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Original Article

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The efficacy of intravitreal ranibizumab injections for treating choroidal neovascularization in wet age-related macular degeneration

Abstract

Aim: To evaluate the efficacy and safety of intravitreal ranibizumab injections for treating choroidal neovascularization associated with wet age-related macular degeneration.
Materials and Methods: This study included 105 eyes of 105 patients who received intravitreal ranibizumab injections for age-related macular degeneration between January 2009 and August 2010, and again between December 2019 and April 2022. Before treatment, color fundus photography, fundus fluorescein angiography, and optical coherence tomography were conducted for assessment. The first three injections were administered at one-month intervals. Additional injections were given if there was a decrease in visual acuity, active leakage observed in fundus fluorescein angiography, an increase in central retinal thickness of more than 100 µm, or the presence of subretinal fluid.
Results: The mean age of the patients was 68.3±6.11 years (range, 60–82 years). The average follow-up period was 14.2±1.3 months (range, 12–18 months). Patients received an average of 4.31±0.44 intravitreal ranibizumab injections (range, 3–6 injections). The mean preoperative best-corrected visual acuity (BCVA) was 0.1 LogMAR, which improved to 0.78 LogMAR postoperatively. BCVA increased (by 1–3 LogMAR) in 45 cases (42.85%), decreased (by 1–3 LogMAR) in 16 cases (15.23%), and remained unchanged in 44 cases (41.9%) at the 12-month follow-up. No cases of endophthalmitis or drug-induced systemic side effects were observed.
Conclusion: Intravitreal ranibizumab injection is a safe and effective treatment for choroidal neovascularization associated with wet age-related macular degeneration.

Keywords: Age-related macular degeneration, choroidal neovascularization, ranibizumab

INTRODUCTION

Age-related macular degeneration (AMD) causes visual impairment and loss due to changes in the choroid, retina, and retinal pigment epithelium (RPE). AMD can present with drusen, RPE changes, geographic atrophy, RPE detachment, subretinal or choroidal neovascularization (CNV), and disciform scars (1). The disease has two forms: atrophic (dry) and exudative (wet). Although AMD typically affects both eyes, they may not be impacted simultaneously or to the same degree (2).

AMD has rapidly become a leading cause of permanent vision loss in developed countries and is the most common cause of central vision loss and legal blindness in individuals over 55 years old (3). A recent meta-analysis found that the prevalence of early AMD increased from 3.5% in individuals aged 55–59 to 17.6% in those aged 85 and older, while late AMD rose from 0.1% to 9.8% in the same age groups (4).

Ranibizumab (Lucentis; Genentech, South San Francisco, CA, USA; Novartis) is a humanized fragment of a mouse monoclonal

antibody produced in Escherichia coli cells using recombinant DNA technology. It was approved for treating wet AMD in the United States in January 2006. Studies have shown that intravitreal ranibizumab injections (IVRI) can improve visual acuity and preserve vision for 1–2 years. Animal studies indicate a half-life of three days, and ranibizumab is a potent, non-selective inhibitor of all VEGF-A isoforms. Each vial (0.3 ml) contains 3 mg of ranibizumab, with a recommended AMD treatment dose of 0.5 mg in 0.05 ml.

This study aimed to evaluate the efficacy and safety of multiple intravitreal ranibizumab injections in the treatment of choroidal neovascularization due to wet age-related macular degeneration.

MATERIALS AND METHODS

The study was conducted using retrospective method. Ethics committee approval was obtained from the Gaziosmanpasa Education and Research Hospital Ethics Committee on September 25, 2024 (approval number: 56). Patient records from the Medical Retina Department at Istanbul Education and Research Hospital (January 2009–August 2010) and from World Eye Hospital (December 2019–April 2022) were retrospectively reviewed for patients who had received IVRI for CNV due to wet AMD. The study included 105 eyes of 105 patients aged over 60 who regularly attended follow-up appointments and were followed for at least 12 months. All cases involved newly diagnosed CNV that had not previously been treated. CNV due to other causes was excluded. CNV types included types 1, 2, and 3.

Before treatment, detailed ocular and systemic histories were obtained. Systemic conditions, including drug allergies, diabetes mellitus, hyperlipidemia, hypertension, and smoking status, as well as ocular conditions, such as previous laser photocoagulation, photodynamic therapy, intraocular surgeries, degenerative retinal disease, uveitis, and glaucoma, were investigated.

Best-corrected visual acuities (BCVA) were assessed using the Snellen chart and converted to LogMAR values before and after injections. All patients underwent anterior segment examinations with a slit-lamp biomicroscope and detailed fundus examinations with a 90D lens. Intraocular pressure was measured using a Goldmann applanation tonometer. Lesion types and sizes were documented with imaging. Fundus photographs and fundus fluorescein angiography (FFA) images were taken, and Fourier-domain optical coherence tomography (OCT) scans were evaluated.

Patient Selection Criteria

- Patients with decreased visual acuity and/or complaints of metamorphopsia.
- Presence of drusen, hemorrhage, or increased macular thickness on ophthalmoscopic examination.
- FFA showing involvement and leakage in the foveal avascular zone.
- More than 50% of the lesion area composed of active CNV.
- CNV size smaller than 12 disc areas.
- IVRI administered to symptomatic AMD cases with intraretinal or subretinal fluid detected on OCT.
- For type 1 membrane cases, criteria indicating recent disease progression included at least a one-line decrease in visual acuity over the last three months, a minimum 10% increase in CNV size, or the presence of newly formed macular hemorrhage or exudate.

Surgical Method

All patients received detailed verbal information and signed informed consent forms before the injections. Injections were performed under sterile conditions in the operating room. The injection area was cleansed with 10% betadine prior to the intravitreal ranibizumab injection. After opening the eyelids with a lid speculum, topical anesthesia was administered using proparacaine hydrochloride, followed by the application of 5% betadine drops. A 30-gauge sterile needle was used to inject 0.05 ml (0.5 mg) of ranibizumab into the vitreous cavity from the upper temporal quadrant, positioned 4.0 mm behind the limbus in patients without cataract surgery and 3.5 mm in those who had undergone cataract surgery. After needle removal, conjunctival compression was applied with a cotton-tipped applicator. Following the injection, the spread of the drug in the vitreous and optic nerve perfusion were assessed using an indirect ophthalmoscope. Topical antibiotic treatment was prescribed for all patients post-injection (4 times/day), and they were informed about the symptoms of endophthalmitis.

Patients received 0.5 mg of IVRI once a month for the first three months. After each injection, patients were followed up on day 1, week 1, month 1, and then monthly. Home monitoring with an Amsler grid was also recommended. At each follow-up, BCVA was measured using the Snellen chart and converted to LogMAR. Fundus images were captured, and OCT was performed. Intraocular inflammation, lens damage, retinal detachment, fluid exudation, hemorrhage, and subretinal fibrosis were recorded. FFA was performed at month three and subsequently as needed to monitor lesion status. Ranibizumab injections were repeated if there was a decrease of more than one line in visual acuity, an increase of more than 100 µm in central retinal thickness on OCT, new hemorrhage observed on examination, or progression of active leakage on FFA (leakage extending beyond the initial CNV boundaries).

Statistical Analyses

Statistical Package for the Social Sciences (SPSS) software was used to analyze the data. Descriptive statistics, including mean and standard deviation, were used for data evaluation. The Mann-Whitney U test was applied to evaluate differences by location, as the data did not meet parametric test conditions.

Differences by CNV type were assessed using the Kruskal-Wallis test. For pre-treatment and post-treatment comparisons, the dependent groups t-test was used when parametric test conditions were met, and the Wilcoxon test was applied when they were not. Repeated measures analysis of variance (ANOVA) was conducted to compare central macular thickness and visual acuity measurements at pre-treatment and post-treatment intervals (month 1, month 3, month 6, and month 12). Statistical significance was set at $p<0.05$.

RESULTS

The study included 105 eyes from 105 patients aged 60 to 82 years (mean age, 68.3±6.11 years) who received IVRI for AMD and were followed for at least 12 months (average follow-up, 14.2±1.3 months). Among the patients, 58 (55.23%) were female, and 47 (44.77%) were male.

The demographic characteristics of the patients are presented in Table 1.

Table 1. Demographic characteristics of patients

Number of eyes	105
Gender	58 (55.23%) female, 47 (44.77%) male
Average age	68.3±6.11
Average follow-up duration (months)	14.2±1.3
Eye color	78 (74.28%) brown, 18 (17.15%) green, 9 (8.57%) blue
Smoking	34 (32.38%)
Hypertension	38 (36.19%)
Lens status	77 (73.33%) phakic, 28 (26.67%) pseudophakic

The average follow-up period was 14.2±1.3 months and the average number of injections was 4.31±0.44 (range, 3–6).

Among the cases, 71 (67.62%) had subfoveal CNV, 22 (20.95%) had juxtafoveal CNV, and 12 (11.43%) had extrafoveal CNV. CNV membrane types included 57 cases (54.28%) with type 1 membrane, 32 cases (30.48%) with type 2 membrane, and 16 cases (15.24%) with type 3 membrane.

Post-treatment CNV sizes (upper limit, 4911 µm; lower limit, 685 µm; mean, 2101.74±1048.18 µm) were significantly smaller than pre-treatment sizes (upper limit, 5894 µm; lower limit, 871 µm; mean, 2789.48±1268.32 µm) ($p<0.001$) (Figure 1).

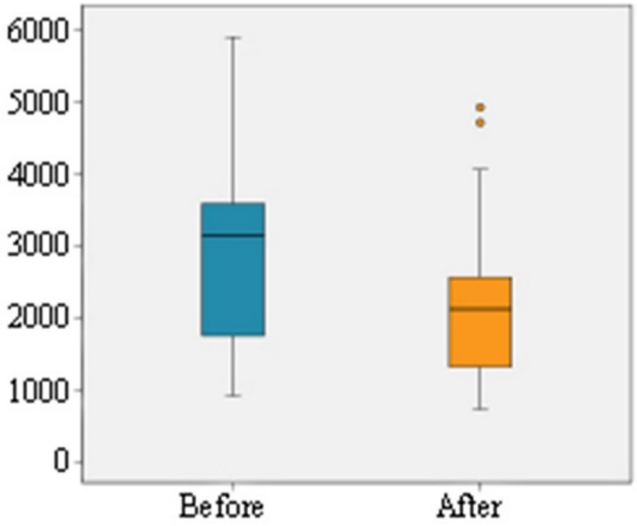

Figure 1. CNV sizes before and after treatment

Cases were divided into two groups based on CNV size as measured by FFA: 27 cases (25.72%) had CNV sizes of 3600 µm or larger, while 78 cases (74.28%) had CNV sizes smaller than 3600 µm. Central macular thickness, measured by OCT, had a mean of 421.82±53.73 µm pre-treatment, 391.4±48.41 µm at month 1 post-treatment, 352.5±48.63 µm at month 3, 354.2±49.32 µm at month 6, and 319.23±42.35 µm at month 12 (Figure 2). Statistically significant reductions in central macular thickness were observed at month 1, month 3, month 6, and month 12 compared to pre-treatment measurements ($p<0.001$).

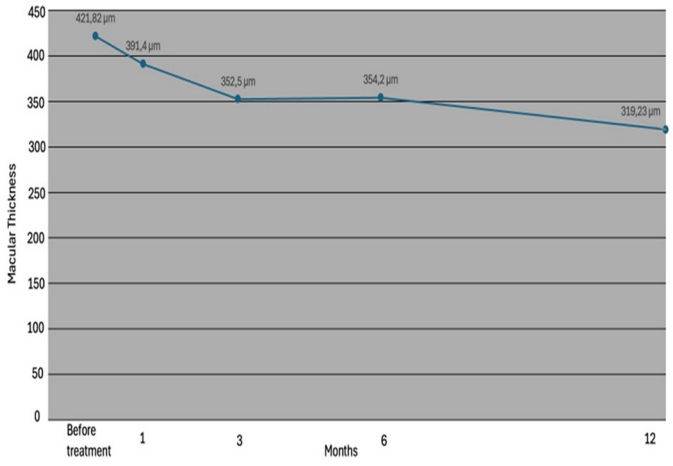

Figure 2. Changes in mean central macular thickness before and after treatment

BCVA measured with the Snellen chart was converted to LogMAR. The mean BCVA (LogMAR) was as follows: 0.93±0.29 before treatment, 0.87±0.41 at 1 month, 0.73±0.41 at 3 months, 0.78±0.43 at 6 months, and 0.79±0.43 at 12 months after treatment. Compared to baseline, there was a statistically significant reduction in LogMAR values at 1 month, 3 months, 6 months, and 12 months post-treatment ($p<0.001$) (Figure 3).

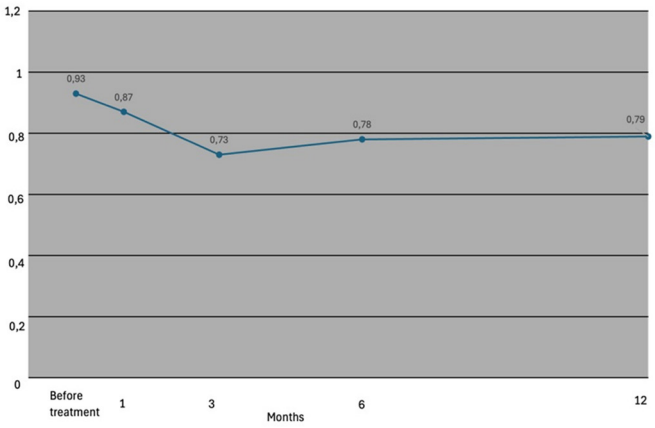

Figure 3. Distribution of mean BCVA by LogMAR before and after treatment

Changes in BCVA after treatment are presented in Table 2. At the 12-month follow-up, BCVA had improved (a reduction of 1–3 LogMAR lines) in 45 cases (42.85%), worsened (an increase of 1–3 LogMAR lines) in 16 cases (15.24%), and remained unchanged in 44 cases (41.91%).

Table 2. Changes in BCVA at 12 months post-treatment

Average BCVA change	Number of cases (n)
Increase (1-3 LogMAR line reduction)	45 (42.85%)
No change	44 (41.91%)
Decrease (1-3 LogMAR line increase)	16 (15.24%)

Table 3 shows BCVA changes before and after treatment based on the location of CNV. For patients with subfoveal CNV, BCVA improved from 1.01±0.29 to 0.87±0.24, while for those with extrafoveal or juxtafoveal CNV, it improved from 0.85±0.42 to 0.58±0.19. Although there was no statistically significant difference in baseline LogMAR values between the two groups, the post-treatment LogMAR value for the subfoveal group was significantly higher than that of the other group (p=0.012). Both groups showed statistically significant reductions in LogMAR values after treatment (p=0.017 for the subfoveal group, p=0.001 for the extrafoveal and juxtafoveal group).

Table 3. Changes in BCVA before and after treatment by CNV location

LogMAR	Subfoveal	Juxtafoveal and extrafoveal
Pre-treatment	1.01±0.29	0.85±0.42
Post-treatment	0.87±0.24	0.58±0.19
P-value	0.017	0.001

Table 4 and Figure 4 display the average BCVA changes (converted to LogMAR) before and after treatment based on lesion size. There was a statistically significant reduction in baseline LogMAR values between the lesion size groups. Among the 24 cases with lesions ≥3600 µm and the 81 cases with lesions <3600 µm, there were significant differences in pre- and post-treatment LogMAR values (p=0.026 and p=0.002, respectively).

Table 4. Changes in BCVA before and after treatment by CNV size

LogMAR	3600 µm and above (24 cases)	Below 3600 µm (81 cases)
Pre-treatment	1.39±0.14	0.83±0.28
Post-treatment	1.24±0.16	0.65±0.23
P-value	0.026	0.002

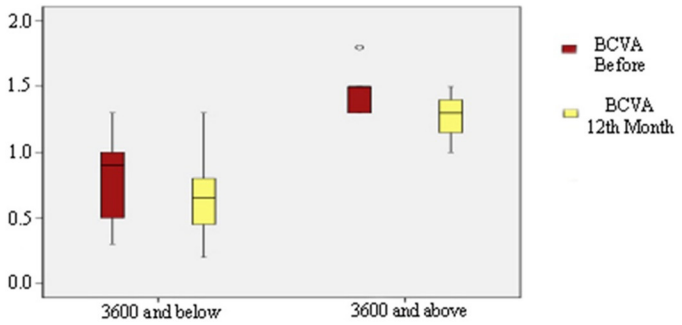

Figure 4. Change in BCVA before and after treatment according to CNV size

Table 5 shows the average BCVA changes (converted to LogMAR) before and after treatment based on CNV type. In Type 1 CNV cases, the LogMAR value decreased from 0.89±0.37 at baseline to 0.73±0.31 at 12 months post-treatment. Similarly, for Type 2 CNV, it decreased from 0.95±0.41 to 0.84±0.39, and for Type 3 CNV, it decreased from 1.19±0.24 to 1.1±0.29. The reductions in LogMAR values after treatment were statistically significant for Type 1 and Type 3 membranes, whereas the decrease for Type 2 membranes was not statistically significant.

Table 5. Changes in BCVA before and after treatment by CNV type

LogMAR	Type 1 CNV	Type 2 CNV	Type 3 CNV
Pre-treatment	0.89±0.37	0.95±0.41	1.19±0.24
Post-treatment	0.73±0.31	0.84±0.39	1.1±0.29
P-value	0.001	0.155	0.039

Table 6 and Figure 5 illustrate the relationship between changes in central macular thickness (CMT) and lesion size. In both groups (lesion size ≥3600 µm and <3600 µm), post-treatment CMT values showed a significant reduction compared to baseline (p<0.01 for both).

Table 6. Changes in central macular thickness before and after treatment by CNV size

Central macular thickness	3600 µm and above (24 cases)	Below 3600 µm (81 cases)
Pre-treatment	509.21±41.03	398.78±18.12
Post-treatment	384.02±42.93	301.91±25.98
P-value	0.003	0.001

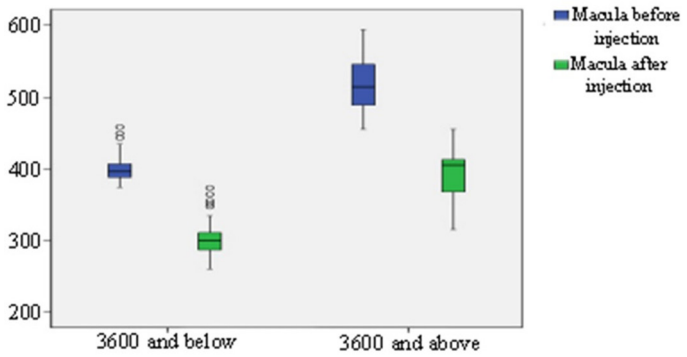

Figure 5. Change in central macular thickness before and after treatment according to CNV size

No complications, such as vitreous hemorrhage, RPE tears, uveitis, lens damage, endophthalmitis, retinal tears or detachment were observed during the study.'

DISCUSSION

Wet AMD is a leading cause of irreversible vision loss in individuals over 50 in developed countries, with a prevalence that increases with age, ranging from 5.8% to 15.1% (5). Various treatment options are available for exudative AMD.

In the Beaver Dam study, the female-to-male ratio was found to be 2:1 (6). In our study, 55.23% of patients were female and 44.77% were male, yielding a female-to-male ratio of 1.23.

The AREDS (Age-Related Eye Disease Study) and Rotterdam studies reported a significant association between a smoking history of 10 pack-years or more and advanced AMD (7, 8). In our study, 34.6% of patients had a smoking history of 10 pack-years or more.

The Blue Mountain study found no significant association between iris color, skin pigmentation, and early or late AMD (9). In our data, most cases (74.28%) had light brown pigmented irises.

Regarding systemic diseases, 38 (36.19%) of the 105 cases had hypertension, and 18 (17.14%) had diabetes mellitus. Research indicates that diabetic retinopathy and higher serum HDL levels are protective factors against AMD, whereas obesity and higher systolic blood pressure increase AMD risk in diabetic patients (10).

The ANCHOR, MARINA, PIER, and PrONTO studies are some of the largest and most significant studies on ranibizumab for treating exudative AMD, with an average number of injections of 13, 13.6, and 5.5 in the first year, respectively. In our study, patients received three ranibizumab injections during the first three months. OCT was performed at each visit to assess recurrence, with additional injections administered as needed. The average number of injections in our study was 4.31±0.44 (range, 3–6).

Another intravitreal treatment option for AMD is bevacizumab injection. Unlike bevacizumab and ranibizumab, pegaptanib is not FDA-approved for AMD treatment; its FDA approval is limited to metastatic colorectal cancers. Although there are no multicenter, randomized, double-blind, placebo-controlled studies, pegaptanib's effectiveness in intravitreal application has been demonstrated in multiple studies. Due to its larger molecular weight compared to ranibizumab, pegaptanib has a longer half-life in the vitreous. While this feature allows for a longer-lasting treatment effect, it also carries a higher risk of systemic and ocular toxicity.

In a study by Spaide et al., 1.25 mg/0.5 cc intravitreal bevacizumab was injected three times at one-month intervals into 266 eyes with large lesions and type 1 or type 3 CNV, where other treatments had previously failed. After three months, the average visual acuity improved from 20/184 to 20/129. Additionally, 38.3% of patients showed vision improvement, 4.7% experienced vision deterioration, and central foveal thickness (CFT) decreased from 340 µm to 213 µm (11).

Avery et al. administered monthly 1.25 mg bevacizumab injections to 81 patients, 78% of whom had previously received FDT and/or pegaptanib with unsuccessful results. After two months, the average visual acuity improved from 20/200 to 20/80, and a significant reduction in CFT was observed. No treatment-related complications were reported (12).

Dhalla et al. evaluated the effectiveness of combined treatment in a series of 24 cases (9 with predominantly classic CNV type and 16 with occult type) who received FDT and 1.25 mg bevacizumab injections every three months. The average lesion diameter was reported as 3042 µm. By the seventh month, an average increase of 2.04 LogMAR lines was observed (2.77 LogMAR lines for type 2, and 1.60 LogMAR lines for type 1). After seven months, 83% of patients had stable vision (type 2, 89%; type 1, 80%), and 67% had an increase of 2.00 LogMAR lines (type 2, 78%; type 1, 60%), with all lesions becoming inactive (13).

Post-intravitreal application, there were no reports of uveitis, endophthalmitis, retinal detachment, or systemic hypertension.

Based on these findings, bevacizumab can be considered a viable anti-VEGF agent for CNV treatment, especially as an adjunct to ranibizumab when additional injections are necessary. In our series, patients who received intravitreal bevacizumab injections at any time before or after treatment were excluded from the study.

In our study, considering type 1, type 2, and type 3 lesions together, vision levels were preserved in 84.75% of 105 eyes after an average follow-up of 14.2±1.3 months, with at least a 15-letter increase observed in 16.7% of cases. By the end of the study, the average increase in visual acuity was 9.4 letters. These results align closely with those reported in the literature. Our study included subfoveal, juxtafoveal, and extrafoveal cases, with no limitations on initial visual acuity. The slightly lower average increase in visual acuity and percentage of vision preservation in our study compared to the literature may be attributed to factors

such as the lower average number of injections, the time elapsed between neovascular AMD onset and hospital admission, low initial visual acuity at presentation, and the potential development of tachyphylaxis to ranibizumab.

The limitation of our study is that some patients who met the selected characteristics left their treatments unfinished or did not attend the required follow-ups.

In cases with type 1 and type 3 membranes, post-treatment LogMAR values significantly decreased compared to pre-treatment values ($p<0.05$). However, no statistically significant reduction was observed in post-treatment LogMAR values for type 2 membranes ($p>0.05$). Additionally, both pre- and post-treatment LogMAR values were significantly lower in type 1 cases compared to type 3 cases ($p<0.05$).

Ernst BJ et al. followed 25 cases diagnosed with subfoveal CNV for 16±3.7 months post-IVRI, evaluating the presence of macular fluid monthly with OCT (14). Re-injections were administered upon recurrence, with an average of 6±2.7 injections during the follow-up period. In our study, changes in visual acuity were assessed at each follow-up, along with the presence of macular fluid and any increase in macular thickness on OCT. Re-injections were performed as needed, minimizing unnecessary injections and associated costs.

The average CMT determined by OCT post-treatment (324.3±47.04 µm) significantly decreased compared to pre-treatment levels (424.8±53.31 µm) ($p<0.05$). In the PIER study, average macular thickness decreased by 20 µm in the sham group, 60 µm in the 0.3 mg IVR group, and 90 µm in the 0.5 mg IVR group.

In our study, OCT results showed that, in examining the relationship between CMT and visual acuity, a rapid decrease in CMT and a corresponding increase in visual acuity were observed within three months post-treatment, with these improvements maintained at 12 months. Similar findings were reported in the MARINA and ANCHOR studies (15,16). Despite the decrease in macular thickness, factors such as RPE dysfunction, atrophy, and subretinal fibrosis development have been proposed as determinants of visual acuity (17).

Ranibizumab does not directly affect existing CNV but inhibits VEGF-induced edema and new blood vessel formation, thereby preventing CNV growth (17). In our study, a significant decrease in average CNV size post-treatment (2101.74±1048.18 µm) compared to pre-treatment (2789.48±1268.32 µm) was observed ($p<0.05$).

Regarding the effect of lesion size on LogMAR values, significant improvements in post-treatment visual acuity were noted in cases with lesion diameters of 3600 µm and above [pre-treatment visual acuity=1.39±0.14, post-treatment visual acuity=1.24±0.16] and in cases with lesion diameters below 3600 µm [pre-treatment visual acuity=0.83±0.28, post-treatment visual acuity=0.65±0.23] ($p<0.05$).

Reported side effects of ranibizumab include vitreous hemorrhage, RPE tears, uveitis, lens damage, endophthalmitis, retinal tears, and retinal detachment (18-20). In the MARINA study, among 716 patients followed for 24 months, 5 (1.0%) cases of possible endophthalmitis and 6 (1.3%) cases of severe uveitis were reported (16).

Konstantinidis L et al. administered 0.5 mg IVRI to 74 eyes of 72 patients with classic CNV AMD between March 2006 and February 2008, reporting 4 (5.4%) cases of RPE tears without pigment epithelium detachment (21).

All patients in our study were informed about the symptoms and risks of endophthalmitis following injections and were strictly cautioned. In our study of 105 cases, no treatment-related complications were observed. This result may be associated with the relatively small sample size in our study. Complications reported in studies by Klein KS and Konstantinidis L may become more apparent in larger case series.

CONCLUSION

In conclusion, IVRI for choroidal neovascularization due to wet AMD resulted in statistically significant reductions in both LogMAR values and central macular thickness from pre- to post-treatment ($p<0.05$). IVRI is an effective and reliable treatment method for wet AMD.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
Ethics committee approval was obtained from the Gaziosmanpasa Training and Research Hospital Ethics Committee on September 25, 2024 (Approval number: 56).

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