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Real-Life Comparison of Off-Label Intravitreal Biosimilar Bevacizumab-awwb and Reference Bevacizumab in Treatment-Naïve Patients with Neovascular Age-Related Macular Degeneration, Diabetic Macular Edema, and Retinal Vein Occlusion

Mehmet Orkun Sevik[1], Simge Gizem Koyu[1], Aslan Aykut[1], Didem Dizdar Yiğit[1], Özlem Şahin[1]

[1] Marmara University Faculty of Medicine, Department of Ophthalmology, Istanbul, Türkiye

Mehmet Orkun SEVİK
0000-0001-7130-4798

Simge Gizem KOYU
0000-0003-2035-1273

Aslan AYKUT
0000-0001-5426-1992

Didem DİZDAR YİĞİT
0000-0001-7309-3293

Özlem ŞAHİN
0000-0003-2907-2852

Correspondence: Mehmet Orkun Sevik
Marmara University Faculty of Medicine, Department of Ophthalmology, Istanbul, Türkiye
Phone: +90 216 625 45 45
E-mail: orkun.sevik@marmara.edu.tr

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ABSTRACT

Purpose: To compare the functional, anatomical, and safety results of intravitreal biosimilar bevacizumab-awwb (IVB-awwb; Mvasi®) and reference bevacizumab (IVB; Altuzan®) in patients with neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), and macular edema secondary to retinal vein occlusion (RVO).

Methods: This non-randomized, retrospective, real-life study included 191 treatment-naïve eyes (62 nAMD, 96 DME, and 33 RVO) of 150 patients receiving three monthly IVB and IVB-awwb loading doses. Baseline and final (one month after the third injection) best-corrected visual acuity (BCVA; logMAR) and central macular thickness (CMT; µm) of the eyes with nAMD, DME, and RVO, disease activity rates for nAMD, and overall endophthalmitis rates were compared between IVB and IVB-awwb groups.

Results: The mean baseline and final BCVA and CMT were comparable for nAMD (32 vs. 30 eyes), DME (47 vs. 49 eyes), and RVO (14 vs. 19 eyes) in IVB and IVB-awwb groups. The final nAMD activity rates were 53.1% and 63.3% in the groups, respectively (p=0.578). In DME eyes, BCVA significantly improved in the IVB group (p=0.002) with no significant difference in the IVB-awwb group (p=0.152), and the mean change in BCVA was -0.18±0.38 and -0.09±0.45 logMAR, respectively (p=0.033). Culture-negative endophthalmitis (n=2; 2.0% overall) was observed only in the IVB-awwb group (p=0.498).

Conclusion: This real-life study suggests that intravitreal biosimilar bevacizumab-awwb could yield comparable or worse but no better results than reference bevacizumab in eyes with nAMD, DME, and macular edema secondary to RVO. Further randomized studies are required to elucidate the efficacy and safety of IVB-awwb.

Keywords: bevacizumab; biosimilar pharmaceuticals; diabetic retinopathy; macular degeneration; macular edema; retinal vein occlusion

ÖZET

Amaç: Neovasküler yaşa bağlı maküla dejenerasyonu (nYBMD), diyabetik maküla ödemi (DMÖ) ve retinal ven tıkanıklığına (RVT) ikincil maküla ödemi olan hastalarda intravitreal biyobenzer bevasizumab-awwb (İVB-awwb) ve referans bevasizumabın (İVB) fonksiyonel, anatomik ve güvenlik sonuçlarını karşılaştırmak.

Yöntem: Bu retrospektif, randomize olmayan gerçek-yaşam çalışmasına, üç ay boyunca aylık İVB ve İVB-awwb yükleme dozu alan 150 hastanın tedavi-naif 191 gözü (62 nYBMD, 96 DMÖ ve 33 RVT) dahil edildi. nYBMD, DMÖ ve RVT'li gözlerin başlangıç ve final (üçüncü enjeksiyondan bir ay sonra) en iyi düzeltilmiş görme keskinlikleri (EİDGK; logMAR) ve merkezi makula kalınlıkları (MMK; µm), nYBMD için hastalık aktivite oranları ve tüm gözlerin endoftalmi oranları İVB ve İVB-awwb grupları arasında karşılaştırıldı.

Bulgular: Neovasküler YBMD'li (32 ve 30 göz), DMÖ'lü (47 ve 49 göz) ve RVT'li (14 ve 19 göz) gözlerin ortalama başlangıç ve final EİDGK ve MMK'leri her iki grupta benzerdi. Final nYBMD aktivite oranları İVB ve İVB-awwb gruplarında sırasıyla %53,1 ve %63,3 idi (p=0,578). DMÖ'lü gözlerde EİDGK, İVB grubunda anlamlı olarak iyileşirken (p=0,002), İVB-awwb grubunda anlamlı fark saptanmadı (p=0,152), EİDGK'deki ortalama değişiklik sırasıyla -0,18±0,38 ve -0,09±0,45 logMAR olarak saptandı (p=0,033). Kültür-negatif endoftalmi (n=2; tüm gözlerin %2,0'si) yalnızca İVB-awwb grubunda gözlendi (p=0,498).

Sonuç: Bu gerçek yaşam çalışması, intravitreal biyobenzer bevacizumab-awwb'nin, nYBMD, DMÖ ve RVT'ye ikincil makula ödemi olan gözlerde referans bevacizumab ile benzer veya daha kötü sonuçlar verebildiğini ancak daha iyi sonuçlar vermediğini göstermektedir. İVB-awwb'nin etkinliğini ve güvenliğini aydınlatmak için randomize çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: bevasizumab; biobenzer farmasötikler; diyabetik retinopati; maküla dejenerasyonu; maküla ödemi; retinal ven tıkanıklığı

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Therapeutic agents containing proteins derived from biotechnology, i.e., biological drugs or biologics, have radically changed the management of many diseases during the last four decades with the expense of high temporal, developmental, and research costs (1). Patent expiration of those original biologics, i.e., reference agents, allowed manufacturers a faster and cheaper way to enter the market through biosimilar products and offered patients more affordable options (2). As a synthesis of definitions, biosimilars are remarkably similar in potency, purity, and safety to currently approved reference biological agents, except for differences in their clinically inactive components (2). Unlike generic drugs identical to the original molecule in structure, they can not be used interchangeably with their references without preclinical and clinical comparison trials (3). Still, once approved for a disease, they can be used for other diseases for which the reference is already being used by extrapolation of indications (4).

The biological agents of vascular endothelial growth factor (VEGF) inhibitors (anti-VEGFs) have revolutionized the anatomical and functional gains from treating several retinal diseases, starting from the non-authorized (off-label) intravitreal use of bevacizumab (Avastin® / Altuzan®, Genentech, CA, USA / Roche, Mannheim, Germany) licensed for metastatic colorectal carcinoma (5). Later, licensed anti-VEGF agents (on-label) for intraocular use, such as ranibizumab (Lucentis®, Genentech, CA, USA) and aflibercept (Eylea®, Regeneron, NY, USA) were manufactured and proven effective in retinal diseases (5). Nevertheless, the economic advantage of bevacizumab and the demonstration of its comparable efficacy and safety with intravitreally approved agents have made it one of the most frequently used anti-VEGF agents in retinal diseases today (6).

The patent expiration of the reference anti-VEGF agents has already resulted in an increased production of their biosimilars (7). Nearly a decade has passed since the first-ever approved ranibizumab biosimilar for intravitreal use, Razumab™ (Intas Pharmaceuticals, Ahmedabad, India) (8, 9). Now, the first-ever both Food and Drug Administration (FDA) and European Medical Agency (EMA) approved ranibizumab biosimilar, ranibizumab-nuna (Byooviz™, Samsung Bioepis, South Korea / Biogen, USA), and aflibercept biosimilar, aflibercept-jbvf (Yesafili™, Biocon Biologics, Bangalore, India) are on the market (9-11). All these intravitreally approved biosimilar agents have comparative studies with their reference biologics and can, therefore, be used interchangeably; however, this is not the case for bevacizumab (8-11). Since bevacizumab is used off-label in ocular diseases, approval of its biosimilar in an extraocular indication cannot be assumed to be extrapolatable to intraocular use without sufficient clinical data (12).

There are several approved bevacizumab biosimilars for extraocular indications, with limited clinical and preclinical studies suggesting safety and efficacy when used intravitreally (13-20). However, to our knowledge, no studies clinically investigate the first-approved bevacizumab biosimilar, bevacizumab-awwb (Mvasi®, Amgen, CA, USA) (21), in its intravitreal application for retinal diseases in treatment-naïve eyes. Therefore, this study aims to compare the functional, anatomical, and safety results of intravitreal biosimilar bevacizumab-awwb (IVB-awwb; Mvasi®, Amgen, CA, USA) and intravitreal reference bevacizumab (IVB; Altuzan®, Roche, Mannheim, Germany) injections in treatment-naive patients with neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), and macular edema secondary to retinal vein occlusion (RVO).

Materials and Methods

This real-life, retrospective, non-randomized, comparative, consecutive case series study was approved by the institutional review board of Marmara University School of Medicine, Istanbul, Turkey (No: 09.2023.873, 09.2023.874, and 09.2023.875 for nAMD, DME, and RVO, respectively). The study adhered to the ethical principles of the latest amendments to the Declaration of Helsinki. All patients routinely provided written informed consent to participate and to have their medical information used in the study at their presentation. Additional informed consent was also obtained from all patients regarding the use of the off-label agents.

Study Population

In Turkey, patients with treatment-naïve retinal disease were obligated to receive three consecutive intravitreal bevacizumab to get reimbursement, according to an official communiqué published by the Social Security Institution on December 28th, 2018 (22, 23). The bevacizumab, used for intravitreal injection, is supplied by the pharmacy of the state hospital, where the injection is performed after the attending physician's approval. As of 2020, the Turkish State Supply Office (SSO) has been carrying out pharmaceutical supplies to hospital

pharmacies at four-month intervals (24). In January 2023, the biosimilar bevacizumab-awwb (Mvasi®, Amgen, CA, USA) was supplied to the pharmacy of Marmara University Pendik Training and Research Hospital by SSO instead of the reference bevacizumab (Altuzan®, Roche, Mannheim, Germany), leaving us to apply IVB-awwb. This study retrospectively included those consecutive patients receiving biosimilar IVB-awwb (IVB-awwb group) from January to April 2023 and consecutive patients receiving reference IVB (IVB group) from the previous SSO supply (September to December 2022) as the comparison group.

Patients who were over 18 years of age, diagnosed either with nAMD, DME, or macular edema secondary to RVO (central [CRVO] or branch retinal vein occlusion [BRVO]), treatment-naïve, treated starting with either IVB-awwb or IVB during the prespecified time intervals, completed three monthly loading doses, and attended the control visit one month after the last loading dose were included in the study. The study exclusion criteria were previous treatment with anti-VEGF or focal, grid, or panretinal laser photocoagulation, intraocular surgery excluding phacoemulsification, phacoemulsification within six months precluding the study, visually significant media opacity (i.e., corneal haze, cataract, posterior capsule opacification, intravitreal hemorrhage, and vitreous condensation), more than seven days deviation from injection appointment, and any missing data.

Patient Examinations

All patients had a comprehensive ophthalmological examination at presentation and one month after the last intravitreal injection, including Snellen best-corrected visual acuity (BCVA) assessment, slit-lamp biomicroscopy, pneumatic tonometry, dilated fundus examination, and spectral-domain optical coherence tomography (SD-OCT; Spectralis®, Heidelberg Inc., Heidelberg, Germany). The retinal diagnoses were made according to the ophthalmic examination, SD-OCT, and, in case of any doubt, fundus fluorescein angiography (Topcon TRC50DX, Topcon, Tokyo, Japan). Indocyanine green angiography (Topcon TRC50DX, Topcon, Tokyo, Japan) was also applied to differentiate nAMD from polypoidal choroidal vasculopathy if necessary. For all eyes, central macular thicknesses (CMT; µm) were measured automatically by the Spectralis® device software after foveal alignment was ensured. Any nAMD lesion with intraretinal fluid, subretinal fluid, or subretinal hyperreflective material in SD-OCT or new hemorrhage on dilated fundus examination is considered active. Any intraretinal or subretinal fluid on SD-OCT in DME and RVO patients is considered persistent after three intravitreal injections. All intravitreal injections were applied in an outpatient clean room under sterile conditions. Both agents were applied in 1.25 mg/0.05 mL doses drawn from separate vials for each eye.

The demographic and clinical characteristics of the patients and their eyes with nAMD, DME, and macular edema secondary to RVO were compared separately between the IVB and IVB-awwb groups. The safety measures were settled as visually significant complications of intravitreal hemorrhage, lenticular touch, and endophthalmitis after the injections, and the rates were compared considering all eyes in the IVB and IVB-awwb groups.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) for macOS version 26.0 (IBM Corp., Armonk, NY, USA) was employed to analyze the data. Inspection of the histogram graphs and the Shapiro-Wilk test were used to determine data distribution. Continuous and categorical variables were expressed in mean±standard deviation (SD) and frequency (n) with percentage (%), respectively. Snellen BCVA values were converted to the logarithm of the minimum angle of resolution (logMAR) values for statistical analysis, and the "counting fingers" and "hand motion" visual acuities were considered 1.85 and 2.30 logMAR, respectively (25). The between-group comparisons were made using Mann-Whitney U or independent samples t-test, and inter-group repeated measures were made using Wilcoxon signed rank test. Three-group comparisons were made with one-way analysis of variance (ANOVA) test, and the Dunn-Bonferroni post-hoc test was applied for multiple comparisons. Pearson Chi-square or Fisher's exact test was used for qualitative comparisons. A two-sided p-value of <0.05 was considered statistically significant, and Bonferroni adjusted p-values (adj. p) were given where appropriate.

Results

One hundred ninety-one eyes of 150 patients (84 [56.0%] females) with a mean age of 66.3±8.2 were included in the study analysis. Of the 191 eyes, 93 (48.7%) were treated with IVB, and 98 (51.3%) were treated with IVB-awwb. The indications for anti-VEGF injection were nAMD in 62 eyes (32.5%) of 50 patients, DME in 96 eyes (50.3%) of 68 patients, and macular edema secondary to RVO in 33 eyes

(17.3%) of 32 patients. The inclusion rates of the second eyes of patients treated with IVB and IVB-awwb were 18.5% (n=5) and 25.0% (n=6) for nAMD patients (p=0.736); 42.4% (n=14) and 35.1% (n=13) for DME patients (p=0.625); and 0% and 5.6% (n=1) for RVO patients (p=1.000), respectively.

The mean age of the patients was significantly different between the disease groups (p<0.001). Of which, nAMD patients (70.9±7.2) was significantly older than DME (64.1±8.0, adj. p<0.001) and RVO (64.2±7.6, adj. p<0.001) patients, with no significant difference between DME and RVO patients (adj. p=1.000). The gender distribution (female, n [%]) was similar amongst the patients with nAMD (26 [52.0%]), DME (40 [58.8%]), and RVO (18 [56.3%]) (p=0.761).

Neovascular Age-Related Macular Degeneration

Of the 62 eyes of 50 patients with nAMD, 32 (51.6%) and 30 (48.4%) were treated with IVB and IVB-awwb, respectively **(Table 1)**. There was no significant difference between the mean age and gender of the treatment groups. The mean BCVA **(Figure 1a)** and CMT **(Figure 2a)** were significantly improved from baseline to final evaluation in IVB and IVB-awwb groups, with no significant intergroup differences **(Table 1)**. The mean change in BCVA and CMT with treatment was also similar between the groups **(Table 1)**.

At the final visit, there were 17 (53.1%) and 19 (63.3%) eyes with active nAMD lesions in IVB and IVB-awwb groups, respectively **(Table 1)**.

Table 1: Demographic and clinical characteristics of the patients and eyes with neovascular age-related macular degeneration.

	IVB Group	IVB-awwb Group	p
Patients, n (%)	27 (54.0)	23 (46.0)	-
Eyes, n (%)	32 (51.6)	30 (48.4)	-
Age, years mean ± SD	70.8 ± 6.9	70.9 ± 7.6	0.962[a]
Gender, n (%) Female Male	15 (55.6) 12 (44.4)	11 (47.8) 12 (52.2)	0.794[b]
BCVA, logMAR			
Baseline mean ± SD Snellen equivalent	1.14 ± 0.74 ~20/250	1.20 ± 0.82 ~20/320	0.949[c]
Final mean ± SD Snellen equivalent	1.04 ± 0.74 ~20/200	1.12 ± 0.86 ~20/250	0.739[c]
p	0.051[d]	0.127[d]	
BCVA change, logMAR mean ± SD	-0.11 ± 0.27	-0.07 ± 0.34	0.747[c]
CMT, µm			
Baseline mean ± SD	423.5 ± 167.9	403.1 ± 147.2	0.730[c]
Final mean ± SD	376.8 ± 157.2	351.3 ± 126.0	0.662[c]
p	**<0.001**[d]	**0.014**[d]	
CMT change, µm mean ± SD	-46.6 ± 64.2	-51.8 ± 109.1	0.703[c]
Final Disease Activity, n (%) Active Inactive	17 (53.1) 15 (46.9)	19 (63.3) 11 (36.7)	0.578[b]

BCVA, best-corrected visual acuity; CMT, central macular thickness; IVB, intravitreal reference bevacizumab; IVB-awwb, intravitreal biosimilar bevacizumab-awwb; logMAR, logarithm of the minimum angle of resolution; SD, standard deviation
[a] Independent samples t-test
[b] Pearson Chi-square with continuity correction
[c] Mann-Whitney U test
[d] Wilcoxon signed rank test
Bold values indicate statistical significance

Table 2: Demographic and clinical characteristics of the patients and eyes with diabetic macular edema.

	IVB Group	IVB-awwb Group	p
Patients, n (%)	33 (48.5)	35 (51.5)	-
Eyes, n (%)	47 (49.0)	49 (51.0)	-
Age, years mean ± SD	62.6 ± 7.7	65.5 ± 8.1	0.126[a]
Gender, n (%) Female Male	19 (57.6) 14 (42.4)	21 (60.0) 14 40.0)	1.000[b]
BCVA, logMAR			
Baseline mean ± SD Snellen equivalent	0.67 ± 0.51 ~20/100	0.70 ± 0.67 ~20/100	0.575[c]
Final mean ± SD Snellen equivalent	0.48 ± 0.43 ~20/63	0.60 ± 0.63 ~20/80	0.771[c]
p	**0.002**[d]	0.152[d]	
BCVA change, logMAR mean ± SD	-0.18 ± 0.38	-0.09 ± 0.45	**0.033**[c]
CMT, µm			
Baseline mean ± SD	426.0 ± 91.4	424.6 ± 122.9	0.994[c]
Final mean ± SD	365.6 ± 115.6	386.3 ± 130.6	0.585[c]
p	**<0.001**[d]	**<0.001**[d]	
CMT change, µm mean ± SD	-60.4 ± 125.1	-38.3 ± 106.4	0.288[c]

BCVA, best-corrected visual acuity; CMT, central macular thickness; IVB, intravitreal reference bevacizumab; IVB-awwb, intravitreal biosimilar bevacizumab-awwb; logMAR, logarithm of the minimum angle of resolution; SD, standard deviation
[a] Independent samples t-test
[b] Pearson Chi-square with continuity correction
[c] Mann-Whitney U test
[d] Wilcoxon signed rank test
Bold values indicate statistical significance

Diabetic Macular Edema

Among the 96 eyes (68 patients) with DME, 47 eyes (49.0%) of 33 patients were treated with IVB, and 49 eyes (51.0%) of 35 patients were treated with IVB-awwb **(Table 2)**. The mean age and gender were similar, and there were no significant differences between the baseline and final BCVA and CMT of the groups **(Table 2)**. The mean CMT was significantly improved with treatment in both groups, with no significant difference in CMT change between them. The DME persistence rates were also similar amongst IVB (30 eyes; 61.2%) and IVB-awwb (26 eyes; 55.3%) groups (p=0.795). However, a statistically significant improvement in BCVA was observed only in the IVB group, and the degree of improvement was significantly greater compared to the IVB-awwb group **(Figures 1b and 2b).**

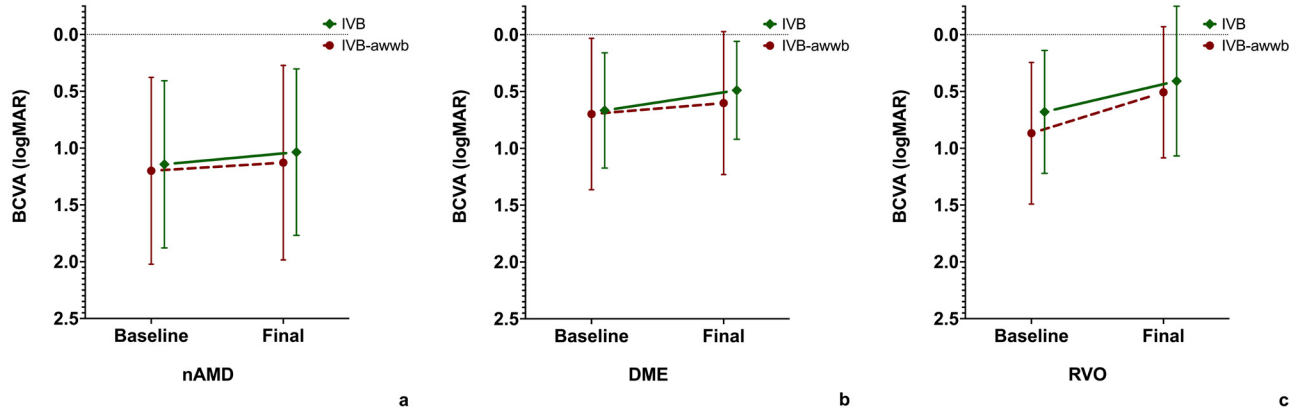

Figure 1: The line graphs of the mean baseline and final best-corrected visual acuity (BCVA) of the eyes included in the study
a. Neovascular age-related macular degeneration (nAMD), **b.** Diabetic macular edema (DME), **c.** Macular edema secondary to retinal vein occlusion (RVO).
BCVA, best-corrected visual acuity; IVB, intravitreal reference bevacizumab; IVB-awwb, intravitreal biosimilar bevacizumab-awwb; logMAR, the logarithm of the minimum angle of resolution.
Error bars indicate standard deviation.

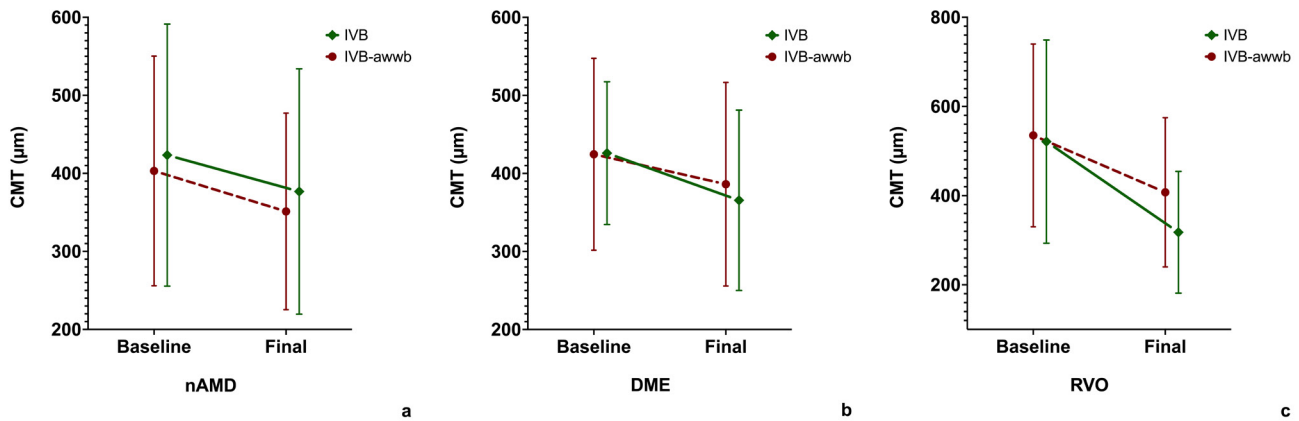

Figure 2: The line graphs of the mean baseline and final central macular thickness (CMT) of the eyes included in the study
a. Neovascular age-related macular degeneration (nAMD), **b.** Diabetic macular edema (DME), **c.** Macular edema secondary to retinal vein occlusion (RVO).
IVB, intravitreal reference bevacizumab; IVB-awwb, intravitreal biosimilar bevacizumab-awwb
Error bars indicate standard deviation.

Retinal Vein Occlusion

There were 14 and 19 eyes of 14 and 18 patients in the IVB and IVB-awwb groups, respectively, with no significant difference in mean age and gender between the patients **(Table 3)**. There were three (21.4%) and six (31.6%) eyes with central retinal vein occlusion in the IVB and IVB-awwb groups, respectively. The mean baseline BCVA and CMT were similar and significantly improved in both groups, with no significant difference in final BCVA **(Figure 1c)** and CMT **(Figure 2c)**. The macular edema persisted in 3 (21.4%) and 7 (36.8%) eyes in IVB and IVB-awwb groups, respectively (p=0.455). The changes in BCVA and CMT were also comparable between the two treatment groups **(Table 3)**.

Table 3: Demographic and clinical characteristics of the patients and eyes with macular edema secondary to retinal vein occlusion.

	IVB Group	IVB-awwb Group	p
Patients, n (%)	14 (43.8)	18 (56.2)	-
Eyes, n (%)	14 (42.4)	19 (57.6)	-
Age, years mean ± SD	65.4 ± 9.1	63.2 ± 6.3	0.441[a]
Gender, n (%) Female Male	5 (35.7) 9 (64.3)	13 (72.2) 5 (27.8)	0.088[b]
The type of RVO, n (%) CRVO BRVO	3 (21.4) 11 (78.6)	6 (31.6) 13 (68.4)	0.698[c]
BCVA, logMAR			
Baseline mean ± SD Snellen equivalent	0.68 ± 0.53 ~20/100	0.87 ± 0.63 ~20/160	0.322[d]
Final mean ± SD Snellen equivalent	0.41 ± 0.66 ~20/50	0.51 ± 0.58 ~20/63	0.163[d]
p	**0.023**[e]	**0.029**[e]	
BCVA change, logMAR mean ± SD	-0.27 ± 0.38	-0.36 ± 0.73	0.855[d]
CMT, µm			
Baseline mean ± SD	521.3 ± 228.0	535.2 ± 204.1	0.716[d]
Final mean ± SD	317.7 ± 136.5	407.4 ± 167.3	0.109[d]
p	**0.001**[e]	**0.009**[e]	
CMT change, µm mean ± SD	-203.6 ± 166.9	-127.8 ± 183.6	0.308[d]

BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CMT, central macular thickness; CRVO, central retinal vein occlusion; IVB, intravitreal reference bevacizumab; IVB-awwb, intravitreal biosimilar bevacizumab-awwb; logMAR, logarithm of the minimum angle of resolution; RVO, retinal vein occlusion; SD, standard deviation
[a] Independent samples t-test
[b] Pearson Chi-square with continuity correction
[c] Fisher's exact test
[d] Mann-Whitney U test
[e] Wilcoxon signed rank test
Bold values indicate statistical significance

Safety

No intravitreal hemorrhage or lenticular touch was encountered during the study period. There were no cases of endophthalmitis in the overall IVB-treated eyes (n=93), but two eyes (2%) from the IVB-awwb-treated eyes (n=98) were diagnosed as endophthalmitis (p=0.498).

Both endophthalmitis patients (a 46-year-old female and a 55-year-old male) had unilateral BRVO with different intravitreal injection application dates. They presented with decreased visual acuity, ocular pain, ciliary injection, and hypopyon three days after the third loading dose of IVB-awwb injections. Same-day vitreous tap and intravitreal antibiotic injections (1 mg/0.1 mL vancomycin and 2.25 mg/0.1 mL ceftazidime) were applied to both patients at their presentation. Their signs were completely regressed after three sessions (once every two days) of intravitreal antibiotic injections with one drop per hour of topical moxifloxacin 0.5% (Moxai®, Abdi İbrahim, İstanbul, Türkiye) and four drops a day of topical prednisolone 1%, without needing pars plana vitrectomy. Vitreous sample cultures were negative for both patients. The BCVA and CMT of both eyes were better than their first presentation at the final visit.

Discussion

This first real-life study assessing intravitreal biosimilar bevacizumab-awwb in comparison to reference bevacizumab in treatment-naïve eyes of nAMD, DME, and RVO patients showed comparable functional and anatomical results in nAMD and RVO, with significantly less BCVA improvement in bevacizumab-awwb treated DME eyes (p=0.033). Although not statistically significant, two cases of culture-negative endophthalmitis were also seen with IVB-awwb, suggesting a questionable sterile intraocular inflammation.

To our knowledge, the first biosimilar bevacizumab with clinical data in intravitreal use was Zybev™ (Zydus Cadila Healthcare Ltd., Ahmedabad, India) (13). In this multicenter retrospective study in India, a single intravitreal injection of 1.25 mg/ 0.05 mL Zybev™ resulted in a significant improvement of BCVA and CMT one month later without any systemic or ocular adverse events in a mixed group of DME, nAMD, and RVO. Later, Agarwal et al. (14) retrospectively evaluated the six-week results of a single injection of the same agent in various retinal diseases. The authors reported an overall significant mean BCVA and CMT improvement considering all patients, without any improvement in BCVA of Coat's disease, choroidal osteoma, and eight cases of BRVO (14). The study also reported no systemic or ocular adverse events (14). In a preclinical study, Lashay et al. (15) reported similar short-term vitreoretinal safety of single intravitreal 2.5 mg/0.1 mL Stivant™ (CinnaGen Co., Tehran, Iran) with electroretinography and histology compared to intravitreal reference bevacizumab in albino rabbits (15). Later, the same group investigated the efficacy of intravitreal 1.25 mg/0.05 mL Stivant™ in patients with nAMD (87 eyes), DME (234 eyes), and RVO-related macular edema (64 eyes) who were either treatment-naïve or without treatment for six months (16). Although CMT significantly improved after the last Stivant™ injection for all indications in this prospective case series, BCVA significantly improved only in RVO patients (16). No systemic or ocular adverse events were reported, except vitreous hemorrhage one day after the injection in a diabetic patient (16).

The ocular safety of another biosimilar bevacizumab, bevacizumab-bvzr (Zirabev®; Pfizer Inc., New York, USA), was evaluated in healthy male cynomolgus monkey eyes in 1.25 mg/0.05 mL biweekly doses of total three intravitreal injections (17). The repeat-dose intravitreal injection of Zirabev® was tolerated locally and systemically, with an ocular safety comparable to controls (17). The first clinical study with intravitreal Zirabev® was reported in a case series of 13 injections for 12 eyes of 9 children with retinopathy of prematurity (ROP, n=7), macular neovascularization (n=3), RVO (n=2), and Coat's disease (n=1) (18). The study revealed a positive clinical response with 0.125 or 0.625 mg/0.025 mL of Zirabev® for ROP and a standard dose of 1.25 mg/0.05 mL for other diagnoses, without post-injection endophthalmitis or intraocular inflammation (18). Recently, a retrospective, single-center, interventional study from India evaluated another biosimilar bevacizumab (Bevatas®, Intas Pharmaceuticals, Ahmedabad, India) in 100 type-1 ROP and 44 aggressive ROP (AROP) eyes (19). The study demonstrated significant benefits from intravitreal 0.625 mg/0.025 mL Bevatas® monotherapy in type-1 ROP but not in AROP, with complete regression rates of 87% and 18.2%, respectively, without any ocular or systemic adverse events (19).

Most recently, a real-life study from Italy assessed the efficacy and safety of three consecutive monthly IVB-awwb (Mvasi®) in nAMD and DME patients who underwent forced substitution from IVB (Avastin®) at the pharmacy level during their maintenance phase of treat-and-extend anti-VEGF treatment (20). For the 80 eyes of 76 nAMD patients receiving a mean of 19.5±11.9 (range, 3-52) IVB, mean BCVA and CMT did not significantly change after the third IVB-awwb injection (20). And the slopes of the linear correlation of CMT over time (in weeks) were similar for IVB (-0.71) and IVB-awwb (-0.98), reflecting comparable (p=0.43) therapeutic activity of the agents (20). The proportions of the treatment intervals reached with the treat-and-extend strategy, as well as retinal fluid score changes, were also similar between the agents (20). Similar results were obtained in 55 eyes of 33 patients with DME receiving a mean of 15.4±7.6 (range, 3-36) IVB after substitution to IVB-awwb (20). The authors reported no ocular or systemic adverse events after cumulatively administering 3496 IVB-awwb injections throughout the study (20). Similarly, the changes of BCVA and CMT were comparable for our patients, except for BCVA change in DME eyes, suggesting at least equivalent efficacy of both agents. However, better improvement in BCVA with IVB in DME eyes could be explained by the fact that our patients were all treatment-naïve and might not have been influenced by the ceiling effect that previously treated eyes, which could have been reached the maximum BCVA of the eye, can get (i.e., no more available visual acuity score to gain).

Regarding safety, our study revealed two (2%) culture-negative endophthalmitis cases in RVO patients managed with local therapy without necessitating pars plana vitrectomy. The fact that the endophthalmitis cases we encountered were culture negative and the functional and anatomical results were relatively favorable increases the likelihood of these cases being sterile endophthalmitis. Yet, considering that we used antibiotics during their treatment, we cannot comment on whether our cases definitely had sterile endophthalmitis. Biosimilar molecules differ from reference agents in their quaternary structures due to biotechnological processes involved in their production through living cells and their inactive components, with even minor unintended modifications resulting in an altered efficacy and safety (2, 7). The importance of this difference regarding safety has been highlighted in the literature with cluster sterile endophthalmitis encountered with some batches of Razumab®, the first on-label intravitreal anti-VEGF biosimilar, resulting in the revision of its formulation (8). Accordingly, the American Academy of Ophthalmology published a policy statement indicating the potential difference in immunogenicity with biosimilars while used intravitreally, strongly recommending against the intravitreal use of off-label bevacizumab biosimilars in the absence of sufficient clinical studies in ophthalmological indications (12).

While interpreting the results of this study, one should consider its non-randomized retrospective design, relatively small sample size, and limited follow-up period. Another limitation is the inclusion of both eyes of eligible patients in the study, given that literature reports suggest bevacizumab injections in one eye may cause changes in the fellow eye (26). However, the inclusion of both eyes in the treatment groups did not differ significantly between the groups. Therefore, this effect is unlikely to influence the study outcomes substantially. Also, this study did not evaluate systemic factors such as hypertension or HbA1c levels, which may influence treatment outcomes in DME and RVO. Future studies should consider these variables. The strength of the study is its head-to-head comparative design in real-life conditions, providing insight into a current affair of national as well as global importance.

Conclusion

This real-life assessment of intravitreal biosimilar bevacizumab-awwb suggests comparable anatomical and functional results to its reference counterpart, with the possibility of questionable immunogenicity to consider. Future randomized comparative studies with more extensive sample sizes may provide clinicians with more information on this subject.

Declarations

Funding

No funding was required during the conduction of this study.

Conflict of Interest

The authors have no potential proprietary or financial interests to disclose.

Ethics Approval

The study protocol was approved by the institutional review board of Marmara University School of Medicine, Istanbul, Turkey (No: 09.2023.873, 09.2023.874, and 09.2023.875).

Data Availability

The data of this study is available from the correspondence author upon reasonable request.

Authors' Contributions

MOS: Conception, design, supervision, funding, materials, data collection, processing, analysis, and interpretation, literature review, writing, and critical review; **SGK:** Conception, design, supervision, materials, data collection and interpretation, literature review, writing, and critical review; **AA:** Conception, design, supervision, data interpretation, and critical review; **DDY:** Conception, design, supervision, data interpretation, literature review, and critical review; **ÖŞ:** Conception, design, supervision, fundings, materials, data analysis and interpretation, and critical review.

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