Real-World Results of Intravitreal Ranibizumab, Bevacizumab, or Triamcinolone for Diabetic Macular Edema

İrem Koç[a]   Sibel Kadayıfçılar[b]   Bora Eldem[b]

[a]Department of Ophthalmology, Ortaköy State Hospital, Aksaray, and [b]Department of Ophthalmology, Hacettepe University School of Medicine, Ankara, Turkey

Abstract

Objective: To compare the visual and anatomical outcomes of intravitreal ranibizumab (group 1), bevacizumab (group 2), and triamcinolone (group 3) for center-involving diabetic macular edema. ***Methods:*** We retrospectively enrolled 275 eyes of 208 consecutive patients. Visual acuity (VA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letters and central macular thickness (CMT) values on optical coherence tomography were extracted. Reported side effects were noted. ***Results:*** At 6 months, the mean changes in VA in group 1, group 2, and group 3 were +4.9, +4.3, and +4.6 letters, respectively ($p = 0.911$). Improvement of CMT at 6 and 24 months was significantly better in group 3 compared to groups 1 and 2 ($p = 0.012$ and $p = 0.001$, respectively). At 24 months, the only independent variable affecting the change in VA was initial VA ($p = 0.020$). Cataract and glaucoma prevalences were higher in group 3 ($p = 0.000$ and $p = 0.001$, respectively). ***Conclusions:*** Three treatment methods had similar effects with regard to improvement in VA; however, intravitreal triamcinolone provided additional anatomical improvement.

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Introduction

Diabetes mellitus (DM) is a chronic, multisystemic, metabolic disease with end-organ complications. Nearly 35% of the diabetic population are affected by diabetic retinopathy (DR), and diabetic macular edema (DME) is the leading cause of vision loss and can be observed in any stage of DR [1, 2]. Several agents, such as intravitreal corticosteroids or anti-VEGF agents including ranibizumab, bevacizumab, or aflibercept, have been proven effective for treatment of DME by numerous landmark studies [3–6]. Randomized controlled trials have been carried out to help clinicians in putting forward an individually tailored treatment regimen. Among intravitreal triamcinolone, ranibizumab, and bevacizumab, ranibizumab is the only agent with United States Food and Drug Administration approval for DME treatment, which was obtained after the pivotal RISE and RIDE studies in 2012 [7]. In daily practice, the choice of agent is challenged by several patient-related factors such as age, systemic diseases, initial best corrected visual acuity (BCVA) as put forward in the Protocol T Study, predisposition for cataract or glaucoma, as well as patient-independent factors including obtainability of the drug and cost of treatment [8]. Here we present our own results of a retrospective evaluation of intravitreal injections of either triamcinolone, ranibiz-

İrem Koç, MD
Ortaköy State Hospital
TR–68400 Aksaray (Turkey)
E-Mail kocirem@gmail.com

umab, or bevacizumab for DME, with the aim of underlining practical real-world differences from randomized controlled trials. As aflibercept and dexamethasone implant are newly reimbursed for DME in our country, patients receiving these agents were not assessed due to short follow-up time.

Methods

In this retrospective study, the hospital records of 275 eyes of 208 patients who underwent at least one injection of either intravitreal ranibizumab (group 1, $n = 101$ eyes), bevacizumab (group 2, $n = 90$ eyes), or triamcinolone (group 3, $n = 84$ eyes) for DME between May 2006 and April 2015 were evaluated. Drug dosage per injection was 0.5 mg, 1.25 mg, and 4 mg for ranibizumab, bevacizumab, and triamcinolone, respectively. Age, sex, smoking status, systemic diseases, type and duration of diabetes, presence of cataract or glaucoma, previous focal or grid laser photocoagulation, initial severity of DR and initial fundus fluorescein angiography (FFA) findings, BCVA in Early Treatment Diabetic Retinopathy Study (ETDRS) letters and central macular thickness (CMT) in optical coherence tomography (OCT) for each visit, presence of serous macular detachment, presence of epiretinal membrane, number of total injections, and number of total visits were noted. The aforementioned data of visits at baseline, 1 month, 2, 3, and 6 months, 1 year, and 2 years were recorded. Every visit within 1 week of the exact monthly period was included for that month. Initial DR severity was classified as mild nonproliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, or proliferative diabetic retinopathy (PDR) by one ophthalmology resident based on color fundus photography and as previously described by the ETDRS Research Group [9]. All patients with PDR were referred to additional panretinal photocoagulation, and any eye with visually obscuring vitreous hemorrhage requiring vitrectomy was excluded from the study as from the time of hemorrhage. Initial macular edema was classified as focal, cystoid, or diffuse based on OCT images. While cystoid and diffuse macular edema classification was made in accordance with previous literature, focal retinal thickenings which did not fit in the previous two categories were classified as focal macular edema [10]. Patients with a follow-up of <6 months or with any etiology of macular edema other than diabetes were excluded. Intravitreal treatment was initiated regardless of BCVA or presence of previous focal/grid laser photocoagulation, but upon presence of edema involving the central macula, with a center subfield thickness measuring ≥250 μm on OCT. Regular FFA, where available, was additionally evaluated by one resident for macular ischemia, where an enlarged foveal avascular zone was labelled ischemic using standard photographs from ETDRS report number 19 [11]. OCT records before the year 2010 were obtained with Stratus OCT™ (Carl Zeiss Meditec, Inc., Dublin, CA, USA), while Heidelberg Spectralis OCT® (Heidelberg Engineering, Heidelberg, Germany) was the choice of imaging device afterwards. Reinjection was performed at the discretion of two retina specialists at postinjection monthly follow-up visits if edema persisted, recurred, or worsened. After three consecutive monthly visits with stable or improving edema, the follow-up interval was set at 2 months. There was no loading dose for any type of treatment; however, a tendency towards two repeat injections following the initial ranibizumab injection was observed, and triamcinolone reinjection was avoided before 4 months although it did not achieve a standard algorithm due to the retrospective nature. All injections were performed by the same retina specialist. The research adhered to the tenets of the Declaration of Helsinki.

Statistical analysis was performed with SPSS 21.0 (IBM SPSS Statistics V21.0). The χ^2 test was used for comparison of qualitative variables, and one-way analysis of variance was performed to compare means between treatment groups, with 95% confidence when assumption of normality was ensured and with Kruskal-Wallis analysis when it was not. Post hoc analysis and pairwise comparisons were performed to specify the group leading to statistical difference. A linear regression model was established to test the variables that significantly affect changes in visual acuity (VA) and CMT at 6 months, 1 year, and 2 years. p values <0.05 were considered significant.

Results

The main demographic characteristics of the three groups are as listed in Table 1. The three groups showed no statistical difference in terms of age, sex, type of diabetes, frequency of systemic conditions (including hypertension, coronary artery disease, and chronic renal disease), type of initial macular edema as seen on OCT, presence of macular ischemia as seen on FFA, and frequency of serous macular detachment at 6 months, 1 year, and 2 years. Out of the 275 eyes included in the study, 184 (66.9%) were followed up for at least 1 year and 92 (33.5%) for at least 2 years. Among the demographic data, duration of DM was significantly higher in group 2 ($p = 0.019$). The mean number of follow-up visits was as listed in Table 1. For the first 6 months, the number of visits was significantly lower in group 3 and for the second 6 months significantly higher in group 1 ($p = 0.024$ and $p = 0.034$, respectively). There was no such significant difference in visit number in the second year of follow-up ($p = 0.933$). The total number of injections was 3.8 ± 2.2 (median: 3), 2.6 ± 1.8 (median: 2), and 1.9 ± 1.3 (median: 2) in groups 1, 2, and 3, respectively, constituting a significant difference in pairwise comparisons ($p = 0.000$ between groups 1 and 3, $p = 0.001$ between groups 2 and 3, and $p = 0.000$ between groups 1 and 2). In the whole group, 100 eyes (48.7%) were treated with at least one session of focal laser photocoagulation before any injection, and 8 eyes (4.0%) had additional focal laser treatment during the study. In total, in group 1, 43 eyes (45.7%), in group 2, 46 eyes (67.6%), and in group 3, 19 eyes (44.2%) received macular laser photocoagulation either before or during the study period ($p = 0.631$). As for the severity of initial DR, the

Table 1. Patient demographics of the treatment groups

	Ranibizumab	Bevacizumab	Triamcinolone
Mean age ± SD	61.1±9.1	60.3±9.7	62.6±9.0
Female to male ratio	0.8	0.9	0.9
Duration of diabetes mellitus, years	15.5±6.1	13.4±4.8	15.0±5.3
Frequency of type 1 diabetes mellitus	7.9%	5.5%	6.0%
Mean initial visual acuity ± SD, letters	49.8±14.3	45.2±15.7	43.6±14.5
Mean initial central macular thickness ± SD, μm	460.0±106.3	484.3±131.8	515.0±119.4
Number of follow-up visits in first 6 months, mean ± SD	3.6±1.2 (1–6)	3.0±0.9 (1–6)	2.8±1.1 (1–6)
Number of follow-up visits in second 6 months, mean ± SD	3.3±1.2 (1–6)	2.7±0.9 (1–4)	2.8±1.0 (1–4)
Number of follow-up visits during 2nd year, mean ± SD	4.6±1.6 (1–7)	4.6±1.8 (2–11)	4.4±1.6 (1–8)
Mild nonproliferative diabetic retinopathy	32.3%	34.3%	33.3%
Moderate nonproliferative diabetic retinopathy	28.0%	26.9%	35.6%
Severe nonproliferative diabetic retinopathy	32.3%	13.4%	17.8%
Proliferative diabetic retinopathy	7.5%	25.4%	13.3%

SD, standard deviation.

frequency of eyes which had severe NPDR in group 1, that of eyes which had PDR in group 2, and that of eyes which had moderate NPDR in group 3 was significantly higher than that of the rest ($p = 0.03$, $p = 0.017$, $p = 0.013$). The frequency distribution of DR severity can be found in Table 1. A previous history of macular laser photocoagulation was present in 45 eyes (66.2%) in group 2, which was significantly higher than in groups 1 and 3 (40.4 and 39.5%, $p = 0.013$). In total, based on initial OCT images, 56 eyes (20.4%) had focal, 79 (28.7%) had cystoid, and 140 (50.9%) had diffuse macular edema. Out of 179 eyes whose FFA images could be evaluated, initial FFA revealed macular ischemia in 26 (14.5%). The frequency distribution of types of macular edema on OCT and the frequency of macular ischemia did not differ significantly between groups ($p = 0.548$ and $p = 0.742$). In the whole cohort, serous macular detachment was detected on OCT in 28.7% of eyes ($n = 79$) initially, 13.5% ($n = 37$) at 6 months, 7.9% ($n = 14$) at 1 year, and 5.5% ($n = 5$) at 2 years. The mean number of injections was 3.1 ± 2.2 in eyes which initially exhibited serous macular detachment and 2.5 ± 1.8 in those which did not ($p = 0.011$). However, the total number of visits did not differ significantly between the two groups (9.9 ± 1.8 and 8.7 ± 1.6, respectively, $p = 0.312$).

The mean VA improvement in ETDRS letters seen at 6 months, 1 year, and 2 years in the three treatment groups revealed no statistical difference ($p = 0.911$, $p = 0.731$, and $p = 0.306$), and mean values were 5.0 ± 11.2, 3.5 ± 11.8, and 7.6 ± 10.1 letters in groups 1, 2, and 3, respectively, at the end of the second year of follow-up. Initial VA was found to be significantly higher in group 1 (49.8 ± 14.3, range 15–80) than in groups 2 and 3 (45.2 ± 15.7, range 5–77, and 43.6 ± 14.5, range 5–80, $p = 0.012$). To further investigate a possible ceiling effect, the gain in VA was again evaluated for the eyes which had initial VA of ≥50 letters. Initially, 52.7% ($n = 145$) of the eyes had VA <50 letters and the remaining 47.3% ($n = 130$) had ≥50 letters. This analysis again revealed no significant difference between treatment groups at 6 months, 1 year, and 2 years ($p = 0.673$, $p = 0.384$, and $p = 0.817$, respectively). For the rest of the cohort with an initial VA <50 letters, the gain in VA in the three treatment groups was statistically indifferent at 6 months, 1 year, and 2 years ($p = 0.998$, $p = 0.967$, and $p = 0.641$, respectively). Quantitative description of gains in VA can be seen in detail in Tables 2 and 3. Table 2 also exhibits the frequency of eyes with a gain or loss in VA of ≥10 letters. After 2 years of follow-up, the three groups showed statistically similar frequencies of eyes gaining ≥10 letters ($p = 0.162$) and losing ≥10 letters ($p = 0.162$) in BCVA. The trend in VA recorded at certain time points in the three treatment groups is demonstrated in Figure 1.

With regard to CMT, initial mean CMT was significantly higher in group 3 than in groups 1 and 2 (515.0 ± 119.4, 460.0 ± 106.3, and 484.3 ± 131.8 μm, respectively, $p = 0.008$), as was improvement in CMT compared to baseline at 6 months, 1 year, and 2 years ($p = 0.014$, $p = 0.014$, and $p = 0.001$, respectively). The changes in CMT over time are as listed in Table 4 and demonstrated in Figure 2.

Table 2. Gain in VA according to treatment from baseline to 6 months, 1 year, and 2 years in letters, followed by frequency of eyes gaining ≥10 letters and frequency of eyes showing ≥10 letters loss in VA

	Ranibizumab			Bevacizumab			Triamcinolone		
	VA gain, letters	VA gain ≥10 letters	VA loss ≥10 letters	VA gain, letters	VA gain ≥10 letters	VA loss ≥10 letters	VA gain, letters	VA gain ≥10 letters	VA loss ≥10 letters
At 6 months	4.9±8.9	24.8%	5.0%	4.3±10.0	27.8%	5.6%	4.6±8.8	28.6%	7.1%
At 1 year	5.4±10.2	35.7%	4.3%	4.1±9.7	25.5%	3.6%	4.1±10.1	28.8%	6.8%
At 2 years	5.0±11.2	21.7%	4.3%	3.5±11.8	22.9%	8.6%	7.6±10.1	47.1%	5.9%

VA, visual acuity.

Table 3. Gain in VA according to treatment from baseline to 6 months, 1 year, and 2 years in letters, in eyes with an initial VA of ≥50 letters, followed by that of eyes with an initial VA <50 letters

	Ranibizumab		Bevacizumab		Triamcinolone	
	≥50 letters	<50 letters	≥50 letters	<50 letters	≥50 letters	<50 letters
At 6 months	4.2±8.6	5.8±9.3	2.7±8.9	5.8±10.7	3.1±8.3	5.7±9.1
At 1 year	5.4±9.8	5.4±12.2	2.5±9.0	6.1±10.6	2.4±11.9	4.5±10.7
At 2 years	2.3±7.4	7.5±13.7	1.8±10.5	5.6±12.2	4.6±14.6	8.9±7.6

VA, visual acuity.

Table 4. Improvement in central macular thickness according to treatment from baseline to 6 months, 1 year, and 2 years in micrometers

	Ranibizumab	Bevacizumab	Triamcinolone
At 6 months	77.9±118.3	74.7±133.9	125.0±119.2
At 1 year	89.4±119.2	89.6±118.7	149.3±146.7
At 2 years	126.9±97.0	83.4±125.9	193.5±125.7

Linear regression analysis was performed to identify factors affecting the amount of changes in VA and CMT at 6 months, 1 year, and 2 years with regard to baseline values. Age, sex, duration of DM, initial VA, initial CMT, presence of serous macular detachment or epiretinal membrane, FFA findings, macular laser photocoagulation status, type of macular edema, initial severity of DR, and type of intravitreal treatment were incorporated into the analysis. Among these tested variables, initial VA and age were found to be inversely proportional to the gain in VA at 6 months and 1 year ($p = 0.011$, $p = 0.015$; $p = 0.046$, $p = 0.039$, respectively). At the end of 2 years, the only significant correlation was found to be the inverse proportion with initial VA ($p = 0.020$). With respect to CMT, the only factor affecting improvement in CMT was initial CMT at all of the three time points of the study, with a positive correlation ($p = 0.000$, $p = 0.000$, and $p = 0.001$, respectively).

When 48 pseudophakic eyes were initially excluded, 11 eyes in group 1 (13.7%), 22 eyes in group 2 (30.6%), and 45 eyes in group 3 (60.0%) either developed visually compromising cataract or underwent cataract surgery during follow-up. The number of eyes which underwent cataract surgery were 5 (6.3%) in group 1, 11 (15.3%) in group 2, and 17 (22.7%) in group 3. All considered, the frequency of cataract development was significantly higher in group 3 compared to groups 1 and 2 ($p = 0.000$ and $p = 0.000$, respectively) and significantly higher in group 2 compared to group 1 ($p = 0.0129$). When eyes having cataract surgery during follow-up were excluded, the frequency of development of visually compromising cataract was similar between groups 1 and 2 ($n = 6$ and $n = 11$, respectively, $p = 0.105$). Among those eyes which were initially pseudophakic or did not develop cataract during follow-up, group 3 showed a remarkably but not significantly higher gain in VA than groups 1 and 2 at the end of 2 years (group 1, 5.5 ± 11.8;

Fig. 1. Course of best corrected visual acuity (BCVA, letters) throughout follow-up in the three treatment groups with visits at baseline, 1 month, 2 months, 3 months, 6 months, 1 year, and 2 years.
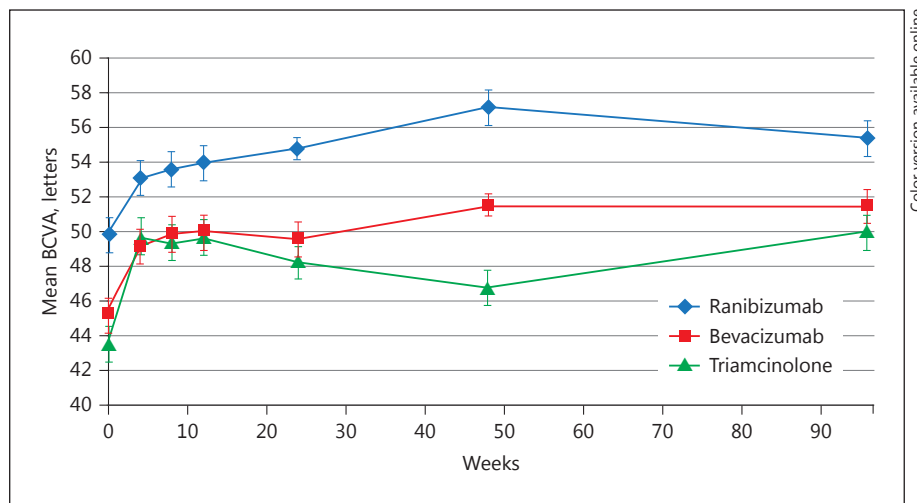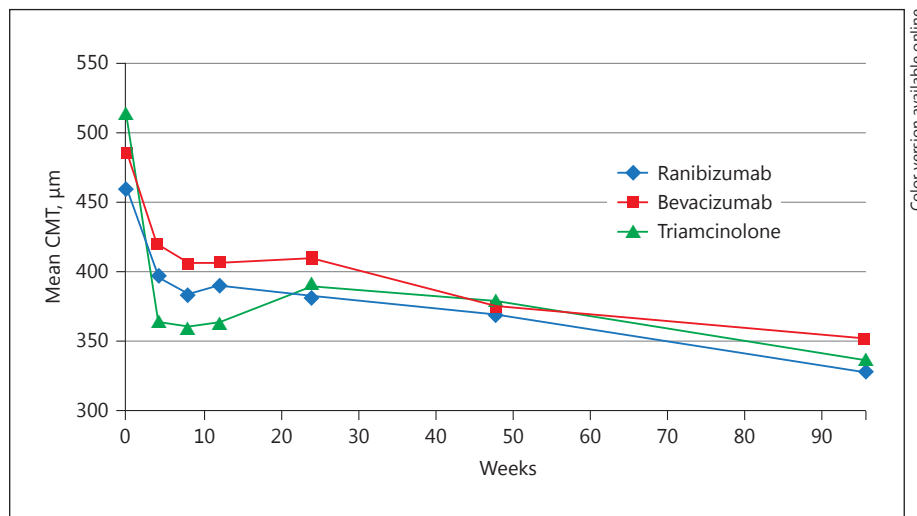

Fig. 2. Course of central macular thickness (CMT, μm) throughout follow-up in the three treatment groups with visits at baseline, 1 month, 2 months, 3 months, 6 months, 1 year, and 2 years.

group 2, 5.7 ± 12.2; group 3, 7.8 ± 10.2; $p = 0.226$). Comparison for this parameter between groups 1 and 2 revealed no statistical significance ($p = 0.388$). The need for topical antiglaucoma agents or surgery was significantly higher in group 3 ($p = 0.001$) and was observed in 5.0% ($n = 5$) of eyes in group 1, in 8.9% ($n = 8$) in group 2, and in 22.6% ($n = 19$) in group 3. Two patients in group 3 required trabeculectomy in the study eye. Development of cataract or permanent increase in intraocular pressure had no significant correlation with respect to the mean number of injections ($p = 0.386$ and $p = 0.417$, respectively). Five patients (2 in group 1, 2 in group 2, and 1 in group 3) deceased from cerebrovascular events after a mean of 14 months of follow-up; the cause was not deemed injection-related due to advanced age of these patients (mean 78 years). One patient in group 1, aged 60, suffered from hypertensive stroke 6 months after the last injection.

Conclusions

The optimum treatment with intravitreal injections in clinical practice is desired to be long-lasting in terms of improving VA and restoring macular anatomy, with a least possible number of injections and number of follow-up visits. Refraining from overtreatment is necessary to avoid injection-related complications and long-term unwanted results such as geographic atrophy or drug-specific complications. Thus, we aimed to report our real-

world experience with three of the most commonly used treatment modalities.

All three groups, ranibizumab, bevacizumab, and triamcinolone, benefited from treatment in terms of improvement in VA and CMT, and the favorable results persisted in the 2 years of follow-up. With linear regression analysis of factors affecting change in VA, at the end of 2 years, the gain in BCVA was found to be inversely proportional to the initial VA in the whole cohort ($p = 0.020$), and the mean final VA was statistically similar among treatment groups (55.4 ± 15.6, 51.5 ± 14.8, and 50.0 ± 15.7, respectively, $p = 0.605$). As for CMT, the eyes with a higher initial CMT were found to be more likely to benefit from anatomical improvement ($p = 0.001$). This is consistent with previous knowledge of worse baseline VA and higher initial CMT being associated with better visual gains; however, CMT has previously not been shown to be predictive of final anatomical outcomes [12].

Although presence of serous macular detachment was not a significant factor in terms of visual gain and anatomical improvement with linear regression analysis, the mean number of injections was significantly higher in eyes which initially exhibited serous macular detachment than in those which did not (3.1 ± 2.2 and 2.5 ± 1.8, respectively, $p = 0.011$). However, the total number of visits did not differ significantly between the two groups (9.9 ± 1.8 and 8.7 ± 1.6, respectively, $p = 0.312$). This suggests a need for a higher number of injections in eyes with serous macular detachment with similar patient adherence to follow-up visits.

The baseline frequency of serous macular detachment was 28.7% ($n = 79$) in the whole cohort and was reduced to 5.5% ($n = 5$) within 2 years. Several studies have reported different prevalences of this finding, and its clinical relevance to DME treatment success is yet to be determined. In a report of cases with both branch retinal vein occlusion and DME, serous macular detachment was shown to be a negative prognostic factor for anatomical improvement [13]. Structural analysis of individual retinal layers in the literature has concluded that eyes with foveal serous macular detachment tend to have a poorer prognosis regarding visual function [14]. Yaya et al. [15] found serous macular detachment in 52.4% of 143 eyes and associated it with systemic hypertension. In our study, serous macular detachment had no significant effect on visual or anatomical improvement in linear regression analysis of 2-year results ($p = 0.699$ and $p = 0.259$, respectively). Additionally, comparison of mean visual gains in the subgroup with serous macular detachment during the first year revealed no significant difference between groups 1, 2, and 3 (4.0, 6.0, and 6.0 letters, respectively, $p = 0.342$). This finding contradicts previous conceptions which favor intravitreal triamcinolone over intravitreal bevacizumab in eyes with serous retinal detachment in terms of visual benefit [16].

Even though baseline CMT was significantly higher in group 3 than in groups 1 and 2, final CMT was statistically similar between the three groups ($p = 0.779$). Thus, in daily practice, eyes with a higher initial CMT could anatomically benefit from corticosteroids, and in pseudophakic eyes without predisposition for glaucoma, corticosteroids as well as ranibizumab and bevacizumab could be of use. The reason for dramatic anatomical improvement rises from the mechanism of action of steroids. Since intravitreal corticosteroids target more than only VEGF of diabetic vasculopathy and act more centrally in the cycle of inflammation than pure anti-VEGF agents, dramatic improvement in macular edema is agreeable. Several other studies with intravitreal dexamethasone implant resulted in better anatomical recovery than bevacizumab alone [17, 18]. Still, with our findings, it is not possible to come to an exact conclusion in terms of a head-to-head comparison of anatomical or functional improvement, due to possible treatment bias caused by lack of a randomized clinical setting and standardized treatment of study drugs.

When the gains in VA in our study groups are compared to previous 2-year results of major reports in the literature, the expanded 2-year results of DRCR.net Protocol I revealed 7 ± 13, 9 ± 14, 2 ± 19, and 8 ± 13 VA gain in letters in the ranibizumab + prompt laser group, the ranibizumab + deferred laser group, the intravitreal triamcinolone group, and the pseudophakic intravitreal triamcinolone subgroup, respectively [4]. Protocol T, a randomized clinical trial of aflibercept, bevacizumab, or ranibizumab, reported a VA score improvement by 12.3 letters with ranibizumab and by 10.0 letters with bevacizumab within 2 years [19]. These values, compared to our real-world 2-year results of VA improvement by 5.0 ± 11.2, 3.5 ± 11.8, and 7.6 ± 10.1 letters with ranibizumab, bevacizumab, and triamcinolone, respectively, overall represent a better functional improvement, which may suggest inadequate treatment.

The adopted type of treatment regimen in our clinic for intravitreal triamcinolone and anti-VEGF agents in DME had been "as needed," and it has shifted from pro re nata to individualized treatment after United States Food and Drug Administration approval of ranibizumab in DME. Dexamethasone implant and aflibercept are other agents that have been licensed and recently reimbursed

for this indication. At present, intravitreal triamcinolone and bevacizumab are still off-label drugs for that purpose. The mean values of the total number of injections revealed a statistical difference, which was caused by a higher mean value in group 1 (3.1 ± 1.9, 2.3 ± 1.5, and 1.7 ± 0.8 in the first year in groups 1, 2, and 3, respectively, $p = 0.001$; 3.8 ± 2.2, 2.6 ± 1.8, and 1.9 ± 1.3 in 2 years in groups 1, 2, and 3, respectively, $p = 0.000$). This finding might represent the aforementioned change of trends over time. Even so, our values of mean number of injections in the first year (3.1 ± 1.9, 2.3 ± 1.5, and 1.7 ± 0.8, respectively, $p = 0.001$) lie far less beyond those in the literature, such as 1-year core studies for ranibizumab or bevacizumab in DME which reported a mean injection of 7 and a median of 9 [20, 21]. As for intravitreal triamcinolone, even though it is known that clinical improvement with a single injection of intravitreal triamcinolone is reversed within 6 months, our mean value for intravitreal triamcinolone injections in 2 years still expresses a lower value than that reported in expanded 2-year results of the DRCR.net Protocol I study, whose median value was 3 over 1 year, and 68% of the study eyes received at least one additional triamcinolone injection between the 1- and 2-year visits [4]. Our significantly lower mean numbers of injections in all groups could be explained by lower adherence to therapy and initial monthly loading doses of anti-VEGF agents, which were applied in a regular manner in these randomized trials. Among real-life studies in the literature, LUMINOUS (registered as NCT01318941 at https://clinicaltrials.gov) is a large-scale, multicenter, prospective study of intravitreal ranibizumab administered for various retinal pathologies, including DME, central and branch retinal vein occlusions, and exudative age-related macular degeneration. Of 1,828 diabetic patients who had follow-up data for 1 year, the mean number of injections was 3.38 and the treatment-naive subgroup had a mean gain in VA of 4.4 ETDRS letters [22]. In another real-world study with retrospective results of anti-VEGF treatment for DME, the average number of injections was 4.2, which is again less than in the landmark studies, but with favorable anatomical results, similar to our findings [23]. A recent retrospective, interventional report of the real-world experience of ranibizumab in a United Kingdom National Health Service setting, however, established a mean number of 7 injections over 12 months, with favorable visual and anatomical benefits (+6.6 letters visual gain and 133.9 μm improvement in central subfield thickness), which is comparable to randomized controlled trials. In that study, the regular injection protocol of three loading doses of ranibizumab followed by pro re nata injections might represent a more homogenous approach than in our report, thus resulting in a higher number of injections. By the end of the second year, our ranibizumab group showed a gain of 5.0 ± 11.2 letters and an improvement of 126.9 ± 97.0 μm in CMT. These findings altogether suggest a slight undertreatment in our cohort [24].

In our retrospective study, all three treatment groups ended up with statistically similar gains in VA and reduction in CMT. Several specific conditions in which one treatment could be preferred over another are determined by several ocular and environmental conditions. For instance, bevacizumab is still a popular choice of treatment, especially due to its low cost, in developing countries. The results for a favorable effect of bevacizumab in visual gain are contradictory. Although its effectiveness has recently been shown not to extend beyond 2 years of follow-up, Protocol T yielded a beneficial effect of bevacizumab even during the second year [19, 25, 26]. Additionally, as previously reported in Protocol T, among eyes with better VA (defined as 20/32 to 20/40), visual gains with intravitreal bevacizumab, ranibizumab, or aflibercept revealed no significant difference at 1 year, and this was shown to persist at 2 years [8, 19]. One should also look for a tendency of glaucoma development or beware of cataract progression before committing for a treatment and avoid adverse events of intravitreal corticosteroids if necessary. Previously DRCR.net Protocol I results of the pseudophakic subgroup of intravitreal triamcinolone-treated eyes showed comparable visual gains in the ranibizumab group, but at the expense of higher risk of intraocular pressure elevation [4]. For cataract development, our results revealed a higher frequency in group 3 compared to groups 1 and 2, as well as a higher frequency in group 2 than in group 1, but the difference between groups 1 and 2 ceased to persist when eyes which underwent cataract surgery were excluded. This prior significant difference among anti-VEGF treated groups could be attributed to higher initial VA in group 1, which might have caused a tendency to delay cataract surgery in ranibizumab-treated eyes. If a treatment modality of intravitreal corticosteroid is to be chosen, one should take into consideration that indications for intravitreal dexamethasone (Ozurdex®, Allergan Inc.) presently include DME, whereas triamcinolone is an off-label agent, and the long-term side effects are more tolerable than those of triamcinolone, with a nearly 13% frequency of intraocular pressure elevation during the first year, which does not last longer than the duration of action of the implant and can be managed with topical antiglaucomatous agents [27].

Our study aimed to point at several conditions, thus differing from large-scale clinical trials. Its limitations lie within the retrospective design, the lack of a standard treatment scheme, the imaging technique and loading dose for anti-VEGF agents, and the relatively shorter duration of follow-up given the chronicity of DM.

Disclosure Statement

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