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Original Article

Aflibercept Treatment Results and Association with Baseline Characteristics in Cases of Newly Diagnosed Neovascular Age-Related Macular Degeneration

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Abstract

Objectives: To evaluate functional and anatomical responses to intravitreal aflibercept (IVA) treatment in newly diagnosed and untreated neovascular age-related macular degeneration (nvAMD) cases and to investigate the effect of baseline lesion characteristics on anatomical responses.

Materials and Methods: This prospective, cross-sectional study included a series of 139 eyes of 133 patients that were diagnosed with active nvAMD and had not been treated. All eyes were subjected to complete ophthalmological examination, spectral-domain optical coherence tomography and fluorescein angiography, and 42 eyes also underwent indocyanine green angiography. IVA treatment was performed using a "treat and extend" regimen after 3 injections at 4-6 weeks intervals. Anatomical and functional responses at 4 weeks after the last injection were evaluated in eyes that completed 3 injections and the subgroup of eyes that completed 6 IVA injections. The effect of baseline lesion characteristics on IVA treatment results was also investigated.

Results: All 139 eyes included in the study received 3 IVA injections (group 1) and 62 received 6 IVA injections. Both groups showed statistically significant improvement in best-corrected visual acuity ($p<0.001$ for both). The rate of complete response was 54.6% and 58.0% in groups 1 and 2, respectively. In group 1, the presence of pigment epithelial detachment (PED) and serous PED were identified as negative initial factors ($p=0.043$, $p=0.005$, respectively). However, none of the baseline characteristics were significantly associated with anatomical response in group 2.

Conclusion: In our study, it was determined that successful anatomical and functional results were achieved with 3 and 6 doses of IVA in eyes with newly-diagnosed and untreated nvAMD. Among baseline characteristics, the presence of PED and serous PED in particular were found to be factors affecting treatment response negatively.

Keywords: Aflibercept, anti-VEGF, neovascular age-related macular degeneration

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Introduction

Intravitreal anti-vascular endothelial growth factor (VEGF) drug therapy has been accepted as a standard treatment method for neovascular age-related macular degeneration (nvAMD). In clinical trials, most eyes have been reported to respond well to anti-VEGF treatments, with improved or preserved visual acuity and anatomical improvement in retinal hemorrhage and/or exudative changes. However, despite these positive results, it is also known that a small proportion of eyes do not respond adequately to anti-VEGF drugs and develop severe vision loss.

Aflibercept, a 115 kDa anti-VEGF drug that first entered clinical use in 2011, is a recombinant fusion protein that both acts as a competitive VEGF inhibitor and binds placental growth factor 1 and 2, which have been shown to play a role in the pathogenesis of AMD.[1] In the VIEW 1 and VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration) studies to determine the efficacy and safety of intravitreal aflibercept (IVA) therapy in eyes with nvAMD, it was reported that a large proportion of eyes had improved and/or maintain visual acuity with 3 consecutive monthly injections followed by continued IVA therapy every 2 months.[2,3]

It is clear that determining the initial lesion characteristics of treatment-resistant and inadequately responsive eyes is important and necessary to facilitate the prediction of functional and anatomical outcomes and to rationalize expectations of IVA therapy in eyes with nvAMD. Making effective changes in treatment and follow-up strategies in clinical practice will only be possible with the guidance of such data.

Therefore, a clinical study was planned to determine the functional and anatomical outcomes obtained with IVA therapy in eyes with newly diagnosed and untreated nvAMD and to investigate the effect of baseline lesion characteristics on treatment outcomes.

Materials and Methods

This clinical study included 139 eyes of 133 consecutive patients with treatment-naive active nvAMD diagnosed in the Retina Unit of the Ege University Faculty of Medicine Ophthalmology Department between February 2015 and April 2017. Patients who were younger than 50 years of age, had previously been treated for nvAMD, had any contraindication to anti-VEGF therapy or developed complications during treatment, and did not adhere to the follow-up and treatment protocol were excluded from the study.

An informed consent form was obtained from each patient and approval was obtained from the Ege University Clinical Research Ethics Committee (decision no: 17-8/11, 70198063-050.06.04). The study was conducted in adherence to the principles of the Declaration of Helsinki.

Before treatment, each patient's age, gender, and best corrected visual acuity (BCVA) values (in decimal) were recorded and all eyes underwent a complete ophthalmological examination as well as spectral-domain optical coherence tomography (SD-OCT) and fluorescein angiography (FA) scans performed using a Heilderberg Spectralis HRA + OCT (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany) device. Indocyanine green angiography (ICGA) was also performed with the same device in patients for whom indocyanine dye could be obtained. According to SD-OCT findings, baseline lesion characteristics, presence and type of pigment epithelial detachment (PED), and nv type based on location (type 1, 2, 3) were recorded. On FA, nv type was determined based on staining properties and the presence of dye leakage in the late phases were recorded. Eyes in which nv type could not be determined due to extensive hemorrhage or scar formation were classified as "undetermined". For eyes with ICGA data, the presence of polypoidal choroidal vasculopathy (PCV) was investigated based on Everest 2 criteria.

Eyes exhibiting fresh hemorrhage on clinical examination or subretinal, intraretinal, and sub-retinal pigment epithelium (RPE) fluid on SD-OCT and leakage on FA were evaluated as having active nvAMD. These eyes were treated with IVA (Eylea; Bayer/Regeneron Pharmaceuticals, Inc., Tarrytown, NY) (2 mg/0.05 cc) injection under fully sterile operating room conditions.

Follow-up examinations were performed 4-6 weeks after treatment and included fundus examination as well as BCVA measurement and reassessment of SD-OCT findings. Eyes with ongoing signs of active disease in examination 1 month after 3 consecutive IVA injections continued treatment at the same intervals, while for those without signs of activation, treatment intervals were extended by adding 2 weeks to the previous interval at each follow-up examination, as per the "treat and extend" protocol. Thereafter, follow-up and treatment were continued at a maximum interval of 3 months between treatments. For eyes that showed signs of reactivation during this treatment protocol, treatment intervals were returned to 4-6 weeks.

Anatomical and functional responses at follow-up examination performed 1 month after the last injection were cross-sectionally analyzed in the eyes that received 3 consecutive IVA injections at 4-6 weeks intervals and those eyes that continued regular follow-up and treatment and completed 6 doses of IVA, and the relationship between treatment outcomes and baseline lesion characteristics was statistically investigated. Eyes with complete regression of signs of activation on SD-OCT were classified anatomically as completely responsive, those with some improvement were classified as partially responsive, and eyes that showed no improvement or worsening were classified as unresponsive/worsening.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 17.0 package software. For statistical analyses, BCVA values were converted from decimal to LogMAR. Numerical variables were tested for normal distribution using Kolmogorov-Simirnov test. Two dependent median values were compared using Wilcoxon test.

Two dependent categorical variables were compared using McNemar test. Differences between independent median values were evaluated with Kruskal-Wallis test. Relationships between independent categorical variables were investigated using chi-square test. Logistic regression analysis was used as a multivariate analysis method. The study was conducted at a confidence level of 95% ($p<0.05$ was accepted as a statistically significant difference).

Results

Of the 133 patients included in the study, 73 (54.9%) were men and 60 (45.1%) were women, 6 (4.5%) had bilateral disease, and the mean age was 71.1±9.5 (51-90) years. All 139 eyes in the study received 3 consecutive injections and were included in group 1, while the 62 eyes that continued regular follow-up and treatment and completed 6 consecutive injections were included in group 2. The demographic characteristics and lens status of the eyes in both groups are shown in Table 1. The eyes in group 2 received 6 IVA injections over a mean of 7.3±0.6 (6-8) months, with a maximum interval of 2.5 months between injections according to the treat and extend protocol.

The baseline SD-OCT, FA, and ICGA lesion features of the eyes in both groups are shown in Table 2. In group 1, according to SD-OCT findings, the most common type of nv was type 1 (59.0%), most eyes had PED (78.4%), and the most common type of PED was fibrovascular (Fv) PED (53.2%). According to the FA characteristics in this group, the most common nv type was occult (51.1%), while PCV was detected in 34 (81.0%) of the 42 eyes (30.2%) that underwent ICGA imaging. In group 2, SD-OCT showed that the most common nv type was type 1 (56.4%), PED was present in 79.0%, and Fv PED was most common (48.4%). FA findings also demonstrated that occult nv was most common in this group (56.5%) and the prevalence of PCV was 84.0% in the 25 eyes (40.3%) eyes that underwent ICGA.

In the cross-sectional evaluation of treatment responses at 1 month after the last injection in the 139 eyes in group 1 who received 3 doses of IVA, 76 eyes (54.6%) were classified as completely responsive, 50 eyes (36.0%) as partially responsive, and 13 eyes (9.4%) as unresponsive/worsening (Figure 1). Similarly, in the cross-sectional evaluation of the 62 eyes in group 2 at 1 month after the last of 6 IVA injections, 36 eyes

Table 2. Baseline SD-OCT, FA, and ICGA lesion characteristics in groups 1 and 2

	Group 1 n (%)	Group 2 n (%)
SD-OCT: nv type		
Type 1	82 (59.0)	35 (56.4)
Type 2	37 (26.6)	15 (24.2)
Type 3	20 (14.4)	12 (19.4)
PED		
PED (-)	30 (21.6)	13 (21.0)
PED (+)	109 (78.4)	49 (79.0)
Serous PED	15 (10.8)	8 (12.9)
Fv PED	74 (53.2)	30 (48.4)
Serous + Fv PED	18 (13.0)	11 (17.7)
Drusenoid PED	2 (1.4)	0 (0)
FA: nv type		
Predominantly classic	36 (25.9)	15 (24.2)
Minimally classic	28 (20.2)	11 (17.7)
Occult	71 (51.1)	35 (56.5)
Undetermined	4 (2.8)	1 (1.6)
ICGA		
Obtained	42 (30.2)	25 (40.3)
PCV (+)	34 (81.0)	21 (84.0)
PCV (-)	8 (19.0)	4 (16.0)
Not obtained	97 (69.8)	37 (59.7)

FA: Fluorescein angiography, SD-OCT: Spectral domain optical coherence tomography, nv: Neovascularization, PED: Pigment epithelial detachment, Fv PED: Fibrovascular PED, ICGA: Indocyanine green angiography, PCV: Polypoidal choroidal vasculopathy

Table 1. Demographic characteristics and lens status of groups 1 and 2

	Group 1	Group 2
Number of patients	133	60
Number of eyes	139	62
Age (years), mean ± SD (min-max)	71.1±9.5 (51-90)	70.6±9.1 (61-89)
Gender, n (%)		
Male	73 (54.9)	31 (51.6)
Female	60 (45.1)	29 (48.4)
Lens status, n (%)		
Phakic	86 (61.9)	38 (61.3)
Pseudophakic	53 (38.1)	24 (38.7)

SD: Standard deviation, min: Minimum, max: Maximum

(58.0%) were classified as completely responsive, 16 (25.8%) as partially responsive, and 10 (16.2%) as unresponsive/worsening (Figure 2).

The mean pre- and post-treatment BCVA values in groups 1 and 2 are shown in Table 3. There were significant increases in mean post-treatment BCVA compared to pre-treatment values in both groups (p<0.001 for both).

The comparison of pre- and post-treatment BCVA and baseline lesion characteristics according to treatment response after 3 IVA injections in the 139 eyes in group 1 is shown in Table 4. There was no significant relationship between mean pre- and post-treatment BCVA values and treatment responses (p=0.786 and p=0.147). In addition, there was no significant relationship between the nv types detected by SD-OCT and FA at diagnosis and treatment responses (p=0.061 and p=0.229). However, the presence of PED at diagnosis was negatively associated with anatomic response (p=0.043) and serous PED had a more negative affect on anatomic response than other PED types (p=0.005). There was no statistically significant relationship between the presence of PCV and treatment response (p>0.999).

The comparison of pre- and post- treatment BCVA and baseline lesion characteristics according to treatment response after 6 IVA injections in the 62 eyes in group 2 is shown in Table 5. There was also no significant relationship between mean pre- and post-treatment BCVA values and treatment responses in this group (p=0.877 and p=0.144). Treatment response did not show a significant association with nv types detected by SD-OCT and FA at diagnosis (p=0.346, p=0.579) or with the presence of PED, PED types (serous, Fv, serous + Fv), and presence of PCV (p=0.734, p=0.579, p=0.666, p=0.538, p=0.801, respectively).

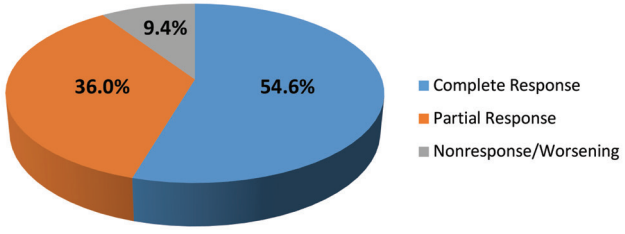

Figure 1. Treatment responses in group 1 after 3 intravitreal aflibercept injections

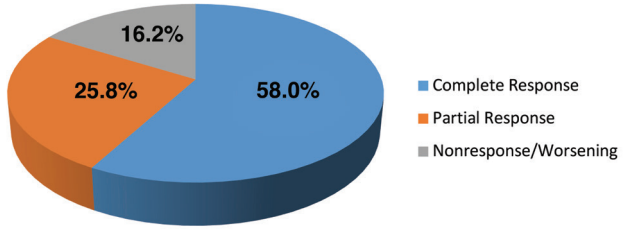

Figure 2. Treatment responses in group 2 after 6 intravitreal aflibercept injections

Discussion

This study evaluated the functional and anatomical results obtained with IVA therapy in newly diagnosed and untreated eyes with nvAMD and investigated the association between these results and baseline lesion characteristics. The results showed that there were statistically significant increases in mean BCVA after treatment in both groups compared to pre-treatment, independent of anatomic treatment response. Our results regarding the increase in BCVA were similar to and consistent with visual acuity improvements in nearly all other clinical trials in eyes with treatment-naive nvAMD treated with aflibercept.[2,3,4,5,6]

In our study, we also evaluated regression of disease activity as another criterion of treatment outcome (i.e., anatomic results) and found that groups 1 and 2 had complete response rates of 54.6% and 58.0%, partial response rates of 36.0% and 25.8%, and nonresponse/worsening rates of 9.4% and 16.2%, respectively. The VIEW 1 and VIEW 2 studies were multicenter, randomized, controlled clinical trials to determine the efficacy and safety of aflibercept therapy and showed that most eyes achieved positive results in both anatomic and functional terms.[2,3] Barthelmes et al.[7] applied the treat-and-extend regimen in 136 eyes diagnosed with treatment-naive nvAMD and reported that inactivation was achieved in 68% of eyes with 3 or fewer injections, while this rate increased to 82% and 90% at the end of 1 and 2 years. In a series of 140 eyes with treatment-naive nvAMD, Kikushima et al.[8] administered 3 monthly aflibercept injections followed by a pro re nata regimen and reported that only 32.9% of the eyes did not require retreatment based on anatomic criteria after 3 months. Minami et al.[9] used an aflibercept regimen of 3 consecutive monthly injections followed by treatment at 2-month intervals in naive nvAMD eyes with good baseline visual acuity and reported a significant increase in visual acuity from month 2, as well as "dry macula" (no exudative findings on OCT) in 80% of eyes after the 3 loading doses and in 66% and 71% at months 6 and 12, respectively. In a similar study, Miyamoto et al.[10] reported anatomical success rates

Table 3. Mean BCVA before and after treatment in groups 1 and 2

	Pre-treatment BCVA (LogMAR), mean ± SD (min-max)	Post-treatment BCVA (LogMAR), mean ± SD (min-max)	p
Group 1	0.80±0.56 (0-2.1)	0.63±0.47 (0-1.8)	<0.001
Group 2	0.68±0.49 (0-2.0)	0.42±0.38 (0-1.3)	<0.001

SD: Standard deviation, min: Minimum, max: Maximum, BCVA: Best corrected visual acuity, LogMAR: Logarithm of the minimum angle of resolution

Table 4. Distribution of BCVA and baseline lesion characteristics in group 1 according to treatment response				
	Complete response (n, %)	**Partial response (n, %)**	**Nonresponse/worsening (n, %)**	**P**
BCVA (LogMAR) mean ± SD (min-max)				
Pre-treatment	0.76±0.53 (0-2.1)	0.81±0.57 (0-1.8)	0.83±0.54 (0.2-1.8)	0.786
Post-treatment	0.57±0.44 (0-1.8)	0.65±0.49 (0-1.8)	0.78±0.39 (0.2-1.8)	0.147
SD-OCT: nv type				
Type 1	41 (53.9)	34 (68.0)	6 (46.2)	
Type 2	23 (30.3)	12 (24.0)	2 (15.4)	0.061
Type 3	12 (15.8)	4 (8.0)	5 (38.4)	
PED				
PED (-)	22 (28.9)	8 (16.0)	0 (0)	
PED (+)	54 (71.1)	42 (84.0)	13 (100.0)	**0.043**[b]
Serous PED	4 (5.3)	10 (20.0)	4 (30.8)	**0.005**[b]
Fv PED	44 (57.9)	25 (50.0)	5 (38.4)	0.168
Serous + Fv PED	6 (7.9)	7 (14.0)	2 (15.4)	0.126
Drusenoid PED	0 (0)	0 (0)	2 (15.4)	
FA: nv type				
Predominantly classic	22 (28.9)	12 (24.0)	2 (15.4)	
Minimally classic	17 (22.4)	7 (14.0)	4 (30.8)	
Occult	37 (48.7)	28 (56.0)	6 (46.2)	0.229
Undetermined	0 (0)	3 (6.0)	1 (7.6)	
ICGA				
Obtained	18 (23.7)	19 (38.0)	6 (46.2)	
PCV (+)	14 (77.8)	15 (78.9)	5 (83.3)	>0.999
PCV (-)	4 (22.2)	4 (21.1)	1 (16.7)	
Not obtained	58 (76.3)	31 (62.0)	7 (53.8)	

SD: Standard deviation, min: Minimum, max: Maximum, BCVA: Best corrected visual acuity, LogMAR: Logarithm of the minimum angle of resolution, FA: Fluorescein angiography, SD-OCT: Spectral domain optical coherence tomography, nv: neovascularization, PED: Pigment epithelial detachment, Fv PED: Fibrovascular PED, ICGA: Indocyanine green angiography, PCV: Polypoidal choroidal vasculopathy

of 37%, 62%, and 81% at months 3, 6, and 12, respectively, in eyes with naive AMD given aflibercept at 2-month intervals following a 3-month loading dose. Looking at studies conducted in our country, Erden et al.[11] evaluated the anatomic and functional efficacy of aflibercept and ranibizumab in nvAMD and observed statistically significant positive changes at the end of 12 months with the pro re nata protocol in the aflibercept arm of the study. Similarly, Unsal et al.[12] investigated the effect of aflibercept therapy on naive eyes with AMD and reported anatomic improvement in 92.1% of the eyes at 12 months with the pro re nata protocol.

Most clinical studies of aflibercept in naive eyes with nvAMD have shown that exudative findings completely or partially regressed and favorable anatomical results were achieved in a large proportion of the eyes, as in our study.[13,14] However, the sizable differences in success rates reported in various studies are also noteworthy. We believe that this variance may be due to differences among the studies in the definition of anatomic success and activation criteria, as well as differences in the treatment regimens used, different baseline lesion characteristics of the eyes, the possibility that case series include different nvYBMD subgroups such as PCV, and that they are conducted in different ethnic populations.[15]

In our study, when the initial SD-OCT, FA, and ICGA lesion characteristics of the eyes in group 1 and group 2 were examined, it was found that based on SD-OCT, the most common type of nv in both groups was type 1 nv (59.0% and 56.4%), that nearly 80% of the eyes had PED, and that approximately 50% of these eyes had Fv PED. Similarly, occult nv accounted for the majority in both groups according to FA characteristics, and rates of PCV were high (81% and 84%) among the eyes that underwent ICGA. In terms of the frequency and distribution of baseline lesion features of the eyes in our study, they had similar characteristics and no differences from other studies, including the high prevalence of PCV.[4,16,17] When our study results were analyzed, it was observed that the

Table 5. Distribution of BCVA and baseline lesion characteristics in group 2 according to treatment response				
	Complete response (n, %)	**Partial response (n, %)**	**Nonresponse/worsening (n, %)**	**P**
BCVA (LogMAR) mean ± SD (min-max)				
Pre-treatment	0.68±0.51 (0-2.0)	0.68±0.43 (0.1-1.3)	0.66±0.46 (0.2-1.8)	0.877
Post-treatment	0.38±0.36 (0-1.3)	0.61±0.48 (0-1.3)	0.54±0.35 (0-1.3)	0.144
SD-OCT: nv type				
Type 1	20 (55.6)	11 (68.7)	4 (40.0)	
Type 2	9 (25.0)	4 (25.0)	2 (20.0)	0.346
Type 3	7 (19.4)	1 (6.3)	4 (40.0)	
PED				
PED (-)	8 (22.2)	3 (18.8)	2 (20.0)	
PED (+)	28 (77.8)	13 (81.2)	8 (80.0)	0.734
Serous PED	6 (16.7)	3 (18.7)	2 (20.0)	0.579
Fv PED	19 (52.8)	8 (50.0)	3 (30.0)	0.666
Serous + Fv PED	3 (8.3)	2 (12.5)	3 (30.0)	0.538
FA: nv type				
Predominantly classic	8 (22.2)	5 (31.3)	2 (20.0)	
Minimally classic	8 (22.2)	1 (6.2)	2 (20.0)	0.579
Occult	20 (55.6)	9 (56.3)	6 (60.0)	
Undetermined	0 (0)	1 (6.2)	0 (0)	
ICGA				
Obtained	15 (41.7)	6 (37.5)	4 (40.0)	
PCV (+)	12 (80.0)	5 (83.3)	4 (100.0)	
PCV (-)	3 (20.0)	1 (16.7)	0 (0)	0.801
Not obtained	21 (58.3)	10 (62.5)	6 (60.0)	

SD: Standard deviation, min: Minimum, max: Maximum, IVA: Intravitreal aflibercept, BCVA: Best corrected visual acuity, LogMAR: Logarithm of the minimum angle of resolution, FA: Fluorescein angiography, SD-OCT: Spectral domain optical coherence tomography, nv: neovascularization, PED: Pigment epithelial detachment, Fv PED: Fibrovascular PED, ICGA: Indocyanine green angiography, PCV: Polypoidal choroidal vasculopathy

presence of PCV at diagnosis was not associated with anatomic response to IVA treatment in group 1 or 2 (p>0.999, p=0.801, respectively). Miyamoto et al.[10] also reported that the presence of PCV did not affect anatomic response to IVA in their study of naive eyes with nvAMD, nearly half of which had PCV, while Ijiri and Sugiyama[18] reported an anatomic success rate of 97% in naive eyes with PCV after 3 consecutive IVA injections.

According to our study results, there was no significant relationship between nv types detected by SD-OCT and FA at diagnosis and treatment response in group 1 or group 2. Vaze et al.[19] did not detect any relationship between the initial FA patterns and anatomic treatment response, as in our study.

In group 1, anatomic responses were poorer in the presence of PED at diagnosis compared to the absence of PED and with serous PED compared to other PED types, whereas there was no significant association between the presence of PED or its subtypes and anatomic response in group 2. In their study, Miyamoto et al.[10] found that detection of PED at diagnosis was associated with inadequate response to IVA therapy, while Ying et al.[20] reported that patients with PED at diagnosis may have functional abnormalities in RPE activity that result in poorer anatomical response. Nagai et al.[21] investigated the reasons for nonresponse to IVA therapy and reported that the presence of serous PED at diagnosis negatively affected anatomic treatment response, similar to our results.

Another striking finding of our study was the similar anatomical response rates obtained in group 1 and group 2. The rate of complete response was 54.6% in group 1 and 58% in group 2. Framme et al.[22] reported that eyes showing complete response on OCT and a functional increase in vision after the first 3 injections continued this success at month 12 of treatment.

Conclusion

Similarly, Nguyen et al.[23] reported that visual response after the fourth injection was the most important factor in predicting visual success at year 3 of treatment and that shorter time to lesion inactivation was associated with better visual outcomes at 3 years; therefore, they concluded that early response may be

useful in predicting long-term outcomes. In our study, the very similar anatomical response rates in groups 1 and 2 supported this view and may be a helpful factor in predicting treatment responses in the longer term.

In conclusion, in this study evaluating the functional and anatomical outcomes with IVA therapy and their association with baseline lesion characteristics in eyes with newly diagnosed, previously untreated nvAMD, we attempted to identify baseline lesion characteristics that will serve as a guide in the prediction of treatment responses in newly diagnosed eyes that will start receiving treatment.

Ethics

Ethics Committee Approval: Ege University Clinical Research Ethics Committee (decision no: 17-8/11, 70198063-050.06.04).

Informed Consent: Obtained.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: P.K., J.M., S.N., F.A., Concept: J.M., Design: J.M., Data Collection or Processing: P.K., J.M., Analysis or Interpretation: P.K., J.M., M.B., Literature Search: P.K., J.M., Writing: P.K., J.M.

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