Original Article

Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Diabetic Macular Edema in Türkiye: 48-Month Data, BOSPHORUS-DME Study Group Report No. 1

Ece Özal[1], Abdullah Özkaya[2], Murat Arıcı[3], Anıl Korkmaz[3], Serhat Ermiş[1], Şerife Çiloğlu Hayat[1], Murat Karapapak[1], Sadık Altan Özal[1], Akın Çakır[4], Gamze Karataş[4], Dilan Yıldız[4], Mehmet Erdoğan[5], İbrahim Koçak[5], Nihat Sayın[5], Veysel Levent Karabaş[6], Ecem Önder Tokuç[6], Semra Tiryaki Demir[7], Mehmet Egemen Karataş[7], Turgay Uçak[7], Mine Öztürk[8], Bengi Demirayak[9], İsmail Umut Onur[10], Mustafa Hepokur[11]

[1]University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[2]Memorial Şişli Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, Beyoğlu Eye Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[4]University of Health Sciences Türkiye, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[5]University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[6]Kocaeli University Faculty of Medicine, Department of Ophthalmology, Kocaeli, Türkiye
[7]University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[8]University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[9]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[10]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Ophthalmology, Tekirdağ, Türkiye
[11]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Ophthalmology, İstanbul, Türkiye

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Address for Correspondence: Ece Özal, University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
E-mail: ecemansuroglu@hotmail.com
ORCID-ID: orcid.org/0000-0002-4251-9308
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Abstract

Objectives: This study aimed to evaluate the 48-month visual and anatomical outcomes, as well as the number of clinic visits and intravitreal injections, in patients treated with three consecutive loading doses of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy for diabetic macular edema (DME) under real-world conditions in Türkiye.

Materials and Methods: In this retrospective, multicenter study conducted by the BOSPHORUS-DME Study Group, the medical records of 2,424 eyes of 1,696 patients who experienced vision loss due to DME and were treated with intravitreal anti-VEGF injections between January 2019 and January 2023 were reviewed. The study was carried out across eight tertiary referral hospitals located on the European side of İstanbul and in the province of Kocaeli. Seven cohort groups were created based on follow-up at baseline and months 3, 6, 12, 18, 24, 36, and 48. Best-corrected visual acuity (BCVA), central macular thickness (CMT), the number of clinic visits and injections, and the rates of anti-VEGF or dexamethasone switching were analyzed.

Results: The study included a total of 2,424 eyes of 1,696 patients (mean age: 60.6±10.0 years; 46.4% female). The mean baseline BCVA and CMT were 0.34±0.24 (decimal) and 400±134 μm, respectively. At month 48, these values improved to 0.49±0.29 ($p<0.0001$) and 324±115 μm ($p<0.0001$). The mean cumulative number of injections at years 1,

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Abstract

2, 3, and 4 were 6.5, 9.6, 12.2, and 15.7, respectively. A switch in anti-VEGF therapy occurred between month 3 and 6 in 43.5% of eyes, mostly due to mandatory transition to on-label agents.

Conclusion: This is the largest and longest real-world study on DME treatment conducted in Türkiye. It demonstrates that visual and anatomical gains can be sustained over a 48-month period. While the overall trend aligns with previous real-world studies, the higher injection frequency in our cohort appears to have contributed to more favorable outcomes. These findings underscore the importance of early intensive therapy and sustained treatment adherence in the real-world management of DME.

Keywords: Aflibercept, anti-VEGF, bevacizumab, diabetic macular edema, intravitreal injection, long-term outcomes, ranibizumab, real-world evidence

Introduction

Diabetic macular edema (DME) is a vision-threatening complication of diabetes and remains one of the leading causes of preventable blindness in the working-age population.[1] The efficacy and safety of anti-vascular endothelial growth factor (anti-VEGF) agents in the treatment of DME have been well established through randomized controlled trials (RCTs),[2,3] and these agents are recommended as first-line therapy in clinical guidelines.[4] The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T study compared the efficacy of intravitreal ranibizumab (Lucentis®, Novartis, Genentech, South San Francisco, CA, USA), aflibercept (Eylea®, Regeneron Pharmaceuticals, Tarrytown, NY, USA), and bevacizumab (Avastin®, Genentech, Roche Group, South San Francisco, CA, USA) for the treatment of DME. When administered according to a structured protocol, all three agents demonstrated comparable visual gains at two years (+12.3, +12.8, and +10.0 ETDRS letters for ranibizumab, aflibercept, and bevacizumab, respectively).[5] However, a five-year extension of the study showed that when patients transitioned to physician-discretion-based treatment in routine clinical practice, best-corrected visual acuity (BCVA) declined between years two and five despite ongoing care.[6]

In recent years, real-world studies derived from diverse clinical settings have gained increasing significance, particularly for chronic diseases like DME that require individualized treatment approaches.[7] However, outcomes in real-world studies often fall short of RCT results due to undertreatment, infrequent monitoring, and suboptimal patient adherence.[8,9,10]

Durukan et al.[11] reported the first large-scale real-world study on DME treatment conducted in the Central Anatolia region of Türkiye, demonstrating lower injection frequencies and modest visual improvements consistent with previous real-world findings. Similarly, Yayla et al.[12] conducted the MARMASIA Study across eight tertiary referral centers on the Asian side of the Marmara region and reported comparable outcomes. Although both studies provided valuable data, they reflected treatment practices prior to 2018 and included follow-up results of up to 36 months.

Building on this foundation, we initiated a multicenter study across eight tertiary referral centers located on the European side of Istanbul and in the Kocaeli province of Türkiye to comprehensively evaluate the real-world outcomes of intravitreal anti-VEGF therapy for DME. The BOSPHORUS-DME study represents the post-2018 treatment era following the reimbursement policy implemented by the Turkish Social Security Institution, which mandated three consecutive loading doses of bevacizumab as the initial therapy and expanded access to on-label anti-VEGF agents.[13] With follow-up data extending up to 48 months, this large and contemporary multicenter cohort provides the most comprehensive assessment to date of visual and anatomical outcomes, injection burden, and patient adherence under real-world clinical conditions in Türkiye. Given the absence of a centralized national ophthalmology database, such multicenter collaborations are crucial for generating reliable real-world data that accurately reflect nationwide clinical practices and long-term treatment outcomes.

Materials and Methods

Study Design

This retrospective, observational, multicenter study included patients with DME who received three consecutive monthly intravitreal anti-VEGF injections between January 2019 and January 2023, with at least three months of follow-up. The BOSPHORUS-DME Study Group comprised 23 retina specialists from eight tertiary centers on the European side of Istanbul and in Kocaeli, Türkiye. Ethics approval was obtained from Kocaeli University Faculty of Medicine Ethics Committee (decision no: KÜ GOKAEK-2025/06/18; date: 13.03.2025; project: 2025/115). The study adhered to the Declaration of Helsinki, and written informed consent was obtained from all participants.

Study Population

The medical records of patients diagnosed with DME, either treatment-naïve or previously treated with intravitreal anti-VEGF injections, were retrospectively reviewed. Patients who had not received any intravitreal injections for DME within the six months prior to inclusion were considered treatment-naïve.

Following the reimbursement regulation issued by the Turkish Social Security Institution on December 28, 2018 (published in the Official Gazette), patients initiating anti-VEGF therapy for DME were required to receive three consecutive intravitreal bevacizumab (IVB) injections as a prerequisite for reimbursement.[13] According to this regulation, alternative anti-VEGF agents (ranibizumab or aflibercept) were permitted only in cases demonstrating non-response or resistance to IVB. Therefore, eyes that had begun treatment prior to this regulation were excluded from the study.

In treatment-naïve eyes, three consecutive monthly IVB (1.25 mg/0.05 mL) injections were administered as the initial loading phase, followed by a pro re nata (PRN) treatment regimen based on anatomical and functional response. In eyes that had received three loading doses of IVB at other centers within the preceding six months, an additional loading phase was performed at the discretion of the treating physician, consisting of three consecutive monthly injections of either IVB or an on-label anti-VEGF agent (ranibizumab 0.5 mg/0.05 mL or aflibercept 2 mg/0.05 mL). Following completion of this loading phase, patients transitioned to PRN therapy and continued to receive additional anti-VEGF injections or adjunctive treatments as clinically indicated throughout the follow-up period. Thus, all eyes included in the study completed a full loading course of three consecutive injections before entering the PRN phase at our centers.

The inclusion criteria were as follows: (1) age ≥18 years, (2) receiving three consecutive loading doses of intravitreal anti-VEGF injections as the initial treatment for DME, and (3) having a minimum follow-up period of three months after the injections. Patients with a history of vitreoretinal surgery or secondary macular edema resulting from other retinal or systemic diseases were excluded from the study. No restrictions were imposed regarding additional procedures performed during follow-up, which could include phacoemulsification, pars plana vitrectomy, panretinal, focal, or grid laser photocoagulation, micropulse laser treatment, or intravitreal dexamethasone implant (IDI; Ozurdex®, AbbVie-Allergan, CA, USA) administration. In cases where both eyes met the inclusion criteria, each eye was analyzed separately.

Data Collection

Medical data were retrospectively collected at baseline and during each follow-up visit up to month 48. Baseline demographic and clinical characteristics included age, sex, stage of diabetic retinopathy (non-proliferative [NPDR] or proliferative [PDR]), and, when applicable, details of intravitreal injections administered within the preceding six months, including the type of agent and the number of injections.

The patients' eyes were divided into seven cohorts according to follow-up duration. Follow-up data were extracted from examinations conducted at months 3, 6, 12, 18, 24, 36, and 48, allowing for a ±2-week window. Because patients with longer follow-up durations also contributed to earlier time points, the cohorts were not independent.

All patients underwent a comprehensive ophthalmologic examination at baseline and during each follow-up visit. The examinations included BCVA assessment using a Snellen chart, intraocular pressure (IOP) measurement with Goldmann applanation tonometry, anterior segment evaluation with slit-lamp biomicroscopy, dilated fundus examination, and optical coherence tomography (OCT) imaging. OCT scans were obtained using one of the following devices, depending on the center: Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany), Cirrus OCT (Zeiss, Dublin, CA, USA), RTVue-100 OCT (Optovue Inc., Fremont, CA, USA), DRI OCT Triton Plus swept-source OCT (Topcon Inc., Tokyo, Japan), or Xephilio WF-OCT S1 (Canon Inc., Tokyo, Japan).

At each visit, BCVA, lens status (phakic or pseudophakic), and OCT parameters were recorded, along with the type of intravitreal agent administered, cumulative number of injections and visits, and the presence of ocular adverse events associated with injection therapy or other procedure-related complications.

All OCT images were centered on the foveola, and central macular thickness (CMT, μm) was automatically calculated using the software of each device. OCT features were classified according to the criteria of the European School for Advanced Studies in Ophthalmology, as follows:[14]

1. Cystic changes: absent (0), mild (1), moderate (2), severe (3);
2. Subretinal fluid: absent (0), present (1);
3. Disorganization of retinal inner layers (DRIL): absent (0), present (1);
4. Integrity of the ellipsoid zone (EZ) and external limiting membrane: intact (0), disrupted (1), absent (2);
5. Hyperreflective foci: <30 (0), ≥30 (1);

6. Vitreoretinal interface: no pathology (0), incomplete posterior vitreous detachment (PVD) (1), complete PVD (2), vitreomacular traction (3), or epiretinal membrane (4);
7. Cyst content: hyporeflective or hyperreflective;
8. Subfoveal hard exudates: present or absent;
9. Foveal depression: present or absent.

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 for Windows (IBM Corp., Armonk, NY, USA). Data distribution was assessed using histogram plots, Shapiro-Wilk, and Kolmogorov-Smirnov tests. Continuous variables were expressed as mean ± standard deviation or median (interquartile range [IQR]: Q1-Q3), while categorical variables were presented as counts (n) and percentages (%). Snellen BCVA values were converted to logarithm of the minimum angle of resolution for statistical analyses.

Depending on data distribution and variable count, dependent variables were analyzed using paired samples t-test or repeated measures analysis of variance (ANOVA), and Wilcoxon signed-rank test or Friedman test. For comparisons involving more than two time points, post-hoc analyses were conducted using Dunn–Bonferroni or SPSS-provided pairwise comparisons for ANOVA and Friedman test, respectively. Bonferroni-adjusted p values are reported as "adj. p" where applicable. Since patients with longer follow-up contributed to multiple cohorts, appropriate dependent tests were used. A two-sided p value <0.05 was considered statistically significant.

Results

Baseline Characteristics

This study included 2,424 eyes of 1,696 patients (mean age: 60.6±10.0 years; range: 19-93), of whom 787 (46.4%) were female. All eyes with at least three months of follow-up were included in the 3-month cohort. As follow-up duration increased, the number of eyes declined across the 6-, 12-, 18-, 24-, 36-, and 48-month cohorts, with 1,878, 1,321, 697, 427, 204, and 86 included, respectively. Cohort-specific baseline characteristics are summarized in Table 1.

Among all eyes, 2,190 (90.3%) were treatment-naïve and 234 (9.7%) had previously received anti-VEGF therapy. All eyes were treated with a PRN regimen following three consecutive monthly loading injections. The mean duration to complete the loading phase was 66±9.5 days (range, 47-90 days). Bevacizumab was the most commonly used initial agent (93.3%), followed by ranibizumab (3.9%) and aflibercept (2.8%). Eyes treated with ranibizumab or aflibercept had received three consecutive bevacizumab injections at other centers within the previous six months.

Most patients (69.9%) had NPDR at baseline. Detailed clinical characteristics per cohort are provided in Table 2, and OCT findings in Table 3. The most frequent cystic pattern was hyporeflective cysts (71.2%), followed by hyperreflective cysts (28.1%). In 0.7% of eyes with cysts, their content could not be assessed. Foveal depression was present in 50.7% and subfoveal hard exudates in 31.5% of the eyes. In addition to these anatomical characteristics, changes in lens status were also observed during follow-up. A total of 262 eyes underwent cataract surgery and were subsequently recorded as pseudophakic.

Functional and Anatomical Results

In the study sample, the mean baseline BCVA (Snellen, decimal) was 0.34±0.24, and the mean CMT was 400±134 µm. BCVA showed gradual, statistically significant improvement at all follow-up points ($p<0.0001$), reaching 0.37±0.25, 0.41±0.26, 0.44±0.27, 0.46±0.28, 0.48±0.28, 0.49±0.29, and 0.49±0.29 at months 3, 6, 12, 18, 24, 36, and 48, respectively. Although modest, these functional gains were largely sustained over time, despite potential undertreatment and compliance issues in routine practice.

CMT also declined consistently to 354±120, 334±112, 324±110, 327±112, 333±137, 324±120, and 324±115 µm at the same respective time points. Despite minor increases at months 18 and 24, all reductions from baseline were significant ($p<0.0001$). These results support the sustained anatomical benefits of anti-VEGF therapy in real-world settings, even with variability in retreatment and monitoring.

Changes in BCVA and CMT over time are illustrated in Figures 1 and 2, respectively.

Number of Visits and Intravitreal Anti-VEGF Injections

The cumulative numbers of intravitreal injections and clinical visits were assessed annually. The average number of visits in years 1 through 4 was 7.5±2.9, 11.2±3.7, 14.7±5.1, and 17.6±5.6, respectively; the corresponding mean number of injections was 6.5±1.7, 9.6±2.8, 12.2±3.9, and 15.7±5.5. Although both visit and injection counts increased over time, the rate of injections slowed notably after the first year. These findings suggest a tendency for reduced adherence to treatment intensity and monitoring over extended follow-up in real-world settings. Detailed data are provided in Table 4.

Anti-VEGF Switch

Between months 3 and 6 of follow-up (i.e., following the initial loading phase), anti-VEGF switching was performed in 813 eyes (43.5%). Among these, 68.1% were switched to an on-label agent, while 31.9% were switched due to poor response. Both the choice of agent and timing of the switch were determined at the discretion of the treating physician. The distribution of switching in the subsequent follow-up intervals was as follows: 255 eyes (19.3%) in months 6-12, 94 eyes (13.6%) in months 12-18, 49 eyes (11.3%) in months 18-24, 17 eyes (7.8%) in months 24-36, and 14 eyes (15.5%) in months 36-48. Detailed information on switch timing and rationale is presented in Table 5.

In selected cases, combination therapy with IDI or a switch to IDI monotherapy was implemented based on the treating physician's clinical assessment. The monthly distribution of IDI usage throughout the follow-up period is summarized in Table 6.

Adverse Events

During the 48-month follow-up period, recorded ocular adverse events included vitreous hemorrhage and elevated IOP. No ocular complications were reported beyond month 36. Importantly, no cases of retinal tear, retinal detachment, or endophthalmitis occurred at any time. The monthly distribution of observed adverse events is summarized in Table 7.

Discussion

This large-scale, multicenter, real-world study presents a comprehensive evaluation of intravitreal anti-VEGF therapy for DME in tertiary centers across the European side of İstanbul and the Kocaeli province of Türkiye. Our findings confirm that anti-VEGF agents are effective in improving visual acuity and reducing CMT. Mean visual acuity increased from 0.34±0.24 Snellen at baseline to 0.49±0.29 at month 48, while mean CMT decreased from 400±134 µm to 324±115 µm over the same period. However, as observed in other real-world studies, visual gains plateaued after the second year, likely due to undertreatment, disease chronicity, and patient adherence issues.[15,16] Treatment patterns varied considerably. Between months 3 and 6, 43.5% of eyes required a switch from the initial anti-VEGF agent, mostly due to a transition to on-label drugs (68.1%).

Table 1. Baseline characteristics of the patients and eyes in each cohort

	Baseline	3-month cohort (whole group)	6-month cohort	12-month cohort	18-month cohort	24-month cohort	36-month cohort	48-month cohort
Eyes, n	2424	2424	1878	1321	697	427	204	86
Age, years, mean ± SD	60.6±10.0	60.6±10.0	60.8±9.9	60.6±10.0	60.2±10.2	59.4±10.7	59.1±10.6	58.4±11.2
Sex, n of patients (%)								
Female	787 (46.4)	787 (46.4)	650 (47.3)	435 (44.2)	225 (42.8)	140 (44)	58 (43.4)	24 (40.0)
Male	909 (53.6)	909 (53.6)	728 (52.7)	549 (55.8)	300 (57.2)	178 (56)	89 (56.6)	36 (60.0)
BCVA, decimal, mean ± SD (range)	0.34±0.24 (0.01-1.0)	0.37±0.25 (0.01-1.0)	0.41±0.26 (0.01-1.0)	0.44±0.27 (0.01-1.0)	0.46±0.28 (0.01-1.0)	0.48±0.28 (0.01-1.0)	0.49±0.29 (0.01-1.0)	0.49±0.29 (0.01-1.0)
CMT, µm, mean ± SD	400±134	354±120	334±112	324±110	327±112	333±137	324±120	324±115

SD: Standard deviation, BCVA: Best corrected visual acuity, CMT: Central macular thickness

Table 2. Baseline clinical characteristics of all patients and eyes

Previous treatment status, n (%)	Treatment-naive	2190 (90.3)
	Previously treated	234 (9.7)
Baseline lens status, n (%)	Phakic	1883 (77.7)
	Pseudophakic	541 (22.3)
Baseline IOP, mmHg, mean ± SD (range)		15.9±3.4 (5-50)
Diabetic retinopathy stage, n (%)	NPDR	1694 (69.9)
	PDR	730 (30.1)
Initial treatment, n (%)	Bevacizumab	2261 (93.3)
	Ranibizumab	95 (3.9)
	Aflibercept	68 (2.8)

IOP: Intraocular pressure. SD: Standard deviation. NPDR: Non-proliferative diabetic retinopathy. PDR: Proliferative diabetic retinopathy

Table 3. Baseline OCT parameters of all patients and eyes		
Cysts, n (%)	Absent (0)	117 (4.7)
	Mild (1)	829 (34.2)
	Moderate (2)	787 (32.5)
	Severe (3)	691 (28.5)
Subretinal fluid, n (%)	Absent (0)	1794 (74.0)
	Present (1)	630 (26.0)
DRIL, n (%)	Absent (0)	1890 (78.0)
	Present (1)	442 (18.2)
	Not evaluated	92 (3.8)
Hyperreflective foci, n (%)	Less than 30 in number (0)	1166 (48.1)
	More than 30 in number (1)	1258 (51.9)
EZ and/or ELM status, n (%)	Intact (0)	1890 (78)
	Disrupted (1)	440 (18.2)
	Absent (2)	62 (2.6)
	Not evaluated	32 (1.3)
Vitreomacular interface disorders, n (%)	No (0)	1493 (61.5)
	Incomplete PVD (1)	403 (16.9)
	Complete PVD (2)	114 (4.7)
	VMT (3)	46 (1.9)
	ERM (4)	368 (15.1)

OCT: Optical coherence tomography. DRIL: Disorganization of the inner retinal layers. EZ: Ellipsoid zone. ELM: External limiting membrane. PVD: Posterior vitreous detachment. VMT: Vitreomacular traction. ERM: Epiretinal membrane

While 31.9% of eyes were switched due to poor response during this period, this rate climbed rapidly, reaching 75% in months 6–12 and 100% after month 24. Additionally, 18.8% of eyes received IDI within the first 6 months, and the cumulative requirement increased to 38.7% by month 48, indicating the need for alternative therapeutic strategies in refractory cases. Bevacizumab was initially administered in 93.3% of eyes, reflecting national reimbursement policies and highlighting the influence of healthcare regulations on clinical decision-making. Adverse events were rare: IOP elevation occurred in 0.4% and vitreous hemorrhage in 0.2% of eyes during the first 3 months, with no such events reported after month 36. Importantly, no cases of endophthalmitis or retinal detachment were detected throughout the study, reaffirming the overall safety of intravitreal therapy.

Intravitreal anti-VEGF injection is widely recognized as the first-line therapy for center-involved DME in most clinical settings.[4] However, in real-world practice, treatment regimens often diverge significantly from those employed in RCTs due to factors such as restricted access to healthcare, the presence of multiple comorbidities, and poor adherence, particularly among elderly patients. Consequently, patients

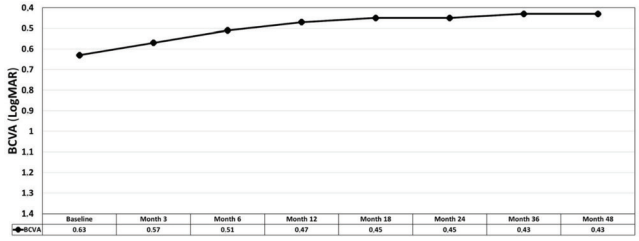

Figure 1. Mean best corrected visual acuity (BCVA) in logMAR over the 48-month follow-up period. Visual acuity improved from a baseline value of 0.63 to 0.43 at both months 36 and 48. All post-treatment time points demonstrated statistically significant improvements compared to baseline (all p<0.0001)
logMAR: Logarithm of the minimum angle of resolution

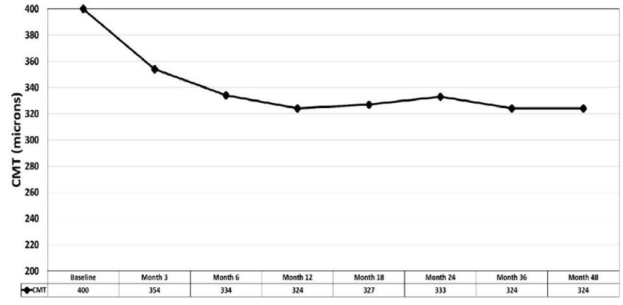

Figure 2. Mean central macular thickness (CMT) over the 48-month follow-up period. CMT decreased from a baseline value of 400 µm to 324 µm at month 48, with the most substantial reduction observed during the initial 6 months of treatment. Although a slight increase was noted at months 18 and 24, the overall reduction in CMT remained statistically significant at all follow-up visits compared to baseline (all p<0.0001)

tend to receive fewer injections and attend fewer follow-up visits than required by the more intensive regimens used in controlled studies. Previous studies have reported a wide range of visual outcomes with anti-VEGF therapy, largely influenced by follow-up duration and injection frequency. Over two years, visual gains of +3.36 letters with 12.4 to 13.1 injections, +3.0 letters with 8.6 injections, and +2.7 letters with 9.1 injections have been documented.[17,18,19] In shorter-term studies, outcomes included gains of +6.6 letters with 6.6 injections in one year and +4.3 to +4.9 letters with 2.6 to 3.8 injections over six months.[20,21] Conversely, in longer follow-up, a four-year study reported a mean gain of +6.6 letters with 7.7 injections.[22] These findings emphasize the heterogeneity of treatment outcomes across studies and underscore the importance of individualized treatment strategies in daily practice. In our study, mean BCVA improved from 0.34±0.24 at baseline to 0.49±0.29 Snellen at month 48, with patients receiving a mean of 15.7 injections during the entire follow-up

Table 4. Visit and intravitreal injection counts				
	12-month cohort (n=1321)	**24-month cohort (n=427)**	**36-month cohort (n=204)**	**48-month cohort (n=86)**
Number of visits, cumulative mean ± SD (range)	7.5±2.9 (2-12)	11.2±3.7 (3-25)	14.7±5.1 (6-35)	17.6±5.6 (7-31)
Number of injections, cumulative mean ± SD (range)	6.5±1.7 (3-12)	9.6±2.8 (3-20)	12.2±3.9 (3-27)	15.7±5.5 (3-36)
SD: Standard deviation				

Table 5. Intravitreal switch rates and reasons			
Time period (months)	**Total eyes switched, n (%)***	**Switched to an on-label agent, n (%)****	**Switched due to poor response, n (%)****
3-6	813 (43.5)	554 (68.1)	259 (31.9)
6-12	255 (19.3)	64 (25.0)	191 (75.0)
12-18	94 (13.6)	14 (13.8)	80 (85.2)
18-24	49 (11.3)	2 (4.0)	47 (96.0)
24-36	17 (7.8)	0 (0.0)	17 (100.0)
36-48	14 (15.5)	0 (0.0)	14 (100.0)
*Total number and percentage of eyes that underwent agent exchange among the eyes being followed within the specified time period; **Percentage of total eyes switched during the time period			

Table 6. Requirement and/or addition of dexamethasone implant	
Time period (months)	**DEX implant requirement/addition, n (%)***
Baseline-6	352 (18.8)
6-12	331 (24.9)
12-18	171 (24.5)
18-24	87 (20.9)
24-36	57 (26.1)
36-48	36 (38.7)
*Cumulative number and percentage of eyes that received a DEX implant during the specified follow-up interval	

Table 7. Ocular adverse effects		
Time period (months)	**VH, n (%)***	**Increase in IOP, n (%)***
Baseline-3	5 (0.2)	12 (0.4)
3-6	3 (0.1)	9 (0.5)
6-12	8 (0.4)	15 (0.7)
12-18	3 (0.1)	4 (0.1)
18-24	1 (<0.1)	4 (<0.1)
24-36	2 (<0.1)	3 (<0.1)
36-48	-	-
*Percentages are based on all eyes at baseline (n=2424). as adverse events could occur at any point during follow-up and might persist or recur across multiple follow-up intervals. Values are not cohort-specific VH: Vitreous hemorrhage. IOP: Intraocular pressure		

period. Notably, the average number of injections in the first year was 6.5, which is higher than those reported in previous large-scale real-world studies from Türkiye. Durukan et al.[11] reported a mean of 4.6 injections, while the MARMASIA Study Group[12] reported a median of 5 injections (IQR: 4-6) (Table 8). This relatively higher treatment intensity in our cohort likely contributed to the favorable early functional and anatomical outcomes. Furthermore, the injection frequency in our cohort surpassed that of international real-world studies, including the German OCEAN study[23] (mean of 4.4 injections) and IRIS Registry data from the United States (approximately 5 injections).[24] These findings highlight the importance of strict adherence to the initial loading phase and regular retreatment to sustain visual and anatomical gains under routine clinical conditions. Nevertheless, as in other real-world reports, the cumulative injection numbers in our study remained considerably lower than those in RCTs, where patients typically received 7-12 injections in the first year and over 20 across two years. In comparison, a recent four-year study by Epstein and Amrén[22] reported declining injection numbers, with patients receiving 4.7, 1.4, 0.7, and 0.9 injections in years 1 through 4, respectively. This treatment gap may stem from the burden of frequent healthcare visits required for DME management, resulting in missed appointments and delayed care. In our cohort, the average number of visits was 7.5, 11.2, 14.7, and 17.6 at

months 12, 24, 36, and 48, respectively, substantially fewer than those observed in tightly controlled clinical trials.[2,25]

The suboptimal treatment adherence observed in our study may be explained by several real-world barriers, such as the need for bilateral injections, limited patient awareness about the importance of intensive therapy, scheduling conflicts, and comorbidities that hinder regular hospital visits. The mean number of injections per patient over 48 months was 15.7, reflecting the difficulty of sustaining long-term, intensive treatment outside of clinical trial conditions. In our cohort, 43.5% of eyes required a switch in anti-VEGF agent between months 3 and 6 of follow-up, which corresponds to the period following the initial 3-month loading phase, and early switching was associated with better visual gains. This is consistent with Maggio et al.,[26] who reported that although switching agents does not always improve outcomes, early therapeutic modifications tend to be more effective. Moreover, dexamethasone implants were needed in some of our patients, particularly those with chronic DME and persistent intraretinal cysts.[18] In the same Maggio et al.[26] study, early steroid use led to greater CMT improvement. Similarly, 18.8% of our patients received dexamethasone implants in the first six months, increasing to 38.7% by month 48. Since inflammation plays a key role in chronic DME, anti-VEGF monotherapy may be insufficient for some patients.

In Türkiye, healthcare reimbursement policies require bevacizumab as the first-line anti-VEGF agent, significantly shaping treatment decisions. In our study, 93.3% of patients received bevacizumab initially. Maggio et al.[26] suggested that the choice of first-line agent influences treatment outcomes, with aflibercept and ranibizumab often producing better results. Similarly, Durukan et al.[11] and Yayla et al.[12] noted that reimbursement restrictions limited both injection frequency and agent selection, potentially compromising long-term visual outcomes.

In our study, mean CMT decreased from 400±134 μm at baseline to 324±115 μm at 48 months. However, BCVA improvement did not always parallel CMT reduction. This supports Maggio et al.,[26] who noted that CMT alone may not predict visual gains, emphasizing the importance of retinal structural integrity. Recent studies suggest that biomarkers like DRIL and EZ integrity are stronger predictors of long-term vision.[18]

Study Limitations

This study has several limitations inherent to its retrospective design. Treatment decisions were made based on the clinical judgment of physicians at each participating center. The analysis included all eyes with available follow-up data of varying durations up to 48 months. However, the number of patients decreased substantially over time, with only 86 eyes remaining under follow-up at month 48. This finding clearly demonstrates the challenges of maintaining long-term anti-VEGF therapy for DME, where the high injection burden, frequent visit requirements, and the chronic nature of the disease constitute major barriers to sustained treatment adherence in real-world

Table 8. Comparison of cumulative intravitreal anti-VEGF injection and clinical visit numbers in real-world studies from Türkiye

	Present study	Durukan et al.[11]	Yayla et al.[12]
Follow-up period (months)	**48**	**36**	**36**
Number of eyes			
Start of therapy	2424	1072	1372
Month 12	1321	495	1185
Month 24	427	293	972
Month 36	204	284	623
Month 48	86	-	-
Number of cumulative intravitreal injections			
Month 12	6.5±1.7	4.6±2.0	5 (4-6)
Month 24	9.6±2.8	7.1±3.1	7 (5-8)
Month 36	12.2±3.9	8.0±4.2	9 (7-10)
Month 48	15.7±5.5	-	-
Number of cumulative visits			
Month 12	7.5±2.9	7.4±2.1	7 (6-10)
Month 24	11.2±3.7	13.2±3.8	11 (9-14)
Month 36	14.7±5.1	18.7±5.7	16 (14-18)
Month 48	17.6±5.6	-	-

Injection and visit numbers reported as mean ± SD or median (range)
anti-VEGF: Anti-vascular endothelial growth factor. SD: Standard deviation

settings. In addition, eyes that showed rapid improvement after short-term treatment or failed to respond despite multiple injections may not have been fully represented in the long-term outcomes. The use of different OCT devices across centers may have introduced minor technical variations in retinal thickness measurements. Finally, systemic and ocular adverse events were not consistently documented throughout the 48-month period. While some were recorded, others were not systematically entered into clinical files.

Conclusion

This large-scale real-world study provides important insights into intravitreal anti-VEGF therapy for DME. Our results were generally consistent with previous real-world studies; however, the superior visual and anatomical outcomes observed in our cohort likely reflect a higher injection frequency. Nevertheless, the outcomes remained below RCT standards; this gap is primarily attributable to undertreatment and delays in routine clinical practice. Building on these findings, future BOSPHORUS-DME reports will explore clinical and anatomical subgroups to strengthen real-world evidence and support more personalized treatment strategies.

Ethics

Ethics Committee Approval: Ethics approval was obtained from Kocaeli University Faculty of Medicine Ethics Committee (decision no: KÜ GOKAEK-2025/06/18; date: 13.03.2025; project: 2025/115).

Informed Consent: Written informed consent was obtained from all participants.

Declarations

Authorship Contributions

Surgical and Medical Practices: All authors, Concept: V.L.K., Design: V.L.K., A.Ö., A.Ç., Data Collection or Processing: All authors, Analysis or Interpretation: All authors, Literature Search: All authors, Writing: E.Ö., S.A.Ö., M.K.

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References

1. Teo ZL, Tham YC, Yu M, Chee ML, Rim TH, Cheung N, Bikbov MM, Wang YX, Tang Y, Lu Y, Wong IY, Ting DSW, Tan GSW, Jonas JB, Sabanayagam C, Wong TY, Cheng CY. Global prevalence of diabetic retinopathy and projection of burden through 2045: systematic review and meta-analysis. Ophthalmology. 2021;128:1580-1591.
2. Heier JS, Korobelnik JF, Brown DM, Schmidt-Erfurth U, Do DV, Midena E, Boyer DS, Terasaki H, Kaiser PK, Marcus DM, Nguyen QD, Jaffe GJ, Slakter JS, Simader C, Soo Y, Schmelter T, Vitti R, Berliner AJ, Zeitz O, Metzig C, Holz FG. Intravitreal aflibercept for diabetic macular edema: 148-week results from the VISTA and VIVID studies. Ophthalmology. 2016;123:2376-2385.
3. Boyer DS, Nguyen QD, Brown DM, Basu K, Ehrlich JS; RIDE and RISE Research Group. Outcomes with as-needed ranibizumab after initial monthly therapy: long-term outcomes of the phase III RIDE and RISE trials. Ophthalmology. 2015;122:2504-2013.e1.
4. Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, Berg K, Chakravarthy U, Gerendas BS, Jonas J, Larsen M, Tadayoni R, Loewenstein A. Guidelines for the management of diabetic macular edema by the European Society of Retina Specialists (EURETINA). Ophthalmologica. 2017;237:185-222.
5. Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, Brucker AJ, Ferris FL, Hampton GR, Jhaveri C, Melia M, Beck RW; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. Ophthalmology. 2016;123:1351-1359.
6. Glassman AR, Wells JA 3rd, Josic K, Maguire MG, Antoszyk AN, Baker C, Beaulieu WT, Elman MJ, Jampol LM, Sun JK. Five-year outcomes after initial aflibercept, bevacizumab, or ranibizumab treatment for diabetic macular edema (protocol T extension study). Ophthalmology. 2020;127:1201-1210.
7. Kim HS, Lee S, Kim JH. Real-world evidence versus randomized controlled trial: clinical research based on electronic medical records. J Korean Med Sci. 2018;33:e213.
8. Choovuthayakorn J, Phinyo P, Tantraworasin A, Kunavisarut P, Patikulsila D, Chaikitmongkol V, Watanachai N, Pathanapitoon K. Intravitreal anti-vascular endothelial growth factor therapy for diabetic macular edema in clinical practice of single center: three-year outcomes. Ophthalmic Res. 2021;64:483-493.
9. Yuen YS, Tan GSW, Gan NY, Too IHK, Mothe RK, Basa P, Shaikh J. Real-world evidence in the management of diabetic macular edema with intravitreal anti-VEGFs in Asia: a systematic literature review. Clin Ophthalmol. 2022;16:3503-3526.
10. Holekamp NM, Campbell J, Almony A, Ingraham H, Marks S, Chandwani H, Cole AL, Kiss S. Vision outcomes following anti-vascular endothelial growth factor treatment of diabetic macular edema in clinical practice. Am J Ophthalmol. 2018;191:83-91.
11. Durukan AH, Unlu N, Onen M, Alp MN, Yeşiltaş YS, Kalayci D, Acar MA, Sekeroglu MA, Citirik M, Altintas AGK, Hazirolan D, Kucukevcilioglu M, Ozdal PC, Toklu Y, Bicer T, Ugurlu N, Budakoglu O, Yazar Z, Ucgun NI, Serdar K, Doguizi S, Erol YO, Atilgan CU, Yorgun MA, Soba DO, Berker N, Baskan C, Yilmaz ES. Anti-vascular endothelial growth factor therapy in diabetic macular edema: real-life outcomes from a multicenter study in Turkey over 36 months. Int Ophthalmol. 2022;42:3777-3787.
12. Yayla U, Sevik MO, Karabaş VL, Şahin Ö, Özkaya A, Yenerel NM, Açıkalın Öncel B, Kaplan FB, Önder Tokuç E, Kanar HS, Kutlutürk Karagöz I, Başaran Emengen E, Demirciler Sönmez A, Aykut A, Limon U, Bozkurt E, Özsoy Saygın I, Aydoğan Gezginaslan T, Aydın Öncü Ö, Türkseven Kumral E, Erçalık NY, Çelik E. Real-world outcomes of intravitreal anti-vascular endothelial growth factor treatment for diabetic macular edema in Türkiye: MARMASIA study group report no. 1. Turk J Ophthalmol. 2023;53:356-368.

13. Birinci Mükerrer Resmi Gazete: Sosyal Güvenlik Kurumu Sağlık Uygulama Tebliğinde Değişiklik Yapılmasına Dair Tebliğ. [Official Gazette First Supplement. Communiqué on the Amendment of the Social Security Institution Health Implementation Communiqué.] 28.12.2018; Available from: https://www.resmigazete.gov.tr/eskiler/2018/12/20181228M1-1.pdf.
14. Panozzo G, Cicinelli MV, Augustin AJ, Battaglia Parodi M, Cunha-Vaz J, Guarnaccia G, Kodjikian L, Jampol LM, Jünemann A, Lanzetta P, Löwenstein A, Midena E, Navarro R, Querques G, Ricci F, Schmidt-Erfurth U, Silva RMD, Sivaprasad S, Varano M, Virgili G, Bandello F. An optical coherence tomography-based grading of diabetic maculopathy proposed by an international expert panel: the European School for Advanced Studies in Ophthalmology classification. Eur J Ophthalmol. 2020;30:8-18.
15. Shimura M, Kitano S, Muramatsu D, Fukushima H, Takamura Y, Matsumoto M, Kokado M, Kogo J, Sasaki M, Morizane Y, Kotake O, Koto T, Sonoda S, Hirano T, Ishikawa H, Mitamura Y, Okamoto F, Kinoshita T, Kimura K, Sugimoto M, Yamashiro K, Suzuki Y, Hikichi T, Washio N, Sato T, Ohkoshi K, Tsujinaka H, Kusuhara S, Kondo M, Takagi H, Murata T, Sakamoto T; Japan Clinical Retina Study (J-CREST) group. Real-world management of treatment-naïve diabetic macular oedema in Japan: two-year visual outcomes with and without anti-VEGF therapy in the STREAT-DME study. Br J Ophthalmol. 2020;104:1209-1215.
16. Virgili G, Curran K, Lucenteforte E, Peto T, Parravano M. Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. Cochrane Database Syst Rev. 2023:CD007419.
17. Ciulla TA, Bracha P, Pollack J, Williams DF. Real-world outcomes of anti-vascular endothelial growth factor therapy in diabetic macular edema in the United States. Ophthalmol Retina. 2018;2:1179-1187.
18. Gandhi JS. Anti-vascular endothelial growth factor treatment for diabetic macular edema in a real-world clinical setting. Am J Ophthalmol. 2019;199:255-256.
19. Hodzic-Hadzibegovic D, Sander BA, Monberg TJ, Larsen M, Lund-Andersen H. Diabetic macular oedema treated with intravitreal anti-vascular endothelial growth factor - 2-4 years follow-up of visual acuity and retinal thickness in 566 patients following Danish national guidelines. Acta Ophthalmol. 2018;96:267-278.
20. Călugăru D, Călugăru M. Real-world outcomes of ranibizumab treatment for diabetic macular edema in a United Kingdom National Health Service Setting. Am J Ophthalmol. 2017;174:175-176.
21. Koç İ, Kadayıfçılar S, Eldem B. Real-world results of intravitreal ranibizumab, bevacizumab, or triamcinolone for diabetic macular edema. Ophthalmologica. 2018;239:85-93.
22. Epstein D, Amrén U. Long-time outcome in patients treated with ranibizumab for diabetic macular edema: a 4-year study. Retina. 2018;38:183-186.
23. Ziemssen F, Wachtlin J, Kuehlewein L, Gamulescu MA, Bertelmann T, Feucht N, Voegeler J, Koch M, Liakopoulos S, Schmitz-Valckenberg S, Spital G; OCEAN study group. Intravitreal ranibizumab therapy for diabetic macular edema in routine practice: two-year real-life data from a non-interventional, multicenter study in Germany. Diabetes Ther. 2018;9:2271-2289.
24. Kuo BL, Tabano D, Garmo V, Kim E, Leng T, Hatfield M, LaPrise A, Singh RP. Long-term treatment patterns for diabetic macular edema: up to 6-year follow-up in the IRIS® Registry. Ophthalmol Retina. 2024;8:1074-1082.
25. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, Gibson A, Sy J, Rundle AC, Hopkins JJ, Rubio RG, Ehrlich JS; RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012;119:789-801.
26. Maggio E, Sartore M, Attanasio M, Maraone G, Guerriero M, Polito A, Pertile G. Anti-vascular endothelial growth factor treatment for diabetic macular edema in a real-world clinical setting. Am J Ophthalmol. 2018;195:209-222.