Real-life experience with ranibizumab and aflibercept in the treatment of neovascular age-related macular degeneration in Turkey

Serhat Ermis[1], *Nursal Melda Yenerel*[2]

ABSTRACT

Purpose: To analyze real-life data pertaining to neovascular age-related macular degeneration (nAMD) treatment with ranibizumab and aflibercept.

Materials and Method: A total of 102 eyes of 102 patients diagnosed with nAMD were analyzed. The following information was retrospectively recorded from the patients' files: best-corrected visual acuity (BCVA) at baseline and at the 1-, 3-, 6-, and 12-month follow-ups; number of injections; central macular thickness (CMT) and presence of intraretinal and subretinal fluid.

Findings: In this study, the mean follow-up period was 12 months. Of the 102 patients, 49% were female. The mean age was 73.74±8.77. Forty-eight percent of the patients were treated with ranibizumab, and 52% were treated with aflibercept. There was no statistically significant difference in the mean number of injections between the ranibizumab group and the aflibercept group ($p > 0.05$), which was 3.65±1.45 and 3.77±1.51, respectively. In the 12-month follow-up period, there was no statistically significant difference in mean BCVA improvement between the two groups ($p > 0.05$). The number of patients with intraretinal fluid decreased by 38.8% in the ranibizumab group and by 24.5% in the aflibercept group ($p > 0.05$). The number of patients with subretinal fluid decreased by 34.7% in the ranibizumab group, while it decreased by 39.6% in the aflibercept group ($p > 0.05$).

Results: In nAMD, both ranibizumab and aflibercept injections reduce CMT, reduce the number of patients with intraretinal and subretinal fluid, and increase BCVA. Consequently, it was concluded that neither ranibizumab nor aflibercept is superior for intravitreal administration.

Keywords: Aflibercept, Ranibizumab, Choroidal neovascularization, Age-related macular degeneration, Real life experience.

INTRODUCTION

Age-related macular degeneration (AMD) is the most common cause of vision loss in the elderly population in developed countries.[1,2] The incidence of AMD increases significantly with age. Only 2.5% of people over the age of 65 years have AMD, compared to 32% of people over 75 years of age.[3] Genetics, environmental factors, metabolic factors, and nutrition play roles in the etiology of the disease with age.[4] AMD is a degenerative and progressive disease of the retinal pigment epithelium (RPE), Bruch's membrane and choriocapillaris. The pathogenesis of the disease is multifactorial: lipofuscin accumulation, chronic inflammation, angiogenesis, chronic oxidative damage, apoptosis, and complement system mutation play roles.[5,6] Neovascular age-related macular degeneration (nAMD), abnormal growth of blood vessels, choroidal neovascularization (CNV), subretinal fluid (SRF), macular edema (ME), and pigmented epithelial detachments (PEDs) lead to accumulation and to 80% of the vision loss due to AMD. The vascular endothelial growth factor (VEGF) accused in pathogenesis is a homodimeric glycoprotein that induces endothelial cell proliferation and migration. It

1- MD, Başakşehir Çam and Sakura City Hospital, Department of Ophthalmology, Istanbul, Türkiye

2- Prof. MD, University of Health Sciences Haydarpasa Education and Research Hospital, Department of Ophthalmology, İstanbul, Türkiye

Received: 01.08.2023
Accepted: 22.11.2023

J Ret-Vit 2024; 33: 32-38

DOİ: 10.37845/ret.vit.2024.33.6

Correspondence Adress:
Serhat Ermis
Başakşehir Çam and Sakura City Hospital, Olympic Boulevard 34480
Başakşehir/İstanbul, Türkiye

Phone: +90 506 728 5543
E-mail: serhatermis88@hotmail.com

is the main activator of angiogenesis and causes increased permeability and lymphangiogenesis.[7-9]

The existing anti-VEGF treatments applied through intravitreal injection include non-indication bevacizumab as well as ranibizumab and aflibercept. International guidelines recommend these anti-VEGF agents as primary treatment for the treatment of nAMD.[10,11]

Ranibizumab (Lucentis, Genentech/Novartis), an antibody fragment capable of binding to all VEGF-A isoforms, has been found to stabilize best-corrected visual acuity (BCVA) and to increase in patients with nAMD.[12,13] The efficacy and safety of ranibizumab therapy for nAMD has been demonstrated in several multicenter studies. In phase III trials, the results from both the minimally classic/occult trial of the anti-VEGF antibody ranibizumab in the treatment of nAMD (MARINA) trial and the anti-VEGF antibody for the treatment of predominantly classic CNV in AMD (ANCHOR) trial allowed ranibizumab to be approved as a therapeutic agent.[12,13] Aflibercept (Eylea Regenener Pharmaceuticals, Tarrytown, New York, USA) is a fusion protein that connects VEGF-A, VEGF-B, and placental growth factor. It is connected with a higher affinity than ranibizumab and bevacizumab, and its intravitreal half-life is longer. For these reasons, aflibercept is at the forefront of the use of CNV therapy unresponsive to other anti-VEGF agents.[14]

We wanted to evaluate the real-life efficacy of these drugs in Turkey which have been demonstrated in randomized controlled studies. In this study, we aimed to present the 12-month visual and anatomical results of intravitreal ranibizumab and aflibercept treatment in patients with nAMD in Turkey, a middle-income country.

PATIENTS AND METHODS

Patients with nAMD who applied to the Retina Unit of our clinic between 2012 and 2017, had not been treated before, and were followed up for at least 12 months were included in this study. Institutional ethics committee approval was obtained for this study. The trial conformed to the tenets of the Declaration of Helsinki.

Exclusion criteria

The following patients were excluded: patients with diabetic retinopathy, optic disk, and other retinal diseases; patients who had previously undergone a pars plan vitrectomy or glaucoma surgery; patients with a uveitis diagnosis or active uveitis; patients who were not followed up for at least 12 months; and patients who could not come to controls.

Data acquisition

Logarithm minimum resolution angle (LogMAR) equivalents of the patients' visual acuity values were obtained with Snellen examination, biomicroscopic examination, stereoscopic fundus examination and spectral-domain optical coherence tomography (SD-OCT; Heidelberg Instruments, Heidelberg, Germany) and the results were recorded at each visit. After the intravitreal injection, the follow-ups were performed at baseline and at 1, 3, 6, and 12 months.

As a treatment protocol, after the diagnosis was made, one dose of ranibizumab or aflibercept treatment was administered, and the controls were treated according to the following reinjection criteria: a visual acuity loss of more than 5 letters (1 line), an increase in central macular thickness (CMT) of ≥100 μm, the presence of intraretinal and/or subretinal fluid, the presence of leakage on fluorescent angiography, and non-previous macular or subretinal hemorrhage foci.[15]

Statistical analysis of data

The Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) software was used for statistical analysis. Descriptive statistics such as the mean, standard deviation, median, frequency, ratio, minimum, maximum were used when comparing quantitative data. Student's t-test and the Mann-Whitney U test were used for two group comparisons of the normally and nonnormally distributed variables used, respectively. The Friedman test was used for in-group comparisons of nonnormally distributed variables. The Bonferroni-Dunn test was used for pairwise comparisons. Pearson's chi-square test was used for comparing qualitative data. Significance was evaluated at the $p < 0.05$ level.

RESULTS

A total of 102 eyes of 102 patients who received intravitreal ranibizumab or aflibercept for nAMD were included in this study. The demographics and characteristics of the patients are shown in Table 1. Of the 102 patients. 49.0% (n = 50) were female, and the mean age was 73.74 ± 8.77 years. Ranibizumab and aflibercept were respectively administered to 48% and 52% of the patients. The mean number of injections in the ranibizumab and aflibercept groups was respectively 3.65 ± 1.45 and 3.77 ± 1.51, with no significant difference between the groups ($p > 0.05$).

Table 1: *Baseline Demographics and Clinical Characteristics of Eyes Treated with Ranibizumab and Aflibercept*

Parameters	Ranibizumab	Aflibercept	p
No. of eyes	49	53	
Mean age (y)	73,61±8,47(46-95)	73,85±9,12(57-93)	[a]0,892
Gender M/F (%)	29/20(59,2/40,8)	23/30(43,4/56,6)	[b]0,111
Baseline BCVA (logMAR)	1,12±0,62 0,2-3,1 (1,1)	1,24±0,83 0,2-3,1 (1,3)	[c]0,805
Baseline CRT (µm)	417,00±100,53 (289-780 (409))	450,36±166,11 (243-1034 (414))	[c]0,642
No. of injections	3,65±1,45(1-7)	3,77±1,51(1-8)	[a]0,683

[a]Student t Test [b]Pearson Chi-Square Test [c]Mann Whitney U Test
Values are presented as mean ± standard deviation (range) or number.
BCVA = best-corrected visual acuity; logMAR = logarithm of minimal angle of resolution; CRT = central retinal thickness.

In all cases, the change in BCVA measurements was found to be statistically significant ($p = 0.006$; $p < 0.01$). The 12-month measurements showed a statistically significant increase of 26.21% compared to the initial measurements ($p = 0.029$; $p < 0.05$). In patients who received ranibizumab injection, the change in BCVA was statistically significant ($p = 0.001$; $p < 0.01$). The 12-month measurements showed a statistically significant increase of 26.86% compared to the initial measurements ($p = 0.017$; $p < 0.05$). In patients who received aflibercept injection, the change in BCVA was not statistically significant ($p = 0.630$; $p > 0.05$) (Figure 1).

The decrease in CMT measurements was statistically significant in both ranibizumab and aflibercept drug groups ($p = 0.001$; $p < 0.01$) (Figure 2).

The results of pairwise comparisons to detect a follow-up that caused a significant change are shown in Table 2.

When the number of patients with intraretinal and subretinal fluid was analyzed according to the drug groups, no statistically significant difference was found ($p > 0.05$).

Gender, right or left eye involvement, total number of visits, fluid localization (intaretinal/subretinal), BCVA, and CMT did not have a significant effect ($p > 0.05$, Wilcoxon's marked sequence test). After 381 injections, no patients who received injection showed serious ocular or systemic side effects.

DISCUSSION

We evaluated our 12-month real-life experience with the use of ranibizumab and aflibercept for nAMD at a

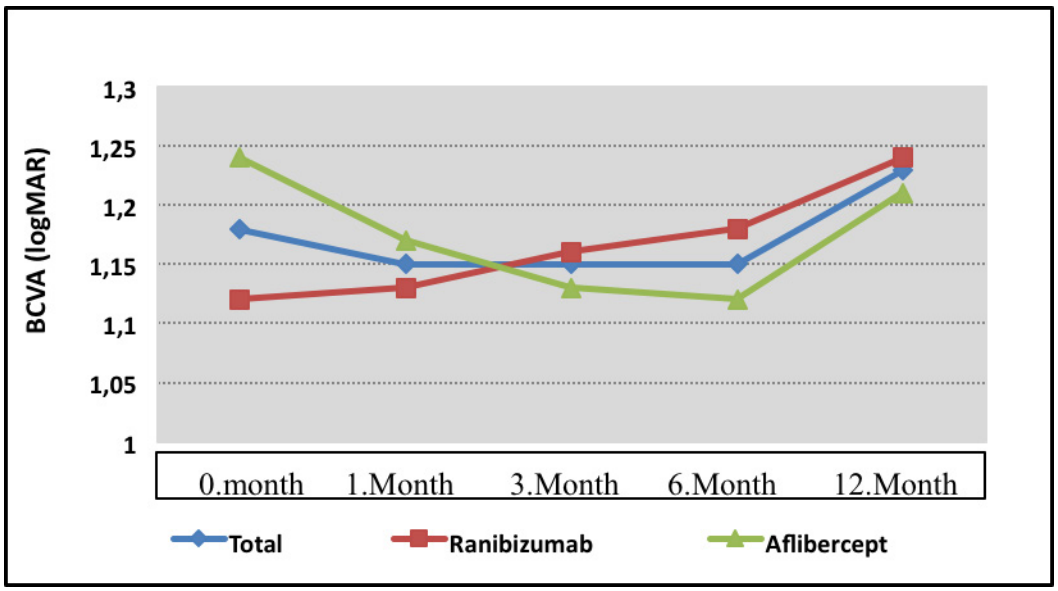

Figure 1: *The changes in mean BCVA in the study group.*

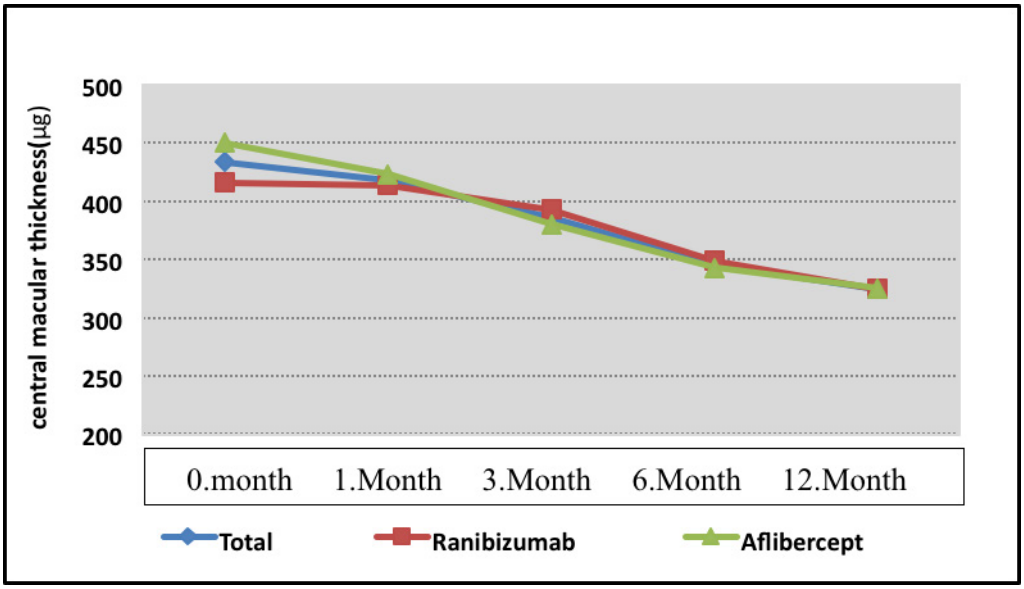

Figure 2: *The changes in central macular thickness in the study group.*

Table 2: *Evaluation of Central Macular Thickness measurements according to the drug used*

CMT (µm)	**Total (n=92)**	**Ranibizumab (n=49)**	**Aflibercept (n=53)**	[a]***p***
0.month	434,33±138,89	417,00±100,53	450,36±166,11	***0,642***
	(243-1034 (409,5))	(289-780 (409))	(243-1034 (414))	
1. month	418,77±127,01	414,31±103,81	422,91±146,12	***0,723***
	(217-965 (389))	(284-759 (390))	(217-965 (380))	
3. month	386,51±113,51	393,10±103,24	380,42±122,91	***0,268***
	(210-790 (367))	(244-790 (378))	(210-780 (343))	
6. month	345,67±102,39	348,98±97,64	342,60±107,44	***0,478***
	(190-810 (323,5))	(190-810 (328))	(204-798 (323))	
12. month	324,98±110,87	324,92±100,02	325,04±121,01	***0,469***
	(175-845 (290))	(225-845 (298))	(175-845 (288))	
[b]***p***	***0,001*****	***0,001*****	***0,001*****	
% change				
0.month-1. month	-2,01±15,34	0,24±14,62	-4,08±15,83	***0,151***
	(-63,6-53,3 (-1,9))	(-34-53,3 (3,4))	(-63,6-26,4 (-3,7))	
[b]***p***	***1,000***	***1,000***	***1,000***	
0. month -3.month	-8,35±19,69	-4,37±19,03	-12,04±19,75	***0,119***
	(-66,4-47,6 (-9,1))	(-42,3-47,6 (-3,8))	(-66,4-23,8 (-10,1))	
[b]***p***	***0,046****	***1,000***	***0,032****	
0. month -6. month	-17,45±19,19	-14,77±18,90	-19,93±19,29	***0,333***
	(-71,4-35,5 (-17,9))	(-54,4-35,5 (-17,5))	(-71,4-26,7 (-18,4))	
[b]***p***	***0,001*****	***0,001*****	***0,001*****	
0. month -12. month	-22,42±20,44	-21,00±16,15	-23,73±23,82	***0,389***
	(-72,9-69,7 (-22,6))	(-54,2-19,2 (-22,3))	(-72,9-69,7 (-24,2))	
[b]***p***	***0,001*****	***0,001*****	***0,001*****	

[ac]Mann Whitney U Test [b]Friedman's Two-way ANOVA Test *p<0,05 **p<0,01
Values are presented as mean ± standard deviation (range) or number.
CMT = central maculer thickness.

retina clinic in Turkey. We obtained results similar to those of other real-life data studies. Although follow-up examinations and injections were not performed properly, the visual and anatomical results were acceptable for real-life practice. When the studies conducted in Japan were examined, the disease was found more frequently in males; by contrast, in the NHANES III and BDES studies, it was more common in females.[16,17] In the AURA study, real-life data were obtained from publications from different countries, and the average number of females in the patient population in England and those in Canada, France, Germany, Ireland, Italy, and Venezuela were compared and found to be similar.[18] Real-life data also validated the NHANES III and BDES studies. [16,17] In the present study, as noted above, 49% of the patients were women. Whether this difference is due to the demographic characteristics of the society or the inclusion criteria of the study remains debatable because no multicenter study with a large enough number of patients to be adapted to the general population has yet been conducted in Turkey.

Randomized controlled studies have provided some guidance on the efficacy of drugs and their practical applications. A phase III MARINA study showed that BCVA was maintained after 2 years. The monthly administration of 0.3 mg and 0.5 mg ranibizumab resulted in a gain of 6.5 and 7.2 letters, respectively, after 24 months, whereas the sham group showed a loss of 10.2 letters.[12] A phase III ANCHOR study compared ranibizumab and photodynamic therapy (PDT). After 24 months, the 0.3 mg and 0.5 mg ranibizumab groups showed a gain of 8.1 and 10.7 letters, respectively, and the PDT group showed a loss of 9.8 letters.[19] A loss of less than 15 letters was found in 89.9% of the 0.3 mg ranibizumab group, 90% of the 0.5 mg ranibizumab group, and 65.7% of the PDT group. (20) In the MARINA study, this was attributed to the exclusion of occult and minimal classic CNV and late referral and diagnosis, with less BCVA gain than in the ANCHOR study. In the second year results of the CATT study comparing monthly and pro re nata (PRN) protocols for ranibizumab and bevacizumab, increases of 8.8 and 6.7 letters were found in the monthly ranibizumab treatment group and with the PRN protocol, respectively.[20] Garweg et al. studied 106 aflibercept and 47 ranibizumab patients and presented real-life data; they reported that the highest visualization level with the administration of ranibizumab was achieved at 12 months, and the visual level reached at 3 months was significantly different from the baseline level.[16] The visual results of our study and other long-term studies showed that BCVA was reduced at the end of 12 months despite treatment.[16,20]

In our study, at the end of 12 months, BCVA decreased from 1.18 logMAR to 1.23 logMAR; however, this was not statistically significant ($p > 0.05$). In addition, the highest BCVA was reached at 3 months. Therefore, these results are in line with the findings reported in the MARINA and ANCHOR studies. When the increase in BCVA and stabilization are evaluated, our study lags behind the abovementioned studies. This can be explained by the fact that the first three loading doses in the treatment protocol of our study were not applied and that some of the retrospectively included patients had a follow-up period of more than 12 months.

In studies in which real-life data were evaluated, the economic level of the countries and the demographic characteristics of the society played a key role in determining the treatment protocol. In the Luminous study, 4444 patients were evaluated for nAMD, and the average number of injections per year was respectively 4.3, 5.5, 4.7, and 5.0 in Germany, Netherlands, Sweden, and Belgium.[21] In the Australian Fight Retinal Blindness database, an average of 7.3 injections in 12 months was recorded in a cohort of 401 patients compatible with the MARINA study cohort for real-life evaluation.[22] In a study in which data were obtained from the IMS Health Lifelink Health plan database between 2008 and 2011, including a total of 11,688 United States patients using anti-VEGF for nAMD, the average number of ranibizumab injections was 6.0 in 2008 and 6.8 in 2010.[23] In a COMPASS study involving 1729 patients in Germany, the average number of injections was 4.5, including 3 loading doses.[24] The multicentered Aura study covering 2227 patients is another important real-life study.[25] Kim et al. conducted a meta-analysis in which they followed patients for more than 3 years; the number of annual visits and injections was respectively 6.8 and 3.6 in Germany, 5.4 and 2.8 in France, and 9.2 and 4.5 in the UK.[17] One study evaluated the 5-year result of ranibizumab treatment for nAMD for 37 patients treated with an average of 60 months of PRN in a real-life clinical environment in Turkey. The average number of visits decreased from 5.9 during the first year to 4.9 in the fifth year. In parallel with the average number of visits, the average number of injections decreased from 3.9 in the first year to 2.3 in the fifth year. The average number of injections was 4.7 (distribution: 3-8) in the first year andse 6 (distribution: 3-12) in the fifth year.[26]

In our study, the average annual number of patients undergoing ranibizumab and aflibercept treatments was respectively 3.65 ± 1.45 (1-7) and 3.77 ± 1.51 (1-8). In contrast to Phase III studies, no difference was seen between the two groups of drugs in terms of injection numbers as our study is based on an injection to be made when necessary after a single dose even if studies on reducing the injection number of aflibercept showed an efficiency duration of longer than a month. When the Phase III studies and other real-life data were taken into consideration, the treatment protocol was the first 3 loading doses, whether for PRN or treat-and-extend (T&E) regimes. Our study had a 1+PRN design considering the patient population of our country and the current insurance policy. Therefore, the number of injections given to the patients was found to be close to each other.

CMT has been determined as an important parameter in the nAMD treatment criteria, and it continues to be an important factor in both PRN and T&E regimens. However, studies show that CMT does not have a direct correlation with visual success. Garweg et al. evaluated real-life data 24 months after the first three loading doses of CMT between the two groups, although more letters were found in the ranibizumab group than in the aflibercept group at 24-month follow-up at the end of the CMT. They reported no difference and similar visual results.[16] Ferrone et al. studied 250 patients and found that CMT changed in patients who were switched from bevacizumab to ranibizumab. However, no improvement was reported in BCVA in correlation with CMT, and a similar situation was observed for patients who were switched from ranibizumab to aflibercept.[27] In our study, although both drug groups provided anatomical improvement by reducing CMT, their effect on BCVA was found to be limited.

The most important elements affecting CMT and visual rehabilitation are changes in the intraretinal and subretinal fluid. Almost all studies with real-life data investigated the presence of intraretinal and subretinal fluids, the thickness of these fluids, and their relationship with visual results. Some studies found no significant difference between the intraretinal and subretinal fluid amounts with ranibizumab and aflibercept.[16,26,27] Similarly, in our study, although the number of patients with intraretinal and subretinal fluid decreased compared to the baseline, there was no statistical difference between the drug groups ($p > 0.05$).

LIMITATION

Our study has some limitations. It suffers from the disadvantages of being a single-center retrospective study. The absence of a control group and the indiscriminate evaluation of nAMD subtypes are another limiting factor. The study has a 1+PRN design owing to the patient population of our country and the insurance policies in the specified period. However, we think that the patient group in this study is a real-life sample as it is a tertiary diagnosis, treatment, and reference center.

In conclusion, a comparison of the intravitreally administered drugs ranibizumab and aflibercept showed that real-life data for both varied between different countries, and they did not exactly match the results of controlled phase III studies.

REFERENCES

1. Leibowitz HM, Krueger DE, Maunder LR, et al. The Framingham Eye Study monograph: An ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration, and visual acuity in a general population of 2631 adults, 1973-5. Surv Ophthalmol 1980;24(Suppl):335-610.
2. Gass JDM. Stereoscopic atlas of macular diseases; diagnosis and treatment. 4th ed. St Louis: CV Mosby Co; 1997:70-2.
3. Abrahám-Marin ML, Cortés-Luna CF, Alvarez-Rivera G, et al. Intravitreal bevacizumab therapy for neovascular age-related macular degeneration: a pilot study. Graefes Arch Clin Exp Ophthalmol 2007;245:651-5. https://doi.org/10.1007/s00417-006-0411-6
4. Vincenyt RLU, Lerner LE, Kaiser PK. Non- Neovascular Age-Related Macular Degeneration. In: Huang D, Kaiser PK, Lowder CY, Traboulsi El, editors. Retinal Imaging. Philadelphia: Mosby Elsevier; 2006:145-51. https://doi.org/10.1016/B978-0-323-02346-7.50016-8
5. Velez-Montoya R, Oliver SCN, Olson JL, et al. Current knowledge and trends in age-related macular degeneration: today's and future treatments. Retina 2013;33:1487-502. https://doi.org/10.1097/IAE.0b013e318271f265
6. Zarbin MA. Pathogenesis of Age-Related Macular Degeneration. In: Bandello F, Querques G, editors. Medical Retina. Basel: Karger; 2012:125-33. https://doi.org/10.1159/000336763
7. Alfaro DV, editor. Age-related macular degeneration: a comprehensive textbook. Lippincott Williams & Wilkins; 2006:44-52.
8. Karaçorlu M, Arf S. Non-Neovasküler Age-Related Macular Degeneration. Medical Retina (Turkish Society of Ophthalmology Publications No:10). İstanbul: Epsilon; 2009:63-72.
9. Hsu ST, Thompson AC, Stinnett SS, et al. Longitudinal Study of Visual Function in Dry Age-Related Macular Degeneration at 12 Months. Ophthalmol Retina 2019;3:637-48. https://doi.org/10.1016/j.oret.2019.03.010

10. Schmidt-Erfurth U, Chong V, Loewenstein A, et al. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). Br J Ophthalmol 2014;98:1144-67. https://doi.org/10.1136/bjophthalmol-2014-305702
11. Chew EY, Benson WE, Boldt HC, et al. American Academy of Ophthalmology Retina Panel: Preferred practice patterns. San Francisco, CA: American Academy of Ophthalmology. American Academy of Ophthalmology Retina/Vitreous Panel: Preferred Practice Pattern Guidelines. Age-Related Macular Degeneration. San Francisco, CA: American Academy of Ophthalmology; 2015.
12. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419-31. https://doi.org/10.1056/NEJMoa054481
13. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432-44. https://doi.org/10.1056/NEJMoa062655
14. Ho VY, Yeh S, Olsen TW, et al. Short-term outcomes of aflibercept for neovascular age-related macular degeneration in eyes previously treated with other vascular endothelial growth factor inhibitors. Am J Ophthalmol 2013;156:23-8.e2. https://doi.org/10.1016/j.ajo.2013.02.009
15. Fung AE, Lalwani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. Am J Ophthalmol 2007;143:566-83. https://doi.org/10.1016/j.ajo.2007.01.028
16. Garweg JG, Gerhardt C, Kodjikian L, et al. Real-Life Experience with Aflibercept and Ranibizumab in the Treatment of Newly Diagnosed Neovascular Age-Related Macular Degeneration over 24 Months. J Ocul Pharmacol Ther 2017;33:567-72. https://doi.org/10.1089/jop.2017.0031
17. Kim LN, Mehta H, Barthelmes D, et al. Metaanalysis of real-world outcomes of intravitreal ranibizumab for the treatment of neovasküler age-related macular degeneration. Retina 2016;36:1418-31. https://doi.org/10.1097/IAE.0000000000001142
18. Hykin P, Chakravarthy U, Lotery A, et al. A retrospective study of the real-life utilization and effectiveness of ranibizumab therapy for neovascular age-related macular degeneration in the UK. Clin Ophthalmol 2016;10:87-96. https://doi.org/10.2147/OPTH.S92627
19. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. Ophthalmology 2009;116:57-65.e5. https://doi.org/10.1016/j.ophtha.2008.10.018
20. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group; Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology 2012;119:1388-98. https://doi.org/10.1016/j.ophtha.2012.03.053
21. Holz FG, Bandello F, Gillies M, et al. Safety of ranibizumab in routine clinical practice: 1-year retrospective pooled analysis of four European neovascular AMD registries within the LUMINOUS programme. Br J Ophthalmol 2013;97:1161-7. https://doi.org/10.1136/bjophthalmol-2013-303232
22. Gillies MC, Walton RJ, Arnold JJ, et al. Comparison of outcomes from a phase 3 study of age-related macular degeneration with a matched, observational cohort. Ophthalmology 2014;121:676-81. https://doi.org/10.1016/j.ophtha.2013.09.050
23. Kiss S, Liu Y, Brown J, et al. Clinical monitoring of patients with age-related macular degeneration treated with intravitreal bevacizumab or ranibizumab. Ophthalmic Surg Lasers Imaging Retina 2014;45:285-91. https://doi.org/10.3928/23258160-20140709-04
24. Wolf A, Kampik A. Efficacy of treatment with ranibizumab in patients with wet age-related macular degeneration in routine clinical care: data from the COMPASS health services research. Graefes Arch Clin Exp Ophthalmol 2014;252:647-55. https://doi.org/10.1007/s00417-013-2562-6
25. Holz FG, Tadayoni R, Beatty S, et al. Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration. Br J Ophthalmol 2015;99:220-6. https://doi.org/10.1136/bjophthalmol-2014-305327
26. Ozkaya A, Alkin Z, Togac M, et al. Five-year Outcomes of Ranibizumab in Neovascular Age-related Macular Degeneration: Real Life Clinical Experience. Korean J Ophthalmol 2017;31:424-30. https://doi.org/10.3341/kjo.2016.0125
27. Ferrone PJ, Anwar F, Naysan J, et al. Early initial clinical experience with intravitreal aflibercept for wet age-related macular degeneration. Br J Ophthalmol 2014;98(Suppl 1):i17-i21. https://doi.org/10.1136/bjophthalmol-2013-304474