Original Article

Aflibercept or ranibizumab for diabetic macular edema

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ABSTRACT

Background: Vascular endothelial growth factor (VEGF) is the primary substance involved in retinal barrier breach. VEGF overexpression may cause diabetic macular edema (DME). Laser photocoagulation of the macula is the standard treatment for DME; however, recently, intravitreal anti-VEGF injections have surpassed laser treatment. Our aim was to evaluate the efficacy of intravitreal injections of aflibercept or ranibizumab for managing treatment-naive DME.

Methods: This single-center, retrospective, interventional, comparative study included eyes with visual impairment due to treatment-naive DME that underwent intravitreal injection of either aflibercept 2 mg/0.05 mL or ranibizumab 0.5 mg/0.05 mL at Al-Azhar University Hospitals, Egypt between March 2023 and January 2024. Demographic data and full ophthalmological examination results at baseline and 1, 3, and 6 months post-injection were collected, including the best-corrected distance visual acuity (BCDVA) in logarithm of the minimum angle of resolution (logMAR) notation, slit-lamp biomicroscopy, dilated fundoscopy, and central subfield thickness (CST) measured using spectral-domain optical coherence tomography.

Results: Overall, the 96 eyes of 96 patients with a median (interquartile range [IQR]) age of 57 (10) (range: 20–74) years and a male-to-female ratio of 1:2.7 were allocated to one of two groups with comparable age, sex, diabetes mellitus duration, and presence of other comorbidities (all P >0.05). There was no statistically significant difference in baseline diabetic retinopathy status or DME type between groups (both P >0.05). In both groups, the median (IQR) BCDVA significantly improved from 0.7 (0.8) logMAR at baseline to 0.4 (0.1) logMAR at 6 months post-injection (both P = 0.001), with no statistically significant difference between groups at all follow-up visits (all P >0.05). The median (IQR) CST significantly decreased in the aflibercept group from 347 (166) μm at baseline to 180 (233) μm at 6 months post-injection, and it decreased in the ranibizumab group from 360 (180) μm at baseline to 190 (224) μm at 6 months post-injection (both P = 0.001), with no statistically significant differences between groups at all follow-up visits (all P >0.05). No serious adverse effects were documented in either group.

Conclusions: Ranibizumab and aflibercept were equally effective in achieving the desired anatomical and functional results in patients with treatment-naive DME in short-term follow-up without significant differences in injection counts between both drugs. Larger prospective, randomized, double-blinded trials with longer follow-up periods are needed to confirm our preliminary results.

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INTRODUCTION

Diabetes mellitus (DM) is a global pandemic that affected >200 million individuals in 2010, and this number is expected to rise by 62% by 2025. Obesity and global life expectancy are inducing this increase [1]. Diabetic macroangiopathy may present as myocardial infarction or stroke, whereas microangiopathy may manifest as diabetic retinopathy (DR), which is the leading cause of blindness in Europe and affects 1.9% of patients with DM [2] a frequent complication of diabetes mellitus (DM. Additionally, 2.64% of individuals with DM have sight-threatening DR. Diabetic macular edema (DME) is the leading cause of blindness in patients with DM and has a 2.19% annual incidence. It results from macular DR, a compromised blood–retina barrier, and metabolic abnormalities caused by hyperglycemia [3-5].

Vascular endothelial growth factor (VEGF) is the primary substance involved in retinal barrier breach. Our understanding of DME pathogenesis has changed with the emergence of anti-VEGF and steroid medications [6]. Since the 1980s, laser photocoagulation of the macula has been the standard treatment for DME. Intravitreal anti-VEGF injections are superior for treating DME, with effectiveness surpassing that of laser therapy; in fact, most USA retinal physicians use anti-VEGF medication to treat DME [7].

Aflibercept and ranibizumab are two anti-VEGF agents. Aflibercept, a 115-kDa dimeric glycoprotein, antagonizes retinal endothelial cell VEGF receptors (VEGFR-1 and VEGFR-2). Aflibercept binds to VEGF-A and placental growth factor more strongly than its natural angiogenic rivals (VEGFR-1 and VEGFR-2) [8]. Aflibercept blocks ligand-induced VEGFR-2 dimerization, preventing intracellular tyrosine kinase domain activation and limiting pathologic angiogenesis [9]. Blocking the VEGF receptor reduces endothelial cell growth, vascular permeability, and neovascularization [9, 10].

Ranibizumab is a 48-kDa humanized monoclonal antibody fragment that is affinity-matured and binds to the receptor-binding site of active VEGF-A [10]. By blocking VEGF-A and its receptors, ranibizumab decreases vascular permeability, neovascularization, and endothelial proliferation. Two ranibizumab molecules can bind to one VEGF dimer owing to its single VEGF-binding site. Due to its small size, ranibizumab is better absorbed into the retina and choroid [11].

Both anti-VEGF agents are safe and effective for DME treatment [12], with aflibercept yielding better anatomical improvement in DME with [13] and without [12] serous retinal detachment. Vision gain persists longer in aflibercept-treated eyes with DME than in ranibizumab-treated eyes [14]. While Ashraf et al. reported similar functional and anatomical improvements using aflibercept or ranibizumab in DME unresponsive to bevacizumab [15], Pessoa et al. observed improvements in central foveal thickness and vision gain with ranibizumab administration, whereas aflibercept yielded improvement only in central foveal thickness [16].

Considering these controversies within the literature regarding anatomical and functional outcomes, this study evaluated the efficacy and safety of intravitreal injection of aflibercept versus ranibizumab for DME management.

METHODS

This single-center, retrospective, interventional, comparative study consecutively included all eligible treatment-naive patients with type II DM with visual impairment due to DME who received either aflibercept or ranibizumab at Al-Azhar University Hospitals, Egypt, between March 2023 and January 2024. Our investigation conformed to the principles of the Helsinki Declaration, and ethical approval was granted by the Institutional Review Board of Al-Azhar University. Written informed consent was obtained from each patient before recruitment.

We included adults aged >18 years meeting our definition of DME (edema within 500 μm of the foveal center, or at least one disc area of swelling, any part of which is within one disc diameter of the foveal center) who received intravitreal aflibercept or ranibizumab [17], with best-corrected distance visual acuity (BCDVA) >20/400 and a minimum follow-up period of 6 months. We excluded those with previous intravitreal or sub-Tenon's steroid injections, intravitreal dexamethasone implants, intravitreal anti-VEGF injections, or focal/grid macular laser photocoagulation for DME management; those with vitreoretinal surface abnormalities or macular edema caused by any medical condition other than type II DM; and those who changed anti-VEGF agents during the study period.

Patient demographics, baseline DR status, DM duration, comorbidities, and glycated hemoglobin levels were documented. Details of full ophthalmological examinations at baseline and 1, 3, and 6 months post-injection were collected, including BCDVA using a Snellen chart (Auto Chart Projector CP 670; Nidek Co., Ltd., Gamagori, Japan) with values converted to logarithm of the minimum angle of resolution (logMAR) notation, anterior and posterior segment examinations under slit-lamp biomicroscopy (Topcon SP-1P, Topcon Medical Inc., Tokyo, Japan), dilated fundus examination using an indirect ophthalmoscope (Keeler Instruments Inc., PA, USA) and a + 20-diopter ancillary lens (VOLK Optical Inc., Mentor, OH, USA), and central subfield thickness (CST) measurements using spectral-domain optical coherence tomography (SD-OCT) (Topcon Corp., Tokyo, Japan).

The DME type was first determined clinically and then based on the SD-OCT findings as follows: cystoid macular edema (CME) was defined as low-reflectivity intraretinal round- or oval-shaped spaces with highly reflective septa separating them; focal DME was defined as an area of retinal thickening <2 disk diameters, not affecting the center of the macula; moderate DME was defined as retinal thickening and/or lipid threatening the fovea; and diffuse DME was defined as increased retinal thickness >200 μm in height and >200 μm in width, with areas of lower reflectivity involving the center of the macula [18-20]. The presence of vitreomacular traction and epiretinal membrane (ERM) at baseline or macular changes at the end of the study (such as, focal macular edema, minimal cystic changes, CME, ERM, and scar) were clinically diagnosed and confirmed by OCT imaging [21, 22].

Eligible patients were allocated to either the aflibercept (aflibercept 2 mg/0.05 mL) (VEGF Trap-Eye, Eylea®; Regeneron, Inc., Tarrytown, NY, USA) or ranibizumab groups (ranibizumab 0.5 mg/0.05 mL) (Lucentis®, Genentech, South San Francisco, CA, USA). The type of anti-VEGF was selected at the treating ophthalmologist's discretion. We followed the treat-and-extend protocol without a fixed loading phase [23].

Intravitreal injections were administered under sterile conditions using topical anesthesia (Benoxinate hydrochloride, BENOX®, E.I.P.I.Co., Cairo, Egypt). The conjunctiva was instilled with commercially available 5% povidone-iodine ophthalmic solution (5% Betadine®, Alcon Laboratories, Fort Worth, TX, USA), and the lids and eyelashes were sterilized with the same solution. An intravitreal anti-VEGF injection was administered for phakic eyes using a 30-gauge needle inserted 4 mm posterior to the inferotemporal limbus; for pseudophakic eyes, an injection was administered 3.5 mm posterior to the same site. A 5% povidone-iodine drop was instilled at injection conclusion [24, 25]. Postoperative care included topical moxifloxacin (Vigamox™;Alcon Inc., Hunenberg, Switzerland) eye drops four times per day for two weeks. Along with side effects, the total number of injections received during the study period was documented.

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Kolmogorov–Smirnov test. Qualitative data were compared using the Chi-square or Fisher's exact tests [26] and are presented as numbers (%). Quantitative data are presented as medians and interquartile ranges (IQRs); independent variables were compared using the Mann–Whitney U test, and paired data were compared using the Friedman and Wilcoxon signed-rank tests [27]. *P*-values <0.05 were considered statistically significant.

RESULTS

In total, 96 eyes of 96 patients with a 1:2.7 male-to-female ratio were allocated to one of two groups with comparable median age, sex distribution, DM duration, and presence of comorbidities (all $P > 0.05$). There was no statistically significant difference in baseline DR status or DME type between the two groups (both $P > 0.05$) (Table 1).

Previous panretinal photocoagulation for DR (n = 13, 24.5%), phacoemulsification (n = 6, 11.3%), and phacovitrectomy (n = 2, 3.8%) were reported only in the aflibercept group. Vitreomacular traction (n = 1, 2.3%) and ERM (n = 1, 2.3%) were detected only in the ranibizumab group (Table 1). Baseline macular hemorrhage was significantly more frequent in the aflibercept group than in the ranibizumab group ($P < 0.05$) (Table 1).

During the study period, the median (IQR) numbers of injections in all participants (n = 96), aflibercept group (n = 53 eyes), and ranibizumab group (n = 43 eyes) were 3 (1), 3 (1), and 2 (2), respectively, and numbers were comparable between the two groups ($P = 0.12$). The median (IQR, range) intervals between the first and last intravitreal injections in all participants (n = 96), the aflibercept group (n = 53 eyes), and ranibizumab group (n = 43 eyes) were 12 (7) (0–24), 12 (4) (4–24), and 12 (20) (0–24) weeks, which were comparable between the two groups ($P = 0.22$).

The median (IQR) BCDVA and CST were significantly improved after the study period and at each follow-up visit compared with baseline in both groups (all $P = 0.001$), with no statistically significant difference noted between the groups at each visit (all $P > 0.05$) (Table 2).

Macular changes at the end of the study were detected in 50 of 96 eyes and included 15.6% (n = 15) with focal macular edema, 24% (n = 23) with minimal cystic changes, 9.4% (n = 9) with CME, 2.1% (n = 2) with macular scar, and 1% (n = 1) with ERM; the proportions of eyes with these changes were comparable between groups ($P > 0.05$) (Table 3). No serious adverse effects were documented throughout the study period.

Table 1. Demographic and baseline clinical characteristics of study participants

Variables	All (n = 96)	Aflibercept (n = 53)	Ranibizumab (n = 43)	*P*-value
Age (y), Median (IQR) (Range)	57 (10) (20 to 74)	58 (9) (20 to 73)	57 (12) (43 to 74)	> 0.99 [a]
Sex (Male/Female), n (%)	26 (27.1) / 70 (72.9)	14 (26.4) / 39 (73.6)	12 (27.9) / 31 (72.1)	0.8 [b]
Laterality (OD / OS), n (%)	48 (50) / 48 (50)	28 (52.8) / 25 (47.2)	21 (48.8) / 22 (51.2)	-
Type of diabetic retinopathy, n (%)				
Mild NPDR	49 (51.0)	26 (49.0)	23 (53.5)	0.7 [b]
Moderate NPDR	40 (41.7)	24 (45.3)	16 (37.2)	
PDR	7 (7.3)	3 (5.7)	4 (9.3)	
History of T2DM, n (%)	96 (100)	53 (100)	43 (100)	0.1 [b]
Duration of T2DM (y), Median (IQR)	15 (10)	15 (10)	15 (10)	> 0.99 [b]
Other comorbidities, n (%)				
HTN	46 (47.9)	22 (41.5)	24 (55.8)	0.7 [b]
IHD	3 (3.1)	1 (1.9)	2 (4.7)	
HTN and IHD	7 (7.3)	3 (5.7)	4 (9.3)	
HTN and renal dialysis	2 (2.1)	1 (1.9)	1 (2.3)	
Previous PRP, n (%)	13 (13.5)	13 (24.5)	0 (0.0)	0.6 [c]
Previous ocular surgery, n (%)				
Phacoemulsification	6 (6.3)	6 (11.3)	0 (0.0)	-
Phacovitrectomy	2 (2.1)	2 (3.8)	0 (0.0)	
Type of baseline macular edema, n (%)				
CME	50 (52.1)	28 (52.8)	22 (51.1)	0.12 [b]
Focal	39 (40.6)	24 (45.3)	15 (34.9)	
Moderate	4 (4.2)	1 (1.9)	3 (7.0)	
Diffuse	3 (3.1)	0 (0.0)	3 (7.0)	
Vitreoretinal interface abnormalities, n (%)				
VMT	1 (1.0)	0 (0.0)	1 (2.3)	-
ERM	1 (1.0)	0 (0.0)	1 (2.3)	
Macular hemorrhage (Yes / No), n (%)	10 (10.4) / 86 (89.6)	9 (17.0) / 44 (83.0)	1 (2.3) / 42 (97.7)	**0.02** [c]

Abbreviations: n, number; y, year; IQR, interquartile range; OD, right eye; OS, left eye; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; T2DM, type II diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; PRP, panretinal photocoagulation; CME, cystoid macular edema; VMT, vitreomacular traction; ERM, epiretinal membrane. Note: P-value < 0.05 is shown in bold; P-value a: P-value is derived from Mann–Whitney U test comparing the aflibercept versus ranibizumab groups; P-value b: P-value is derived from chi-square test comparing the aflibercept versus ranibizumab groups; P-value c is derived from Fisher's exact test comparing the aflibercept versus ranibizumab groups; Aflibercept, aflibercept group receiving intravitreal injection of aflibercept 2 mg/0.05 mL; Ranibizumab, ranibizumab group receiving intravitreal injection of ranibizumab 0.5 mg/0.05 mL.

Table 2. BCDVA and central subfield thickness changes during study period

Variable	Aflibercept (n = 53)	*P*-value [b]	Ranibizumab (n = 43)	*P*-value [b]	*P*-value [c]
BCDVA (logMAR) , Median (IQR)					
Baseline	0.7 (0.8)	-	0.7 (0.5)	-	0.8
After 1-month	0.4 (0.4)	**0.001**	0.4 (0.3)	**0.001**	0.5
After 3-month	0.4 (0.4)	**0.001**	0.4 (0.3)	**0.001**	0.6
After 6-month	0.4 (0.1)	**0.001**	0.4 (0.1)	**0.001**	0.1
***P*-value [a]**	**0.001**		**0.001**		
Central subfield thickness (μm), Median (IQR)					
Baseline	347 (166)	-	360 (180)	-	0.1
After 1-month	320 (144)	**0.001**	329 (196)	**0.001**	0.3
After 3-month	274 (111)	**0.001**	280 (149)	**0.001**	0.9
After 6-month	180 (233)	**0.001**	190 (224)	**0.001**	0.7
***P*-value [a]**	**0.001**		**0.001**		

Abbreviations: BCDVA, best-corrected distance visual acuity; n, number; logMAR, the logarithm of the minimum angle of resolution; IQR, interquartile range; μm, micrometer. Note: P-values < 0.05 are shown in bold; P-value a, P-value is derived from Friedman test comparing throughout the follow-up in either group; P-value b, P-value is derived from Wilcoxon signed-rank test comparing each post-injection visit with the baseline in either group; P-value c, P-value is derived from Mann–Whitney U test comparing the aflibercept versus ranibizumab groups at each visit; Aflibercept, aflibercept group receiving intravitreal injection of aflibercept 2 mg/0.05 mL; Ranibizumab, ranibizumab group receiving intravitreal injection of ranibizumab 0.5 mg/0.05 mL.

Table 3. Types of macular changes at 6 months after anti-VEGF injection

Macular changes, n (%)	All (n = 50 out of 96)	Aflibercept (n = 28 out of 53)	Ranibizumab (n =22 out of 43)	*P*-value
Focal macular edema	15 (15.6)	9 (17.0)	6 (14.0)	0.8
Minimal cystic changes	23 (24.0)	14 (26.4)	9 (20.9)	
CME	9 (9.4)	4 (7.5)	5 (11.6)	
Macular scar	2 (2.1)	1 (1.9)	1 (2.3)	
ERM	1 (1.0)	0 (0.0)	1 (2.3)	

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor; n, number of eyes; %, percentage; CME, cystoid macular edema; ERM, epiretinal membrane. Note: P-value is derived from chi-square test comparing the aflibercept versus ranibizumab groups; Aflibercept, aflibercept group receiving intravitreal injection of aflibercept 2 mg/0.05 mL; Ranibizumab, ranibizumab group receiving intravitreal injection of ranibizumab 0.5 mg/0.05 mL.

DISCUSSION

We observed comparable functional and anatomical improvements in managing treatment-naive DME in patients with type II DM, 6 months post-intravitreal injections of aflibercept or ranibizumab, with similar safety profiles.

VEGF is a crucial mediator in DME development. Recently, intravitreal injections of anti-VEGF agents have become the standard DME treatment [28]. Ranibizumab is a Fab fragment of a monoclonal anti-VEGF antibody and binds to the receptor site of active VEGF-A glycoprotein, antagonizing its function. The recombinant fusion protein aflibercept binds to placental growth factor and VEGF isoforms A and B; it is a relatively new anti-VEGF drug [29, 30] with a longer intraocular half-life than that of ranibizumab [31], explaining the lower median number of injections in aflibercept-treated eyes. Although this difference was statistically insignificant at the end of the study. We observed comparable intervals between the first and last intravitreal injections in the aflibercept- and ranibizumab-treated eyes. Similar to Babiuch et al. [32] and Fauser et al [33], the median (IQR) age of our participants was 57 (10) years and females outnumbered males.

We found a significant improvement in BCDVA in both study groups during the study period and at each follow-up visit compared with baseline, without statistically significant differences between groups at any time point. Similar improvements have been observed in previous studies. According to Pham et al. [34], ranibizumab (37%) and aflibercept (39%) had similar odds of achieving visual gain over 2 years of therapy [34]. Demircan et al. [28] documented mean (standard deviation) baseline BCDVAs for aflibercept and ranibizumab groups of 0.67 (0.38) logMAR and 0.73 (0.34) logMAR, respectively. On the last visit, the BCDVA improved in the aflibercept group to 0.58 (0.38) logMAR and in the ranibizumab group to 0.67 (0.37) logMAR, though this difference was not significant. In Demircan et al. [28], the aflibercept group improvements may have been superior because the patients were administered ranibizumab first and then changed to aflibercept.

The median (IQR) CST significantly improved over our study period and at each follow-up visit compared with baseline in both groups, with no statistically significant differences noted between the two groups at each visit. This is consistent with the findings of Alsaedi et al. [35], who observed a significant reduction in CST after injection of both anti-VEGF agents, with comparable outcomes for both drugs. Demircan et al. [28] found no differences between the two groups in central macular thickness improvement at the intermediate visit. However, they detected a significant difference in reduction between the two groups at the last visit, with more improvements in the aflibercept group than in the ranibizumab group [28]. Our results and those of Demircan et al. [28] are dissimilar, as in their study the eyes in the aflibercept group were first injected with ranibizumab and then switched to aflibercept, causing cumulative efficacy with the two injected drugs.

We observed no significant difference in BCDVA improvement or CST decrease between the two treatment groups at any time point in our study, corroborating the findings of Protocol T, which found that ranibizumab and aflibercept had comparable anatomical and functional effects on DME [36, 37]. However, studies with longer follow-up periods may reveal subtle differences in efficacy of these anti-VEGF agents. Table 4 summarizes the outcomes of studies published over the last 12 years pertaining to anti-VEGF DME management [12-16, 28, 36-68]. Our research demonstrated that ranibizumab and aflibercept were equally effective in achieving the desired short-term anatomical and functional results in the management of treatment-naive DME. Limitations of our study included the retrospective design, limited sample size, and short follow-up period. In addition, we included only treatment-naive eyes. Thus, the results cannot be generalized. Long-term, prospective, randomized trials could clarify how well aflibercept injections reverse the effects of prior treatments on visual and anatomical outcomes in patients with persistent DME. Whether aflibercept or ranibizumab would be preferable to initial bevacizumab remains unclear based on the results of the current investigation. Clinicians should consider treatment availability, treatment costs, and the development of novel modalities when managing DME. An increasing number of studies are applying artificial intelligence in targeted therapies for DME [69].

Using the baseline characteristics of DME, a trained artificial neural network revealed good precision in predicting visual prognosis with intravitreal ranibizumab [70]. Further validation studies may support the application of artificial intelligence in precise prognostication after administration of the available anti-VEGF agents and aid in personalized treatment selection in managing this potentially blinding condition.

Table 4. Studies of intravitreal anti-VEGF agents in managing DME [12-16, 28, 36-68]

Author (Year)	Study design	Participants	Anti-VEGFs	Outcomes
Nguyen et al. (2012) [38]	Two parallel, phase 3, multicenter, double-masked, sham injection–controlled, RCT.	Patients with vision loss from DME.	Ranibizumab.	Ranibizumab improved vision and macular edema with low rates of ocular and non-ocular side effects.
Do et al. (2012) [39]	Double-masked, multicenter, phase 2 RCT.	Center-involved DME in patients with DM.	VEGF-Trap-Eye.	Different dosing regimens of VEGF-Trap-Eye were compared with laser photocoagulation. All VEGF Trap-Eye groups experienced significant improvements in visual acuity at 6 months, which was maintained or improved over the past 12 months.
Wells et al. (2015) [36]	RCT.	Center-involved DME in patients with DM.	Aflibercept, ranibizumab, or bevacizumab.	All three anti-VEGF agents improved vision, but the relative effect depended on baseline vision.
Elman et al. (2015) [40]	Multicenter RCT.	Center-involved DME in patients with DM.	Ranibizumab.	Five-year data revealed that initiating intravitreal ranibizumab with focal/grid laser is not superior to postponing laser treatment for ≥24 weeks in eyes with DME.
Brown et al. (2015) [41]	Two similarly designed phase 3 RCT: VISTA^{DME} and VIVID^{DME}.	Center-involved DME in patients with type 1 or 2 DM.	Aflibercept.	Functional and anatomical superiority of aflibercept over laser therapy at 52 weeks persisted to week 100.
Schmid et al. (2015) [42]	A comparative study.	Patients with age-related macular degeneration, DME, and retinal vein occlusion.	Ranibizumab and aflibercept.	Anti-VEGF agents did not differ in cost, injection frequency, or clinical outcomes.
Vandekerckhove (2015) [43]	A prospective case study.	Patient with type I DM and bilateral refractory DME.	Aflibercept and ranibizumab.	The study reported the effectiveness of switching intravitreal ranibizumab to aflibercept in managing treatment-resistant DME.
Wells et al. (2016) [37]	RCT.	Center-involved DME in patients with DM.	Aflibercept, bevacizumab, or ranibizumab.	All three anti-VEGFs improved visual acuity from baseline to 2 years, and aflibercept had a greater effect than ranibizumab and bevacizumab in eyes with worse initial visual acuity.
Wells et al. (2016) [44]	The post-hoc, exploratory analyses of RCT data.	Patients with DME.	Aflibercept, ranibizumab, or bevacizumab.	For eyes with terrible initial visual acuity, intravitreal aflibercept had an advantage over ranibizumab and bevacizumab.
Shimizu et al. (2017) [14]	A retrospective review of medical records.	Patients with DME.	Aflibercept or ranibizumab.	Both were effective, with the effects of aflibercept persisting longer than those of ranibizumab. Aflibercept may be effective in the anatomical improvement of DME in eyes refractory to ranibizumab.
Ashraf et al. (2017) [15]	A retrospective study.	Patients with DME unresponsive to bevacizumab.	Ranibizumab or aflibercept.	The effect of early switching to ranibizumab or aflibercept in DME unresponsive to bevacizumab was evaluated, and both anti-VEGF agents were effective.
Wykoff et al. (2017) [45]	Phase 4, multicenter, open-label extension study.	Sixty patients with clinically relevant DME completing VISTA^{DME}.	Aflibercept.	Vision gains attained during the 3-year VISTA ^{DME} trial were maintained through this extension study; treatment frequency was reduced, while 30% of eyes had no clinically relevant DME and did not receive aflibercept.
Blinder et al. (2017) [46]	A multicenter, retrospective, chart review.	Patients with DME or macular edema due to retinal vein occlusion.	Bevacizumab, ranibizumab, or aflibercept.	The frequency of anti-VEGF injections decreased, with lower efficacy than that shown in the ranibizumab registration trials. Most patients with DME had suboptimal gains in visual acuity.

Countinued Table 4. Studies of intravitreal anti-VEGF agents in managing DME [12-16, 28, 36-68]

Author (Year)	Study design	Participants	Anti-VEGFs	Outcomes
Demircan et al. (2018) [28]	A retrospective comparative study.	Patients with persistent DME.	Ranibizumab or aflibercept.	The study evaluated the differences in visual and anatomical results between ranibizumab-treated patients with persistent DME who continued ranibizumab and those who switched to aflibercept. Functional outcomes were similar in both groups, but anatomical outcome was superior in the switched group.
Bressler et al. (2018) [47]	The post hoc analyses of a RCT, the DRCR.net Protocol T.	Patients with DME.	Aflibercept, ranibizumab, or bevacizumab.	Persistent center-involved DME was more likely with bevacizumab than with aflibercept or ranibizumab.
Morioka et al. (2018) [48]	RCT.	Patients with DME.	Aflibercept, ranibizumab, or triamcinolone.	The study assessed anterior flare intensity and central retinal thickness following intravitreal injections of aflibercept, ranibizumab, or triamcinolone acetonide. Central retinal thickness improved after all treatments, but the flare decreased only in eyes treated with triamcinolone acetonide.
Kaldirim et al. (2019) [13]	A prospective, non-randomized-cohort study.	Treatment naive eyes with DME and serous retinal detachment.	Ranibizumab or aflibercept.	Aflibercept was more effective than ranibizumab and required fewer injections.
Bressler et al. (2019) [49]	The post hoc analyses of a RCT, the DRCR.net Protocol T.	Patients with DME.	Aflibercept, bevacizumab, or ranibizumab.	The study examined associations between visual acuity and central subfield thickness changes for each of the three anti-VEGF agents. Only a small proportion of the variation in changes in visual acuity were explained by changes in central subfield thickness.
Ozkaya et al. (2020) [50]	A retrospective, comparative study.	Patients with DME associated with subfoveal retinal detachment.	Aflibercept or ranibizumab.	Both were effective in functional and anatomical improvement, however, aflibercept was more effective than ranibizumab in subfoveal retinal detachment resolution at the 12th month.
Holbach et al. (2020) [51]	A retrospective study.	Patients with treatment naive DME.	Aflibercept or ranibizumab.	Both anti-VEGF agents showed good safety and efficacy in DME treatment regarding functional and anatomical improvement under real-life conditions after 12 months. For eyes with worse initial visual acuity, aflibercept was more effective in visual acuity improvement.
Chujo et al. (2020) [52]	A retrospective study.	Patients with DME.	Aflibercept or ranibizumab.	The treat-and-extend regime using ranibizumab or aflibercept was equally effective both functionally and anatomically without significant differences in injection counts between both drugs.
Sarda et al. (2020) [53]	A prospective single-center study.	Patients with treatment naive DME.	Aflibercept or ranibizumab.	The central subfield choroidal thickness decreased after five injections of both anti-VEGF agents, especially aflibercept.
Chatzirallis et al. (2020) [54]	A prospective randomized study.	Patients with DME.	Aflibercept or ranibizumab.	The anti-VEGF agents had comparable anatomical and functional outcomes in an 18-month follow-up period.
Bhandari et al. (2020) [55]	A retrospective analysis of data from the prospectively designed observational databases in Australia, New Zealand, and Switzerland.	Patients with treatment-naive DME.	Aflibercept or ranibizumab.	Both anti-VEGF agents were effective. However, for eyes with worse initial visual acuity or thicker baseline maculae, aflibercept yielded better outcomes.
Pessoa et al. (2021) [16]	A single-center retrospective comparative study.	Patients with DME unresponsive to bevacizumab.	Aflibercept or ranibizumab.	Ranibizumab yielded both anatomical and functional improvements, and aflibercept only anatomical improvement.
Comet et al. (2021) [56]	A comparative study.	Patients with treatment naive DME.	Ranibizumab, aflibercept, or IDI.	All drugs were functionally and anatomically effective in DEM management.
Turkseven et al. (2021) [57]	A retrospective study.	Patients with DME and previously vitrectomized eyes.	Ranibizumab or aflibercept.	Both anti-VEGF agents were effective with comparable functional and anatomical outcomes.

Countinued Table 4. Studies of intravitreal anti-VEGF agents in managing DME [12-16, 28, 36-68]

Author (Year)	Study design	Participants	Anti-VEGFs	Outcomes
Tsai and Cheng (2021) [58]	A retrospective comparative study.	Patients with DME.	Aflibercept or ranibizumab.	Both anti-VEGF agents yielded anatomical and functional improvements. In aflibercept-treated eyes, vision was maintained more effectively with less recurrence of subretinal fluid at 12 months in real-world settings.
Korkmaz et al. (2021) [59]	A retrospective study.	Patients with treatment naive DME.	Ranibizumab, aflibercept, or IDI.	Functional and anatomical improvements were significant in all treatment groups.
Asikgarip and Yenerel (2021) [60]	A retrospective study.	Patients with treatment naive DME.	Aflibercept or ranibizumab.	Both anti-VEGF agents caused a significant narrowing of retinal vessels after three loading doses at monthly intervals.
Gabrielle et al. (2022) [12]	A retrospective study.	Patients with treatment naive DME.	Aflibercept or ranibizumab.	Both anti-VEGF agents were effective and safe over 3 years of follow-up after the start of treatment. Aflibercept yielded a higher reduction in central subfield thickness than ranibizumab.
Jhaveri et al. (2022) [61]	RCT.	Center-involved DME in patients with DM.	Aflibercept or bevacizumab.	There was no significant difference in functional outcomes between aflibercept monotherapy and bevacizumab treatment switched to aflibercept during a 2-year follow-up.
Atas et al. (2022) [62]	A retrospective comparative study.	Patients with treatment naive DME without adequate response to three consecutive bevacizumab injections.	Aflibercept or ranibizumab.	Both anti-VEGF agents produced significant functional and anatomical improvements. Early treatment switching in eyes with inadequate response to bevacizumab could improve visual and anatomical outcomes.
Alshalan et al. (2022) [63]	A retrospective cohort study.	Center-involved DME in patients with DM.	Aflibercept or ranibizumab.	The study assessed the impact of age on the anatomical and functional outcomes of intravitreal anti-VEGF agents. Age significantly influenced the anatomical outcome, as the younger age group experienced more reduction in central subfield thickness than the older age group.
Akbas et al. (2023) [64]	A retrospective study.	Patients with DME.	Aflibercept or ranibizumab.	The aflibercept group had significantly better functional outcome at year 1; however, this difference did not persist in years 2 and 3. Despite the comparable mean total number of injections between groups, the need for adjuvant steroid treatment was higher in the ranibizumab group than in the aflibercept group.
Kaya et al. (2023) [65]	A retrospective study.	Patients with treatment naive DME.	Aflibercept or ranibizumab.	The mean number of injections as well as anatomical and functional improvements were comparable using ranibizumab or aflibercept monotherapy. Eyes with worse baseline vision had a more significant visual gain in the aflibercept group than in the ranibizumab group.
Isik et al. (2023) [66]	A single-center retrospective comparative study.	Patients with treatment naive DME.	Aflibercept or ranibizumab.	In a real-world setting, both anti-VEGF agents had comparable functional and anatomical outcomes as first-line DME treatments, with similar injection numbers. Despite fewer injections, the real-world setting had functional and anatomical outcomes comparable to those of RCTs.
Sirakaya et al. (2023) [67]	A retrospective comparative study.	Patients with treatment naive DME and serous retinal detachment.	Aflibercept, ranibizumab, or bevacizumab.	In the first 3 months, central retinal thickness and serous retinal detachment height were better in the aflibercept-treated eyes than in the other two anti-VEGF-treated eyes. However, evaluating the anatomical and functional outcomes after 6 months, we determined that all were equally effective.
Yayla et al. (2023) [68]	A retrospective, real-world study.	Patients with DME.	Aflibercept, ranibizumab, bevacizumab, or IDI.	Gains in visual acuity were poorer than those in RCTs because of the lower number of injections in real-life setting. However, with lower baseline visual acuity and higher IDI combination rates, these gains were relatively superior to those of similar real-life studies.

Abbreviations: anti-VEGF, anti-vascular endothelial growth factor; DME, diabetic macular edema; RCT, randomized controlled trial; DM, diabetes mellitus; VEGF, vascular endothelial growth factor; VISTA-DME, Study of Intravitreal Aflibercept Injection (IAI; EYLEA®; BAY86-5321) in Patients With DME; VIVID-DME, Intravitreal Aflibercept Injection in Vision Impairment Due to DME; DM, diabetes mellitus; DRCR, Diabetic Retinopathy Clinical Research Network; IDI, intravitreal dexamethasone implant.

CONCLUSIONS

Ranibizumab and aflibercept are equally effective in achieving the desired anatomical and functional results in treatment-naive DME management over 6 months, with similar safety profiles and without significant differences in injection counts between both drugs. Larger prospective, randomized, double-blinded trials with longer follow-up periods are needed to confirm our preliminary results.

ETHICAL DECLARATIONS

Ethical approval: Our investigation conformed to the principles of the Helsinki Declaration, and ethical approval was granted by the Institutional Review Board of Al-Azhar University. Written informed consent was obtained from each patient before recruitment.
Conflict of interest: None.

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