Prognostic Value of Retinal Pigment Epithelium Elevation in Anatomical Success After Loading Phase in Neovascular Age-Related Macular Degeneration Treated with Bevacizumab

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ABSTRACT

Purpose: To determine the value of retinal pigment epithelium (RPE) elevation area and volume in the prognosis of neovascular age related macular degeneration (nAMD).

Materials and Methods: Twenty-five eyes of 25 treatment naive nAMD patients (13 male,12 female) were included in this retrospective study. AMD cases with classical choroidal neovascularization (CNV) demonstrated by fundus flourescein angiography were included in the study. Two groups were divided according to the presence of subretinal fluid (SRF) (group 1) and absence of SRF (group 2) at the first visit after 3 months of anti-VEGF (Bevacizumab) loading. Best corrected visual acuity (BCVA), intraocular pressure values, center macular thickness (CMT), SRF height, center 3 and 5 mm RPE elevation area and volume were evaluated.

Results: There were 13 patients in group 1 and there was no difference in age and gender between the groups. There was no significant correlation between the delta value of RPE elevation areas and volumes before and after treatment and the change in BCVA values. According to the results obtained from the Univariate risk analysis, CMT, RPE elevation area 3mm, RPE elevation area 5mm and RPE elevation volume 3mm (p:0.028, p:0.002, p:0.044, and p:0.059, respectively) were included in the logistic regression analysis model. In logistic regression analysis, it was observed that baseline RPE elevation area 3mm was significantly associated with the presence of subretinal fluid after the loading phase (OR:6.062, CI:1.173-31.335, p:0.032).

Conclusion: The RPE elevation area at the central 3 mm at the first presentation may have value as a marker in determining the prognosis of nAMD.

Keywords: Bevacizumab, Neovascular age related macular degeneration, Retinal pigment epithelium elevation.

INTRODUCTION

Neovascular age-related macular degeneration (nAMD) is the most common cause of blindness in the elderly population in developed countries.[1] Anti-vascular endothelial growth factor (anti-VEGF) therapies are used as standard treatment in nAMD therapy.[2] Although anti-VEGF therapies make an important contribution to the management of nAMD, one quarter of the cases may be unresponsive to treatment. Therefore, various biomarkers have been studied to predict the response of the treatment in nAMD. Subgroup analyzes of the MARINA and ANCHOR studies showed that baseline visual acuity and patient age were a determining factor on visual acuity at the end of treatment. [3, 4] Namura et al. have investigated the relationship between vitreoretinal interface and nAMD, it was reported that more injections were required in eyes with vitreoretinal interface disease,[5] and in another study, the presence of outer retinal tubulation (ORT) was associated with poor prognosis.[6] In the HARBOR study, the protective effect of subretinal fluid aganist geographic atrophy was shown.[7] Additionally, CATT study, intraretinal fluid was associated with poor outcome.[8] The role of markers such as external limiting membrane (ELM) status, lipofuscin accumulation, choroidal thickness, etc. has been investigated in determining the prognosis of nAMD.[9]

It has been shown in the ANCHOR and MARINA studies

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that the small size of choroidal neovascularization is also associated with a good prognosis.[3, 4] A positive association between choroidal neovascularization (CNV) size and the extent of ellipsoid zone (EZ) destruction with poor visual outcome has also been reported.[4, 10] In addition, degenerative changes in the retinal pigment epithelium (RPE) layer are considered a sign of disease progression, and photoreceptors are lost at the end of this process, which is one of the indicators of poor prognosis.[11, 12] One of the degenerative changes in nAMD is the elevation of the RPE caused by drusen formed by deposits between the RPE and Bruch's membrane, and by CNV developing in the sub-RPE.[13] The aim of this study is to determine the value of retinal pigment epithelium (RPE) elevation area or volume in the prognosis of nAMD.

MATERIALS AND METHODS

Total 25 eyes of 25 treatment naive nAMD patients (13 male, 12 female) were included in this retrospective study. AMD cases with classical CNV demonstrated by fundus fluorescein angiography (FFA) were included in the study. None of the eyes had any other retinochoroidal disorder (occult CNV, pachychoroidal vasculopathy, myopic CNV, etc.). A total of 3 intravitreal doses of 0.05 ml bevacizumab were administered to all eyes at 4-week intervals (loading phase). Two groups were divided according to the presence of SRF (group 1) and absence of SRF (group 2) at the first visit after 3 months of anti-VEGF loading. Best corrected visual acuity (BCVA) and intraocular pressure (IOP) values were noted at each follow-up examination. In addition, center macular thickness (CMT), subretinal fluid height (SRFH) (if any/present), center 3 and 5 mm RPE elevation area and volume were evaluated with optical coherence tomography (OCT) (SD-OCT, Zeiss Cirrus HD OCT 5000)(figure 1). All subjects were informed about the study procedure, and written consent was obtained. The study followed the tenets of the Helsinki Declaration and was approved by the institutional ethics committee.

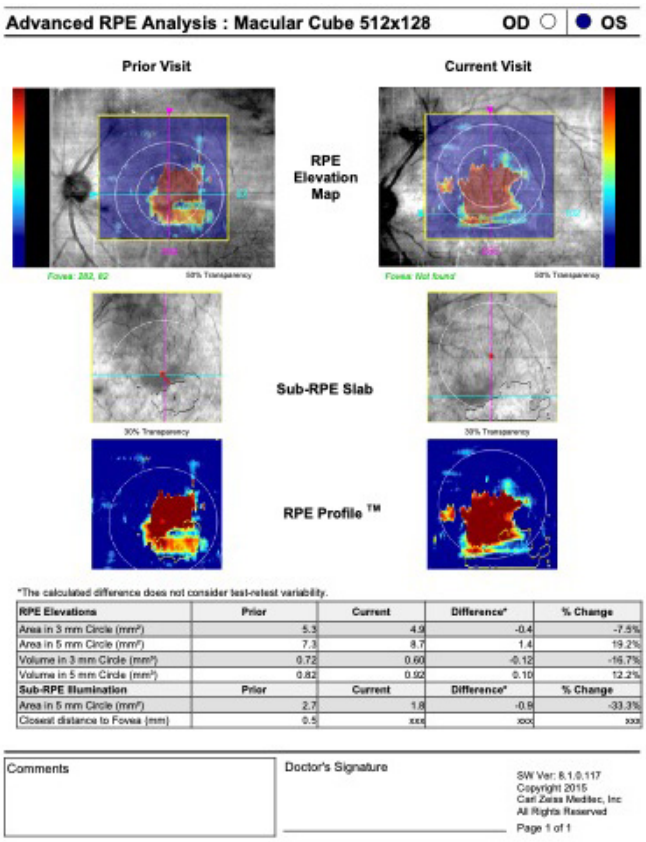

Figure 1: *OCT image showing the retinal pigment epithelium elevation area and volume at the central 3 mm and 5 mm at baseline and after loading dose.*

Statistical analysis

Analysis were performed using the SPSS statistical software for Windows, version 21, released in 2012 (IBM, Armonk, NY, USA). The descriptive statistics are expressed as means ± standard deviations for variables with normal distributions, medians (interquartile range for non-normal distributions), and the number of cases and percentages (%) for nominal variables. The Kolmogorov-Smirnov distribution test was used to examine the normal distribution. Pearson Chi-square test and Fisher's Exact test were used for comparison of descriptive statistics, as well as qualitative data. Mann-Whitney U test was performed for comparison of non-normally distributed quantitative data of two groups. When the relationship between parameters were investigated, Pearson's correlation test was used for normally distributed data, and Spearman's correlation test was used for non normally distributed data. Univariate risk analysis and logistic regression analysis were used to analyze the factors leading to the persistence of subretinal fluid after 3 months of loading. The results were evaluated at 95% confidence interval, $p < 0.05$ significance level.

RESULTS

There were 13 patients in group 1, and the mean age was 69.4±11.2 years. The mean age of group 2 was 73.2±5.1 years and there was no significant difference between the two groups (p:0.298). There were 8 males in both groups and the genders were similar (p:0.990). Table 1 and 2 show the distribution of BCVA, IOP values and OCT parameters of the eyes according to the groups after the initial and loading dose, and the comparison of these values between the groups. There was no significant relationship between baseline RPE elevation areas and volumes and BCVA values ($p>0.05$ for all). There was no significant correlation between the delta value of RPE elevation areas and volumes before and after treatment and the change in BCVA values ($p>0.05$ for all). When the relationship between visual gain

Table 1: *Baseline BCVA, IOP, and OCT parameters values of the groups and their comparison.*

	Group 1	Group 2	p value
	Median (IQR)		
BCVA (logMAR)	-1.41 (-1.65;-1.0)	-0.69 (-1.65;-0.61)	0.295
IOP (mmHg)	15 (14;16)	16 (15;19)	0.210
CMT	395 (319;471)	292 (234;335)	**0.007**
Rpe el. area 3mm	3.95 (2.12;4.27)	1.30 (0.40;2.85)	**0.005**
Rpe el. area 5mm	5.55 (2.77;7.87)	2.90 (0.45;4.75)	0.052
Rpe el. volume 3mm	0.39 (0.10;0.82)	0.04 (0.02;0.42)	**0.019**
Rpe el. volume 5mm	0.47 (0.13;1.24)	0.11 (0.02;0.52)	0.077
SRFH	138 (95;243)	89 (68;163)	0.331

BCVA: Best corrected visual acuity, IOP: Intraocular pressure,
OCT: Optical coherence tomography, IQR: Interquartile range
Rpe el: Retina pigment epithelium elevation, SRFH: Subretinal fluid height

Table 2: *BCVA, IOP, and OCT parameters values of the groups after the loading dose and their comparison.*

	Group 1	Group 2	p value
	Median (IQR)		
BCVA (logMAR)	-0.67 (-1.07;-0.37)	-0.69 (-0.82;-0.35)	0.605
IOP (mmHg)	16.0 (15.0;17.0)	16.0 (13.5;18.2)	0.962
CMT	325 (254;420)	202 (189;229)	**0.002**
Rpe el. area 3mm	3.55 (1.55;4.12)	0.70 (0.35;1.65)	**0.010**
Rpe el. area 5mm	4.70 (2.42;7.37)	0.70 (0.35;3.90)	**0.014**
Rpe el. volume 3mm	0.21 (0.07;0.58)	0.03 (0.015;0.12)	**0.010**
Rpe el. volume 5mm	0.35 (0.11;0.83)	0.03 (0.01;0.34)	**0.016**
SRFH	82 (64;134)	0.0	

BCVA: Best corrected visual acuity, IOP: Intraocular pressure,
OCT: Optical coherence tomography, IQR: Interquartile range
Rpe el: Retina pigment epithelium elevation, SRFH: Subretinal fluid height

and demographic and baseline anatomical parameters was examined, it was observed that only age was a risk factor on visual gain (p:0.039).

Age, gender, baseline CMT, RPE area 3mm, RPE area 5mm, RPE volume 3mm, RPE volume 5mm and SRFH were evaluated in the univariate risk analysis. Of these parameters, CMT, RPE elevation area 3mm, RPE elevation area 5mm and RPE elevation volume 3mm (p:0.028, p:0.002, p:0.044, and p:0.059, respectively) were included in the logistic regression analysis model. In logistic regression analysis, it was observed that baseline RPE elevation area 3mm was significantly associated with the presence of subretinal fluid after the loading phase (OR: 6.062, CI:1.173-31.335, p:0.032).

DISCUSSION

In nAMD, many demographic and structural parameters have been the subject of research in order to predict the visual or anatomical course of the disease. Multicenter studies have shown that there is an association between advanced age and poor visual prognosis. Many studies investigating the prognosis in nAMD have shown the relationship between advanced age and poor visual prognosis.[14] When the gender distribution, which is another demographic data, is examined, although there is no significant difference between the genders, it was reported that the visual gain was higher in female at the end of 5 years in the CATT study.[15] In the current study, when the relationship between visual prognosis and demographic and anatomical data was examined, it was observed that there was a significant relationship only between the change in visual acuity and age at baseline. In addition,

there was no significant difference between the genders in terms of anatomical integrity obtained at the end of the loading dose.

Previous studies have also examined the relationship between some anatomical data and prognosis.Apart from these, the relationship between some anatomical data and prognosis was examined. In the PrONTO study, a correlation was reported between retinal thickness and VA change at 3 months.[16] While evaluating the CMT, we noted the automatized values of the OCT device, which also includes the SRF height in the measurement. Therefore, the lack of correlation between visual prognosis and retinal thickness in this study can be explained in this way. For example As well as, the ANCHOR, MARINA, CATT, and VIEW studies, which also investigated the relationship between CNV size and visual prognosis, have shown that smaller CNV size is associated with better visual prognosis. [14] In the HAWK, HARRIER, and FLUID studies, increased SRF volume has been shown to be associated with poor visual prognosis.[17, 18] Besides, the CATT study mentioned the negative relationship between the presence of RPE elevation and visual prognosis. [19] In the current study, we did not calculate SRF volume or CNV size as we investigated the effect of RPE elevation on prognosis. However, when we investigated the relationship between SRF height and dry macula, there was no significant relationship. In addition, in this study, in which RPE elevation areas and volumes were investigated numerically rather than the presence of RPE elevation, we could not detect a significant relationship between RPE elevation areas and volumes and visual prognosis. This may be due to the small sample size and/or short follow-up time. In the PrONTO study, a correlation was reported between retinal thickness and VA change at 3 months. The CATT study also mentioned the negative relationship between the presence of RPE elevation and visual prognosis. In the current study, when the relationship between visual prognosis and demographic and anatomical data was examined, it was observed that there was a significant relationship only between the change in visual acuity and age at baseline. While evaluating the CMT, we noted the automatized values of the OCT device, which also includes the SRF height in the measurement. Therefore, the lack of correlation between visual prognosis and retinal thickness in this study can be explained in this way. Apart from these, we did not calculate SRF volume or CNV size in this study as we investigated the effect of RPE elevation on prognosis. However, we could not detect a significant relationship between RPE elevation areas and volumes and visual prognosis. This may be due to the small sample size and/or short follow-up time. Although we could not find a relationship between visual prognosis and initial anatomical factors, when risk factors for dry macula were investigated, we observed that obtaining a dry macula after the loading phase was significantly associated with the initial 3 mm RPE elevation area.However, when the risk factors for dry macula were investigated, we observed that RPE elevation area 3mm was significantly associated with dry macula after the loading phase.

Maintaining the functional gain and anatomical stability achieved at the end of the anti-VEGF loading phase in nAMD is the goal of treatment. [20, 21] There are two approaches in the treatment of the nAMD as pro re nata (PRN) and treat and extend (TAE).[22] In the PRN regimen, monthly clinical visits are planned after the anti-VEGF loading dose and repeated anti-VEGF injections were applied when relapsed. However, delay in treatment is possible with the PRN regimen, which can cause irreversible damage to the neurosensory retina. In the TAE regimen, monthly fixed injections are applied until complete remission is achieved, and then a protocol that extends the visit and treatment intervals is applied. However, approximately one-third of patients with dry macula after the loading phase did not require additional treatment for recurrence in the first 12 months. [23] In these patients, when the TAE regimen is applied, unnecessary anti-VEGF injections will be made. In the present study, it was observed that the initial RPE area was associated with the dry macula after the loading phase. Therefore, the RPE area may be considered as an indicator for which treatment regimen can be chosen initially.

This study has some limitations, first of which is the relatively small sample size. This also caused the failure to investigate other factors (ORT, subretinal hyperreflective material, ELM and EZ status, etc.) that might affect the prognosis. The second major limitation was the evaluation of only the changes in the 3-month follow-up period, which led to a limitation in investigating the factors that may affect the visual prognosis. In conclusion, the RPE elevation area at the central 3 mm at the first presentation may have value as a marker in determining the prognosis of nAMD. Contributions can be made to the management of treatment by evaluating the possible relationship between RPE elevation and nAMD prognosis with 52 or 104 week follow-up results.

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Disclosure of interest

The author MUI report no conflicts of interest. The author EY report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

Ethical approval

All procedures involving human participants were in accordance with the ethical standards of our institution's research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individuals included in the study.

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