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Original Article

Ranibizumab or Aflibercept Monotherapies in Treatment-Naive Eyes with Diabetic Macular Edema: A Head-to-Head Comparison in Real-Life Experience

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Abstract

Objectives: To compare the functional and anatomical outcomes of ranibizumab and aflibercept monotherapies given according to a pro re nata (PRN) protocol in treatment-naive eyes with diabetic macular edema (DME) in a real-life clinical setting.

Materials and Methods: The medical charts of treatment-naive patients with center-involved DME retrieved from our institutional database were reviewed in this retrospective cohort study. A total of 512 treatment-naive eyes with DME underwent either ranibizumab (Group I; 308 eyes) or aflibercept (Group II; 204 eyes) monotherapy and 462 patients were included. The primary outcome was visual gain over 12 months.

Results: The mean number of intravitreal injections within the first year was 4.34±1.83 and 4.39±2.12 in Group I and II, respectively (p=0.260). The mean best corrected visual acuity (BCVA) improvement at 12 months was +5.7 and +6.5 ETDRS letters in Group I and II, respectively (p=0.321). However, among eyes with a BCVA score less than 69 ETDRS letters (54% of the study population), visual gain was more prominent in Group II (+15.2 vs. +12.1 ETDRS letters; p<0.001). Statistically significant decreases in central foveal thickness were observed with both ranibizumab and aflibercept monotherapy (p<0.001), with no significant difference between the groups (p=0.148).

Conclusion: No statistically significant difference was found in visual outcomes at 12-month follow-up between ranibizumab and aflibercept monotherapies using a PRN protocol, although there was a tendency toward slightly better functional and anatomic prognosis in the aflibercept arm.

Keywords: Aflibercept, diabetic macular edema, pro re nata protocol, ranibizumab

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Introduction

Diabetic macular edema (DME) is one of the most common complications of diabetes mellitus (DM) and the leading cause of visual deterioration in the working-age population.[1] Approximately 21 million individuals suffer from DME globally, and this number is predicted to increase to 100 million by year 2030.[2] About 7% of all diabetics develop DME, with an exact frequency of 8.9% in patients with type 1 DM and 4.7% in patients with type 2 DM.[1,3] According to a previous study published in 2005, the DME prevalence in Türkiye was found to be 3.4% in all diabetics, 9.7% in type 1 DM, and 2.4% in type 2 DM.[4] Acan et al.[5] performed an optical coherence tomography (OCT)-based screening of diabetics with or without the diagnosis of retinopathy and reported a prevalence of 15.3% for DME among diabetic patients in 2012. DME has a multifactorial pathogenesis including capillary endothelial dysfunction with increased inflammation, cellular hypoxia and related oxidative stress, secretion of inflammatory cytokines secondary to capillary ischemia, and blood-retinal barrier breakdown. However, the most important cause of diabetic maculopathy is vascular endothelial growth factor (VEGF) overexpression.[6,7]

The management of DME has evolved over the years. Before the turn of the century, laser photocoagulation therapy was the standard treatment for DME and proliferative diabetic retinopathy (PDR), but visual improvement could not be sustained over the long term.[8,9] The pursuit of new treatments in response to the increased burden of DME resulted in the introduction of agents to block VEGF, which plays an important role in its pathophysiology. Based on randomized clinical trials that proved the efficacy and safety of intravitreal anti-VEGF agents in macular edema, it is now well accepted that they are superior to laser therapy for the treatment of DME.[10,11,12,13,14,15] Today, the first-line therapy for DME is intravitreal injection of anti-VEGF drugs including bevacizumab, ranibizumab, and aflibercept.[13,14,15] Twenty-four-month results from the Diabetic Retinopathy Clinical Research Network (DRCR.net) indicated that all anti-VEGF agents were effective in improving visual acuity and reducing central foveal thickness (CFT). For the treatment of DME, approximately 7-12 injections within the first year and 3-6 injections in the second year have been recommended for better anatomic and functional outcomes.[11,16,17] However, recent real-life data apart from randomized clinical trials have shown fewer annual numbers for intravitreal shots according to patient comorbidities, and this may cause under-treatment.[18,19] The aim of this study was to present anatomical and functional outcomes at the end of 12-month follow-up in treatment-naive eyes that received intravitreal monotherapy with either ranibizumab or aflibercept for DME as a real-life experience of our tertiary referral center located in Western Türkiye.

Materials and Methods

This retrospective, single-center, observational study included all 565 eligible eyes of 512 treatment-naive patients with DME who received either ranibizumab or aflibercept monotherapy between January 2015 and December 2019 and were followed up at least 12 months. Written informed consent was obtained from all patients about the side effects of the drug and the injection procedure before the administration of intravitreal anti-VEGF injections. The protocol of this study was approved by the institutional ethics committee and complied with the ethical principles stated in the Declaration of Helsinki and local regulations.

Patients older than 18 years of age with a diagnosis of either type 1 or type 2 DM were included in the study. Patients who were previously treated for DME with intravitreal steroid or anti-VEGF injections or grid/focal laser photocoagulation, patients with macular ischemia and other ophthalmic disorders except for refractive errors, patients with a history of any intraocular surgeries other than phacoemulsification as well as those who underwent cataract surgery in the last 12 months were excluded. Another 50 patients were excluded because they missed follow-up visits at least three times in a year. Thus, the study was completed with the remaining 512 eyes of 462 patients. The study population was divided into two groups based on the intravitreal anti-VEGF monotherapy they received. When needed in patients with PDR, salvage laser therapy was performed in a scatter panretinal photocoagulation (PRP) pattern using the Volk transequator contact lens in four sessions at 2-week intervals. We evaluated the anatomical and functional outcomes of 512 eyes at the first year of follow-up.

We recorded demographic data including DM duration, glycated hemoglobin (HbA1c) levels, and other comorbidities for each participant. Results of ophthalmological examinations including best-corrected visual acuity (BCVA) assessments with ETDRS (Early Treatment of Diabetic Retinopathy Study) chart, slit-lamp biomicroscopy, intraocular pressure (IOP) measurements using Goldmann applanation tonometer, dilated fundoscopy with a 90D non-contact lens or indirect binocular ophthalmoscope, and spectral-domain (SD) OCT scans (Spectralis; Heidelberg Engineering, Heidelberg, Germany) performed at baseline and all follow-up visits scheduled at 4-week intervals, as well as findings in fluorescein angiography (FA) performed at baseline and at follow-up visits when needed, were recorded in detail. We diagnosed DME according to clinical examination and confirmed the diagnosis with FA and SD-OCT scans at baseline. All study eyes received intravitreal anti-VEGF monotherapy according to a pro re nata (PRN) protocol after three loading doses. Additional injections were administered in eyes with persistent macular edema or a loss in BCVA of 5 ETDRS letters or more between two consecutive visits, as well as those with CFT greater than 300 µm or more than 10% increase in CFT. All intravitreal anti-VEGF injections were administered in the operating theater using topical anesthesia with 0.5% proparacaine hydrochloride (Alcon Laboratories, Inc., Ft. Worth, TX, USA). Before the injection, 5% povidone iodine was instilled in the lower fornix and left for at least five minutes. After the periocular skin and eyelids were wiped with a 10% povidone iodine solution, a sterile eye speculum was placed. Either 0.5 mg/0.05 mL ranibizumab (Lucentis®, Novartis,

Basel, Switzerland) or 2 mg/0.05 mL aflibercept (Eylea®, Bayer, Leverkusen, Germany) was injected in the superotemporal quadrant at a distance of 3.5 to 4.0 mm from the limbus with 30-gauge needle. After injection, a sterile cotton swab was used to apply pressure to injection site while withdrawing the needle to prevent drug reflux and vitreous prolapse. We applied 5% povidone iodine to the ocular surface after the injection, and the patient was prescribed a topical 0.3% ofloxacin drop (Exocine; Allergan Laboratories, İstanbul, Türkiye) 4 times a day for 4 days.

Statistical Analysis

The data were stored in a computer database and analyzed using SPSS version 22.0 statistical software (IBM Corp, Armonk, NY, USA). The descriptive data of the patients were expressed as mean, standard deviation, or percentage. The normality of data distributions was checked with Kolmogorov-Smirnov analysis, then Wilcoxon rank-sum test, Student's t-test, chi-square test, and Fisher exact test were used as appropriate to compare baseline characteristics between ranibizumab- and aflibercept-treated eyes. To test for differences between the groups and to adjust for age and gender, an analysis of covariance was performed with diagnosis and sex as fixed variables and age as a co-variate. Mean change in BCVA and CFT from baseline was calculated, along with 95% confidence intervals (CIs) and nominal p values, using paired t tests. A probability value of <0.05 was considered statistically significant.

Results

Baseline Findings

Of the total 462 treatment-naive patients with a mean age of 63.7±9.8 years (range, 21-79), 209 (45.2%) were female and 253 (54.8%) were male. The mean duration of DM was 14.1±7.8 years (range, 1-40) and the mean HbA1c concentration was 7.5±1.3% (range, 8.6-6.2%). Group I consisted of 308 eyes (60.2%) of 280 patients who received intravitreal ranibizumab monotherapy, and Group II consisted of 204 eyes (39.8%) of 182 patients who received intravitreal aflibercept monotherapy. Patient compliance, defined as a complete attendance to all scheduled visits, was over 90% in both study arms through month 12. There was no statistically significant difference in age or gender distribution between the groups (p=0.815 and p=0.642, respectively). No statistically significant difference was found in either mean duration of DM or mean HbA1c level between eyes treated with intravitreal ranibizumab and aflibercept monotherapies (p=0.215 and p=0.312, respectively). Similarly, mean duration from DM onset to DME diagnosis did not differ significantly between the treatment groups (p=0.463). Mean BCVA and CFT scores at baseline were 55.7±10.8 ETDRS letters (range, 38-75) and 426.9±160.5 µm (range, 301-823), respectively, in the entire study population. There was no statistical difference in terms of baseline BCVA and CFT scores between the eyes included in the treatment groups (p=0.647 and p=0.586, respectively). Demographics and baseline ophthalmologic findings are summarized in Table 1.

Visual Outcomes at 12 Months

In both treatment arms, visual acuity started to improve at the first post-injection visit scheduled 1 month after the initial intravitreal shot. Statistically significant increases in BCVA were found for both the ranibizumab monotherapy group (+3.1 ETDRS letters; 95% CI: 1.2-5.8) and aflibercept monotherapy group (+3.7 ETDRS letters; 95% CI: 1.4-6.5) when compared to baseline scores (p=0.020 and p=0.010, respectively). Mean BCVA continued to increase steadily in both treatment arms up to the last follow-up visit (p<0.05 at all time points). Although the mean improvement in BCVA at month 12 was higher with aflibercept monotherapy (+6.5 ETDRS letters; 95% CI: 4.1-7.6) than with ranibizumab monotherapy (+5.7 ETDRS letters; 95% CI: 3.4-6.8), this did not reach statistical significance (p=0.321). Figure 1 shows the mean ETDRS letter gains in both treatment groups at all monthly visits within the first year of follow-up.

A subgroup analysis including eyes with an initial BCVA lower than 69 ETDRS letters, which corresponds to <20/50 in Snellen equivalent (54% of the study population), revealed significantly greater visual gains over baseline with aflibercept monotherapy than ranibizumab monotherapy at month 6 (+13.5 vs. +10.6 ETDRS letters, respectively; p=0.023) and month 12 (+15.2 versus +12.1 ETDRS letters, respectively; p<0.001) (Figure 2).

Table 1. Baseline characteristics of patients in each treatment arm

	Ranibizumab arm	Aflibercept arm	Overall
No. of patients	280	182	462
No. of eyes	308	204	512
Age (years), mean (SD)	64.7 (10.4)	63.1 (10.6)	63.8 (10.5)
Female gender, n (%)	124 (46)	85 (44)	209 (45)
Diabetes duration (years), mean (SD)	14.2 (8.1)	13.9 (7.4)	14.1 (7.8)
HbA1c (%), mean (SD)	7.6 (1.3)	7.4 (1.2)	7.5 (1.3)
Diabetes type, n (%) Type 1 Type 2	 32 (12) 236 (88)	 19 (10) 175 (90)	 45 (10) 411 (90)
Diabetic retinopathy grade, n (%) Non-proliferative Proliferative	 276 (90) 32 (10)	 182 (89) 22 (11)	 458 (90) 54 (10)
Salvage PRP laser requirement, n (%)	32 (10)	22 (11)	54 (10)
Baseline BCVA (letters), mean (SD)	54.6 (11.6)	56.8 (9.9)	55.7 (10.8)
Baseline BCVA (letters) ≤69, n (%)	162 (53)	116 (57)	278 (54)
CFT (µm), mean (SD)	431.3 (158.4)	422.6 (162.5)	426.9 (160.5)

BCVA: Best corrected visual acuity, CFT: Central foveal thickness, PRP: Panretinal laser photocoagulation, SD: Standard deviation

Anatomical Outcomes at 12 Months

Comparing with baseline values, statistically significant reduction in CFT was observed for both study groups at all follow-up visits ($p<0.05$ at all time points). Although the decrease in CFT score was more prominent with aflibercept monotherapy than ranibizumab monotherapy, the mean change in CFT did not differ significantly between the two study arms at any follow-up visit ($p>0.05$ at all time points). Figure 3 depicts monthly changes in mean CFT values in both treatment groups within the first year of follow-up.

In the subgroup analysis of eyes with an initial BCVA lower than 69 ETDRS letters, the decrease in mean CFT was 156.4±128.5 µm and 198.7±134.3 µm at month 12 in eyes treated with ranibizumab and aflibercept monotherapies, respectively. Differences in CFT reduction were statistically significant between the two treatment arms at month 8 and each monthly visit thereafter (Figure 4).

Treatments and Visits During 12-Month Follow-up

The mean number of intravitreal injections and follow-up visits in eyes that completed the 12-month follow-up were 4.34±1.83 injections (range, 3-8) and 6.8±2.1 visits (range, 5-12) for the ranibizumab arm, versus 4.39±2.12 injections (range, 3-8) and 6.7±1.9 visits (range, 5-11) for the aflibercept arm ($p=0.260$ and $p=0.160$, respectively). During follow-up, 44 eyes of 42 patients with PDR underwent salvage laser therapy with PRP completed in four sessions. No statistically significant difference was found in the need for salvage laser therapy between the treatment groups ($p=0.124$).

Noncompletion Rate at Month 12

A total of 53 eyes (9.3%) of 50 patients missed more than two follow-up visits within the first year. The noncompletion rate was lower in the ranibizumab group (29 eyes, 9.4%) than the aflibercept group (24 eyes, 11.8%), but the difference did not reach statistical significance ($p=0.560$). The mean time of the first missed follow-up visit was 136.2±16.4 days (range, 65-202 days) and 128.5±11.7 (range, 62-196 days) days in the ranibizumab and aflibercept groups, respectively.

Systemic and Ocular Adverse Events

The rate of serious adverse events was similar between both treatment groups at the end of 12-month follow-up ($p=0.460$). Thromboembolic problems including cardiac and cerebrovascular events were seen in 1 (0.36%) of the eyes that received ranibizumab monotherapy, and 1 (0.55%) that received aflibercept monotherapy ($p=0.840$). Infectious endophthalmitis

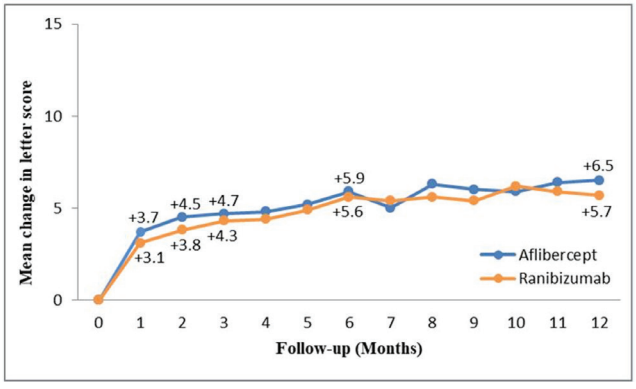

Figure 1. Mean change in visual acuity in ETDRS letter scores from baseline through month 12 in each treatment arm
ETDRS: Early Treatment Diabetic Retinopathy Study

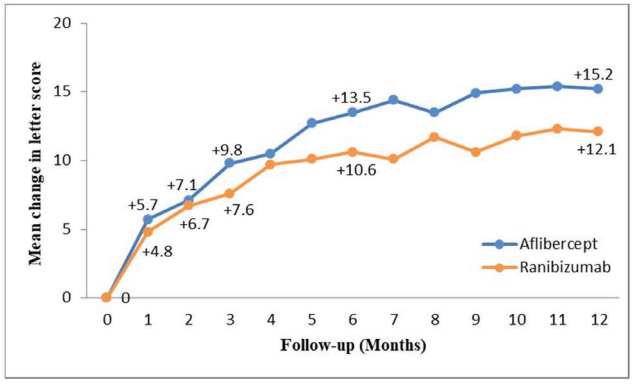

Figure 2. Mean change in visual acuity letter scores from baseline through month 12 in each treatment arm in eyes with initial best corrected visual acuity lower than 69 ETDRS letters
ETDRS: Early Treatment Diabetic Retinopathy Study

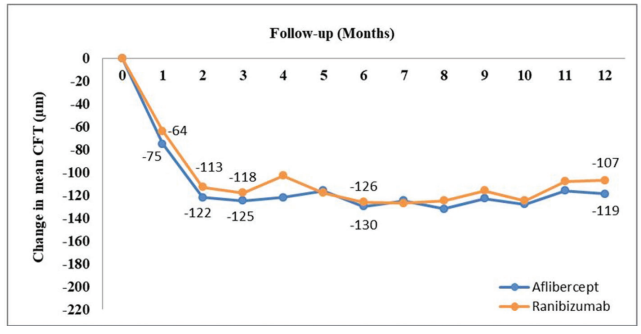

Figure 3. Mean change in central foveal thickness (CFT) over 12 months in each treatment arm

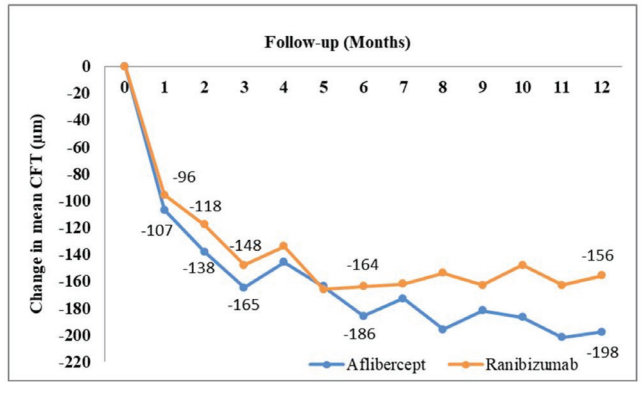

Figure 4. Mean change in CFT across 12 months in each treatment arm in eyes with initial best corrected visual acuity lower than 69 ETDRS letters
CFT: Central foveal thickness, ETDRS: Early Treatment Diabetic Retinopathy Study

occurred only in one eye, which received intravitreal ranibizumab injection, and noninfectious inflammation occurred in one eye treated with aflibercept monotherapy. Treatment-related retinal detachment or vitreous hemorrhage were not detected in either study arm. During 12 months of follow-up, IOP elevation of 5 mmHg or more over baseline was seen in 22 (7.1%) of the 308 eyes treated with intravitreal ranibizumab monotherapy and 14 (6.9%) of the 204 eyes that received intravitreal aflibercept monotherapy, but none required filtration surgery.

Discussion

Various randomized controlled clinical studies have reported improved functional prognosis with good anatomic prognosis after intravitreal anti-VEGF therapy in eyes with DME.[16,20,21,22] However, recent real-life data apart from randomized clinical trials has also shown favorable visual and anatomic outcomes with fewer intravitreal injections annually.[15,21,23,24,25,26] In the real-life OCEAN study including treatment-naive eyes with DME, the authors reported a mean visual acuity gain of +4.1 ETDRS letters with a mean of 4.5 intravitreal ranibizumab injections in the first year of follow-up.[26] Another real-life experience of eyes with DME revealed a mean BCVA improvement of +7.8 ETDRS letters at month 12 with a mean of 7.6 intravitreal aflibercept injections.[15] In this study, we present a head-to-head comparison of ranibizumab and aflibercept monotherapies in a cohort of treatment-naive eyes with DME. Based on the real-life experience in our tertiary referral center, eyes in the ranibizumab and aflibercept treatment groups received similar numbers of intravitreal injections (4.34 vs. 4.39, respectively) within 12-month follow-up, and both provided successful functional and anatomic outcomes in patients with DME. Similar functional outcomes were observed at 12-month follow-up with ranibizumab and aflibercept monotherapies (visual gain of +5.7 vs. +6.5 ETDRS letters, respectively). However, subgroup analysis of eyes with poorer baseline visual acuity revealed statistically significant superiority of aflibercept over ranibizumab (+15.2 vs. +12.1 ETDRS letters, respectively) at the end of the first year of treatment.

Our results support a Cochrane meta-analysis showing that treatment with aflibercept conferred some advantages in visual and anatomic outcomes over ranibizumab in patients with DME at 1-year follow-up.[18] Based on the Protocol T cohort, DRCR.net also reported slightly superior visual outcomes in the aflibercept arm compared with the ranibizumab arm in eyes with DME at the end of their first year of follow-up (+13.3 vs. +11.2 ETDRS letters, respectively).[16] Additionally, among study eyes with initial visual acuity lower than 69 ETDRS letters (Snellen equivalent of 20/50 or worse), statistically better visual prognosis at month 12 was reported in eyes treated with aflibercept injections compared to those treated with ranibizumab (+18.9 vs. +14.2 ETDRS letters, respectively).[16] According to the evaluation of entire study populations, visual acuity gains differed by approximately 1 ETDRS line between the DRCR.net Protocol T study and our real-life results. However, our 1-year visual outcomes were similar to those in the DRCR.net Protocol T study for eyes with initial BCVA less than 69 ETDRS letters.

Major randomized controlled clinical trials and real-life experience studies have reported significant CFT reductions with both ranibizumab and aflibercept monotherapies in eyes with DME.[15,16,18,20,21,23,27] Although the intravitreal administration of both drugs has similar effects on CFT, Bhandari et al.[23] and the 1-year results of the Protocol T study[16] demonstrated better anatomic outcomes (mean CFT reduction) with aflibercept than ranibizumab. Consistent with the literature, we also found that aflibercept provided significantly greater CFT reduction among eyes with a baseline BCVA less than 69 ETDRS letters after month 8 of follow-up.

A higher number of intravitreal injections necessitates more frequent follow-up visits and extra medical costs, both of which decrease patient comfort. Recent studies have reported that approximately 20% of DME patients were noncompliant to routine outpatient visits and treatment with intravitreal anti-VEGF injections after the first year of follow-up.[19,23,24,25,26,28] Contributing factors to poor compliance may differ according to disease and between communities. Patient compliance defined as complete attendance to all scheduled visits was 92.2% in the ranibizumab arm and 90.2% in the aflibercept arm of our study. We observed that patients first missed scheduled visits after month 4 of follow-up. Possible reasons for noncompliance include comorbidities, patient age, the high visit burden due to the need for frequent diabetes monitoring in patients with DME or PDR, and also the associated extra medical costs.[19,29] Holekamp et al.[30] suggested that patients would lose motivation to attend scheduled follow-up visits when faced with problems related to health insurance reimbursement and personal finances. Therefore, previously published real-life studies have demonstrated that real-world settings do not always permit continued and intensive treatment protocols like those defined in randomized controlled clinical trials. In contrast to many randomized clinical studies, several real-life clinical studies have reported smaller annual intravitreal injection numbers, as physicians often prefer a flexible dosing regimen instead of a fixed dosing regimen.

Study Limitations

The limitations of this study are its retrospective nature, the lack of randomization, being single-centered, and having a follow-up period limited to 12 months. We compared only ranibizumab and aflibercept treatment, which have a large quantity of patient data. Furthermore, we did not divide the patients according to the severity and stage of nonproliferative diabetic retinopathy. Unlike in randomized clinical trials, treatment decisions in routine clinical practice are made based on clinical experience with the different treatment regimens clinicians use for patients with DME. The strength of our study is that we reported a real-life experience in a large cohort from a single center, which allows us to make a head-to-head comparison of ranibizumab and aflibercept monotherapies in treatment-naive eyes with DME.

Conclusion

Our real-life experience revealed the effectiveness and safety of both ranibizumab and aflibercept monotherapies performed using a PRN protocol in the treatment of DME, despite fewer intravitreal administrations per year than recommended in randomized controlled clinical trials. Head-to-head comparison of ranibizumab and aflibercept in the present study indicated a tendency for better functional and anatomic prognosis at month 12 in DME treated with aflibercept monotherapy. Intravitreal aflibercept treatment showed significant superiority over ranibizumab monotherapy in eyes with lower initial visual acuity.

Ethics

Ethics Committee Approval: The protocol of this study was approved by the institutional ethics committee and complied with the ethical principles stated in the Declaration of Helsinki and local regulations.

Peer-review: Externally peer reviewed.

Authorship Contributions

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

Conflict of Interest: No conflict of interest was declared by the authors.

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