Single-Centre Real Life Data of Patients Treated with Intravitreal Injection for Neovascular Age-Related Macular Degeneration

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ABSTRACT

Purpose: To evaluate the real-life intravtreal anti vascular endothelial growth factor (anti-VEGF) treatment and follow-up data in patients with neovascular age-related macular degeneration (AMD).

Methods: One hundred and five eyes of 102 patients with newly diagnosed AMD receiving intravitreal anti-VEGF injections with Pro Re Nata (PRN) treatment regimen were retrospectively analysed. Mean number of visits and injections, best corrected visual acuity (BCVA), and central macular thickness (CMT) were evaluated during follow-up period.

Results: The mean follow-up period was 21.9±8.7 months. The mean number of visits and injections was 9.34±2.38 and 5.74±1.69, at the end of the first year respectively, and 15.46±6.19 and 8.45±3.66 at the end of the follow-up respectively. At baseline, at the first year of treatment and at the end of follow-up, BCVA was 0.60±0.34, 0.51±0.31, 0.62±0.38 LogMAR and CMT was 366.16±116.75 µm, 332.75±101.75 µm and 315.37±96.53 µm, respectively. At the end of the first year, BCVA was significantly higher than at baseline (p=0.002), whereas no difference was found at the end of follow-up compared to baseline (p=0.94). Mean CMT decreased gradually throughout the treatment. At the end of the follow-up CMT was significantly lower compared to both the baseline and at the first year of treatment(p<0.001 and p=0.003,respectively). In a multivariable regression model older age, male gender, presence of cronic obstrucive pulmonary disease and low baseline BCVA increase the possibility of unexpected treatment outcome (loss of vision or failure to gain vision).

Conclusion: A significant improvement in both CMT and BCVA was observed at the one-year follow-up. Although the anatomical success was maintained with a decrease in CMT at the end of the follow-up period, the functional success in BCVA was not preserved.

Keywords: Age-related macular degeneration, intravitreal injection, vascular endothelial growth factor

INTRODUCTION

Age-related macular degeneration (AMD) is a progressive, degenerative retinal disease that causes severe, irreversible vision loss, most commonly in people over age 50.[1] There are two types of AMD: dry (non-neovascular), which accounts for 90% of patients and has a better visual prognosis, and wet (neovascular), which accounts for 10% of patients and causes the majority of instances of blindness.[2] .The role of vascular endothelial growth factor (VEGF) in the pathogenesis of neovascular AMD was first demonstrated in 1983.[3] Subsequently, many animal and clinical studies have demonstrated the key role of VEGF in the development of choroidal neovascularization(CNV).[4] There are three molecules that target VEGF and are globally accepted for intravitreal use when treating neovascular AMD: bevacizumab, a recombinant humanized monoclonal antibody; ranibizumab, a monoclonal antibody fragment; and aflibercept, a recombinant fusion protein composed of

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Received: 25.01.2025
Accepted: 24.03.2025
J Ret-Vit 2025; 34: 91-99
DOI:10.37845/ret.vit.2025.34.15

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the binding domains of VEGF receptors 1 and 2 and the Fc portion of human IgG1 immunoglobulin.[5] There are three treatment regimens that are universally recognised: Monthly fixed injections, Pro Re Nata (PRN), and treat-and-extend.[6]

Our study aimed to present real-life data on treatment efficacy and safety in neovascular AMD patients receiving anti-VEGF treatment with PRN regimen in our clinic.

MATERIALS AND METHODS

This study included 105 eyes of 102 patients who were diagnosed with neovascular AMD between January 2021 and June 2024, had not received any previous treatment, and could be followed up for at least 12 months. Medical records of patients diagnosed with neovascular AMD who received intravitreal anti-VEGF injections were retrospectively analysed. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Research and Ethics Committee (approval number: 2024-48). In the power analysis, the sample size was calculated as 90 individuals for an alpha ratio of %5 and a beta ratio (power) of %80. Written informed consent was obtained from all participants. Patients with diabetic retinopathy, hypertensive retinopathy, retinal vein occlusion, glaucoma, uveitis, conditions predisposing for CNV (such as high myopia, angioid streaks, and central serous chorioretinopathy), and patients previously treated for AMD were excluded from the study. Patients were also excluded from the study if they missed 3 consecutive months of follow-up.

The best corrected visual acuity (BCVA) was determined at the initial examination and detailed anterior and posterior biomicroscopic examinations were performed. Intraocular pressure (IOP) was measured via Goldmann applanation tonometry. Optical coherence tomography (OCT) (Heidelberg Engineering GmbH, Heidelberg, Germany) and fundus fluorescein angiography (FFA) (Topcon Medical Systems, Inc., Oakland, New Jersey) were performed to confirm the presence of CNV. OCT and FFA images of a patient with neovascular AMD are shown in Figure 1. Intravitreal bevacizumab (Altuzan®, Roche Diagnostics GmbH, Mannheim, Germany) was administered to all patients who have intraretinal and/or subretinal fluid on OCT and CNV on FFA, as 1 injection per month for the first 3 months according to the Turkish Health Implementation Communiqué. Patients who responded to bevacizumab continued to be treated with bevacizumab. Switch of intravitreal injection from bevacizumab to ranibizumab (Lucentis®, Novartis Pharma, Stein, Switzerland), or

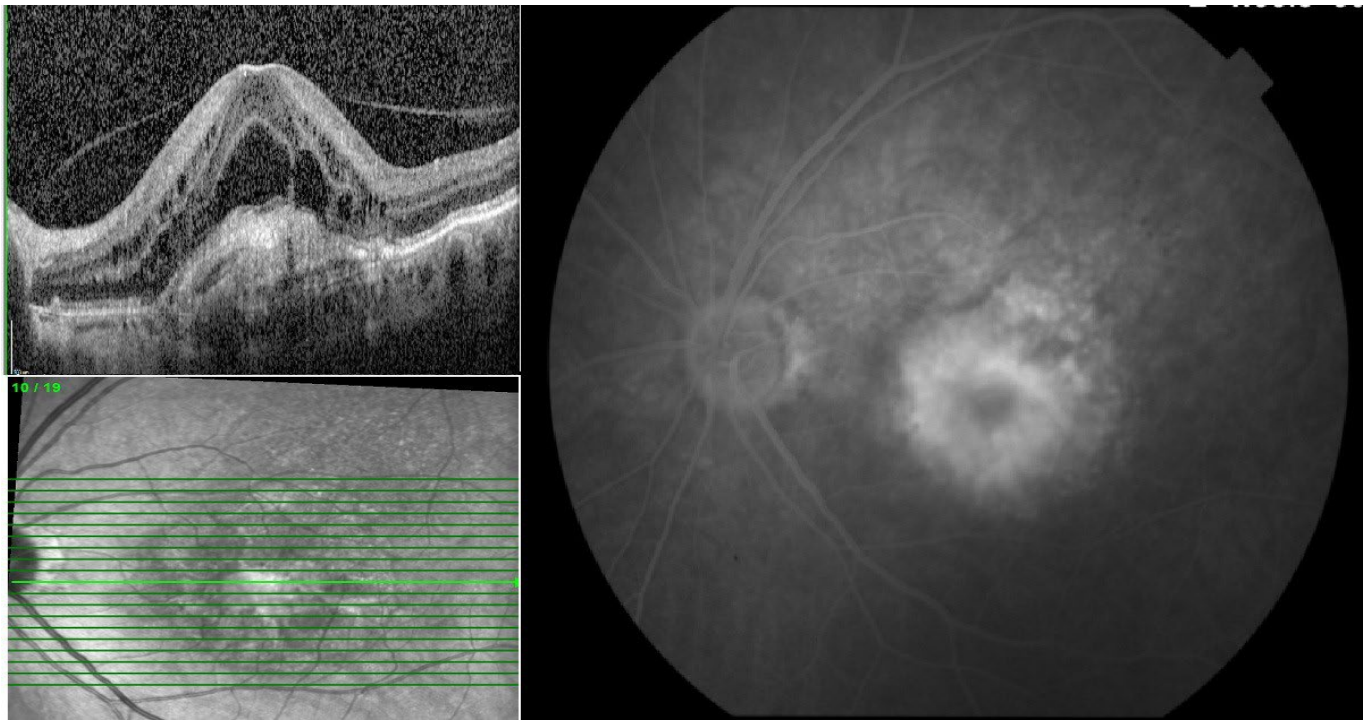

Figure 1: *OCT and FFA images of a patient with neovascular AMD*

aflibercept (Eyelea®, Bayer, Regeneron Pharmaceuticals Inc, New York, USA) was decided based on a decrease in BCVA, presence of macular hemorrhage on funduscopic examination, increase of intraretinal and/or subretinal fluid on OCT, increase in central macular thickness (CMT). It was up to the clinician to decide whether to use ranibizumab or aflibercept when switching from bevacizumab to other anti-VEGFs.

We intended to follow up and treat the patients with the PRN regimen. The treatment and follow-up protocols were explained to the patients and they were told not to miss any monthly visits.

All injections were performed under operating room conditions after topical anesthesia with 0.5% proparacaine (Alcaine, Alcon Pharmaceuticals, Rijksweg, Belgium), ocular surface cleaning with 10% povidone-iodine and conjunctival surface cleaning with 5% povidone-iodine for at least 3 minutes. Injections were performed 4 mm posterior to the limbus in phakic patients and 3.5 mm posterior to the limbus in pseudophakic patients using a 30-gauge needle from the superior temporal region to the pars plana. The doses of anti-VEGF agents are 1.25 mg/50 µL for bevacizumab, 0.5 mg/50 µL for ranibizumab, and 2.0 mg/50 µL for aflibercept.

From the retrospectively analysed patient files, data on age, sex, follow-up period, number of visits, number of injections, and anti-VEGF molecule in the injection were obtained. Best corrected visual acuity, IOP, and CMT were compared at baseline, at the end of the first year, and at the end of the follow-up period. Best corrected visual acuity values were obtained using Snellen visual charts and converted to Log-MAR equivalents for statistical analysis.

STATISTICAL ANALYSIS

Statistical analyses were performed using the SPSS version 22 package (IBM Corporation, Somers, New NY, USA). The Kolmogrov-Smirnov test was used to assess the conformity of the data to normal distribution. Data showing normal distribution were analysed by repeated measures ANOVA test. Non-normally distributed data were analysed using Friedman's test for repeated measures and the Wilcoxon test with Bonferroni correction for pairwise comparisons. The chi-square test was used for categorical data. Data was expressed as mean and standard deviation. $P<0.05$ was considered significant. Multivariable logistic regression analysis was done and odds ratios (OR) with 95% confidence intervals (CI) were determined to estimate the relative risk.

RESULTS

A total of 105 eyes of 102 patients were included in our study, 60 males (58.8%) and 42 females (41.2%), with a mean age of 72.03 ± 8.31 years. There were 32 patients with diabetes mellitus, 41 patients with hypertension, 11 patients with chronic obstructive pulmonary disease (COPD), and 21 patients with coronary artery disease. There were 76 phakic eyes (72.4%) and 29 pseudophakic eyes (27.6%). Thirty-one eyes (29.5%) had a follow-up of one year and 74 eyes (70.5%) had a follow-up of more than one year. The mean follow-up was 21.94±8.70 months (12-40 months). At the end of the first year, the mean number of visits was 9.34±2.38 and the mean number of injections was 5.74±1.69 (bevacizumab, ranibizumab, aflibercept; 4.06±1.28, 0.82±1.47, 0.87±1.64, respectively). The final mean number of visits was 15.46±6.19 and the mean number of injections was 8.45±3.66 (bevacizumab, ranibizumab, aflibercept; 4.61±2.10, 2.00±3.26, 1.85±3.59, respectively) (Table 1). The mean log-MAR BCVA was 0.60±0.34 before treatment, 0.51±0.31 at the end of the first year, and 0.62±0.38 at the end of follow-up (Figure 2). Mean BCVA was significantly higher at the end of the first year of treatment compared to both pre-treatment and at the end of the follow-up period ($p=0.002$ and $p<0.001$, respectively). No statistically significant difference was found between pre-treatment and at the end of the follow-up period($p=0.94$). Mean CMT values were 366.16±116.75 µm, 332.75±101.75 µm, and 315.37±96.53 µm before treatment, at the end of the first year, and at the end of follow-up, respectively (Figure 3). Mean CMT was significantly lower at the end of follow-up compared to both pre-treatment and at the end of the first year of treatment ($p<0.001$ and $p=0.003$, respectively). At the end of the first year of treatment, mean CMT was significantly lower than pre-treatment ($p<0.001$). The mean IOP was 15.45±2.81 mmHg before treatment, 15.18±2.75 mmHg at the end of the first year, and 15.51±2.84 mmHg at the end of the follow-up. There was no statistically significant difference ($p>0.05$) in mean IOP before treatment, at the end of the first year, and at the end of follow-up (Table 2).

Table 1: Demographic characteristics, duration of follow-up and mean number of visits and injections of the participants	
Age (mean ± SD), years	72,03±8,31
Sex (%F / %M)	%41,2 / %58,8
Systemic Disease	
Diabetes Mellitus Hypertension Chronic Obstructive Pulmonary Disease Coronary Artery Disease	32/102 41/102 11/102 21/103
Lens (%phakic / % pseudophakic)	%72,4 / %27,6
Follow up period (mean ± SD), months	21,94±8,70
Mean number of visits (1st year/end of follow up)	9,34±2,38 / 15,46±6,19
Mean number of injections (1st year/end of follow up)	5,74±1,69 / 8,45±3,66
Bevacizumab (1st year/end of follow up)	4,06±1,28 / 4,61±2,10
Ranibizumab (1st year/end of follow up)	0,82±1,47 / 2,00±3,26
Aflibercept (1st year/end of follow up)	0,87±1,64 / 1,85±3,59
SD: Standart Deviation F/M: Female / Male	

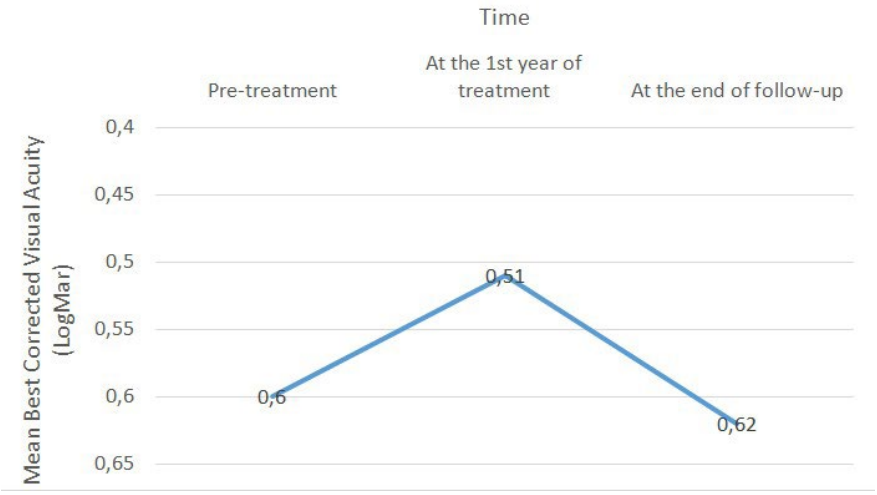

Figure 2: *Mean BCVA during follw-up period*

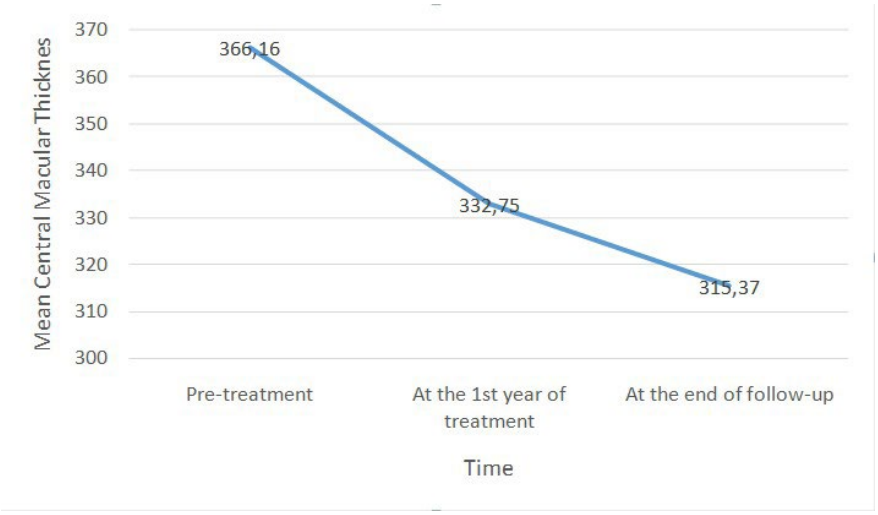

Figure 3: *Mean CMT during follw-up period*

Table 2: Mean BCVA, CMT and IOP values of all participants at the baseline, at the first year of treatment and at the end of the follow-up period

	Baseline	**End of the first year**	**End of the follow-up**	**P** **End of the 1st year/ baseline**	**P** **End of the follow-up / baseline**	**P** **End of the 1st year / End of the follow-up**
BCVA, logMAR	0,60±0,34	0,51±0,31	0,62±0,38	**0,002**	0,94	**< 0,001**
CMT, µm	366,16±116,75	332,75±101,75	315,37±96,53	**<0.001**	**<0.001**	**0,003**
IOP, mmHg	15,45±2,81	15,18±2,75	15,51±2,84	0.873	0.842	0.799

BCVA: Best corrected visual acuity
logMAR: Logarithm of the Minimum Angle of Resolution
CMT: Central macular thickness
µm: Micrometer
IOP: Intraocular preassure

When 74 eyes with more than one year of follow-up were analysed separately, the mean BCVA was 0.53±0.31, the mean CMT was 354.70±92.72 µm, and the mean IOP was 15.54±2.81 mmHg before treatment. At the end of the first year of treatment, the mean BCVA was 0.46±0.28, the mean CMT was 340.41±10.18 µm, and the mean IOP was 15.10±2.65 mmHg. At the end of the follow-up period, the mean BCVA was 0.60 ± 0.40, the mean CMT was 315.75 ± 101.06 µm, and the mean IOP was 15.58 ± 2.78 mm Hg. At the end of the first year, the mean number of visits was 9.08 ± 2.39 and the mean total number of injections was 5.68 ± 1.70 (bevacizumab, ranibizumab, aflibercept; 3.82 ± 1.07, 0.95 ± 1.53, 0.90 ± 1.76, respectively). At the end of the follow-up period, the mean number of visits was 17.77 ± 5.86, the mean follow-up period was 26.10 ± 6.95 months, and the mean number of injections was 9.54 ± 3.72 (bevacizumab, ranibizumab, aflibercept; 4.60 ± 2.30, 2.63 ± 3.62, 2.29 ± 4.12, respectively). When the mean CMT values of 74 eyes with more than one year of follow-up were compared, the mean CMT value at the end of the first year was statistically significantly lower than pre-treatment (p=0.023), and the mean CMT value at the end of follow-up was significantly lower than both pre-treatment and at the end of the first year of treatment (p<0.001 and p=0.003, respectively). When comparing the BCVA values of 74 eyes with more than 1 year of follow-up, it was found that the BCVA values were statistically significantly higher at the first year of treatment compared to both the pretreatment and the end of follow-up (p=0.01 and p<0.001, respectively), whereas no statistically significant difference was found between the end of follow-up and the pre-treatment (p=0.23). No statistically significant difference was found for mean IOP (p>0.05) (Table 3).

Table 3: Mean BCVA, CMT and IOP at baseline, at the first year of treatment and at the end of the follow-up period in participants with more than 1 year of follow-up

	Baseline	**End of the first year**	**End of the follow-up**	**P** **End of the 1st year/ baseline**	**P** **End of the follow-up / baseline**	**P** **End of the 1st year / End of the follow-up**
BCVA, logMAR	0,53±0,31	0,46±0,28	0,60±0,40	**0,01**	0,23	**< 0,001**
CMT, µm	354,70±92,72	340,41±10,18	315,75±101,06	**0,023**	**<0,001**	**0,003**
IOP, mmHg	15,54±2,81	15,10±2,65	15,58±2,78	0.986	0.941	0.893

BCVA: Best corrected visual acuity logMAR: Logarithm of the Minimum Angle of Resolution
CMT: Central macular thickness
µm: Micrometer
IOP: Intraocular preassure

Multivariable logistic regression analysis was done in order to evaluate the impact of baseline patient characteristics on unexpected treatment outcome (loss of vision or failure to gain vision) at the end of follow-up (Table 4). Being over 80 years old at the time of diagnosis increases the likelihood of an unexpected outcome by 2.24 times compared to being under 70 years old (p=0.03). Male sex increases the odds of an unexpected outcome by 1.6 times (p=0.03), and COPD is associated with a 1.96-fold increase in the odds of an unexpected outcome (p=0.04). If the initial BCVA is worse than 0.50 logMar, the probability of an unexpected outcome increases 1.68 times (p=0.01).

Table 4: Multivariable logistic regression analysis to evaluate the impact of baseline patient characteristics on unexpected treatment outcome (loss of vision or failure to gain vision) at the end of follow-up.

Baseline Characteristics	**Odds Ratio for unexpected treatment outcome (95 % CI)[1]**	**P**
Age (years)		
<70	1	
70-79	1.65 (0.93-3.16)	**0.04**
≥80	2.24 (1.12-4.65)	**0.03**
Sex		
Female	1	
Male	1.6 (0.9-2.1)	**0.03**
Systemic Disease		
Diabetes Mellitus	1.44 (0.96-2.31)	0.44
Hypertension	1.23 (0.77-2.43)	0.76
COPD	1.96 (0.95-3.12)	**0.04**
CAD	0.98 (0.83-1.97)	0.12
BCVA (logMar)		
≤0.50 logMar	1	
>0.50 logMar	1.68 (0.89-2.31)	**0.01**

CI : Confidence Interval

COPD: Chronic Obstructive Pulmonary Disease
CAD: Coronary Artery Disease
BCVA: Best Corrected Visual Acuity
logMAR: Logarithm of the Minimum Angle of Resolution

[1]Each Odds ratio and *P* value is adjusted for all other characteristics listed in the table.

DISCUSSION

Age-related macular degeneration, which is a common condition all over the world, can lead to loss of vision. Following the introduction of anti-VEGF agents for the treatment of neovascular AMD, many studies have been conducted to determine the dose, time of administration, and frequency of injections. Different treatment regimens have been established. There are three treatment regimens that are generally accepted: Monthly fixed injections, PRN, and treat-and-extend. In the monthly fixed injection regime, the patient is evaluated and treated with intravitreal injections every month. As monthly injections in this regimen increased the cost of treatment, the PRN regimen was introduced. In the PRN regimen, patients are still examined every month, but intravitreal anti-VEGF injections are only administered when necessary.[6] Many studies have shown that when patients are examined monthly with no missed visits, the visual outcome of the PRN regimen is as successful as the monthly fixed injection regimen.[7,8] The HORIZON study also showed that the lack of strict monthly follow-up in the PRN regimen reduced treatment success.[9] The PRN regimen reduces the number of injections and the cost of treatment, but the number of visits remains the same due to strict monthly patient follow-up. The treat and extend protocol is designed to minimise the number of injections and clinic visits. This protocol includes a maintenance phase in which the interval between both visits and injections is progressively extended depending on the presence or absence of disease activity.[6] In an ideal PRN regimen, 12-13 visits annually should be performed, as in prospective randomised clinical trials.[10-13] In addition, prospective randomised controlled trials have shown that at least 8-9 injections should be performed in the first year of treatment to achieve the best visual outcome.[14,15] However, trials with real-life data have shown that such strict follow-up and frequent injections are impossible, and that the average number of annual visits and injections is less. Retrospective analysis of neovascular AMD patients by Togac et al. showed that the mean number of visits and injections was 5.83 and 4.70 for the first year and 4.68 and 2.08 for the second year, respectively.[16] In the AURA study, which retrospectively evaluated the efficacy of ranibizumab treatment for neovascular AMD and presented real-life data, the mean number of visits was 10.4 in the first year and 8.0 in the second year, and the mean number

of injections was 9.0 in the first year and 5.8 in the second year.[17] In a retrospective study of 2227 neovascular AMD patients from 8 countries, Holz et al. showed that the mean number of visits was 8.6 and 4.9 in the first and second years, respectively, while the mean number of injections was 5.0 and 2.2 in the first and second years, respectively.[18] Brynskov et al published a 10-year follow-up of 4678 eyes of 3668 neovascular AMD patients treated with a PRN regimen and showed that the mean number of intravitreal anti-VEGF injections was 5.4 in the first year and 4.3 in the following years.[19] In the multicentre LUMINOUS study, which evaluated the efficacy of ranibizumab treatment for neovascular AMD, the mean number of intravitreal injections at one year varied from 4.3 to 5.7.[20] In a multicentre study conducted by the Bosphorus Retina Study Group with PRN treatment protocol, 880 eyes of 783 patients were examined and at the end of the first year the mean number of visits was 6.9±2.5 and the mean number of intravitreal injections was 4.1±1.9.[21] In our study, at the end of the first year, the mean number of visits was 9.34±2.38 and the mean number of intravitreal injections was 5.74±1.69. Although patients should be seen every month with the PRN regimen, we think that visits were interrupted due to the high patient load of our retina clinic, patients' inability to reach the appointment, and unknown factors related to the patient. At the end of the mean follow-up period (21.94±8.70 months), the mean number of visits was 15.46±6.19 and the mean number of injections was 8.45±3.66.

In the ANCHOR study, ranibizumab 0.5 mg/mL administered monthly resulted in an average gain of 11.3 letters at the end of the first year. Continuation of monthly ranibizumab maintained the efficacy of the treatment and 10.7 letters were gained at the end of the second year.[22]

Monthly injections of bevacizumab and ranibizumab were compared with the PRN regimen in the CATT and IVAN studies. It was shown that both the PRN and monthly injection regimens provided similar improvement in visual acuity for both ranibizumab and bevacizumab.[13,15] However, in real life, considering the number of visits and injections, it is not easy to implement monthly fixed injections and ideal PRN treatment regimens due to the large number of patients, the physical conditions of the hospitals and the non-compliance of the patients. In the study by Hykin et al, which presented real-life data, an average of 9 ranibizumab injections could be administered over 2 years with the PRN regimen, with an average gain of 6.1 letters at the end of the first year and an average gain of only 4.0 letters at the end of the second year.[17] In an international multicentre study, the average number of injections over 2 years was only 7.2, and these injections resulted in a gain of 2.7 letters at the end of the first year and 0.3 letters at the end of the second year.[18] Although CMT was lower in both the first and second year of treatment compared to baseline, there was no significant difference in BCVA in the first and second year compared to baseline in a study by Arrigo et al. presenting real-life data from 439 neovascular AMD patients.[23] Nicolo et al. presented 3-year follow-up results of anti-VEGF treatment with a PRN regimen. Mean CMT decreased with treatment and remained significantly lower than baseline for 3 years. Although anatomical success was maintained over three years in the study, letter gain decreased after the first year and mean BCVA was lower than baseline at the end of the third year.[24]

In our study, mean CMT was significantly lower at the end of the first year and at the end of the follow-up period compared to baseline. BCVA was significantly higher at the end of the first year of treatment compared to baseline. However, while treatment success was maintained anatomically, there was no significant difference in BCVA at the end of follow-up compared to baseline. Although subretinal/intraretinal fluid and CMT are reduced by intravitreal anti-VEGF injections, cellular damage continues and macular atrophy and fibrosis may develop as a result of mechanisms such as inflammation and complement activation that play a role in the pathophysiology of AMD. The decrease in the number of visits after the first year and the under-treatment due to the decrease in patient compliance may be another reason for the decrease in BCVA after the first year. When the baseline characteristics of the patients are analysed, older age, male gender, presence of COPD and low baseline BCVA increase the possibility of unexpected treatment outcome. Our study has some limitations: the number of patients and the follow-up period were slightly small, and the effect of anti-VEGF agents was not analysed separately. However, our study is valuable because it presents real-life data on anti-VEGF treatment and questions the applicability of treatment regimens.

CONCLUSION

Although we have tried to follow up and treat our patients on a PRN regimen in our clinic, the average number of injections and visits was lower than that reported in randomised controlled clinical trials in the literature. This may have been due to the large number of patients, inadequate physical conditions, or interruptions of visits by patients. The number of visits and injections in our study were compatible with other real-world trials. As it is difficult to implement frequent visits and treatment protocols as in randomised controlled trials, new real-life studies are needed to find optimal follow-up and treatment regimens.

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