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

Yayla et al. Diabetic Macular Edema in Real World

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Abstract

Objectives: This study aims 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 provides an overview of outcomes during routine clinical practice in Turkey.

Materials and Methods: This retrospective, real-world study included 1372 eyes (854 patients) treated in a *pro-re-nata* protocol by 21 ophthalmologists from 8 tertiary clinics on the Asian Side of the Marmara Region of Turkey (The MARMASIA Study Group). Five cohort groups were established by collecting the patients' baseline and 3rd-, 6th-, 12th-, 24th-, and 36th-month follow-up data, of which each subsequent cohort may comprise the previous. Changes in best-corrected visual acuity (BCVA, approximate ETDRS letters) and central macular thickness (CMT, µm), number of visits and IVI, and anti-VEGF switch and intravitreal dexamethasone implant (IDI) combination rates 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±180.3µm. 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 -215.4µm at the 3rd-, 6th-, 12th-, 24th-, and 36th-month visits ($p<0.001$ for all). The number of median cumulative anti-VEGF IVI were 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 Turkey demonstrated BCVA gains inferior to randomized-controlled trials mainly due to lower number of IVI. However, those gains were relatively superior to other real-life study counterparts by lower baseline BCVA of the study population and higher IDI combination rates.

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

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, RCT's design, which controls the variability of the data while ensuring its quality with restrictive eligibility criteria, withholds their replicability and reproducibility in clinical practice.[2] Therefore, real-world evidence (RVE) 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.[5-15] 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 treating DME, similar results could not be obtained in their respective interstudy arms, even though they included patients with similar demographics and disease characteristics in each.[9,12] These two examples alone demonstrate the need for complementary studies in real-life settings for DME treatment.

Furthermore, the five-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 different modalities could be applied to DME patients in routine clinical practice at clinician discretion after two years of protocol-defined follow-up and re-treatment.[14-16] From two to five years, those patients were shown to lose best-corrected visual acuity (BCVA) even though they preserved central macular thickness (CMT) at a protocol depending on clinician discretion.[16] Also, several RWE studies, even systematic reviews and meta-analyses of them report the anatomical and functional effectivity of anti-VEGF agents in DME but with less impressive results than RCTs, mainly due to undertreatment, less frequent monitoring, and lower patient compliance.[17-27]

Recently, Durukan et al.[27] published the first large-scale RWE study of DME treatment from the Central Anatolian Region of Turkey, reporting 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 the intravitreal anti-VEGF treatment of DME in 8 tertiary reference centers located on the ASIAn Side of the MARMara Region of Turkey (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, including 22 ophthalmologists experienced in retinal diseases from 8 tertiary clinics in 3 cities (Istanbul, Kocaeli, and Sakarya) on the Asian Side of the Marmara Region of Turkey. The Institutional Review Board of XXX approved the study protocol (No: GOKAEK-2022/07.19). The study followed the 1964 and later amendments of the Declaration of Helsinki ethical principles. In addition, written informed consent was routinely provided by all patients at their first presentation to the corresponding clinics about having their medical information used in the study analysis. 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 had a follow-up of at least three months were retrospectively screened and included in the study. In Turkey, for

treatment-naive DME patients to receive reimbursement from the Turkish Social Security Institution (SSI), it has been made mandatory to start the treatment with three loading doses of IVB injections with the "Communiqué Amending the SSI Health Implementation Communiqué" published on December 28, 2018.[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 in 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 files. The study inclusion criteria were established as being at the age of 18 years or older, having 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, at least three months of follow-up, and having at least four or more visits per year for the patients who had a follow-up of more than one year. The patients who had a phacoemulsification surgery one month before and pan-retinal, focal, or grid laser photocoagulation, or micropulse laser in the previous four months before the study enrolment, 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 the previous intravitreal therapy with anti-VEGFs or corticosteroids, presenting BCVA, whether or not applied loading doses of intravitreal anti-VEGFs, and use of intravitreal dexamethasone implant (IDI; Ozurdex®, Abbvie-Allergan, CA, USA), pan-retinal, focal, or grid laser photocoagulation, or micropulse laser, as well as phacoemulsification and PPV surgeries at any point of the follow-up.

Baseline and Follow-up Data

The baseline demographics and medical information of the patients included age, gender, duration of diabetes mellitus (DM), treatment of DM (none, oral antidiabetic drugs [OAD], insulin, or combination of OAD and insulin), accompanying disorders (none, hypertension [HT], coronary artery disease [CAD], cerebrovascular accident [CVA], and chronic kidney disease [HD] leading to hemodialysis [HD]), history of glaucoma, antiglaucomatous use (if any, classified as prostaglandin analogs and others), previous anti-VEGF IVI (if any; numbers and agents), previous pan-retinal photocoagulation and previous PPV history.

Five retrospective cohort groups were formed so that subsequent cohorts may also include patients from the previous cohorts by taking the 3rd, 6th, 12th, 24th, and 36th month (±2 weeks for each) examinations as follow-up data of the patients. All patients had a comprehensive ophthalmic examination in 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 applied at clinicians' discretion if there was suspicion of new neovascularization or persistent peripheral retinal ischemia.

BCVA, lenticular status (as pseudophakic or phakic), DR grading (as nonproliferative [NPDR] or proliferative [PDR]), and OCT parameters were collected from specified visits. OCT parameters of particular importance were settled as the following: CMT (μm, automatically calculated by corresponding OCT device's software after foveal alignment ensured by the clinician); DME pattern (classified as diffuse/spongious, cystoid, diffuse/spongious plus subretinal fluid [SRF], and cystoid plus SRF); cystic pattern according to the European School for Advanced Studies in Ophthalmology (ESASO) classification[29] (as absent [0], mild [1], moderate [1], or severe [2]); largest cyst diameter (μm, measured manually by corresponding

OCT device's software); SRF height (µm, measured manually by corresponding OCT device software from the outer surface of the photoreceptor layer and the inner surface of the retinal pigment epithelium); the presence of disorganization of retinal inner layers (DRIL, defined as more than 500 µm of the foveal area in the horizontal plane[30]); continuity (classified as interrupted, partially preserved, totally preserved, or indiscernible) of the ellipsoid zone (EZ) and the external limiting membrane (ELM); the presence of epiretinal membrane (ERM) and the status of the posterior hyaloid (as attached, detached, or indiscernible).

Additional information collected at each follow-up visit were; the intravitreal anti-VEGF agent used, treatment protocol (defined as 3+PRN if three loading dose was applied and 1+PRN if not applied), number of cumulative injections, number of cumulative visits, stabilization of the macula (defined as first visit time as months when the injection deferred according to PRN protocol), the first stabilization time of the macula, application of phacoemulsification, PPV, and pan-retinal, focal, and grid laser photocoagulation, and micropulse laser and their application times (months), and presence of intravitreal hemorrhage (IVH) and neovascular glaucoma (NVG), as well as any other complications and adverse events.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) software for Windows version 22.0 (IBM Crop., 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 (SD) or median (interquartile range [IQR] as the value at quartile 25 – quartile 75), and categorical data were presented as frequency (n) and percentage (%). Snellen BCVA values were converted to the 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. Also, logMAR values were converted to approximate Early Treatment Diabetic Retinopathy Study (ETDRS) letter score by using the formula "logMAR = 1.7 - (0.02)(ETDRS letter score)" as suggested by Beck et al.[31] Since the logMAR values of 1.7 and higher give a negative value, 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 1372 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 three 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.

Eight hundred eighteen (59.6%) of the eyes included in the study 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 pan-retinal laser photocoagulation, and 35 (2.6%) had a history of PPV.

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

The baseline characteristics of the patients and their 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 six-month period, BCVA gradually declined after six months despite the progressive decrease in CMT.

BCVA, best-corrected visual acuity; CMT, central macular thickness; ETDRS, early treatment diabetic retinopathy study; logMAR, logarithm of the minimum angle of resolution.

Error bars indicate standard deviation.

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 three years. The mean change in letter scores from baseline was 7.6±17.3 at the 3rd ($p<0.001$), 9.1±19.0 at the 6th (adj. $p<0.001$), 8.0±21.2 at the 12th (adj. $p<0.001$), 8.6±23.0 at the 24th (adj. $p<0.001$), and 8.4±85.4 letters at the 36th-month (adj. $p<0.001$) visits. And the mean letter score changes from the subsequent visits were 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 3rd, 6th, 12th, 24th, and 36th-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 the 3rd ($p<0.001$), -140.0±181.1 at the 6th (adj. $p<0.001$), -147.9±211.6 at the 12th (adj. $p<0.001$), -167.3±196.4 at the 24th (adj. $p<0.001$), and -215.4±221.7 µm at the 36th-month (adj. $p<0.001$) visits. And the mean CMT changes from the previous visit were -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 3rd, 6th, 12th, 24th, and 36th-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 number of median visits and intravitreal anti-VEGF injections in each cohort stratified by study visits. The number of median cumulative number of visits were 2 (2-2), 4 (4-5), 7 (6-10), 11 (9-14), and 16 (14-18), and intravitreal anti-VEGF injections were 3 (2-3), 3 (3-4), 5 (4-6), 7 (5-8), and 9 (7-10) in 3-, 6-, 12-, 24-, and 36-month cohorts, respectively. Number of median injections per year decreased from 5 (4-6) in 1st year to 2 (1-3) in the 2nd ($p<0.001$) and 2 (1-3) in the 3rd year ($p<0.001$; adj. $p<0.001$, adj. $p<0.001$, and adj. $p=1.000$ for 1st vs. 2nd, 1st vs. 3rd, and 2nd vs. 3rd year, respectively).

Anti-VEGF Switch and Additional Treatments

Anti-VEGF agent switches were made during the study period in a total of 254 eyes (18.5%) during the study period, of which 229 (90.2%) of them were intentional at the clinician's discretion. Fifty-one (20.1%) of the anti-VEGF agent switches were between 3 to 6 months, 97 (38.2%) were between 6 to 12 months, 66 (26.0%) were between 12 to 24 months, and 40 (15.7%) were between 24 to 36 months periods. 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**.

Four hundred eighty of 1372 eyes (35.0%) had combination therapy with at least one IDI injection in the entire cohort with a mean of 2.4±1.4 (range, 1-9) injections. While none of the eyes had IDI injection in the 3-month cohort, 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 were phacoemulsification in 315 (23.0%), PPV in 68 (5.0%), pan-retinal laser photocoagulation in 444 (32.4%), only focal or grid laser photocoagulation in 267 (19.5%), focal and grid laser photocoagulation in 192 (14.0%), and micropulse laser in 44 (3.2%) eyes.

Adverse Events

During the study period, encountered ocular adverse events were IVH in 98 (7.1%), NVG in 22 (1.6%), increased intraocular pressure in 2 (0.1%), rhegmatogenous retinal detachment in 2 (0.1%), and endophthalmitis in 1 (0.1%) eyes.

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

Discussion

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

The results of one of the earliest RCTs compared the effectivity of an anti-VEGF agent (ranibizumab) against macular focal/grid laser photocoagulation (READ-2) was similar to our study regarding the 6th and 24th-month results of the 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 more than two months on a PRN basis differentiates READ-2 from other RCTs regarding the risk of possible undertreatment.[32,33] Moreover, the 3rd 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 number of IVI of 5.4 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.[35-37] However, the reported 12-, 24- and 36-month functional and anatomical results of the RESTORE study were even worse than our results, with much more number of IVI throughout the study period **(Table 4)**.[35-37] These results can be explained by the fact that the ratio of eyes with an initial BCVA of 60 or fewer letters in the RESTORE study is relatively low (33.0% and 27.7% in 12- and 24-36-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.[35-37] Yet, the mean visual gains of the lower-seeing eyes (≤60 letters) were reported to be +8.2 and +10.5 letters in the 12- and 24-month results.[35,36]

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

that when the protocol-defined re-treatment with IVR continued, mean visual gain at 1 year could be maintained for 5 years with progressively diminishing number of injections.[40] The open-label extension study of RISE/RIDE studies also showed that visual and anatomical gains achieved after monthly IVR were maintained with a 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 maintained visual gains by IVA through 12 and 24 months with individualized PRN treatment protocol with reduced IVI frequency.[43,44] Those 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.[45-48] 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-up and injections to avoid undertreatment.[17-27,49-63]

The prospective, non-interventional RWE of the OCEAN Study Group from Germany reported mean number of IVR injections of 4.4 and 5.5 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 IVI and visual gains than in our study could be attributed to the OCEAN study's fewer OCT evaluations at follow-up visits due to reimbursement issues in Germany, which 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 up to months 12 and 24, respectively).[49] The prospective BOREAL-DME study from France reported mean BCVA gains of +7.4 and +4.1 with mean cumulative anti-VEGF IVI of 5.1 and 7.6 in 12 and 36 months, respectively.[20,50] Recently, the two-year prospective APOLLON study from France reported higher number of mean cumulative IVA injections of 7.6 and 11.6 in 12 and 24 months, leading to +6.5 and +3.9 mean letter gains, respectively.[51,52] Relatively lower visual improvements despite number of convenient IVI in the 2nd year of the APOLLON study were attributed to structural changes related to the long-lasting DME in previously treated patients by the authors.[52] One-year results of the global LUMINOUS study prospectively evaluating the efficacy of IVR on any indications in real-life settings showed that BCVA change from baseline in DME patients differs between -0.3 to +6.9 letters with means of 2.2 to 6.0 number of IVR among countries.[53] Also, 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 of DME patients, 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 IVI per year gradually decreased from 6.1 in the 1st year to 3.0, 2.6, and 1.8 in the 2nd, 3rd, and 4th years, respectively.[54] The authors also reported an increase of 1.01 letters for every extra anti-VEGF IVI adjusted for age and baseline BCVA, further emphasizing the importance of number of IVI 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 the 2nd and 4th-year number of visits with means of 4.7, 1.4, 0.7, and 0.9 number of IVI per year in 1st, 2nd, 3rd, and 4th 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 the study period.[56] Other studies from different countries

reported mean cumulative BCVA gains of +3.0-11.2[17-19,21-23,26,57-61,63], +2.3-10.0[18,19,21,22,58,60,62,63] and +3.0-6.9[19,21,58] letters with number of mean cumulative IVI of 3.1-8.0[17-19,21-23,26,57-61,63], 5.0-12.8[18,19,21,22,58,60,62,63], and 9.0-12.5[19,21,58] in 1st, 2nd, and 3rd years, respectively.

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 with better baseline BCVAs in those studies compared to ours (51.4 letters). For example, the prospective RWEs such as OCEAN, 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 they do not have any regarding exclusion criteria.[20,49-53] Similar differences also can be seen in relatively large-scale retrospective RWEs from Denmark, Sweden, and Moorfields with baseline BCVAs of 64.9, 60.8, and 61.0, respectively.[54-56]

Recently, Durukan AH 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 IVI per year in the mutually exclusive groups of DME patients from Turkey followed up for 12, 24, and 36 months, respectively. Those findings align with our results regarding numver of IVI of all cohorts and mean letter gains in the 1st 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 excluding the eyes below the 20/400 Snellen visual acuity by Durukan AH et al.[27], resulting in a mean overall baseline BCVA of 55.6 letters, which is lower 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 they had since there were also fewer reductions in CMTs from baseline, especially at 24- and 36-months.[27] Furthermore, although they did not stratify it according to the cohorts, 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 12-, 24-, and 36-month cohorts, respectively), which might explain our BCVA letter gains and CMT reductions.[27] In another study recently published in Turkey, the number of mean visits in both groups at 12 months (6.8±2.1 and 6.7±1.9) was similar to those in our study.[64]

While not allowed in RCTs evaluating anti-VEGFs in DME treatment, the anti-VEGF switch and IDI combination rates and their effects on study outcomes are often ignored in RWEs, or if they are not already an exclusion criterion, those eyes are removed from the outcome analysis.[19,51-54,56,57,60] Of the DME RWE studies reporting treatment switch rates, the rates of switching index agent to any other anti-VEGF ranges between 8.5 to 20.9%[20,23,50,60], and switching to IDI ranges between 3.9 to 26.7%[20,23,27,50,55] depending on the follow-up time. Our study's overall anti-VEGF switch rate is comparable to those reported studies; however, the IDI combination rates are relatively higher. An RWE study of IDI for DME comparing treatment-naive and refractory eyes, i.e., IRGREL-DEX Study, showed that the BCVA of the refractory eyes was improved by a mean of +7.3 letters and the mean CMT reduced from 565 to 313 µm in 24 months with a mean of 3.1 (range, 1-4) IDI while 16.9% of the patients also receiving IVI of anti-VEGFs.[65] Although we did not explicitly investigate the reason for the IDI combination, 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 result in different studies with several intravitreal agents reporting various macular laser ratios at particular time intervals as well as specific study dates **(Table 3)**.[5,8-12,14,15,36-41] Nevertheless, the overall macular laser ratios of our study (33.5%) appear comparable to the rates used for salvage therapy in RCTs. The TURK-DEM real-life registry study demonstrated that the most common DME treatment

preferences among Turkish retina specialists were laser photocoagulation (32.1%) and intravitreal anti-VEGF injection (31.8%), followed by the combination of them (30.8%) between the years of 2013 and 2014.[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 has been demonstrated to be non-inferior to macular laser in treating DME with slightly higher treatment rates.[67] There are also numerous reports of its additive effects, such as reducing the need for re-injection as a combination therapy with anti-VEGFs.[68,69] Therefore, although the gains in such a subgroup of patients are beyond the scope of this report, the use of micropulse laser therapy in this real-life DME treatment study (n=44, 3.2%) as adjunctive therapy is worth mentioning.

Several limitations should be considered while interpreting the results of this study. First of all, its retrospective, observational nature preventing randomization and intervention reduces the reliability of effectiveness parameters. Similarly, the selected time intervals for assessing treatment outcomes were arbitrary rather than scheduled as in RCTs, which may not have coincided with an actual effect. Also, the possibility of under-reporting any complication can not 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 the actual BCVA. Finally, study population included the patients who were treated before 2018 and according to drug remibursment rules at that time. The reimbursment rules changed after 2018 and patients with DME in Turkey has been treated according to new reimbursment rules so far. So, real world-data might have been changed in Turkey. However, the study's relatively large sample size from a diverse DME patient population, the inclusion of different treatment modalities as a whole, no exclusion criteria regarding visual acuity mirroring routine clinical practice, and the provision of complete data without using any imputation method for missing data can be considered strengths of the study.

In conclusion, this largest-scale RWE study from Turkey 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 RCTs. Furthermore, the study results also point out that the number of lower IVI are the probable reason, as in other RWE studies. Future reports from the MARMASIA Study Group will focus on specific groups of patients with evaluated particular disease characteristics, which will expectedly increase the literature knowledge on the real-life DME treatment.

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Table 1. Baseline characteristics of the patients and their 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 Male	 455 (53.3) 399 (46.7)	 447 (53.3) 391 (46.7)	 385 (53.3) 337 (46.7)	 325 (55.9) 256 (44.1)	 203 (56.2) 158 (43.8)
DM duration, 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 OAD Insulin Combination	 3 (0.4) 306 (35.8) 483 (56.6) 62 (7.3)	 3 (0.4) 302 (36.0) 471 (56.2) 62 (7.4)	 3 (0.4) 257 (35.6) 404 (56.0) 58 (8.0)	 2 (0.3) 215 (37.0) 327 (56.3) 37 (6.4)	 0 (0.0) 123 (34.1) 288 (63.2) 10 (2.8)
Accompanying disorders, n (%) None HT CAD CVA CKD	 347 (40.6) 481 (56.3) 115 (13.5) 7 (0.8) 37 (4.3)	 343 (40.9) 469 (56.0) 113 (13.5) 6 (0.7) 36 (4.3)	 296 (41.0) 402 (55.7) 98 (13.6) 5 (0.7) 31 (4.3)	 245 (42.2) 315 (54.2) 71 (12.2) 4 (0.7) 22 (3.8)	 146 (40.4) 198 (54.8) 51 (14.1) 2 (0.6) 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)
Lenticular status, n (%) Phakic Pseudophakic	1056 (77.0) 316 (23.0)	1040 (76.9) 312 (23.1)	911 (76.9) 274 (23.1)	742 (76.3) 230 (23.7)	467 (75.0) 156 (25.0)
DR grade, n (%) NPDR PDR	999 (72.8) 373 (27.2)	985 (72.9) 367 (27.1)	865 (73.0) 320 (27.0)	709 (72.9) 263 (27.1)	486 (78.0) 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 Previously treated	818 (59.6) 554 (40.4)	805 (59.5) 547 (40.5)	694 (58.6) 491 (41.4)	537 (55.2) 435 (44.8)	339 (54.4) 284 (45.6)
Treatment protocol, n (%) 1+PRN 3+PRN	525 (38.3) 847 (61.7)	522 (38.6) 830 (61.4)	470 (39.7) 715 (60.3)	409 (42.1) 563 (57.9)	213 (34.2) 410 (65.8)
Initial anti-VEGF agent, n (%) Bevacizumab Ranibizumab Aflibercept	60 (4.4) 893 (65.1) 419 (30.5)	60 (4.4) 876 (64.8) 416 (30.8)	59 (5.0) 787 (66.4) 339 (28.6)	58 (6.0) 631 (64.9) 283 (29.1)	57 (9.1) 359 (57.6) 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, the logarithm of the minimum angle of resolution; NPDR, nonproliferative diabetic retinopathy; OAD, oral antidiabetic; PDR, proliferative diabetic retinopathy; PGA, prostaglandin analogs; PRN, pro re nata; SD, standard deviation

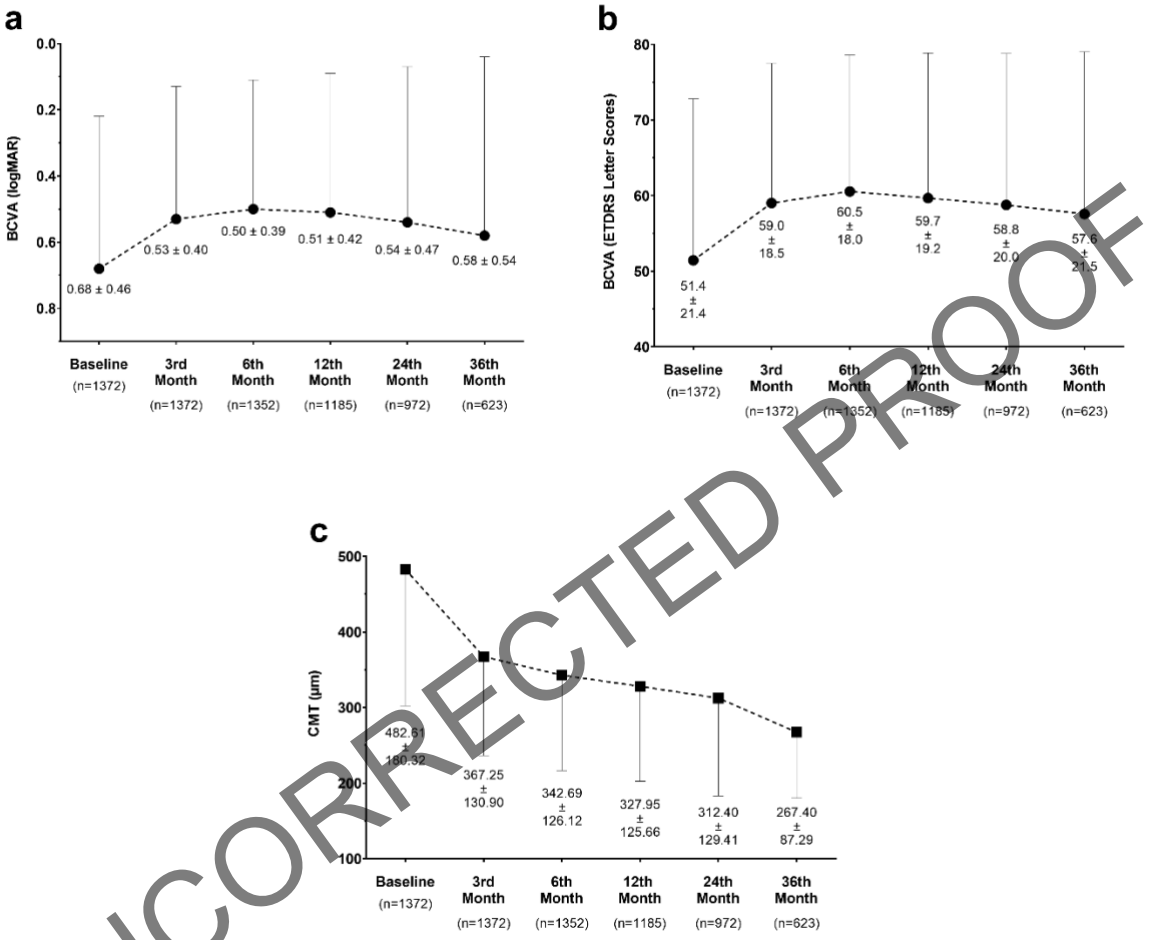

Figure 1. Best-corrected visual acuity **(a & b)** and central macular thickness **(c)** of the eyes during the study period.

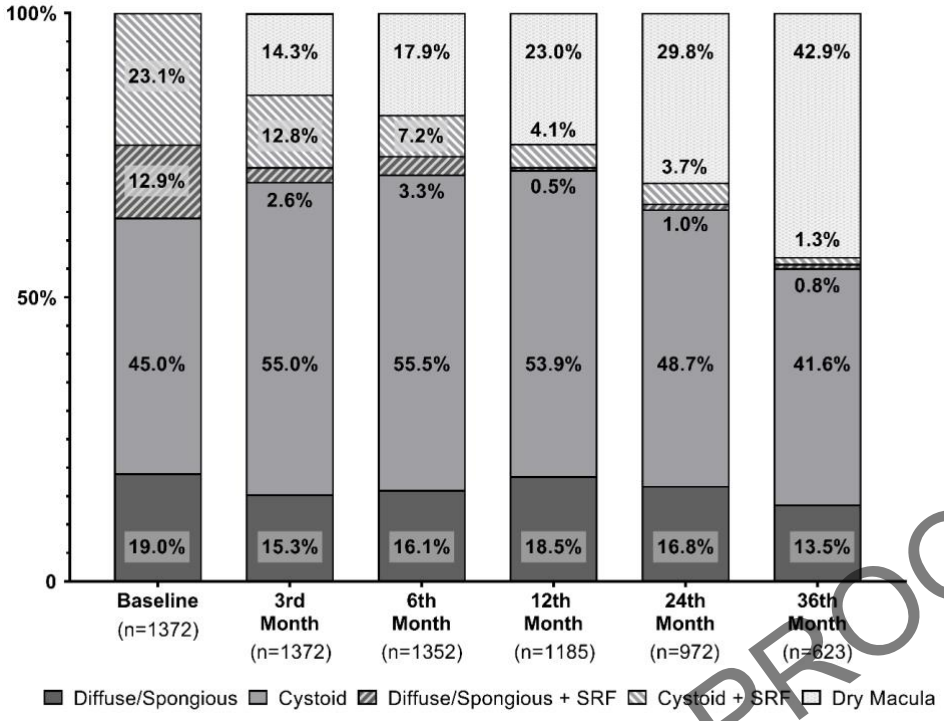

Figure 2. Diabetic macular edema patterns and dry macula rates during the study period. SRF, subretinal fluid.

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 3rd-Month					
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 6th-Month					
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 12th-Month					

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)	-	-	5 (4-6)	5 (4-6)	5 (4-6)
Per-year	-	-	5 (4-6)	5 (4-6)	5 (4-6)
Cumulative					
At 24th-Month					
Visits, median (IQR)					
Per-year	-	-	-	4 (4-5)	4 (4-5)
Cumulative	-	-	-	11 (9-14)	10 (9-13)
Injections*, median (IQR)	-	-	-	2 (1-3)	2 (1-3)
Per-year	-	-	-	7 (5-8)	7 (6-8)
Cumulative					
At 36th-Month					
Visits, median (IQR)					
Per-year	-	-	-	-	5 (4-7)
Cumulative	-	-	-	-	16 (14-18)
Injections*, median (IQR)	-	-	-	-	2 (1-3)
Per-year	-	-	-	-	9 (7-10)
Cumulative					

IQR, interquartile range.
*Injections include only intravitreal anti-vascular endothelial growth factors.

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 IVI** n (IQR)	**Number of Visits** n (IQR)
		Baseline	**Final**	**Change**	**Baseline**	**Final**	**Change**		
6-month cohort	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)
IDI (-)	1223 (90.5)	**<0.001**	0.073	**0.001**	**<0.001**	0.891	**<0.001**	0.131	**0.005**
p[a]									
12-month cohort	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)
IDI (-)	877 (74.0)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.356	**<0.001**	**0.001**	**<0.001**
p[a]									
24-month cohort	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)
IDI (-)	572 (58.8)	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.001**	**<0.001**	**<0.001**	**<0.001**
p[a]									

36-month cohort	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)
IDI (-)	344 (55.2)	**<0.001**	**0.002**	**0.018**	**<0.001**	0.136	**<0.001**	**<0.001**	0.977
p[a]									

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

a Mann-Whitney U test

Bold values indicate statistical significance

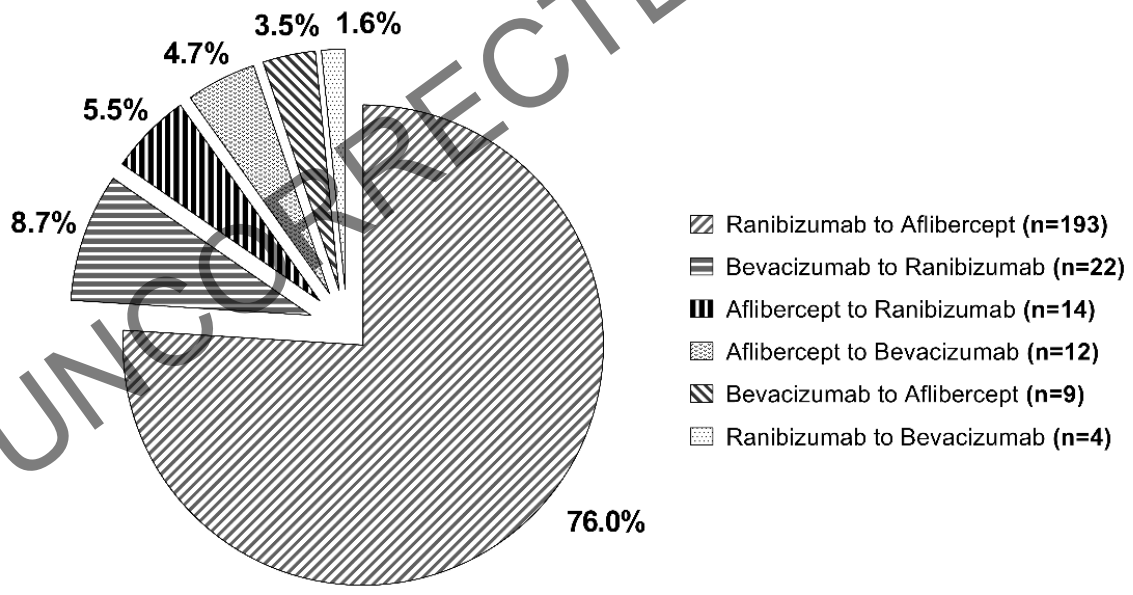

Figure 3. The rates of the switches between intravitreal anti-vascular endothelial growth factor agents during the study period.

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]	188	+9.0[a]	-137.0[a]	9.0[a]	30.0
12-months[5]	139	+9.0[a]	-150.0[a]	12.0[a]	42.0
24-months[38]	147	+10.0[a]	-155.0[a]	15.0[a]	46.0
36-months[39]	111	+10.0[a]	-165.0[a]	17.0[a]	44.0
60-months[40]					
DRCR.net Protocol T					
12-months[14]	206	+9.7[a]	-101.0[a]	10.0[b]	56.0
IVB	206	+11.2[a]	-147.0[a]	10.0[b]	46.0
IVR	208	+13.3[a]	-169.0[a]	9.0[b]	37.0
IVA					
24-months[15]	185	+10.0[a]	-126.0[a]	16.0[b]	64.0
IVB	191	+12.3[a]	-149.0[a]	15.0[b]	52.0
IVR	201	+12.8[a]	-171.0[a]	15.0[b]	41.0

IVA					
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]

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

[a] The mean values were given

[b] The median values were given

[c] Ranibizumab only group.

[d] Manually calculated from the supplementary Table 2B of the original article by Nguyen QD 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] The ratio of eyes having met the additional treatment criteria regardless of having the treatment