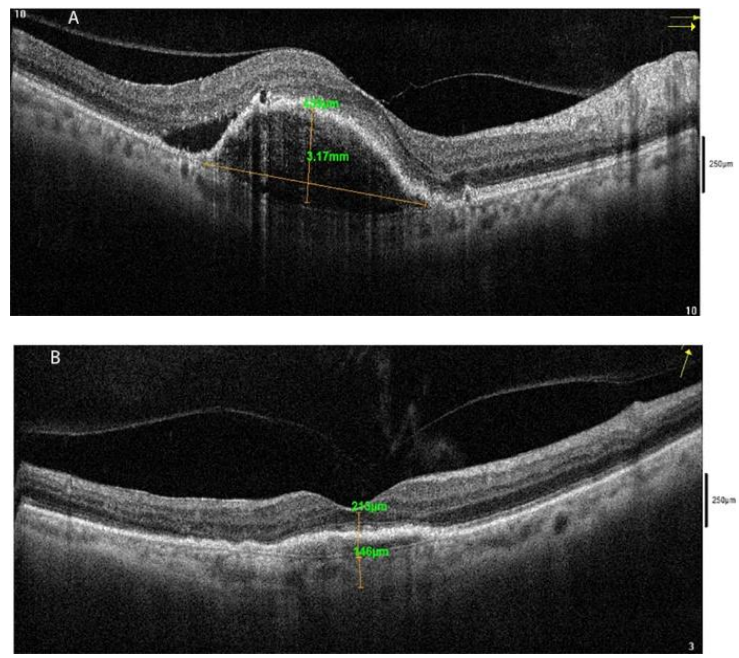
500.34±286.62 µm to 366.14±238.10 µm, CCT decreased from 251.55±74.44 µm to 197.09±50.36 (p<0.001 for both). IRF or SRF were significantly regressed (p=0.008 and p=0.032). The proportion of eyes with both IRF and SRF decreased from 30.9% to 23.8% (p=0.631). After treatment, PED resolved completely in 9 eyes (21.4%) and PED decreased in 22 eyes (52%3).

3.3. Changes in Morphological Features of Macular Neovascularization (MNV) in Optical Coherence Tomography Angiography (OCTA)

Changes in morphological features of MNV in OCTA were given in Table 3. After three doses of IVB, branching decreased from 23.8% (n=10) of patients to 11.9% (n=5) (p=0.044), loops (n=5) completely regressed (p<0.001), hypointense halo decreased from 7.1% (n=3) of patients to 4.6% (n=2) (p=0.323), open circuit pattern decreased from 23.8% (n=10) to 4.6% (n=2) (p<0.001). Seafan and medusa NV were present in 2.3% (n=1) and 4.6% (n=2) of patients, however did not differ. The pruned tree NV increased from 11.9% (n=5) to 33.3% (n=12) (p<0.001). Closed circuit pattern increased from 33.3% (n=14) to 38% (n=18) (p=0.083).

Figure 1

A) Measurement of pigment epithelial detachment (PED) height and width at optical coherence tomography (OCT)
B) Measurement of central macular thickness (CMT) and central choroidal thickness (CCT) after three loading doses of intravitreal bevacizumab in the same patient



4. Discussions

Worsening of visual acuity during the natural course emphasizes the clinical implication of PED. Approximately 50% of patients with newly diagnosed untreated PED experienced a loss of more than 15 letters during observation period of 1 year.[19] However, there is no consensus on the therapeutic effect or even the need for active treatment for PED.

Shima et al.[20] reported that after combined photodynamic therapy (PDT) and IVB, and followed 1-year, PED resolved in 12 eyes (55%) and decreased in ten eyes (45%), however Axer-Siegel R et al.[21] found that eyes with AMD with severe PED due to BCVA more than 56% worsened and had a low percentage eyes with anatomical success after PDT. Bolz et al.[22] successfully treated nine eyes with AMD with three systemic bevacizumab treatments in 2 weeks intervals; BCVA recovered and height of PED decreased significantly at 3 months but regression of PED was slower than regression of

intra- or subretinal oedema. Abi-Ayad N et al.[23] reported that sytemic bevacizumab therapy appears to be safe and effective in the treatment of retinal angiomatous proliferation (RAP) associated with PED during this short follow-up period of 3 months. They observed improvement of in BCVA and total regression on PED in OCT.

Intravitreal anti-VEGFs are still the most commonly used agents in nAMDs with PED. In a study, the 12-month follow-up of groups with PED treated with ranibizumab and aflibercept were compared, and they reported that final visual acuity and parameters of PED were better in aflibercept group.[14] Post Hoc analysis from the HABOR Trial, after a single ranibizumab injection, 35.5% of PEDs were flattened, 17.3% of them were flattened at 2 months, in other words, almost half of the PEDs were flattened after the 2nd injection, but this flattening was not reflected in visual acuity.[24] Twenty eight naive eyes with PED and sub- or juxtafoveal occult CNV as a result of nAMD and additional IRF and/or SRF were treated with IVB. During follow up time (37.9±18.3 weeks), mean PED height decreases in 50% of patients.[25] In another study, after 12 months of ranibizumab or aflibercept (with first three monthly loading doses) treatment, the mean PED height decreased from 453±261 µm at baseline to 230±142, the proportion of complete PED resolution after treatment was 19.3% (39 eyes).[26] Similarly, in present study, after three loading doses of IVB, 21.4% of PED completely regressed and 52.3% of PED decreased. The mean PED height (from 323.46±189.80 µm to 274.79±199.80 µm), width (from 1639.87±1037.44 µm to 1599.01±993.88 µm) and area (from 2.90±2.76 mm^2 to 2.24±2.38 mm^2) decreased.

Particularly, fibrovascular PED in AMD is associated with type 1 CNV, which can be visualized by FA and SD-OCT.[2] OCTA was found to have a sensitivity of 76%, specificity of 61%, positive predictive value of 83%, and negative predictive value of 50% for detecting vascularized PEDs. False positive cases in non-vascularized PED caused by projection or flow artifacts from the reflective material. False-negative cases were seen in eyes with minimal exudation on structural OCT, and also those showing retinal pigment epithelial tears [27]. In this study, we examined MNVs which shape were able to categorize (like branching, loops, hypointense halo etc.) in OCTA. In this study, although 64.3 % (n=27) eyes had fibrovascular PED, only 30.9% (n= 13) had MNV that could be categorized. After three loading doses, branching decreased from 23.8% of patients to 11.9%, loops completely regressed, hypointense halo decreased from 7.1% of patients to 4.6%, open circuit pattern decreased from 23.8% to 4.6%. Seafan and medusa NV were present in 2.3% and 4.6% of patients, however did not differ. The pruned tree NV increased from 11.9% to 33.3%. Closed circuit pattern increased from 33.3% to 38%. Three loading doses of IVB were found to alter the shape of MNVs associated with PED.

Limitations of this study; retrospective pattern, small simple size, single anti-VEGF (bevacizumab), short treatment period (three loading dose).

5. Conclusions

After three loading doses of IVB, PED height and area were significantly reduced and also 21.4% of PED completely regressed and 52.3% of PED decreased. Macular NV with PED, particularly brancing, loops had regressed, and most of the pruned tree formations were increased and some of the open circuit pattern were converted to closed circuit pattern. As a result, three loading doses IVB decreased the size of PEDs and changed morfological feature of MNVs with PED.

Statement of ethics

Ethics committee approval (number: 2011-KAEK-25 2023/08-06) was obtained from Bursa Yuksek Ihtisas Training and Research Hospital Local Ethics Committee.

Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

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