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Original Article

A 5-Year Analysis of Optical Coherence Tomography Biomarkers in The Visual Outcomes of an As-Needed Treatment Algorithm for Neovascular Age-Related Macular Degeneration

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Abstract

Objectives: This study aimed to predict the visual course of patients with neovascular age-related macular degeneration by analyzing data from a 5-year observational study and to identify biomarkers that have an impact on visual prognosis.

Methods: The present study comprised a total of 104 patients who received the PRN treatment regimen between March 2015 and March 2021. Best-corrected visual acuity (BCVA) and optical coherence tomography findings were evaluated. Multinomial logistic regression models were used to determine predictors of BCVA at 12, 24, and 60 months.

Results: Better BCVA and thicker macula at baseline, decreased BCVA at month 3, and persistence of IRF at month 3 were correlated with decreased BCVA at month 12 (all $p<0.05$). At 24 month, a decline in BCVA was associated with specific baseline characteristics, including better BCVA, absence of pigment epithelial detachment (PED), and presence of intraretinal cystoid fluid (IRF) (all $p<0.01$). Similarly, decreased BCVA and thicker macula in the 3rd month were associated with worse BCVA. At the 60-month visit, better baseline BCVA, absence of PED, presence of IRF at baseline, and persistence of IRF at month 3 were associated with a reduction in BCVA (all $p<0.05$). The visual prognosis had no correlation with the number of injections.

Conclusion: This 5-year real-life study identified prognostic markers that cause a decline in visual acuity. The use of these markers has the potential to be valuable in preserving visual gain, irrespective of the number of injections.

Keywords: Anti-vascular endothelial growth factor, Biomarkers, Neovascular age-related macular degeneration, Real-life, Visual prognosis

Introduction

In the year 2020, age-related macular degeneration (AMD) was listed as one of the primary causes of loss of vision in people aged 50 and over worldwide (18 million cases) (1). In the case of neovascular AMD (nAMD), the development of subretinal or sub-retinal pigment epithelium (RPE) choroidal neovascularization (NV) can irreversibly reduce visual acuity (VA) (2).

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Intravitreal anti-vascular endothelial growth factor (VEGF) injection therapy has been demonstrated to minimize macular complications by suppressing neovascular membrane formation (2-6). However, despite the use of these agents, only some patients achieve the desired VA gain and anatomic improvement. Therefore, some studies have been undertaken to predict the treatment response of patients with nAMD. In these studies, biomarkers (age, genetic factors, initial VA) and optical coherence tomography (OCT)-based markers (status of vitreomacular interface, presence of fibrovascular or serous pigment epithelial detachment (PED), subretinal and intraretinal fluid, hyperreflective foci [HF]) were thoroughly investigated to identify the characteristics of patients requiring intensive treatment (5-7). Personalized disease prognosis can be achieved by describing probable prognostic factors using biomarkers.

The objective of our study was to ascertain the prognostic factors and biomarkers that affect visual outcomes by analyzing real-life data and establishing criteria for creating personalized disease prognoses for treatment-naïve patients. This study represents the first investigation, to the best of our knowledge, to provide 5 years of real-life data in Türkiye, with the aim of identifying biomarkers that can be used to predict visual outcomes of nAMD treatment.

Methods

This retrospective study was conducted in the medical retina department of a tertiary care center between March 2015 and 2021. The medical records of patients who received intravitreal anti-VEGF injections for nAMD were reviewed. The study followed the tenets of the Declaration of Helsinki and it was approved by the ethics committee of Ankara Training and Research Hospital. Informed consent was obtained from all participants. The trial registration number (retrospectively registered) was E-21-687 (August 18, 2021).

The study comprised a series of patients aged 50 years and over who underwent intravitreal injection of anti-VEGFs for nAMD, with a 5-year follow-up period. The study excluded all patients who had any disease causing choroidal neovascular membrane formation other than AMD, any retinal and corneal pathology affecting VA, and image quality. In addition, patients with a history of intraocular surgery, except uncomplicated phacoemulsification with intraocular lens implantation, and a history of uveitis and any hereditary retinal disease were excluded.

Following the administration of 3-month loading doses of aflibercept (Eylea®, Bayer, Berlin, Germany) or ranibizumab (Lucentis®; Genentech/Roche, USA), the treatment algorithm was adapted to an as-needed (PRN) basis. OCT follow-ups were conducted at 4–6-week intervals to monitor patient progress. We performed retreatment when there was a decrease of one or more lines in VA due to disease activity, persistence of intraretinal or subretinal fluid (SRF), an increase of more than 100 µm in central macular thickness (CMT), or development of new-onset macular hemorrhage. A decreased VA due to central atrophy was not an indication for injection.

All patients underwent a complete ophthalmic examination, including medical and family history, best-corrected visual acuity (BCVA, measured on an early treatment diabetic retinopathy study [ETDRS] chart converted to logarithm of the minimum angle of resolution [logMAR]), intraocular pressure measurement, slit-lamp biomicroscopy, and dilated fundus examination using a 90 D lens during the follow-up. OCT (Heidelberg Engineering, Franklin, MA 02038, USA) and fundus fluorescein angiography (Carl Zeiss Meditec, Inc., Dublin, CA) were performed in all patients with AMD. The types of choroidal NV (CNV) were recorded. CMT measurements were obtained using spectral domain OCT. The BCVA and CMT values, as well as the OCT findings (presence of PED, intraretinal, and SRF), were evaluated at the baseline visit and at 3, 6, 12, 24, and 60 months. The extent of VA (logMAR) changes over time was determined by calculating the differences between eye-specific logMAR averages at initial and at every visit. The total number of injections administered and the total number of visits made by patients were meticulously calculated.

Cross-sectional images were analyzed using built-in software, and automated software was used to segment the retinal layers in foveal scans. Retinal thickness map analysis was performed using spectralis software on nine subfields according to the ETDRS definitions. CMT was measured as the average of all points within the inner circle of 1 mm radius. The presence of SRF, intraretinal cystoid fluid, PED, and HF was evaluated on OCT scans within 3 mm fovea at the baseline visit. The vitreomacular interface was classified according to the classification system established by the ınternational vitreomacular traction (VMT) study group. This classification was based on OCT images. OCT markers were evaluated for their effects on VA at 12, 24, and 60th months.

The clinical factors assessed included the patient's age, sex, and visual acuity as well as the findings of the OCT scan at baseline and at 3 months. The influence of these factors on the final visual outcomes at 12, 24, and 60 months was analyzed.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 27 software. (SPSS, Inc. Chicago, IL). Descriptive statistics are given as mean±standard deviation or median (minimum-maximum) for continuous variables and frequency (%) for categorical variables. The assessment of normality was conducted by Kolmogorov–

Smirnov test. Multinomial logistic regression models were used to identify predictors of VA at 12, 24, and 60 months. Patients were categorized into three groups according to the degree of change in their BCVAs, as outlined in the following sentence. An absolute difference of <0.2 logMAR was deemed to be a non-clinically relevant change, whereas an increase of 0.2 logMAR or greater was considered a decrease in VA, and a decrease of 0.2 logMAR or greater was regarded as an improvement in VA (7). The dependent variables were the BCVA status at 12, 24, and 60 months (decreased was defined as "1," a non-clinically relevant change was defined as "2," and increased was defined as "3"). The independent variables were baseline clinical and OCT findings. Numerical values (e.g., baseline BCVA, age, CMT) were included as continuous variables in the multinominal regression analysis. P<0.05 was considered to be statistically significant.

Results

A total of 223 patients who were followed up in the retina outpatient clinic and received regular treatment between March 2015 and March 2021 were identified. However, the current study incorporated a total of 104 eyes from 104 patients, with consistent longitudinal follow-up for 5 years. Fifty patients were male and 54 were female; the mean age of the patients was 71.66±9.28 (51–92) years. Angiographically, the CNV lesions were occult in 45%, minimally classic in 28.9%, predominantly classic in 17.7%, and retinal angiomatous proliferation in 8.4%. Table 1 presents a comprehensive overview of the patients' demographic characteristics, while Figure 1 illustrates the mean number of visits and injections.

The mean BCVA was 0.40 (0.00–3.0) logMAR at baseline. The mean VA changes at 3, 6, 12, 24, and 60th months were −0.07, −0.09, −0.05, 0.0, and +0.025 logMAR, respectively. The

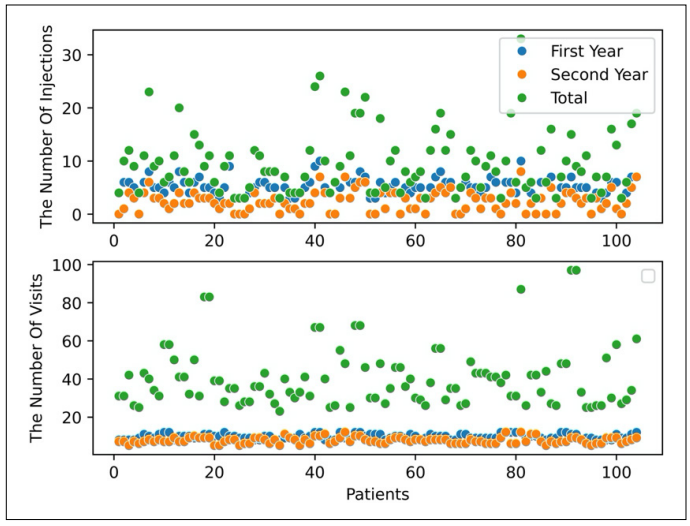

Figure 1. The mean number of visits and injections.

Table 1. Summary of the data of the study group

No. of patients/eyes at the beginning of study	**104/104**
Mean age (range, year)	71.66±9.28 (51–93)
Gender Male/Female (%)	50/54 (48/52)
Type of CNV lesion	
Type 1	47 eyes (45.1%)
Type 2	30 eyes (28.8% minimally classic)
	19 eyes (18.2% predominantly classic)
Type 3	8 eyes (8.2% RAP)
Anti-VEGF agents	
Ranibizumab/Aflibercept/(eyes)	93/11
The mean number of injections (mean±SD/median, minimum-maximum)	
1st year	5.2±1.5/5 (3–10)
2nd year	2.6±2.0/2.5 (0–8)
During the follow-up period	9.75±5.9/9 (3–33)
The mean number of visits (mean±SD/median, minimum-maximum)	
1st year	9.8±1.4/9.5 (8–12)
2nd year	7.6±1.7/7 (5–12)
During the follow-up period	40.16±15.5/38 (22–97)

SD: Standard deviation; VEGF: Vascular endothelial growth factor; CNV: Choroidal neovascularization; RAP: Retinal angiomatous proliferation.

mean baseline CMT was 302.5 (204–948) µm, and the mean CMT change at 3, 6, 12, 24, and 60th months after treatment was −27.50, −11, −6.5,+14.50, +7.50 µm, respectively (Fig. 2).

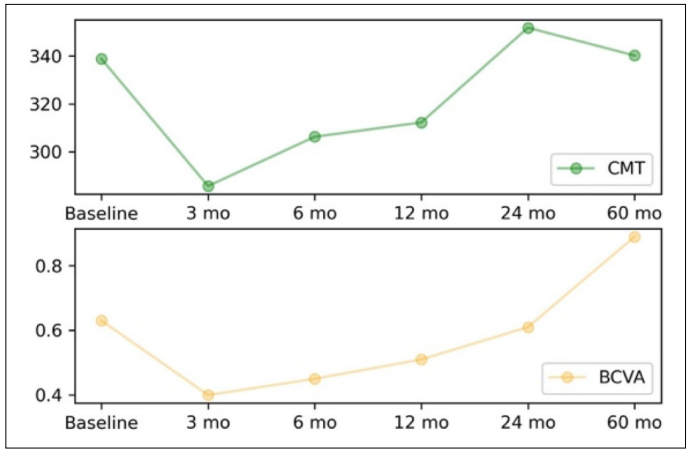

Figure 2. The mean visual acuity and central macular thickness changes during the follow-up.

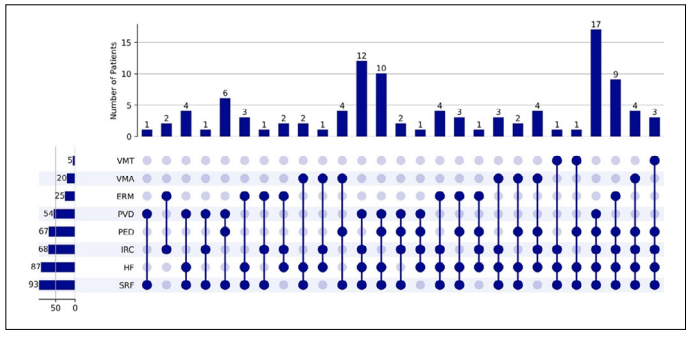

Figure 3. OCT findings of the patients at baseline visit.

OCT: Optical coherence tomography, PED: Pigment epithelial detachment, IRC: Intraretinal cystoid fluid, SRF: Subretinal fluid, HF: Hyper-reflective foci, ERM: Epiretinal membrane, PVD: Posterior vitreous detachment, VMA: Vitreomacular adhesion, VMT: Vitreomacular traction.

The most common OCT findings at baseline visit were SRF (91.6%), HF (79.4%), PED (57%), and intraretinal fluid/cyst (54.1%). Figure 3 shows the OCT findings of patients at the baseline visit.

Multinomial logistic regression analysis was conducted to evaluate the combined impact of clinical and OCT biomarkers at baseline and after 3 monthly loading doses on BCVA status at 12, 24, and 60 months. Better baseline BCVA ($p<0.001$), thicker macula at baseline ($p=0.013$), decreased BCVA at the 3rd month ($p<0.001$), and IRF resistance at month 3 ($p<0.001$) were found to be associated with decreased BCVA at the 12th month. At the 24 months, a statistically significant correlation was observed between the decreased BCVA and several baseline characteristics. These included better baseline BCVA ($p<0.001$), absence of PED ($p=0.008$), and presence of IRF ($p=0.006$). Furthermore, decreased BCVA ($p=0.005$), thicker CMT ($p=0.017$) at the 3rd month, and persistence of IRF at the 3rd month were identified as significant factors associated with decreased BCVA. At the 60 months, a better baseline BCVA ($p=0.01$), absence of PED ($p=0.026$), presence of IRF ($p=0.019$) at baseline, and persistence of IRF at month 3 ($p=0.002$) were linked to a decline in BCVA (Table 2 and Fig. 4).

Discussion

In this study, the real-world data of anti-VEGF agents used in the treatment of AMD over a 5-year follow-up period were evaluated. Furthermore, we identified biomarkers and OCT markers that may affect BCVA at 12, 24, and 60 months.

An extensive number of studies have been conducted to evaluate the outcomes of PRN and Treat-and-Extend (T and E) regimens, as compared with monthly injections. The number of injections in PRN studies was lower than that in T and E regimens. Almost all previous studies demon-

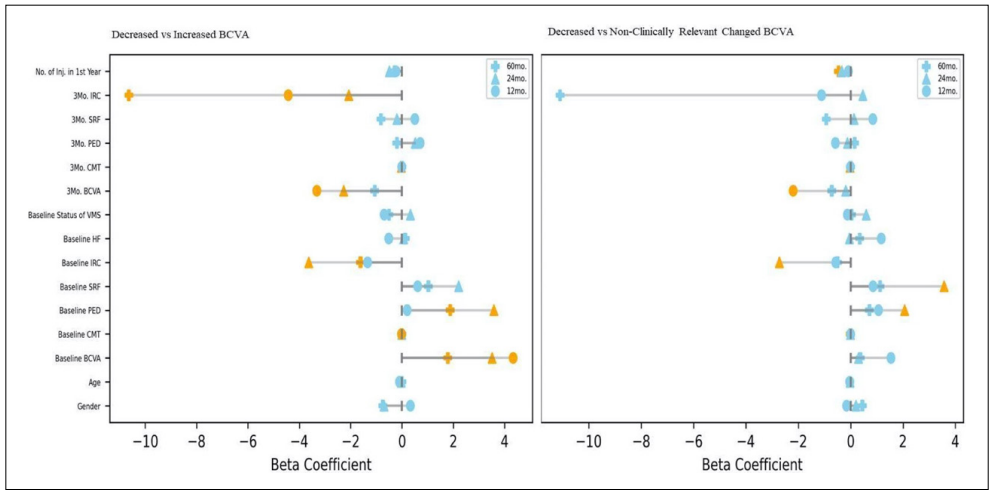

Figure 4. The results of the multinomial logistic regression analysis (The statistical significance of the results is indicated by the use of orange icons, while non-significant results are represented by blue icons).

Table 2. The results of multinominal regression analysis

	Decreased BCVA versus Increased BCVA						Decreased BCVA versus Unchanged BCVA					
	12 Mo		24 Mo		60 Mo		12 Mo		24 Mo		60 Mo	
	p	Odds ratio	p	Odds ratio	p	Odds ratio	p	Odds ratio	p	Odds ratio	p	Odds ratio
Gender	0.74	1.39	0.52	0.50	0.35	0.48	0.83	0.86	0.79	1.23	0.49	1.57
Age	0.08	0.91	0.62	0.97	0.95	1.00	0.42	0.97	0.68	0.98	0.26	0.96
Baseline BCVA	0.00	76.09	0.00	33.54	0.01	5.98	0.32	4.67	0.82	1.36	0.63	1.45
Baseline CMT	0.02	0.98	0.58	1.00	0.43	1.00	0.37	1.00	0.48	1.00	0.01	0.99
Baseline PED	0.85	1.22	0.01	36.02	0.02	6.56	0.16	2.90	0.02	7.87	0.30	2.06
Baseline SRF	0.62	1.85	0.16	9.13	0.43	2.80	0.37	2.36	0.01	35.55	0.21	3.07
Baseline IRC	0.21	0.26	0.01	0.03	0.04	0.20	0.47	0.57	0.02	0.07	0.47	0.61
Baseline HF	0.63	0.60	0.96	1.07	0.88	1.14	0.17	3.22	0.97	0.96	0.66	1.42
Baseline status of the vitreomacular surface	0.25	0.50	0.60	1.40	0.28	0.60	0.77	0.88	0.24	1.81	0.92	1.04
3 Mo. BCVA	0.00	0.04	0.01	0.10	0.27	0.35	0.04	0.11	0.87	0.83	0.47	0.49
3Mo. CMT	0.47	0.99	0.02	0.98	0.92	1.00	0.30	0.99	0.01	0.98	0.68	1.00
3Mo. PED	0.55	2.04	0.66	1.68	0.81	0.82	0.52	0.56	0.90	0.89	0.84	1.16
3Mo. SRF	0.69	1.66	0.88	0.82	0.40	0.44	0.39	2.34	0.90	1.14	0.28	0.39
3Mo. IRC	0.03	0.01	0.04	0.13	0.04	0.00	0.45	0.33	0.75	1.60	0.80	0.00
No. of injections in 1st year	0.49	0.80	0.19	0.61	0.23	0.75	0.74	0.92	0.27	0.71	0.04	0.63

BCVA: Best-corrected visual acuity, PED: Pigment epithelial detachment, IRC: Intraretinal cystoid fluid, SRF: Subretinal fluid, CMT: Central macular thickness, Mo: month, HF: Hyper-reflective foci.

strated that as injections increased, patients gained more letters and demonstrated excellent vision maintenance (5-7). The mean number of injections in the initial year of treatment was 5.2, which is consistent with the findings of other studies (8,9). In the subsequent year under the PRN regimen, this number decreased to an average of 2.6 injections. The findings of this study indicate that the number of injections in the 1st year of treatment has no effect on visual prognosis. However, although visual acuity stability was maintained during the first 2 years of treatment, it was not sustained at 60 months. One potential strategy to address this issue could be to determine the frequency of injections based on the prognostic factors identified in the present study.

We analyzed prognostic indicators at baseline and at month 3 to predict individual treatment prognosis. In previous studies, patient age has been reported as a biomarker of treatment response. In most of these studies, younger patient age was correlated with good final VA results (2,3,5,10,11). In the current study, patient age was not correlated with BCVA during follow-up. The mean age of our patients was 71.66 and the proportion of patients aged <65 years was only 23%, indicating that our patients predominantly comprised elderly individuals.

Wang et al.(12) reported that men exhibited a 2.19-fold increased risk of reinjection than women. Similarly, the 5-year follow-up results of the comparison of AMD treatment trial (CATT) study demonstrated that, compared to men, women were more likely to gain a minimum of 15 letters (13). In the current study, there was no difference in the follow-up between females and males. These results match those observed in previous studies (14,15).

Another important predictor of visual improvement was the baseline VA level. A number of studies correlated poor baseline VA with better visual outcomes at year 1 and year 2; however, some studies reported better baseline VA as a predictor of better final VA (4,5,16,17). In our study, poor baseline VA had a significantly positive effect on VA level in all visits. However, even if patients with poor baseline VA seem to gain more VA, they will have poorer final VA. Several reports have shown that initiating treatment early is one of the significant factors for improved visual outcomes (18,19).

As demonstrated in preceding studies, the BCVA level following three loading doses has been identified as a significant predictor of the final visual outcome (5,11). The present study's findings provide further evidence in support of this hypothesis, thereby demonstrating a positive correlation between VA levels following three loading doses and VA levels at 12, 24, and 60 months. The BCVA level achieved after three loading doses was valuable for predicting long-term visual prognosis.

OCT-based biomarkers are used to predict visual prognosis while assessing treatment response. At present, CMT is not used as a monitoring or retreatment indicator. Therefore, evaluating CMT alone is insufficient to distinguish subtle changes in retinal compartments. Furthermore, there was a weak correlation between VA and retinal thickness. Our results indicate that baseline CMT significantly affects VA at month 12, but not at 24 and 60 months. However, a thick macula after three loading doses affected the BCVA at month 24. A thicker central macula may unfortunately lead to morphological changes in the retinal layers, resulting in a poorer long-term visual prognosis.

Another significant biomarker investigated in previous studies is the location of fluid within the retinal layers, including intraretinal and SRF. In most of the previous studies, the presence of SRF at baseline and during follow-up was associated with favorable visual outcomes (20,21). While there are studies showing that SRF <200 μm can be tolerated with no negative effect on VA, there are also studies showing a progressive decrease in retinal sensitivity in eyes with SRF (22,23). The present study found no statistically significant correlation between the presence of SRF at baseline or at 3 months and subsequent visual prognosis during follow-up. In contrast, a number of earlier studies have shown that the existence of IRF at baseline and throughout the follow-up period is indicative of a poor final visual prognosis (13,14,21). Our findings align with those of numerous preceding studies, which have demonstrated a correlation between the presence of baseline IRF and a decline in BCVA over time. Similarly, the results of the multinomial logistic regression analysis in our study indicated that the presence of IRF following loading doses has a negative predictive value for visual gain.

The presence of PED and its persistence after loading are prognostic factors evaluated in previous studies. The association between the presence of PED at the baseline visit and visual outcomes has been reported in previous studies (14). Some reports indicate no significant association with the risk of inferior visual outcomes, whereas others specifically state that PED width predicts disease progression (24,25). In addition, it has been documented that fibrovascular or vascularized PED may result in a less favorable visual outcome. Nonetheless, certain studies have indicated a possibility that the presence or persistence of PED may be associated with relatively good VA (26). The present study found that the presence of PED at baseline had no effect on VA at 12 months. However, it was linked to better VA at 24 and 60 months. The present study did not concentrate on a comparison between serous and fibrovascular PEDs; however, the majority of the observed PEDs in the current study fell under the serous category.

The vitreomacular interface status has been considered an important risk factor in previous reports. In the literature, eyes with vitreomacular adhesion (VMA) had lower VA than those with PVD; these eyes also required more intensive treatment (14,27). Post hoc analysis of the MONT BLANC and CATT studies showed that there was no significant change in BCVA gains among the VMA, VMT, and RELEASE groups, but eyes with VMA and VMT required an increased number of injections to obtain favorable visual outcomes (22,28). In this study, the most common vitreomacular interface change was VMA. No correlation was observed between vitreomacular interface status at baseline and mean BCVA during the 60-month follow-up. In accordance with the existing literature, eyes with VMA, VMT, and epiretinal membrane required a higher average number of injections during follow-up than eyes with PVD (10 vs. 8 injections), although this was not statistically significant.

HF, another OCT finding, are small, well-defined dots located in the neurosensory retina and within the RPE (29,30). Coscas et al.(31) reported that poor BCVA at baseline was significantly correlated with the continuation of HFs after intravitreal injections. Some studies noted that HFs could be a biomarker of less VA gain, especially if they did not resolve with treatment (29-31). The presence of HF was found to have no effect on VA at 12, 24, and 60 months in this study. This study did not investigate the persistence of HF after injection but rather the relationship between the presence of HF at baseline and short- and long-term visual outcomes. These findings indicate that there is insufficient evidence to conclude that HF has an effect on visual prognosis.

The retrospective design of the study constitutes its primary limitation. Second, the potential effects of different anti-VEGF drugs were not addressed. Moreover, while a qualitative assessment of OCT parameters, including fluid, PED, and HF, was performed, a quantitative analysis of subretinal and intraretinal fluid volume, PED, and HF was not conducted. It may be useful to adopt a quantitative assessment approach to quantify the effectiveness of anti-VEGF treatment and the progression of AMD.

Conclusion

This study identified prognostic factors and OCT biomarkers affecting visual outcomes over a 5-year follow-up period in a real-world setting. The results indicated that lower baseline VA, absence of IRF, presence of PED at baseline, and lower macular thickness at baseline were predictive of better VA in the initial years following injections. Similarly, better BCVA at 3 months, absence of intraretinal fluid and the presence of PED, and reduced CMT at 3 months were significant prognostic markers for favorable visual outcomes in the initial 2 years following injections. The findings of our study indicate that the number of 1st year injections had no discernible effect on either short or long-term visual prognosis. In the present study, as in real-life studies, a decline in VA in patients treated with PRN regimens in the latter years of treatment was also observed. However, the use of favorable prognostic indicators, such as improved BCVA, absence of IRF, and a thinner macula following three loading doses, in conjunction with poor prognostic markers, including better baseline BCVA, absence of PED, and presence of IRF at the initial visit, may prove beneficial in preserving VA, regardless of the number of injections administered. This enables the creation of a personalized visual prognosis. Furthermore, when deciding on retreatment in a PRN regimen, it may be helpful to consider indicators affecting the visual prognosis. These indicators include the presence of IRF and its persistence after loading doses, thick macula persistence at 3 months, and inadequate visual improvement after loading doses. For this purpose, longitudinal studies with follow-up periods exceeding 5 years should be conducted with larger patient populations.

Disclosures

Ethics Committee Approval: This study was approved by the Ankara Training and Research Hospital Ethics Committee (Date:18.08.2021 Number: E-21-687).

Informed Consent: Written informed consent was obtained from all patients.

Conflict of Interest: None declared.

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Peer-review: Externally peer-reviewed.

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