EPIRETINAL MEMBRANES IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

Effect on Outcomes of Anti-vascular Endothelial Growth Factor Therapy

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Purpose: To investigate the role of epiretinal membrane (ERM) on outcomes of anti-vascular endothelial growth factor therapy in patients with neovascular age-related macular degeneration (nAMD).

Methods: This study is a retrospective observational case series and was conducted at the Gazi University School of Medicine, Ankara, Turkey. The reports of the patients with a diagnosis of new-onset nAMD, who were aged at least 50 years and treated with intravitreal anti-vascular endothelial growth factors (ranibizumab or bevacuzimab) between October 2010 and September 2013 in our retina clinic, were reviewed for the vitreomacular interface changes.

Results: The study included 90 eyes of 90 patients with nAMD. The mean age of the patients was 70 ± 7.5 years, with 35 (38.9%) being male and 55 (61.1%) being female. According to the examinations with optical coherence tomography and B-mode ultrasonography, 43 patients had "concurrent" vitreomacular adhesion (30 focal, 13 broad; Group 1). Twenty-nine patients had complete posterior vitreous detachment (Group 2) and 18 patients (Group 3) had ERM. The number of injections was highest for the patients with ERM (Group 3), and this difference was statistically significant ($P < 0.001$). The mean interval between injections and the mean longest interval were shorter in Group 3 ($P < 0.05$).

Conclusion: The presence of ERM in association with nAMD seems to increase the number of anti-vascular endothelial growth factor injections and decrease the injection intervals for the treatment of nAMD. Although the anatomical and functional results are similar in eyes with or without ERM, the increased need for anti-vascular endothelial growth factors may mean that these membranes may decrease the penetration of the drugs through these membranes, which may act as a physical barrier. Additionally, increased inflammation in patients with ERM probably requires more frequent injections.

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Neovascular age-related macular degeneration (nAMD) is the leading cause of visual impairment among the elderly in the world, and the late stages of the disease have a severe negative impact on visual function. After widespread introduction of anti-vascular endothelial growth factor (anti-VEGF) treatment, retinal specialists have been able to improve vision in nAMD with an otherwise poor natural history.[1]

Debates continue about optimal treatment regimen for patients with AMD. Meta-analysis of older trials recommended monthly treatment as the most effective therapy.[2] However, many physicians administer anti-VEGF in a pro re nata (PRN) regimen. For an effective PRN strategy, the factors determining outcome and treatment should be identified. Among the

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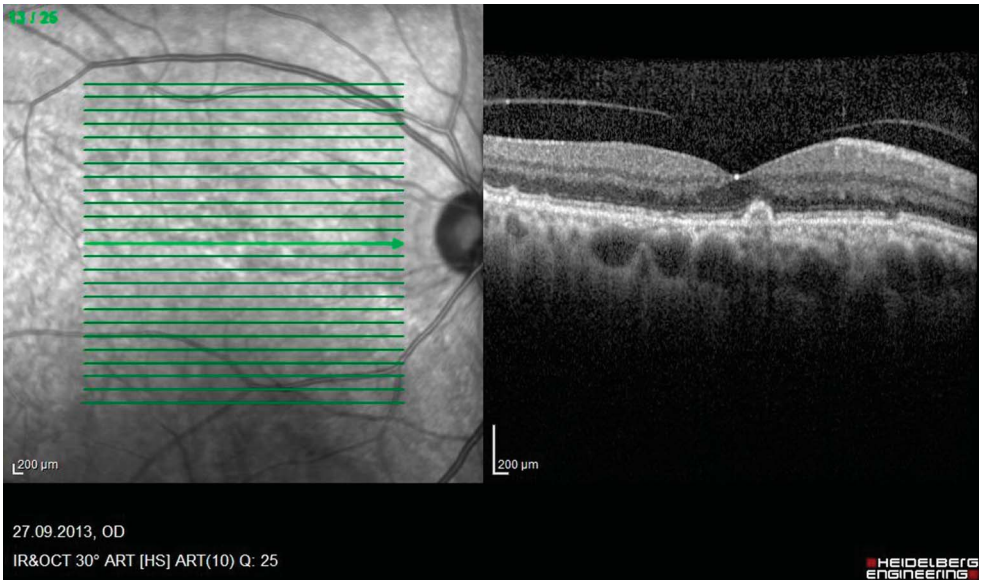

Fig. 1. Optical coherence tomography scan illustrating VMA.

factors, vitreous is supposed to play an important role in nAMD.[3–6] Several hypotheses have been forwarded accusing attached posterior vitreous as a stimulator of pathology localized in the retinal pigment epithelium.[7] Traction forces were suspected to contribute development and poor prognosis of nAMD. Vitreomacular interface (VMI) changes of patients with AMD, such as posterior vitreous detachment (PVD), vitreomacular adhesion (VMA), and vitreomacular traction have been addressed in several clinical studies using optical coherence tomography (OCT).[3,6,8–10] However, the role of epiretinal membrane (ERM) has not been investigated in the concept of vitreomacular interface disorders in patients with nAMD.

Vitreomacular adhesion is characterized by an elevation of the cortical vitreous above the retinal surface, with the vitreous remaining attached within a 3-mm radius of the fovea. The angle between the vitreous and the inner retinal surface is acute, and the retina displays no change in contour or morphologic features on OCT because of the vitreous adhesion. People with VMA generally experience no visual impairment, and the finding is normal in the natural course of PVD. With time, the vitreous may separate spontaneously from the inner retina, usually without incident.[11]

The aim of this study is to elucidate whether the presence of ERM may contribute additional problem in patients with nAMD treated with anti-VEGFs.

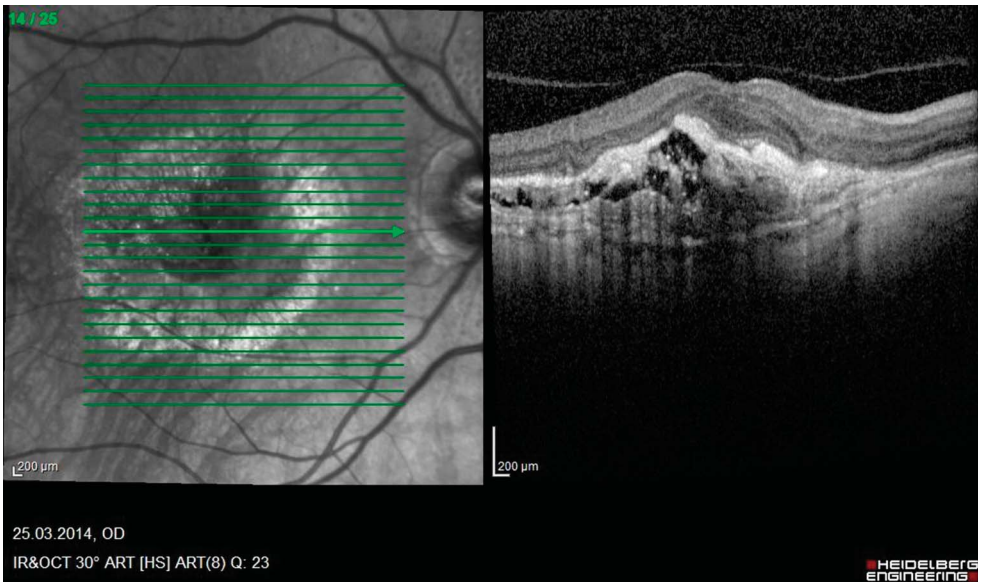

Fig. 2. Optical coherence tomography scan illustrating PVD.

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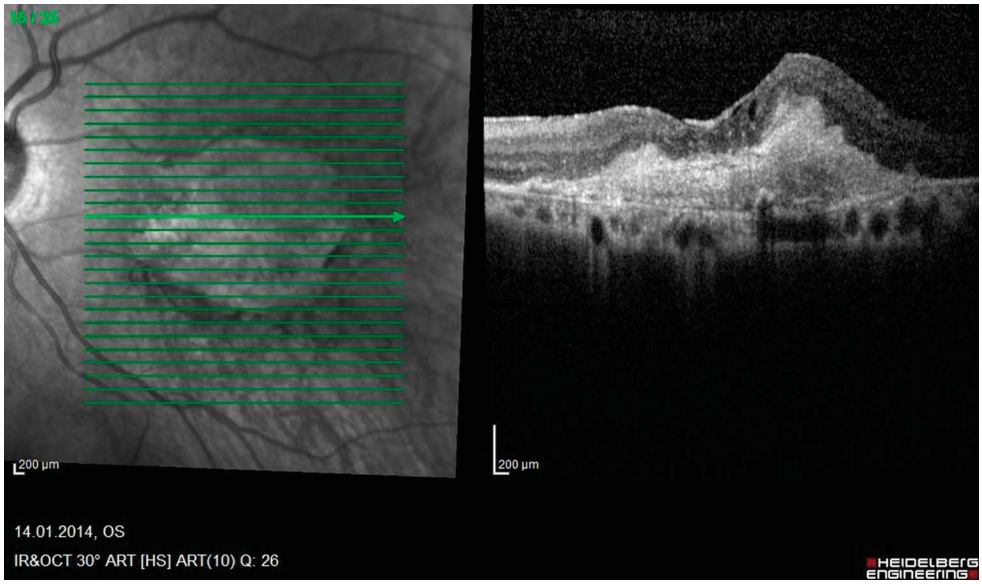

Fig. 3. Optical coherence tomography scan illustrating ERM with no sign of PVD.

Methods

This study is a retrospective observational case series and was conducted at the Gazi University School of Medicine, Ankara, Turkey. The study was approved by the Institutional Review Board and Ethics Committee of Gazi University Hospital.

The reports of the patients with a diagnosis of new-onset nAMD, who were aged at least 50 years and treated with intravitreal anti-VEGFs (ranibizumab or bevacuzimab) between October 2010 and September 2013 in our retina clinic, were reviewed for the vitreomacular interface changes. Both fluorescein angiography and OCT were obtained as a part of the routine practice during the first diagnosis in all patients with nAMD. Patients with choroidal neovascularization (CNV) caused by other pathologies than AMD (idiopathic or myopic CNV) were not included. Patients with visually significant cataract or corneal disease, the best-corrected visual acuity (BCVA) <20/200, advanced glaucomatous damage, other retinal vascular diseases, history of any previous injection or other treatment modalities, such as photodynamic therapy and transpupillary thermotherapy, and a previous vitrectomy or trabeculectomy surgery in the eye with nAMD were excluded from the study. Furthermore, patients without minimum follow-up of 6 months were also excluded. Initial treatment was given as a loading dose over 3 months with monthly intravitreal injections of anti-VEGF. Patients were followed up monthly after the loading treatment and given additional injections when the lesion is active as in PRN regimen. Fluorescein angiography (before treatment and when needed in indeterminate cases during follow-ups) and OCT (before treatment and at every visit) (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) were performed. The presence of subretinal or intraretinal fluid in OCT, the presence of a new hemorrhage associated with the lesion, fluorescein angiography-staining pattern, increase in the size

Table 1. Baseline Characteristics of the Patients in Three Groups

	Group 1 (n = 43)	Group 2 (n = 29)	Group 3 (n = 18)	*P* (ANOVA)
Age (years)	70.5 ± 1.3	70.3 ± 1.3	69.11 ± 1.3	0.919
Sex (M/F)	18/25	11/18	6/12	0.274
CNV type (occult/classical)	34/9	20/9	13/5	0.651
Follow-up time (month)	31.5 ± 3.2	25.1 ± 2.5	29.72 ± 0.4	0.274
BCVA (baseline) (logMAR)	0.5 (0.1–1)	0.5 (0.1–1)	0.3 (0–1)	0.204
CFT (μm) (baseline)	252 (140–651)	271 (126–1,000)	255 (175–600)	0.525
Lesion size (cm^2) (baseline)	9.97 (0.21–71.37)	10.23 (0.65–33.12)	11.29 (1.38–37.31)	0.230
No. injections	8.32 ± 4.7	6.87 ± 3.3	11.6 ± 2.9	<**0.001**
Injection intervals (weeks)	7.59 (4–10.7)	7.2 (4–12.2)	6.12 (4–9.1)	<**0.032**
Longest interval between injections (weeks)	10.7	12.2	9.1	<**0.012**

ANOVA, analysis of variance; CFT, central foveal thickness; CNV, choroidal neovascularization.

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Table 2. BCVA Measurements at Each Follow-up

	BCVA (logMAR) (Median; Min–Max)			
	Group 1	Group 2	Group 3	*P* (ANOVA)
Baseline	0.5 (0.1–1)	0.5 (0.1–1)	0.3 (0–1)	0.204
Third month	0.5 (0–2)	0.7 (0–2)	0.3 (0–2)	0.484
Last visit	0.5 (0–2)	0.7 (0–2)	0.45 (0–2)	0.545

ANOVA, analysis of variance.

of the lesion (lesion area in fluorescein angiography), and worsening of objective (measured) visual acuity by three or more Snellen lines were used as activity criteria.

The clinical charts of patients were reviewed for age, sex, BCVA, lesion characteristics, including type of nAMD, follow-up time, total number of injections, injection intervals and extension, signs of nAMD control, and VMI characteristics determined by spectral domain OCT. All patients were imaged by the same experienced technician. Horizontal cross-sectional spectral domain OCT scans of the foveal region were examined to measure the central foveal thickness and to determine the presence of VMI changes. For analysis, patients were divided into three groups based on their first visit slit-lamp biomicroscopy and spectral domain OCT; Group 1 had VMA, Group 2 had complete PVD (confirmed by slit-lamp biomicroscopy or B-scan ultrasonography), and Group 3 had ERM in addition to VMA. Vitreomacular adhesion was defined as vitreous adhesion to central macula with no demonstrable retinal morphologic changes and subclassified as focal or broad by the size of the adhesion.[11] Patients with partial PVD with no vitreomacular contact were also included in VMA group. We omitted patients with vitreomacular traction at baseline and the ones with VMI change, such as additional PVD or ERM, during follow-up period; 24 patients were excluded because of these conditions.

Statistical Analysis

Statistical analysis was performed by using the software SPSS 16.0. Continuous data are given as mean ± SD or median (minimum to maximum), categorical variables are given as number of cases and percentages (%). Significance of the difference between mean values and medians for three groups were tested by analysis of variance test. For comparing time-dependent clinical measurements during follow-up time, repeated-measures variance analysis was used. Categorical variables were compared by Pearson chi-square test. The criterion for statistical significance was $P < 0.05$.

Results

The study included 90 eyes of 90 patients with nAMD. The mean age of the patients was 70 ± 7.5 years, with 35 (38.9%) being male and 55 (61.1%) being female. According to the examinations with OCT and B-mode ultrasonography, 43 patients had "concurrent"[11] VMA (30 focal, 13 broad; Group 1) (Figure 1), 29 patients had complete PVD (Group 2) (Figure 2), and 18 patients (Group 3) had ERM (Figure 3) ($P > 0.05$). The mean follow-up time was similar ($P > 0.05$), and it was at least 2 years for all groups. There was also no significant difference between the baseline lesion size, OCT findings, and the best-corrected visual acuities of any groups (Table 1). The number of injections was highest for the patients with ERM (Group 3), and this difference was statistically significant ($P < 0.001$). The mean interval between injections and the mean longest interval were shorter in Group 3 ($P < 0.032$, $P < 0.012$, respectively).

There was no significant difference in the BCVA at baseline, after loading dose, and at the end of the follow-up time among the groups (Table 2). Additionally, the change in BCVA compared with baseline at each visit was also not different between groups (Table 3). The CFT and lesion size measurements were also taken at baseline, third month, and at the end. Neither separately nor in comparison with baseline, any difference was found between groups (Tables 4–7).

Discussion

Despite improvements in visual acuity with anti-VEGF therapy, a subset of patients with nAMD continue

Table 3. Time-Dependent Change in the BCVA

	Change in the BCVA (logMAR) (Median; Min–Max)			
	Group 1	Group 2	Group 3	*P* (ANOVA)
Third month – baseline	0.00 (–1 to 1)	0.00 (–0.7 to 0.78)	0.00 (–0.50 to 1.30)	0.934
Last visit – baseline	0.00 (–1 to 1.78)	0.00 (–0.70 to 1.90)	0.05 (–0.60 to 1.30)	0.918

ANOVA, analysis of variance.

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Table 4. CFT Measurements at Each Follow-up

	CFT (μm) (Median; Min–Max)			
	Group 1	Group 2	Group 3	*P* (ANOVA)
Baseline	252 (140–651)	271 (126–1,000)	255 (175–600)	0.525
Third month	180 (90–640)	180 (116–500)	201.5 (96–660)	0.987
Last visit	160 (52–620)	157 (45–652)	187 (90–521)	0.633

ANOVA, analysis of variance; CFT, central foveal thickness.

to lose vision and to display leakage from CNV, even with regular intravitreal anti-VEGF therapy.[12–15] Previous studies have demonstrated that the percentage of PVD is lower and VMA is more frequently observed in eyes with nAMD than in controls or eyes with dry type AMD.[3,6–8] Additionally, VMA was suggested to be related with progression in patients with nAMD.[16] This study investigated vitreous configuration and the presence of ERM as relevant factors for the efficacy of anti-VEGF treatment.

In this study, OCT revealed ERM in 19% of patients. When analyzed according to the frequency of anti-VEGF injections and injection intervals, which reflect the quality of response assessed by OCT, patients with ERM required 11.6 ± 2.9 anti-VEGF injections with 6.12 weeks of mean injection interval. This relatively poor response demonstrates the importance of ERM in the management of patients with nAMD.

Vitreomacular adhesion was described in previous studies in eyes with nAMD, significantly more frequent than in eyes with nonexudative AMD or control eyes.[3,4,7] Weber-Krause and Eckardt[8] demonstrated that ultrasound examinations of patients with AMD showed a higher rate of persisting posterior vitreous attachment compared with those without AMD. In another study, 80% of patients with nAMD were found to have a central vitreoretinal adhesion during vitrectomy performed for subretinal CNV extraction.[17] They also speculated that vitreomacular traction might enforce degenerative processes or even lead to enlargement of CNV. Schmidt et al[18] claimed patients with nAMD and VMA might profit from pharmacological or surgical removal of the vitreous. In an OCT study, 77% of patients with nAMD showed abnormalities of the VMI (ERMs, retinal thickening, and retinal distortion).[19] These findings may support the idea of poor prognosis in patients with nAMD with VMI disorders.

To date, there are few reports of the effect of VMI configuration on anti-VEGF treatment. All studies consider VMA or PVD in the prognosis of nAMD and include small populations and retreatment regimens without standardized protocol. To the best of our knowledge, this study that obeys the novel classification scheme reported by the International Vitreomacular Traction Study Group[11] is the only one providing the effects of ERM on the anti-VEGF treatment of patients with nAMD. Lee and Koh[20] demonstrated results of a loading plus PRN regimen with anti-VEGF (OCT-based retreatment; 3.87 ± 1.77 injections/12 months), resulting in inferior BCVA outcomes of eyes with VMA compared with eyes without VMA. The authors postulated a negative association between VMA and visual outcome of anti-VEGF in nAMD. However, on the basis of the results of PRN treatment, we suggest that VMA without ERM may not represent a disadvantage for anti-VEGF therapy because these patients also achieved favorable outcomes with appropriate treatment regimen.

Previous investigators proposed several possible mechanisms to explain the effect of VMA on the progression of typical AMD: gel liquefaction that goes beyond the degree of vitreoretinal dehiscence results in anomalous PVD.[21] Chronic inflammation is thought to be involved in the cause of choroidal neovascularization in typical AMD.[22–24] Vitreomacular traction induces macular edema through dynamic traction caused by posterior vitreous cortex. The macula is cut off from its blood supply, leading to ischemia-induced VEGF release and the development of CNV.[25] Tong et al[26] demonstrated that VEGF concentrations in aqueous humor were increased in patients with

Table 5. Time-Dependent Change in the CFT

	Change in the CFT (μm) (Median; Min–Max)			
	Group 1	Group 2	Group 3	*P* (ANOVA)
Third month – baseline	–41.5 (–433 to 360)	–50 (–500 to 314)	–40.5 (–450 to 80)	0.513
Last visit – baseline	–87 (–472 to 340)	–84 (–955 to 422)	–55 (–510 to 270)	0.904

ANOVA, analysis of variance; CFT, central foveal thickness.

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Table 6. Lesion Size Measurements at Each Follow-up

	Lesion Size (mm^2) (Median; Min–Max)			
	Group 1	Group 2	Group 3	*P* (ANOVA)
Baseline	9.97 (0.21–36.75)	10.23 (0.65–33.12)	11.29 (1.38–37.31)	0.230
Third month	10.63 (0–33.03)	8.36 (0.32–27.35)	14.42 (0–48.79)	0.183
Last visit	12.03 (0–88.34)	9.68 (0–47.10)	14.86 (0–37.31)	0.871

ANOVA, analysis of variance.

Table 7. Time-Dependent Change in Lesion Size

	Change in Lesion Size (mm^2) (Median; Min–Max)			
	Group 1	Group 2	Group 3	*P* (ANOVA)
Third month – baseline	0.00 (–8.25 to 9.70)	0.00 (–20.3 to 9.87)	–0.2 (–17.6 to 41.99)	0.353
Last visit – baseline	0.00 (–11.30 to 58.09)	0.00 (–20.3 to 29.62)	–0.18 (–13 to 6.82)	0.332

ANOVA, analysis of variance.

nAMD. Posterior vitreous detachment has been suggested to increase the intravitreal concentration of molecular oxygen and thereby reduces the VEGF level.[27,28] Vitreomacular adhesion with chronic inflammation in patients with nAMD may have greater effect on the VMI and lead to more frequent adhesion of posterior hyaloid. Vitreous adhesion on the retinal surface is regarded as risk factor for proliferative complications, such as proliferative vitreoretinopathy and epiretinal gliosis.[29] Frequently, these proliferations in the macular area induce an additional edema, which further decreases visual acuity.[30,31] However, a follow-up examination of our patients revealed no significant difference between the change of lesion size, OCT findings, and the BCVA of any groups.

We hypothesize that, in most cases, ERM is not considered at baseline because most clinicians concentrate on other parameters, such as hemorrhage, presence of fluid, and pigment epithelial detachments in the setting of nAMD. In this study, ERM seems to have a significant influence on anti-VEGF treatment and should be assessed when using PRN protocol. The mechanism to explain this result may be a possible inherent inflammation to nAMD may lead to formation of ERM, and this increased inflammation probably requires more frequent injections. Another potential explanation may be that the traction may disrupt the architecture of the retinal pigment epithelium (RPE), the Bruch membrane, and the retinal photoreceptor layer that may result in a decrease in effectiveness of anti-VEGF agents. Additionally, these membranes may decrease the penetration of the drugs through these membranes, which may act as a physical barrier. However, further studies are needed to clarify how the presence of ERM contributes to the number of injections and injection interval.

There are a number of limitations of the current study. The study is retrospective study with no prior diagnostic criteria. The study was not planned to demonstrate whether VMA and ERM were the cause or the result of nAMD. It is necessary to determine whether VMA and ERM are indeed pathogenic factors in development of nAMD.

In conclusion, the presence of ERM in eyes with nAMD seems to be associated with an increase in the number of anti-VEGF injections and decrease in the injection intervals for the treatment of nAMD. Although the anatomical and functional results are similar in eyes with or without ERM, the increased need for anti-VEGFs may mean that these membranes, probably as a result of inflammation in nAMD patients, may decrease the penetration of the drugs through these membranes, which may act as a physical barrier.

Key words: AMD, epiretinal membrane, vitreomacular interface.

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