Original Article

Real-World Outcomes of Intravitreal Anti-Vascular Endothelial Growth Factor Treatment for Diabetic Macular Edema in Türkiye: MARMASIA Study Group Report No. 1

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Abstract

Objectives: This study aimed to report the demographic and clinical characteristics of diabetic macular edema (DME) patients treated with intravitreal injection (IVI) of anti-vascular endothelial growth factors (anti-VEGF) and provide an overview of outcomes during routine clinical practice in Türkiye.

Materials and Methods: This retrospective, real-world study included 1,372 eyes (854 patients) treated with a pro re nata protocol by 21 ophthalmologists from 8 tertiary clinics on the Asian side of the Marmara region of Türkiye (MARMASIA Study Group). Five cohort groups were established by collecting the patients' baseline and 3, 6, 12, 24, and 36-month follow-up data, where each subsequent cohort may include the previous. Changes in best-corrected visual acuity (BCVA, approximate ETDRS letters) and central macular thickness (CMT, µm), number of visits and IVI, and rates of anti-VEGF switch and intravitreal dexamethasone implant (IDI) combination were evaluated.

Results: The 3, 6, 12, 24, and 36-month cohorts included 1372 (854), 1352 (838), 1185 (722), 972 (581), and 623 (361) eyes (patients), respectively. The mean baseline BCVA and CMT were 51.4±21.4 letters and 482.6±180.3 µm. The mean changes from baseline in BCVA were +7.6, +9.1, +8.0, +8.6, and +8.4 letters, and in CMT were -115.4, -140.0, -147.9, -167.3, and -215.4 µm at the 3, 6, 12, 24, and 36-month visits ($p<0.001$ for all). The median cumulative number of anti-VEGF IVI was 3.0, 3.0, 5.0, 7.0, and 9.0, respectively. The overall anti-VEGF switch and IDI combination rates were 18.5% (253/1372 eyes) and 35.0% (480/1372 eyes), respectively.

Conclusion: This largest real-life study of DME from Türkiye demonstrated BCVA gains inferior to randomized controlled trials, mainly due to the lower number of IVI. However, with the lower baseline BCVA and higher IDI combination rates in our cohorts, these gains were relatively superior to other real-life study counterparts.

Keywords: Anti-VEGF, diabetic macular edema, intravitreal injection, real-life study, routine clinical practice

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Introduction

Traditionally, the data considered in evidence-based retinal disease management guidelines have been primarily, if not exclusively, dependent on the gold standard, randomized controlled trial (RCT)-based "efficacy" studies.[1] However, the design of RCTs, which utilizes restrictive eligibility criteria to control data variability while ensuring quality, limits their replicability and reproducibility in clinical practice.[2] Therefore, real-world evidence (RWE) from diversified routine clinical practice has recently received significant attention worldwide, particularly in diseases that require more individualized treatment, such as diabetic macular edema (DME).[3,4]

DME is the leading vision-threatening complication of diabetic retinopathy (DR). It has been shown to be anatomically and functionally responsive to intravitreal anti-vascular endothelial growth factors (anti-VEGF) and corticosteroids in numerous milestone RCTs.[5,6,7,8,9,10,11,12,13,14,15] However, even considering two well-designed RCTs, RISE/RIDE and VIVID/VISTA, the former evaluating intravitreal ranibizumab (IVR; Lucentis®, Genentech, CA, USA) and the latter intravitreal aflibercept (IVA; Eylea®, Regeneron, NY, USA) in the treatment of DME, similar results could not be obtained in their respective study arms, even though they both included patients with similar demographics and disease characteristics.[9,12] These two examples alone demonstrate the need for complementary studies of DME treatment in real-life settings.

Furthermore, the 5-year extension study of Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T, the first RCT to compare IVR, IVA, and intravitreal bevacizumab (IVB; Avastin®, Genentech, CA, USA) in treating DME, showed that after 2 years of protocol-defined follow-up and re-treatment, DME patients may receive different modalities at clinician discretion in routine clinical practice.[14,15,16] Those patients were shown to lose best-corrected visual acuity (BCVA) between 2 and 5 years, even though they preserved central macular thickness (CMT) with a protocol chosen at clinician discretion.[16] Also, several RWE studies, even systematic reviews and meta-analyses, report anatomical and functional effectiveness of anti-VEGF agents in DME but with less impressive results than in RCTs, mainly due to undertreatment, less frequent monitoring, and lower patient compliance.[17,18,19,20,21,22,23,24,25,26,27]

Recently, Durukan et al.[27] published the first large-scale RWE study of DME treatment from the Central Anatolia region of Türkiye, reporting a similar lower number of injections and gains like other RWE studies on DME. Therefore, we established a multicenter collaboration to further evaluate the real-world outcomes of intravitreal anti-VEGF treatment of DME in 8 tertiary reference centers located on the ASIAn side of the MARMara region of Türkiye (MARMASIA Study Group). This first report by the MARMASIA Study Group aims to demonstrate the demographic and clinical features of the evaluated DME patients and provide an overview of the treatment outcomes.

Materials and Methods

This descriptive, retrospective, observational, multicenter, real-world study was conducted by the MARMASIA Study Group, which includes 22 ophthalmologists experienced in retinal diseases from 8 tertiary clinics in 3 cities (İstanbul, Kocaeli, and Sakarya) on the Asian side of the Marmara region of Türkiye. The Institutional Review Board of Kocaeli University Faculty of Medicine approved the study protocol (no: GOKAEK-2022/07.19, date: 14.04.2022). The study followed the ethical principles of the 1964 Declaration of Helsinki and later amendments. In addition, written informed consent for the use of their medical data for research purposes was routinely obtained from all patients at their first presentation to the participating clinics. The study is registered on ClinicalTrials.gov (number: NCT05472376).

Study Population

Patients who had received at least one intravitreal injection (IVI) of any anti-VEGF agent (IVR, IVA, or IVB) for DME between January 2015 and December 2018 and was followed up for at least 3 months were retrospectively screened and included in the study. In Türkiye, for treatment-naive DME patients to receive reimbursement from the Turkish Social Security Institution, it was made mandatory as of December 28, 2018 to start treatment with three loading doses of IVB injections.[28] Accordingly, the reimbursement of anti-VEGFs approved for intraocular use (i.e., IVR and IVA) could only be obtained by patients in case of failure of treatment with IVB.[28] Therefore, patients whose treatment started after this date were excluded from the study. The patients' demographics, clinical characteristics, and follow-up information were collected retrospectively from electronic or traditional patient records.

The study inclusion criteria were established as being 18 years of age or older, having received at least one IVB (1.25 mg/0.05 mL), IVR (0.5 mg/0.05 mL), or IVA (2 mg/0.05 mL) injection as initial treatment for DME during the specified dates, having at least 3 months of follow-up, and having at least four or more visits per year for patients who were followed up for more than one year. Patients who underwent phacoemulsification surgery within the previous month and panretinal, focal, or grid laser photocoagulation or micropulse laser treatment in the previous 4 months before study enrollment, as well as patients who had any intraocular surgery other than phacoemulsification and pars plana vitrectomy (PPV) during the study period were excluded from the study. If eligible, both eyes of the patients were included in the study analysis separately. There were no restrictions on previous intravitreal therapy with anti-VEGFs or corticosteroids, presenting BCVA, whether loading doses of intravitreal anti-VEGFs were administered, the use of intravitreal dexamethasone implant (IDI; Ozurdex®, Abbvie-Allergan, CA, USA), micropulse laser, panretinal, focal, or grid laser photocoagulation, and undergoing phacoemulsification or PPV at any point during follow-up.

Baseline and Follow-up Data

The baseline demographics and medical information of the patients included age, gender, duration of diabetes mellitus, treatment of diabetes mellitus (none, oral antidiabetic drugs, insulin, or combination of oral antidiabetic drugs and insulin), comorbidities (none, hypertension, coronary artery disease, cerebrovascular accident, and chronic kidney disease leading to hemodialysis), history of glaucoma, antiglaucoma drug use (classified as prostaglandin analogs and others), previous anti-VEGF IVI (number of injections and agents), previous panretinal photocoagulation, and previous PPV history.

Five retrospective cohort groups were formed so that subsequent cohorts may also include patients from the previous cohorts by using examinations performed at 3, 6, 12, 24, and 36 months (±2 weeks) as follow-up data. All patients underwent comprehensive ophthalmic examination at baseline and follow-up visits, including BCVA assessment with an electronic Snellen chart, Goldmann applanation tonometry, slit-lamp biomicroscopy, dilated fundus examination, and optical coherence tomography (OCT) scans obtained by either Spectralis (Heidelberg Eng., Heidelberg, Germany), RS-3000 (Nidek, Gamagori, Japan), or RTVue-100 (Optovue Inc., CA, USA) OCT devices, depending on the availability in each clinic. We used the follow-up software feature of these devices to ensure the accuracy of the measurement positions. In addition, fundus fluorescein angiography was performed at clinicians' discretion if there was suspicion of new neovascularization or persistent peripheral retinal ischemia.

BCVA, lens status (pseudophakic or phakic), DR grading (non-proliferative or proliferative), and OCT parameters from the specified follow-up visits were collected. The OCT parameters of particular importance were as follows:

1. CMT (µm), automatically calculated by the software of the corresponding OCT device after foveal alignment was ensured by the clinician;

2. DME pattern, classified as diffuse/spongious, cystoid, diffuse/spongious plus subretinal fluid (SRF), and cystoid plus SRF;

3. Cystic pattern according to the European School for Advanced Studies in Ophthalmology classification:[29] absent (0), mild (1), moderate (2), or severe (3);

4. Largest cyst diameter (µm), measured manually by the corresponding OCT device software;

5. SRF height (µm), measured manually by the corresponding OCT device software from the outer surface of the photoreceptor layer to the inner surface of the retinal pigment epithelium;

6. Presence of disorganization of the retinal inner layers (DRIL), defined as the horizontal distance (µm) in which it was not possible to identify the boundaries between the inner nuclear layer, outer plexiform layer, and ganglion cell-inner plexiform layer complex;[30]

7. Continuity of the ellipsoid zone and external limiting membrane, classified as interrupted, partially preserved, totally preserved, or indiscernible;

8. Presence of epiretinal membrane;

9. Status of the posterior hyaloid, classified as attached, detached, or indiscernible.

Additional information collected at each follow-up visit included the intravitreal anti-VEGF agent used; treatment protocol (defined as 3+ pro re nata [PRN] if three loading doses were given and 1+PRN if not); cumulative number of injections; cumulative number of visits; stabilization time of the macula (defined as the first visit [in months] that injection was deferred according to the PRN protocol); the application and timing (months) of phacoemulsification, PPV, panretinal, focal, and grid laser photocoagulation, and micropulse laser, and presence of intravitreal hemorrhage, neovascular glaucoma, and any other complications and adverse events.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) software for Windows version 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical data analysis. Data distribution was determined by histogram plots and the Shapiro-Wilk and Kolmogorov-Smirnov tests. Continuous data were presented as mean ± standard deviation or median (interquartile range [IQR], expressed as 25th and 75th quartile values), and categorical data were presented as frequency (n) and percentage (%). Snellen BCVA values were converted to logarithm of the minimum angle of resolution (logMAR) values for statistical analysis, and the logMAR equivalent value for "counting fingers" and "hand motion" were assumed to be 2.10 and 3.10, respectively. LogMAR values were also converted to approximate Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores using the formula "ETDRS letter score = 1.7 - logMAR) / 0.02" as suggested by Beck et al.[31] As logMAR values of 1.7 and higher give a negative value, the ETDRS letter scores of eyes higher than 1.6 logMAR were accepted as 0 (zero). Dependent variables were evaluated with paired samples t-test or repeated measures analysis of variance (ANOVA), and Wilcoxon signed rank test or Friedman test, depending on the data distribution and variable counts. Post-hoc analyses of more than two dependent variables were conducted with Dunn-Bonferroni post-hoc test and pairwise comparisons provided by the SPSS software for repeated measures ANOVA and Friedman test, respectively. The p values for post-hoc analysis were adjusted with Bonferroni correction and given as "adj. p" value where appropriate. A two-sided p value of less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

The study included 1,372 eyes of 854 patients with a mean age of 62.7±8.7 (range, 30-94) years (455 [53.3%] females). All patients (eyes) had at least 3 months of follow-up and were included in the 3-month cohort, and there were 838 (1352), 722 (1185), 581 (972), and 361 (623) patients (eyes) in the 6-, 12-, 24-, and 36-month cohorts, respectively.

Of the 1,372 eyes in the study, 818 (59.6%) were treatment-naïve and 554 (40.4%) had previously been treated with a

mean of 4.3±3.0 (range, 1-24) anti-VEGF injections. Only 28 eyes (2.0%) were previously treated with intravitreal steroid injections (dexamethasone implant or triamcinolone acetonide) in combination with anti-VEGF agents. Also, 377 eyes (27.5%) had a history of panretinal laser photocoagulation, and 35 (2.6%) had a history of PPV.

The treatment protocol was 1+PRN in 525 eyes (38.3%) and and 3+PRN in 847 eyes (61.7%). The initial anti-VEGF agent used during the study period was bevacizumab in 60 eyes (4.4%), ranibizumab in 893 eyes (65.1%), and aflibercept in 419 eyes (30.5%).

The baseline characteristics of the patients and eyes in each cohort are given in Table 1.

Functional and Anatomical Outcomes

The mean BCVA and CMT of the eyes in the whole cohort during the study period are given in Figure 1. While BCVA increased and CMT decreased in the first 6-month period, BCVA gradually declined after 6 months despite the progressive decrease in CMT.

The mean baseline and final approximate ETDRS letter scores of the eyes were 51.4±21.4 and 57.6±21.5, with a mean change of 8.4±25.6 letters in 3 years. The mean change in letter scores from baseline was 7.6±17.3 at 3 months (p<0.001), 9.1±19.0 at 6 months (adj. p<0.001), 8.0±21.2 at 12 months (adj. p<0.001), 8.6±23.0 at 24 months (adj. p<0.001), and 8.4±85.4 letters at 36 months (adj. p<0.001). The mean letter score change from the previous visit was 7.6±17.3 (p<0.001), 1.5±11.9 (adj. p<0.001), -0.6±14.0 (adj. p=1.000), 0.3±14.8 (adj.p=1.000), and 0.2±0.4 (adj. p=1.000) letters at the 3-, 6-, 12-, 24-, and 36-month visits, respectively.

The mean baseline CMT of 482.6±180.3 µm was decreased to 267.4±87.3 µm at the last follow-up visit, with a mean change of -215.4±221.7 µm. The mean CMT changes from the baseline visit were -115.4±150.1 at 3 months (p<0.001), -140.0±181.1 at 6 months (adj. p<0.001), -147.9±211.6 at 12 months (adj. p<0.001), -167.3±196.4 at 24 months (adj. p<0.001), and -215.4±221.7 µm at 36 months (adj. p<0.001). The mean change in CMT from the previous visit was -115.4±150.1 (p<0.001), -24.6±123.1 (adj. p<0.001), -15.1±141.5 (adj. p=0.003), -15.5±147.6 (p<0.001), and -44.6±127.0 (p<0.001) µm at the 3-, 6-, 12-, 24-, and 36-month visits, respectively.

The most common baseline DME type was cystoid (n=617, 45%), followed by cystoid plus SRS (n=317, 23.1%), diffuse/spongious (n=261, 19%), and diffuse/spongious plus SRF (n=177, 12.9%). At the last follow-up visit, 42.9% (267/623) of the eyes had dry macula. DME pattern and dry macula rates during the study period are given in Figure 2.

Number of Visits and Intravitreal Anti-VEGF Injections

Table 2 displays the median number of visits and intravitreal anti-VEGF injections in each cohort stratified by study visits. In 3-, 6-, 12-, 24-, and 36-month cohorts, the median (IQR) cumulative number of visits was 2 (2-2), 4 (4-5), 7 (6-10), 11 (9-14), and 16 (14-18), and the median number of anti-VEGF IVIs was 3 (2-3), 3 (3-4), 5 (4-6), 7 (5-8), and 9 (7-10), respectively. The median number of injections per year decreased from 5 (4-6) in the first year to 2 (1-3) in the second (p<0.001) and 2 (1-3) in the third year (adj. p<0.001 for first vs. second and third years and adj. p=1.000 for second vs. third year).

Anti-VEGF Switch and Additional Treatments

The anti-VEGF agent was switched in a total of 254 eyes (18.5%) during the study period, of which 229 (90.2%) of the switches were intentional at the clinician's discretion. Fifty-one (20.1%) of the anti-VEGF agent switches occurred between 3 and 6 months, 97 (38.2%) between 6 and 12 months, 66 (26.0%) between 12 and 24 months, and 40 (15.7%) between 24 and 36 months of follow-up. The most frequent anti-VEGF agent switch was from ranibizumab to aflibercept (n=193, 76%). The rates of switches between anti-VEGF agents are given in Figure 3.

Of the 1372 eyes, 480 (35.0%) in the entire cohort had combination therapy with at least one IDI injection (mean: 2.4±1.4 injections, range, 1-9). While none of the eyes in the 3-month cohort had IDI injection, the cumulative rates of combination with IDI injection were 9.5% (129/1352), 26.0% (308/1185), 41.2% (400/972), and 44.8% (279/623) in the 6-, 12-, 24-, and 36-month cohorts, respectively. Combination with IDI resulted in significantly more BCVA letter gains and CMT reductions in all cohorts (Table 3).

Additional treatments employed at any time during the study period included panretinal laser photocoagulation in 444 eyes (32.4%), phacoemulsification in 315 eyes (23.0%), only focal or grid laser photocoagulation in 267 eyes (19.5%), focal and grid laser photocoagulation in 192 eyes (14.0%), PPV in 68 eyes (5.0%), and micropulse laser in 44 eyes (3.2%).

Adverse Events

Ocular adverse events encountered during the study period were intravitreal hemorrhage in 98 eyes (7.1%), neovascular glaucoma in 22 eyes (1.6%), increased intraocular pressure in 2 eyes (0.15%), rhegmatogenous retinal detachment in 2 eyes (0.15%), and endophthalmitis in 1 eye (0.07%).

Systemic adverse events that could be associated with anti-VEGFs were acute myocardial infarction in 5 patients (0.6%) and cerebrovascular accident in 1 patient (0.1%).

Discussion

This first report of the largest-scale RWE study of DME treatment from Türkiye demonstrates lower overall number of injections and visual gains than in RCTs (Table 4), supporting the findings from various other countries. Moreover, it provides insight into the rates of macular laser, anti-VEGF agent switch, and steroid combination in the treatment of DME at clinician discretion in real life.

One of the earliest RCTs comparing the efficacy of an anti-VEGF agent (ranibizumab) against macular focal/grid laser photocoagulation (READ-2) had results similar to those at 6 and 24 months in our IVR-only group (+7.2 and +7.7 letters, respectively).[32,33] However, its small sample size and the established treatment protocol obligating IVR at a frequency of

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

	3-Month cohort (whole group)	6-month cohort	12-month cohort	24-month cohort	36-month cohort
Patients (eyes), n	854 (1372)	838 (1352)	722 (1185)	581 (972)	361 (623)
Age, years, mean ± SD	62.7±8.7	62.8±8.7	62.9±8.8	63.3±8.8	63.8±8.2
Sex, n (%)					
Female	455 (53.3)	447 (53.3)	385 (53.3)	325 (55.9)	203 (56.2)
Male	399 (46.7)	391 (46.7)	337 (46.7)	256 (44.1)	158 (43.8)
DM duration, years, mean ± SD	16.3±6.6	16.3±6.6	16.5±6.6	16.7±6.5	16.8±6.2
DM treatment, n (%)					
None	3 (0.4)	3 (0.4)	3 (0.4)	2 (0.3)	0 (0.0)
OAD	306 (35.8)	302 (36.0)	257 (35.6)	215 (37.0)	123 (34.1)
Insulin	483 (56.6)	471 (56.2)	404 (56.0)	327 (56.3)	288 (63.2)
Combination	62 (7.3)	62 (7.4)	58 (8.0)	37 (6.4)	10 (2.8)
Accompanying disorders, n (%)					
None	347 (40.6)	343 (40.9)	296 (41.0)	245 (42.2)	146 (40.4)
HT	481 (56.3)	469 (56.0)	402 (55.7)	315 (54.2)	198 (54.8)
CAD	115 (13.5)	113 (13.5)	98 (13.6)	71 (12.2)	51 (14.1)
CVA	7 (0.8)	6 (0.7)	5 (0.7)	4 (0.7)	2 (0.6)
CKD	37 (4.3)	36 (4.3)	31 (4.3)	22 (3.8)	19 (5.3)
BCVA, logMAR, mean ± SD	0.68±0.46	0.68±0.46	0.68±0.46	0.71±0.47	0.72±0.45
Glaucoma history, n (%)	148 (10.8)	146 (10.8)	127 (10.7)	114 (11.7)	65 (10.4)
PGA use, n (%)	49 (3.6)	49 (3.6)	41 (3.5)	37 (3.8)	23 (3.7)
Lens status, n (%)					
Phakic	1056 (77.0)	1040 (76.9)	911 (76.9)	742 (76.3)	467 (75.0)
Pseudophakic	316 (23.0)	312 (23.1)	274 (23.1)	230 (23.7)	156 (25.0)
DR grade, n (%)					
NPDR	999 (72.8)	985 (72.9)	865 (73.0)	709 (72.9)	486 (78.0)
PDR	373 (27.2)	367 (27.1)	320 (27.0)	263 (27.1)	137 (22.0)
CMT, µm, mean ± SD	482.61±180.32	482.70±180.83	475.88±178.62	479.68±185.47	482.79±196.13
Previous DME treatment, n (%)					
Treatment-naive	818 (59.6)	805 (59.5)	694 (58.6)	537 (55.2)	339 (54.4)
Previously treated	554 (40.4)	547 (40.5)	491 (41.4)	435 (44.8)	284 (45.6)
Treatment protocol, n (%)					
1+PRN	525 (38.3)	522 (38.6)	470 (39.7)	409 (42.1)	213 (34.2)
3+PRN	847 (61.7)	830 (61.4)	715 (60.3)	563 (57.9)	410 (65.8)
Initial anti-VEGF agent, n (%)					
Bevacizumab	60 (4.4)	60 (4.4)	59 (5.0)	58 (6.0)	57 (9.1)
Ranibizumab	893 (65.1)	876 (64.8)	787 (66.4)	631 (64.9)	359 (57.6)
Aflibercept	419 (30.5)	416 (30.8)	339 (28.6)	283 (29.1)	207 (33.2)

Anti-VEGF: Anti-vascular growth factor, BCVA: Best corrected visual acuity, CAD: Coronary artery disease, CKD: Chronic kidney disease, CVA: Cerebrovascular accident, DM: Diabetes mellitus, DME: Diabetic macular edema, DR: Diabetic retinopathy, HT: Hypertension, logMAR: Logarithm of the minimum angle of resolution, NPDR: Non-proliferative diabetic retinopathy, OAD: Oral antidiabetic, PDR: Proliferative diabetic retinopathy, PGA: Prostaglandin analogs, PRN: Pro re nata, SD: Standard deviation

more than 2 months on a PRN basis differentiates READ-2 from other RCTs regarding the risk of possible undertreatment.[32,33] Moreover, the 3-year extension period of the trial allowing monthly follow-up and PRN IVR injections resulted in a +10.3 mean letter gain from baseline with a mean of 5.4 IVIs during the third year (cumulative mean of 14.7 IVIs), further supporting undertreatment in the earlier study period.[34] The subsequent RESTORE study adopted a treatment protocol of monthly PRN IVR injections after starting with three loading doses.[35,36,37] However, the reported 12-, 24-, and 36-month functional and anatomical results of the RESTORE study were even worse than our results, with a much higher number of IVIs throughout the study period (Table 4).[35,36,37] These results can be explained by the fact that the proportion of eyes with an initial BCVA of 60 or fewer letters was relatively lower in the RESTORE study (33.0% and 27.7% in 12- and 24- to 36-month results, respectively) compared to our study (61.4%). Those ratios could have resulted in a so-called ceiling effect due to the higher proportion of better-seeing eyes in the RESTORE study.[35,36,37] However, the mean visual gains in the worse-seeing eyes (≤60 letters) were reported to be +8.2 and +10.5 letters in the 12- and 24-month results.[35,36]

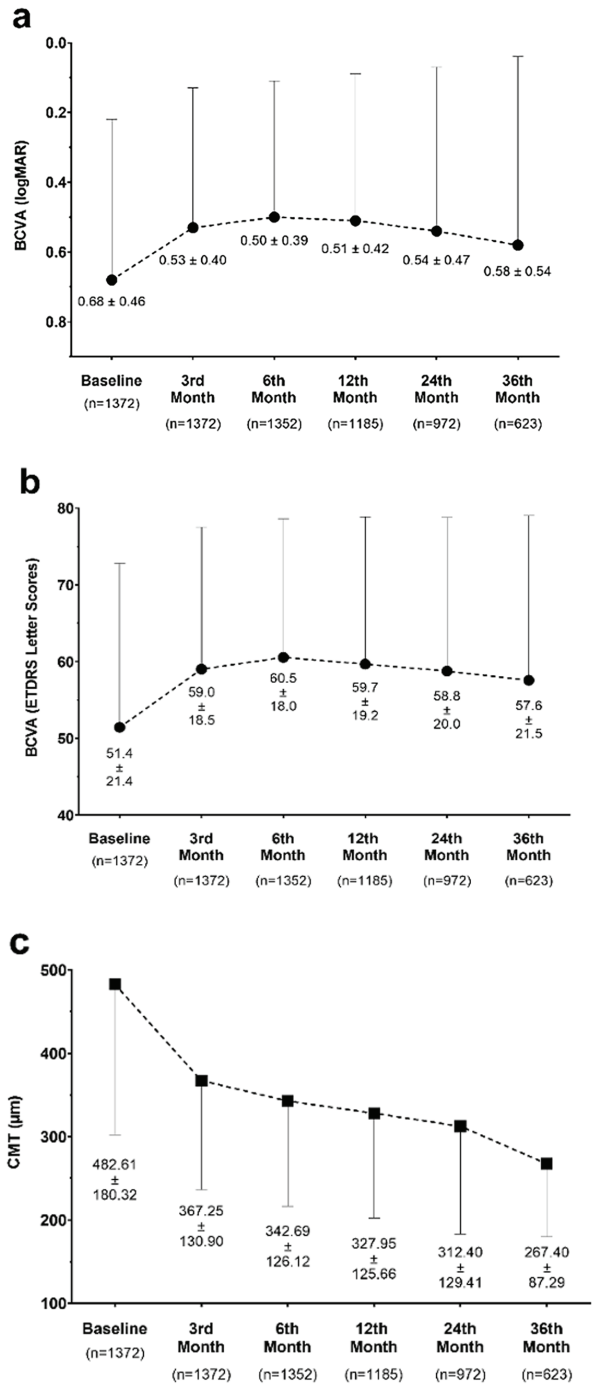

Figure 1. Best corrected visual acuity in logMAR (a) and ETDRS letter scores (b) and central macular thickness (c) of the eyes during the study period. Error bars indicate standard deviation

BCVA: Best corrected visual acuity, CMT: Central macular thickness, ETDRS: Early treatment diabetic retinopathy study, logMAR: Logarithm of the minimum angle of resolution

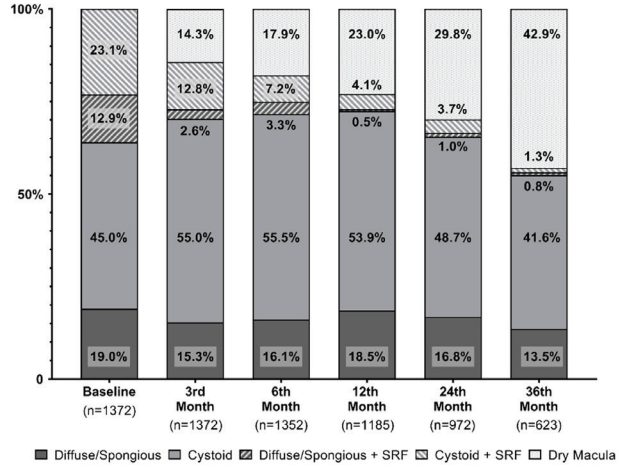

Figure 2. Diabetic macular edema patterns and dry macula rates during the study period

SRF: Subretinal fluid

The DRCR.net Protocol I study was a 5-year multicenter RCT comparing four treatments for DME (IVR plus deferred [after 24 weeks] vs. IVR plus prompt [within 1 week] macular laser photocoagulation vs. intravitreal triamcinolone plus prompt vs. intravitreal sham injections plus prompt macular laser photocoagulation) with protocol-defined re-treatment and follow-up criteria.[5,38,39,40] It was the first study providing level-1 evidence on the efficacy of an anti-VEGF agent (i.e., ranibizumab) for DME treatment, demonstrating improved and sustained BCVA for up to 5 years.[5,38,39,40] Although the injection frequencies per year gradually decreased during the study period, the number of cumulative injections, as well as letter gains, were also higher than in RWE studies like ours.[5,38,39,40] Further milestone RCTs comparing intravitreal anti-VEGF agents to sham and laser treatments also resulted in similar outcomes (Table 4).[8,9,10,11,12,41] Another DRCR.net study, Protocol T, was a 2-year RCT comparing the efficacies of PRN IVB, IVR, and IVA in DME, with protocol-defined re-treatment criteria, a salvage regimen, and scheduled visits (every 4 weeks in the first year and every 4 to 16 weeks in the second year depending on treatment response).[14,15] The 1- and 2-year results of Protocol T also demonstrated greater visual gains with a higher number of IVIs than in RWE studies and our report (Table 4).[14,15] However, the 5-year extension study of Protocol T after the randomized trial ended at the end of the second year showed that between 2 and 5 years, the median number of anti-VEGF IVIs was 4 (0-12), with only 68% of patients receiving at least one injection.[16] Moreover, although BCVA improved by 7.4 letters from baseline, patients were shown to have lost 4.7 letters from year 2 to 5.[16] On the other hand, the Protocol I study showed that when protocol-defined re-treatment with IVR continued, the mean visual gain at 1 year could be maintained for 5 years with a progressively diminishing number of injections.[40] The open-label extension study of RISE/RIDE trials also showed that the visual and anatomical gains achieved after monthly IVR were maintained

Table 2. Number of visits and intravitreal anti-vascular endothelial growth factor injections in each cohort

	3-month cohort (n=1372)	6-month cohort (n=1352)	12-month cohort (n=1185)	24-month cohort (n=972)	36-month cohort (n=623)
At 3 months					
Visits, median (IQR)					
Per year	-	-	-	-	-
Cumulative	2 (2-2)	2 (2-2)	2 (2-2)	2 (2-2)	2 (2-2)
Injections*, median (IQR)					
Per year	-	-	-	-	-
Cumulative	3 (2-3)	3 (2-3)	3 (2-3)	3 (1-3)	3 (2-3)
At 6 months					
Visits, median (IQR)					
Per year	-	-	-	-	-
Cumulative	-	4 (4-5)	4 (4-5)	4 (4-5)	4 (4-5)
Injections*, median (IQR)					
Per year	-	-	-	-	-
Cumulative	-	3 (3-4)	3 (3-4)	3 (3-4)	3 (3-4)
At 12 months					
Visits, median (IQR)					
Per year	-	-	7 (6-10)	7 (6-9)	7 (6-9)
Cumulative	-	-	7 (6-10)	7 (6-9)	7 (6-9)
Injections*, median (IQR)					
Per year	-	-	5 (4-6)	5 (4-6)	5 (4-6)
Cumulative	-	-	5 (4-6)	5 (4-6)	5 (4-6)
At 24 months					
Visits, median (IQR)					
Per year	-	-	-	4 (4-5)	4 (4-5)
Cumulative	-	-	-	11 (9-14)	10 (9-13)
Injections*, median (IQR)					
Per year	-	-	-	2 (1-3)	2 (1-3)
Cumulative	-	-	-	7 (5-8)	7 (6-8)
At 36 months					
Visits, median (IQR)					
Per year	-	-	-	-	5 (4-7)
Cumulative	-	-	-	-	16 (14-18)
Injections*, median (IQR)					
Per year	-	-	-	-	2 (1-3)
Cumulative	-	-	-	-	9 (7-10)

*Injections include only intravitreal anti-vascular endothelial growth factors. IQR: Interquartile range

with protocol-defined PRN re-treatment and follow-up criteria up to a mean of 14.1 months of follow-up.[42] Likewise, the open-label extension study of VISTA (i.e., the ENDURANCE study), showed similar visual gains maintained by IVA through 12 and 24 months with an individualized PRN treatment protocol with reduced IVI frequency.[43,44] The differences between extension studies with and without protocol-defined re-treatment and follow-up criteria support the findings of undertreatment and lower visual gains in RWE studies.

During their treatment course in routine clinical practice, DME patients were shown to be affected more by patient-related non-adherence than other macular pathologies, as they usually have multiple comorbidities and a disease requiring individualized treatment patterns.[45,46,47,48] Numerous prospective and retrospective RWE studies involving these patients have provided complementary information about the effectiveness of intravitreal anti-VEGF agents on DME, particularly emphasizing the importance of number of follow-ups and injections to avoid undertreatment.[17,18,19,20,21,22,23,24,25,26,27,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63]

The prospective, non-interventional RWE of the OCEAN Study Group from Germany reported a mean of 4.4 and 5.5 IVR injections in 12 and 24 months, leading to mean BCVA gains of +4.0 and +5.2 letters from baseline, respectively.[49] They stated that BCVA changes from baseline were slightly greater in those receiving 7 or more injections (+6.3 and +6.1 letters in 12 and 24 months, respectively).[49] The relatively lower number of IVIs and visual gains than in our study could be attributed to the fewer OCT evaluations at follow-up visits in the OCEAN study due to reimbursement issues in Germany.[49] In contrast, OCT was employed in all follow-up visits in our study as a main contributor to the IVI decision (mean cumulative evaluations of 4.1 and 7.5 vs. 7.8 and 12.3 at 12 and 24 months, respectively). The prospective BOREAL-DME study from France reported mean

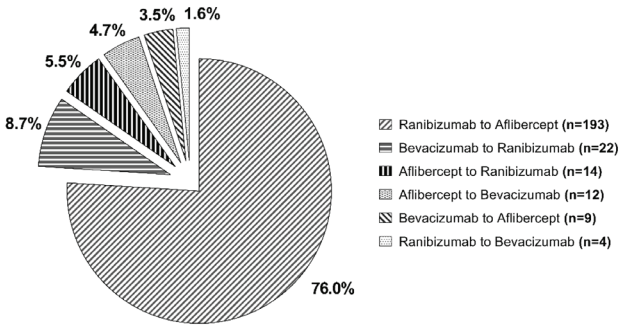

Figure 3. Rates of switches between intravitreal anti-vascular endothelial growth factor agents during the study period

BCVA gains of +7.4 and +4.1 with a cumulative mean of 5.1 and 7.6 anti-VEGF IVIs in 12 and 36 months, respectively.[20,50] Recently, the 2-year prospective APOLLON study from France reported a higher mean cumulative number of IVA injections (7.6 and 11.6) in 12 and 24 months, leading to +6.5 and +3.9 mean letter gains, respectively.[51,52] The authors attributed the relatively smaller visual improvements despite a higher number of IVIs at 2 years in the APOLLON study to structural changes related to the long-standing DME in previously treated patients.[52] One-year results of the global LUMINOUS study, which prospectively evaluated the effectiveness of IVR for any indications in real-life settings, showed that BCVA change from baseline in DME patients differs between -0.3 to +6.9 letters with mean numbers of IVR injections ranging from 2.2 to 6.0 among countries.[53] Additionally, better visual gains were observed in patients receiving 5 or more IVR injections (including loading doses) in the first year.[53]

In a 4-year retrospective RWE study from Denmark including 566 eyes with DME, the mean changes in BCVA and CMT from baseline to 12, 24, 36, and 48 months were reported as +3.9, +3.5, +2.7, +1.8, and +2.3 letters and -102.6, -106.9, -105.9, and -131.6 µm, respectively.[54] The mean number of IVIs per year gradually decreased from 6.1 in the first year to 3.0, 2.6, and 1.8 in the second, third, and fourth years, respectively.[54] The authors also reported an increase of 1.01 letters for every extra anti-VEGF IVI when adjusted for age and baseline BCVA, further emphasizing the importance of number of IVIs in visual prognosis.[54] Another 4-year retrospective RWE study from Sweden with a much smaller sample size of 102 eyes reported an improvement of +7.0 and +6.6 letters at 2 and 4 years with a mean of 4.7, 1.4, 0.7, and 0.9 IVIs per year in the first, second, third, and fourth years of the study, respectively.[55] A retrospective RWE study from Moorfields reported mean BCVA changes of +5.2, +4.8, +3.4, and +2.5 letters with mean cumulative IVI rates of 6.4, 8.9, 11.1, and 14.0 during 12, 24, 36, and 48 months of follow-up.[56] Other studies from different countries reported mean cumulative BCVA gains of +3.0-11.2 letters at 1 year with a mean of 3.1-8.0 IVIs,[17,18,19,21,22,23,26,57,58,59,60,61,63] +2.3-10.0 letters at 2 years with a mean of 5.0-12.8 IVIs,[18,19,21,22,58,60,62,63] and +3.0-6.9 letters at 3 years with a mean of 9.0-12.5 IVIs.[19,21,58]

Apart from demonstrating lower visual gains from RCTs due to lower injection frequencies and undertreatment, we observed relatively better BCVA letter gains than most RWE studies mentioned above. The probable reason is the so-called ceiling effect resulting from fewer gainable letters because of the better baseline BCVAs in those studies compared to ours (51.4 letters). For example, prospective RWEs such as the OCEAN,

Table 3. Outcomes of combination therapy with intravitreal dexamethasone implant in study cohorts

	Eyes n (%)	BCVA mean ± SD letters			CMT mean ± SD µm			Number of anti-VEGF IVIs n (IQR)	Number of visits n (IQR)
		Baseline	Final	Change	Baseline	Final	Change		
6-month cohort									
IDI (+)	1352 (100)	41.2±23.0	58.2±18.2	17.0±25.1	602.1±216.0	343.8±116.4	-258.3±251.7	3 (3-4)	4 (4-5)
IDI (-)	129 (9.5)	52.5±21.0	60.8±18.0	8.3±18.1	470.1±172.1	342.6±127.4	-127.5±167.2	3 (3-4)	4 (3-5)
p[a]	1223 (90.5)	**<0.001**	0.073	**0.001**	**<0.001**	0.891	**<0.001**	0.131	**0.005**
12-month cohort									
IDI (+)	1185 (100)	41.6±21.4	55.5±18.3	13.9±25.7	579.0±210.0	330.5±119.1	-248.5±252.4	5 (4-6)	7 (6-9)
IDI (-)	308 (26.0)	55.2±20.4	61.2±19.3	6.0±19.0	439.7±150.4	327.1±128.0	-112.6±182.8	5 (4-6)	8 (6-10)
p[a]	877 (74.0)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.356	**<0.001**	**0.001**	**<0.001**
24-month cohort									
IDI (+)	972 (100)	43.0±21.1	56.0±19.0	13.0±25.9	554.2±210.8	339.5±152.7	-214.7±236.2	7 (6-8)	10 (9-13)
IDI (-)	400 (41.2)	55.2±20.7	60.7±20.6	5.5±20.1	472.6±144.4	293.5±106.4	-134.1±154.7	6 (5-8)	11 (9-15)
p[a]	572 (58.8)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.001**	**<0.001**	**<0.001**	**<0.001**
36-month cohort									
IDI (+)	623 (100)	43.0±21.4	54.4±22.6	11.6±27.5	549.5±229.4	274.3±92.0	-275.2±261.4	9 (8-11)	16 (14-17)
IDI (-)	279 (44.8)	54.2±20.5	60.1±20.2	5.9±23.4	428.7±143.3	261.8±83.0	-166.9±168.6	9 (7-10)	16 (14-18)
p[a]	344 (55.2)	**<0.001**	**0.002**	**0.018**	**<0.001**	0.136	**<0.001**	**<0.001**	0.977

[a]Mann-Whitney U test. Bold values indicate statistical significance. Anti-VEGF: Anti-vascular endothelial growth factor, BCVA: Best corrected visual acuity, CMT: Central macular thickness, IDI: Intravitreal dexamethasone implant, IQR: Interquartile range, SD: Standard deviation

Table 4. Functional and anatomical gains, number of intravitreal injections, and macular laser rates in selected milestone randomized controlled trials

	Eyes (n)	BCVA change from baseline (ETDRS letters)	CMT change from baseline (µm)	Number of cumulative intravitreal injections (n)	Macular laser rates (%)
Our study					33.5 (overall)
3 months	1372	+7.6[a]	-115.4[a]	3.0[b]	
6 months	1352	+9.1[a]	-140.0[a]	3.0[b]	
12 months	1185	+8.0[a]	-147.9[a]	5.0[b]	
24 months	972	+8.6[a]	-167.3[a]	7.0[b]	
36 months	623	+8.4[a]	-215.4[a]	9.0[b]	
BOLT					
12 months[6]	42	+8.0[b]	-130.0[a]	9.0[b]	-
24 months[7]	37	+8.6[a]	-146.0[a]	13.0[b]	-
READ-2[c]					
6 months[32]	37	+7.2[a]	-106.7[a]	4.0[a]	-
24 months[33]	33	+7.7[a]	-78.9[a,d]	9.3[a]	-
36 months[34]	28	+10.3[a]	-132.0[a]	14.7[a]	-
RESTORE[c]					
12 months[35]	115	+6.8[a]	-118.7[a]	7.0[b]/7.0[a]	-
24 months[36]	83	+7.9[a]	-140.6[a]	10.0[b]/11.3[a]	16.9
36 months[37]	83	+8.0[a]	-142.9[a]	14.2[a]	24.1
RISE[e]					
24 months[8]	125	+11.9[a]	-253.1[a]	24.0[b]/20.9[a]	35.2
36 months[9]	125	+11.0[a]	-269.1[a]	34.0[b]/28.5[a]	37.6
RIDE[e]					
24 months[8]	127	+12.0[a]	-270.7[a]	24.0[b]/21.9[a]	19.7
36 months[9]	127	+11.4[a]	-266.7[a]	34.0[b]/30.4[a]	21.3
DRCR.net Protocol I[f]					
12 months[5]	188	+9.0[a]	-137.0[a]	9.0[a]	30.0
24 months[38]	139	+9.0[a]	-150.0[a]	12.0[a]	42.0
36 months[39]	147	+10.0[a]	-155.0[a]	15.0[a]	46.0
60 months[40]	111	+10.0[a]	-165.0[a]	17.0[a]	44.0
DRCR.net Protocol T					
12 months[14]					
IVB	206	+9.7[a]	-101.0[a]	10.0[b]	56.0
IVR	206	+11.2[a]	-147.0[a]	10.0[b]	46.0
IVA	208	+13.3[a]	-169.0[a]	9.0[b]	37.0
24 months[15]					
IVB	185	+10.0[a]	-126.0[a]	16.0[b]	64.0
IVR	191	+12.3[a]	-149.0[a]	15.0[b]	52.0
IVA	201	+12.8[a]	-171.0[a]	15.0[b]	41.0
VIVID					
52 weeks[10]	136[g]/135[h]	+10.5[g]/+10.7[h]	-195.0[g]/-192.4[h]	12.2[a,g]/ 8.7[a,h]	4.4[g]/8.1[h]
100 weeks[11]	136[g]/135[h]	+11.4[g]/+9.4[h]	-211.8[g]/195.8[h]	22.6[a,g]/13.6[a,h]	7.4[g]/11.1[h]
148 weeks[12]	136[g]/135[h]	+10.3[g]/+11.7[h]	-221.3[g]/-222.4[h]	32.0[a,g]/18.1[a,h]	7.4[g]/11.9[h]
VISTA					
52 weeks[10]	154[g]/151[h]	+12.5[g]/+10.7[h]	-185.9[g]/-183.1[h]	11.8[a,g]/8.4[a,h]	2.6[g]/0.7[h]
100 weeks[11]	155[g]/152[h]	+11.5[g]/+11.1[h]	-191.4[g]/-191.1[h]	21.3[a,g]/13.5[a,h]	3.2[g]/8.6[h]
148 weeks[12]	155[g]/152[h]	+10.4[g]/+10.5[h]	-204.6[g]/-212.7[h]	29.6[a,g]/18.1[a,h]	4.5[g]/10.5[h]
VIVID-east					
52 weeks[41]	122[g]/116[h]	+13.6[g]/+13.1[h]	-231.1[g]/-232.0[h]	12.6[g]/8.7[h]	7.1[g,i]/6.2[h,i]

[a]Mean value, [b]Median value, [c]Ranibizumab only group, [d]Manually calculated from Supplementary Table 2B of the original article by Nguyen et al.[33], [e]Ranibizumab 0.5 mg group, [f]Ranibizumab plus deferred laser group, [g]Aflibercept 2 mg intravitreal injections every 4 weeks, [h]Aflibercept 2 mg intravitreal injections every 8 weeks after 5 initial monthly dosing, [i]Proportion of eyes meeting the criteria for additional treatment, regardless of whether they received the treatment. ETDRS: Early treatment diabetic retinopathy study, CMT: Central macular thickness, IVA: Intravitreal aflibercept, IVB: Intravitreal bevacizumab, IVR: Intravitreal ranibizumab, DRCR.net: Diabetic Retinopathy Clinical Research Network

BOREAL-DME, APOLLON, and global LUMINOUS studies had patients with mean baseline BCVAs of 60.6, 59.2, 62.7, and 57.7 letters, respectively, even if they did not have any related exclusion criteria.[20,49,50,51,52,53] Similar differences also can be seen in relatively large-scale retrospective RWE from Denmark, Sweden, and Moorfields with baseline BCVAs of 64.9, 60.8, and 61.0, respectively.[54,55,56]

Recently, Durukan et al.[27] reported +8.3, +5.3, and +4.4 mean letter gains and -105.5, -107.7, and -114.3 µm CMT reductions compared to baseline with a mean of 4.6±2.0, 2.3±1.9, and 1.8±1.8 anti-VEGF IVIs per year in mutually exclusive groups of DME patients from Türkiye followed up for 12, 24, and 36 months, respectively. Those findings align with our results regarding IVI numbers of all cohorts and mean letter gains in the first year (8.0). However, better mean letter gains were observed in our 24- and 36-month cohorts (8.6 and 8.4, respectively), as well as better CMT reductions in all our cohorts. This discrepancy in BCVA gains could have resulted from Durukan et al.[27] excluding the eyes with visual acuity worse than 20/400 Snellen, resulting in a mean overall baseline BCVA of 55.6 letters, which is higher than ours. Also, although they stated that there were no significant differences in BCVA gains of the cohorts at any time, another reason could be the mutually exclusive nature of the cohort groups and adjunctive therapies the patients received, since there were also smaller reductions in CMT from baseline, especially at 24 and 36 months.[27] Furthermore, although they did not stratify according to cohort, the overall IDI combination rate (23.6%) was also lower than the corresponding cumulative IDI combination rates in our study (26.0%, 41.2%, and 44.8% for the 12-, 24-, and 36-month cohorts, respectively), which might explain our better BCVA letter gains and CMT reductions.[27] In another study recently published in Türkiye, the number of mean visits in both groups at 12 months (6.8±2.1 and 6.7±1.9) was similar to that in our study.[64]

While not allowed in RCTs evaluating anti-VEGFs in DME treatment, anti-VEGF switch and IDI combination rates and their effects on study outcomes are often ignored in RWE, or if they are not already an exclusion criterion, those eyes are removed from the outcome analysis.[19,51,52,53,54,56,57,60] Of the DME RWE studies reporting treatment switch rates, the rates of switching the index agent to any other anti-VEGF ranges from 8.5 to 20.9%[20,23,50,60] and rates of switching to IDI range from 3.9 to 26.7%[20,23,27,50,55] depending on the follow-up time. The overall anti-VEGF switch rate in our study is comparable to those reported studies, but the IDI combination rates are relatively higher. An RWE study of IDI for DME comparing treatment-naive and refractory eyes (i.e., the IRGREL-DEX Study) showed that the BCVA of the refractory eyes was improved by a mean of +7.3 letters and the mean CMT decreased from 565 to 313 µm in 24 months with a mean of 3.1 IDIs (range, 1-4), while 16.9% of the patients also received IVIs of anti-VEGFs.[65] Although we did not explicitly investigate the reason for IDI combination in our cohort, if these patients are considered resistant to anti-VEGFs, the results can be regarded as comparable to the IRGREL-DEX study.

The variable macular laser rescue treatment criteria of RCTs have resulted in different studies with several intravitreal agents reporting macular laser rates at various time intervals and during specific study dates (Table 4).[5,8,9,10,11,12,14,15,36,37,38,39,40,41] Nevertheless, the overall macular laser treatment rate in our study (33.5%) appears comparable to the rates of salvage therapy in RCTs. The TURK-DEM real-life registry study demonstrated that between the years of 2013 and 2014, the most common DME treatment preferences among Turkish retina specialists were laser photocoagulation (32.1%) and intravitreal anti-VEGF injection (31.8%), followed by their combination (30.8%).[66] As can be appreciated from our current study, those preferences seem to change with the growing literature supporting the superior outcomes of anti-VEGF agents and the risk of limiting visual gain potential by laser-induced iatrogenic structural damage.[40] Recently, subthreshold micropulse laser was shown to be non-inferior to macular laser in treating DME, with a slightly higher treatment rate.[67] There are also numerous reports of its additive effects as a combination therapy with anti-VEGFs, such as reducing the need for re-injection.[68,69] Therefore, although the gains in such a subgroup of patients are beyond the scope of this report, the use of micropulse laser as adjunctive therapy in this real-life DME treatment study (n=44, 3.2%) is worth mentioning.

Study Limitations

Several limitations should be considered while interpreting the results of this study. First of all, its retrospective, observational nature prevented randomization and intervention, reducing the reliability of effectiveness parameters. Similarly, the selected time intervals for assessing treatment outcomes were arbitrary rather than scheduled as in RCTs and may not have coincided with an actual effect. Also, the possibility of under-reporting any complication cannot be eliminated due to the retrospective data collection from patient files. Similarly, unstandardized re-treatment indications from different clinics would have affected the number of overall treatments and visits. Visual acuity evaluated in routine clinical practice may not reflect actual BCVA. Finally, the study population included patients who were treated before 2018 and according to drug reimbursement rules at that time. The reimbursement rules changed after 2018, and patients with DME in Türkiye have been treated according to the new reimbursement rules since that time. This may have altered the real-world data in Türkiye. However, strengths of the study are the relatively large sample size from a diverse DME patient population, the inclusion of different treatment modalities as a whole, the absence of exclusion criteria related to visual acuity (mirroring routine clinical practice), and the provision of complete data without using any imputation method for missing data.

Conclusion

This largest-scale RWE study from Türkiye provides further insights into the treatment of DME initiated with anti-VEGF agents, supporting the observations of less satisfactory anatomical

and functional real-life outcomes than in RCTs. Furthermore, our results also suggest that the lower number of IVIs is the probable reason, as in other RWE studies. Future reports from the MARMASIA Study Group will focus on specific groups of patients with particular disease characteristics, which is expected to increase the literature data on real-life DME treatment.

Ethics

Ethics Committee Approval: Kocaeli University Faculty of Medicine approved the study protocol (no: GOKAEK-2022/07.19, date: 14.04.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: MARMASIA Study Group, Concept: V.L.K., Design: V.L.K., A.Ö., Ö.Ş., Data Collection or Processing: MARMASIA Study Group, Analysis or Interpretation: MARMASIA Study Group, Literature Search: MARMASIA Study Group, Writing: U.Y., M.O.S.

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

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