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Short-term effectiveness of intravitreal Ziv-Aflibercept for the treatment of macular edema secondary to retinal vein occlusion

Efectividad a corto plazo de Ziv-Aflibercept intravítreo para el tratamiento del edema macular secundario a la oclusión de la vena retiniana

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SUMMARY

Objective: To determine the short-term effectiveness of intravitreal Ziv-Aflibercept (IV-ZA) for the treatment of macular edema secondary to retinal vein occlusion (MESRVO). ***Methods:*** A retrospective, single-arm cohort study was conducted, including patients diagnosed with MESRVO. All received six monthly doses of IV-ZA. Data was collected before treatment and one month after the final dose. The main outcome measures were best-corrected visual acuity (BCVA, LogMAR) and central macular thickness (CMT). Summary statistics were presented, and the Wilcoxon signed-rank test with continuity correction was used; $p < 0.05$ was considered statistically significant. Data were analyzed using R Studio. ***Results:*** Twenty-six eyes from 25 patients were included (69% with central retinal vein occlusion and 31% with branch retinal vein occlusion). Sixty-eight

percent were male, with a mean age of 63.9 ± 13.4 years. Baseline BCVA was 2 (0.3–2.09) LogMAR, improving to 1 (0.09–2) LogMAR (p < 0.01). Baseline CMT was 671 (392–1174) μm, decreasing to 207 (137–325) μm after treatment (p < 0.01). A total of 92.3% of eyes achieved a CMT below 300 μm after therapy. No ocular or systemic adverse events were reported. ***Conclusions:*** Six-monthly doses of IV-ZA were effective for the short-term management of MESRVO, showing significant visual and anatomical improvement. IV-ZA may represent a safe and cost-effective therapeutic alternative.

KEYWORDS: Retinal vein occlusion, Macular edema, Intravitreal Injection, Angiogenesis inhibitors.

RESUMEN

***Objetivo*:** Determinar la efectividad a corto plazo de Ziv-Aflibercept intravítreo (ZA-IV) para el tratamiento del edema macular secundario a oclusión venosa retiniana (EMSOVR). ***Material y métodos*:** Estudio de cohorte retrospectivo de un solo brazo. Se incluyeron pacientes con diagnóstico de EMSOVR. Se trató con 6 dosis mensuales de ZA-IV. Los datos se recopilaron antes del tratamiento y un mes después de la última dosis. Las principales medidas de resultado son la agudeza visual mejor corregida (AVMC) en LogMAR y el grosor macular central (GMC). Se presentaron medidas de resumen y se utilizó la prueba de rangos con signo de Wilcoxon con continuidad de corrección; p < 0,05 se consideró estadísticamente significativo. Se procesaron los datos en R Studio. ***Resultados*:** Se incluyeron 26 ojos de 25 pacientes (69% con oclusión de la vena central de la retina y 31% con oclusión de la rama venosa de la retina). El 68% eran varones, edad media de 63,9 ± 13,4 años. La AVMC basal fue de 2 (0,3-2,09) LogMAR y final de 1 (0,09-2) LogMAR (p<0,01). El GMC basal fue de 671 (392-1174) μm y el GMC final fue 207 (137-325) μm (p<0,01). El 92,3% de los ojos incluidos presentó un GMC inferior a 300 μm luego del tratamiento. No se reportaron efectos adversos sistémicos ni oculares. ***Conclusiones*:** El uso de 6 dosis de ZA-IV en un régimen mensual fue eficaz para el tratamiento a corto plazo del EMSOVR y podría considerarse una buena alternativa terapéutica.

PALABRAS CLAVE: Oclusión venosa retiniana, efectividad, edema macular, inyecciones intravítreas, inhibidores de la angiogénesis.

INTRODUCTION

Vein occlusions represent the second most frequent retinal vascular disease after diabetic retinopathy, with a prevalence of 5.2 cases per 1000 people (0.52%). Vein occlusions are classified into central retinal vein occlusions (CRVO) with a prevalence of 0.8 cases per 1000 people (0.08%) and branch retinal vein occlusion (BRVO) with a prevalence of 4.4 per 1000 people (0.44%). Macular edema secondary to retinal vein occlusions (MESRVO) constitutes a main cause of decreased vision in these patients. [1–3]

Ischemia caused by a retinal vein occlusion leads to an increase in levels of vascular endothelial growth factor (VEGF), which plays a key role in the physiopathology of macular edema, by increasing retinal vessels permeability and promoting vascular leakage [2,4–7]. Prompt treatment of macular edema secondary to vein occlusions avoids the progressive neurodegeneration that occurs in these patients [8]. Currently, anti-VEGF intravitreal injections are considered first-line treatment. Ranibizumab and Aflibercept are FDA-approved for the treatment of macular edema secondary to branch and central retinal vein occlusions. [1,9-11]

Ziv-Aflibercept is a recombinant fusion protein that binds to VEGF receptors 1 and 2. As a structural isomer of Aflibercept, it targets all the VEGF subtypes, including placental growth factor, and demonstrates similar efficacy. It has FDA approval for the treatment of metastatic colorectal carcinoma, but its ophthalmologic use is off label. [1,4,9,12,13]

Intravitreal Ziv-Aflibercept (IV-ZA) has been reported to be a safe drug with favorable structural and functional results in cases of diverse pathologies such as diabetic macular edema, age-related macular degeneration, and retinal vein occlusions. Adverse effects reported from the use of IV-ZA were very similar to those of intravitreal Ranibizumab and Aflibercept. [3,4,12,14-17]

In addition to its established efficacy and safety profile, IV-ZA offers a significant economic advantage that enhances treatment accessibility, particularly in low- and middle-income countries. The approximate cost per intravitreal dose is USD 50 for Bevacizumab, USD 25–30 for IV-ZA, and USD 1,800–2,000 for Aflibercept. Both Bevacizumab and Ziv-Aflibercept require aseptic repackaging prior to intravitreal administration. Owing to its comparable molecular structure and pharmacodynamic properties to Aflibercept, Ziv-Aflibercept represents a cost-effective and practical therapeutic alternative for the management of retinal vascular diseases. [2,3,5,16,18]

The main objectives of most studies that evaluate the effectiveness of intravitreal medications for the management of macular edema secondary to vein occlusions are the evaluation of macular thickness and visual acuity, but this does not demonstrate anatomical changes. In this study, we considered that this is insufficient to quantify the response to treatment. Advances in tomographic image resolution have enabled the use of tomographic biomarkers to evaluate prognostic factors for treatment response in greater detail, both functionally and anatomically. Therefore, the objective of this study was to assess the effectiveness of IV-ZA in treating MESRVO, using anatomical biomarkers (via Optical Coherence Tomography) and functional outcomes (best-corrected visual acuity, BCVA).

METHODS

This was a retrospective, observational, single-center, single-arm cohort study conducted at the Mexican Institute of Ophthalmology in Querétaro, Mexico, between the months of March and October 2021.

We included patients with macular edema secondary to retinal vein occlusions (central and/or branch retinal vein) from the Retinal and Vitreous Department of our institution, who have had a recent diagnosis of secondary macular edema and who have been treated for the first time with intravitreal Ziv-Aflibercept 1.25 mg/0.05 ml (Sanofi) for 6 months (1 dose per month). We excluded patients with diabetic macular edema or any other cause different from retinal vein occlusion, patients who had previously received antiangiogenic treatment, vitrectomized patients, history of intermediate or posterior uveitis, myopia greater than 6 diopters, patients with proliferative diabetic retinopathy, neovascular glaucoma, patients with renal failure in hemodialysis, media opacities (vitreous hemorrhage, dense cataract, corneal opacity) that do not allow the evaluation of the posterior pole through indirect ophthalmoscopy or that do not allow a satisfactory image by Optic Coherence Tomography (OCT).

The application protocol was similar to that of Bevacizumab [1,5,10,14]. First, the compounding of the medication was carried out under sterile conditions and in a laminar flow hood. From the 100 mg/4ml vial of Ziv-Aflibercept, doses of 1.25 mg / 0.05 ml are obtained in 0.5ml syringes with a 31G / 6mm needle. The application of the medication was carried out in an exclusive environment for intravitreal procedures. The palpebral and periocular region was washed with 10% povidone-iodine for 3 minutes, then 5% povidone-iodine was applied in the conjunctival sac for 30 seconds. Sterile gloves and drapes were used, as well as a blepharostat. Adverse events, such as endophthalmitis, intraocular inflammation, or increased intraocular pressure, were monitored during follow-up visits.

Macular edema was confirmed through spectral domain OCT (REVO NX 130, Optopol) using a protocol of horizontal line scan in the foveal center. Prior to the first intravitreal injection, we collected data on BCVA and baseline tomography. The same data was collected post-treatment one month after the sixth dose. BCVA was measured by an optometrist who performed subjective refraction with trial lenses and a Snellen chart at 3 meters and transformed the data to LogMAR for statistical analysis.

Outcome measures were classified as follows:

- Primary outcome: Change in best-corrected visual acuity (BCVA) measured in LogMAR scale before and after treatment.

- Secondary outcomes: Changes in tomographic biomarkers (central macular thickness [CMT], macular cube volume [MCV], cyst size, integrity of EZ/ELM, DRIL, hyper-reflective foci, subretinal fluid [SRF], and vitreoretinal ratio).

We considered BCVA improvement with a clinically relevant minimal difference of 0.2 in LogMAR scale between the visual acuity values before and after the therapeutic intervention (equivalent to 1.5 to 2 Snellen lines of vision). A minimal clinically relevant difference of 0.2 in the LogMAR scale (equivalent to 1.5–2 Snellen lines) was considered significant, based on previous studies and expert consensus. [19]

To quantify the treatment effects in anatomical terms, data was obtained from the following tomographic biomarkers: central macular thickness (CMT) (um) (to consider edema, a criterion of mean ± 2 SD was used, which includes 95% of the population, taking as a normal limit value greater than 300 µm), macular cube volume (MCV) (mm^3), cyst size, integrity of the ellipsoid zone/external limiting membrane (EZ/ELM), disorganization of retinal inner layers (DRIL), presence of hyper-reflective foci, presence of subretinal fluid (SRF), vitreoretinal ratio. Data was also collected on occlusion types classified as ischemic, non-ischemic, and undetermined, according to the areas of ischemia (CRVO: 10-disc areas; BRVO: 5-disc areas) shown in fluorescein angiography.

The information collected was made available in a database designed by Microsoft Excel 2020. We then evaluated the database quality, avoiding the presence of lost, illegible data or bad digitizing. Normality of continuous variables was assessed using the Shapiro-Wilk test. For normally distributed data, paired Student's t-tests were used; otherwise, Wilcoxon signed-rank tests were applied. Categorical variables were analyzed using McNemar's Chi-squared test. Statistical significance was set at $p < 0.05$. Subgroup analyses were performed to assess the impact of occlusion type (ischemic vs. non-ischemic) on treatment outcomes. The data was processed in the graphical interface JAMOVI version 2.2 in the R version 4.1 programming language.

The study was approved by the Institutional Ethics Committee for its implementation with the registration number: CI/IMO-011/2021. The Declaration of Helsinki principles were respected.

RESULTS

A total of 25 patients were included, representing a total of 26 eyes. Seventeen (68%) patients were male. The mean age was 63.9 ± 13.4 years. The left eye (80%; n=21) was more frequently affected. Eighteen (70%) of eyes presented central retinal vein occlusion. Systemic comorbidities included hypertension (54%; n=14) and type 2 diabetes mellitus (42%; n=11). These conditions were managed per standard care during the study period. The most common type of vein occlusion was obstruction of the central retinal vein (69%; n=18). The characteristics of occlusion type according to ischemia grade are shown in table 1. Functional and tomographic characteristics according to occlusion type at the beginning and after the 6th dose of IV-ZA for macular edema secondary to vein occlusions are summarized in tables 2 and 3.

After analyzing the vein occlusions, we evidenced an improvement in the posterior visual capacity after the sixth dose of treatment, being statistically significant (from LogMAR 2 (0.3-2.09) to LogMAR 1 (0,09-2)) ($p< 0.01$) (Graphic 1). Likewise, we observed a noticeable decrease in the MCT (from 671 (392-1174) µm to 207 (137-325) µm) ($p<0.01$), and MCV, also with statistically significant results (from 14.1 (8.3-19.9) mm^3 to 7.7 (5.8-13.2) mm^3) ($p<0.01$) (see Graphics 2 and 3). 92,3% of eyes included presented a macular thickness below 300 µm after treatment.

Among the patients affected by central retinal vein occlusion, we observed visual capacity improvement in 50% of cases. In contrast, in patients with branch retinal vein occlusion, we evidenced improvement in 62% of patients.

There was a significant change in decrease of the disruption of EZ/ELM layer ($p<0.01$) as well as a decrease in DRIL ($p<0.001$). However, at the subretinal fluid level, statistical significance was not estimated despite the significant change in the reduction of SRF. We did not observe changes in the hyperreflective foci after treatment ($p=0.102$). The bivariate analysis could not be estimated for the changes in the variables- cysts and vitreoretinal ratio.

Bivariate and multivariate analyses were performed to assess associations between baseline tomographic biomarkers (e.g., EZ/ELM disruption, DRIL, SRF) and post-treatment visual improvement. No significant associations were identified, suggesting that other factors may influence treatment outcomes.

Regarding safety, no patient presented ocular adverse reactions (such as endophthalmitis or uveitis) or serious systemic adverse reactions (such as death, anaphylactic shock, or stroke) during the treatment period.

Figure 1 shows tomography of the macula of 3 patients after the use of 6 doses of intravitreal Ziv-Aflibercept for macular edema secondary to vein occlusions.

Table 1. Types of occlusions according to the degree of ischemia.

	Central retinal vein occlusion (n=18)	Branch retinal vein occlusion (n=8)	p value**
Degree of ischemia according to FAG			
- No data	2 (10%)	0 (0%)	0.24
- Ischemic	3 (20%)	4 (50%)	
- Non-ischemic	11(60%)	4 (59%)	
- Indeterminate	2 (10%)	0 (0%)	

FAG: fluorescein angiography. ** Pearson chi-square

Table 2. Characteristics of patients with central vein occlusion.

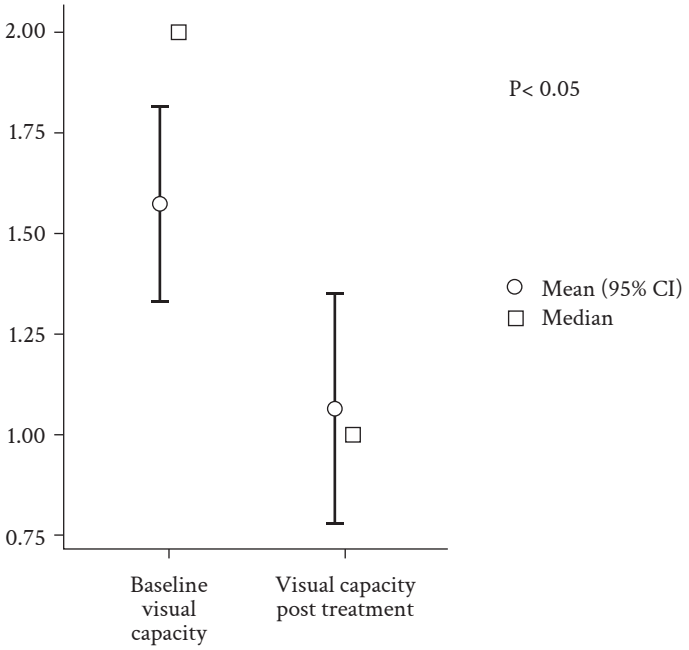
	Pre	Post	p value
	n (%)	n (%)	
BCVA median (range)	1.6 (0.30 - 2.09)	1.2 (0.09 - 2.00)	0.004*
MCT median (range)	680 (534 - 935)	202 (180 - 220)	0.001*
Cysts (C)			
Absent	0 (0.0%)	10 (55.5%)	NE**
Mild (0-100 um)	1 (5.6%)	5 (27.8%)	
Moderate (101-200 um)	3 (16.7%)	2 (11.1%)	
Severe (> 200 um)	14 (77.7%)	1 (5.6%)	
ZE / MLE (E)			
Intact	2 (11.1%)	3 (16.7%)	0.04**
Disruption	1 (5.6%)	7 (38.9%)	
Absent	15 (83.3%)	8 (44.4%)	
DRIL (D)			
Absent	1 (5.6%)	12 (66.7%)	0.001**
Present	17 (94.4%)	6 (33.3%)	
Hyperreflective foci (H)			
Absent	12 (66.7%)	16 (88.9%)	0.1**
Present	6 (33.3%)	2 (11.1%)	
Sub-retinal fluid (F)			
Absent	3 (16.7%)	18 (100.0%)	NE**
Present	15 (83.3%)	0 (0.0%)	
Vitreoretinal relationship (V)			
Absent of STVM	10 (55.5%)	11 (61.1%)	NE**
PVD incomplete	2 (11.1%)	2 (11.1%)	
PVD complete	2 (11.1%)	2 (11.1%)	
VMTS	1 (5.6%)	0 (0.0%)	
ERM	3 (16.7%)	3 (16.7%)	

BCVA: Best Correct Visual Acuity; MCT: Macular Central Thickness; ZE/MLE: Ellipsoid layer/External Limitin; DRIL: Disorganization of the Internal Layers of the Retina; VMTS: Vitreous Macular Traction Syndrome; PVD: Posterior Vitreous Detachment; ERM: Epiretinal Membrane.
NE: not estimable; * Wilcoxon-signed rank test; **McNemar test

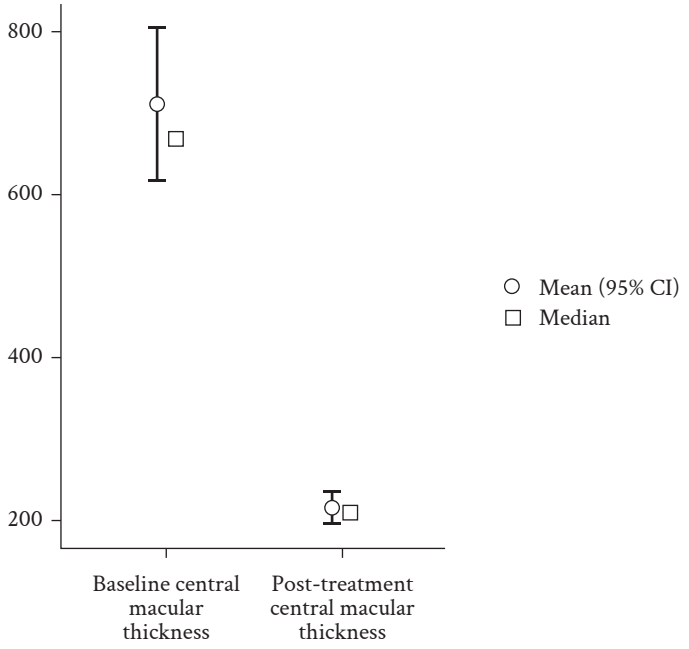
Table 3. Characteristics of patients with branch venous occlusion.

	Pre	Post	p value
	n (%)	n (%)	
BCVA	1.3 (0.39 - 2.00)	0.6 (0.17 - 2.00)	0.021*
MCT	699 (438 - 1036)	236.1 (137 - 325)	0.001*
Cysts (C)			
Absent	0 (0.0%)	6 (75.0%)	NE**
Mild (0-100 um)	0 (0.0%)	0 (0.0%)	
Moderate (101-200 um)	0 (0.0%)	2 (25.0%)	
Severe (> 200 um)	8 (100.0%)	0 (0.0%)	
ZE / MLE (E)			
Intact	1 (12.5%)	3 (37.5%)	NE**
Disruption	2 (25.0%)	5 (62.5%)	
Absent	5 (62.5%)	0 (0.0%)	
DRIL (D)			
Absent	0 (0.0%)	6 (75.0%)	NE**
Present	8 (100.0%)	2 (25.0%)	
Hyperreflective foci (H)			
Absent	8 (100.0%)	8 (100.0%)	NE**
Present	0 (0.0%)	0 (0.0%)	
Subretinal Fluid (F)			
Absent	2 (25.0%)	8 (100.0%)	NE**
Present	6 (75.0%)	0 (0.0%)	
Vitreoretinal relationship (V)			
Absent of VMTS	6 (75.0%)	5 (62.5%)	NE**
PVD incomplete	1 (12.5%)	1 (12.5%)	
PVD complete	0 (0%)	1 (12.5%)	
VMTS	1 (12.5%)	0 (0.0%)	
ERM	0 (0.0%)	1 (12.5%)	

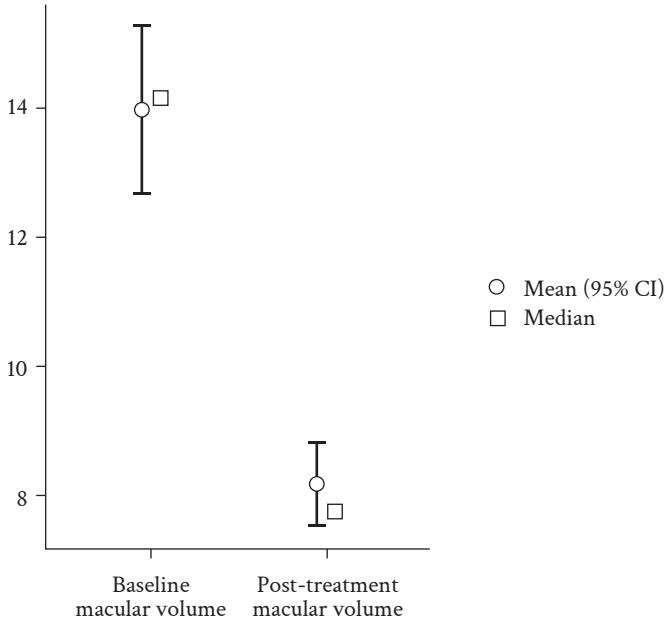
BCVA: Best Correct Visual Acuity; MCT: Macular Central Thickness; ZE/MLE: Ellipsoid layer/External Limitin; DRIL: Disorganization of the Internal Layers of the Retina; VMTS: Vitreous Macular Traction Syndrome; PVD: Posterior Vitreous Detachment; ERM: Epiretinal Membrane.
NE: not estimable; * Wilcoxon-signed rank test; **McNemar test



Graphic 1. Visual capacity (LogMAR) at the beginning and after the 6th dose of intravitreal Ziv-Aflibercept.



Graphic 2. Macular thickness capacity (μm) at baseline and after the 6th dose of intravitreal Ziv-Aflibercept.



Graphic 3. Macular volume (mm^3) at baseline and after the 6th dose of intravitreal Ziv-Aflibercept.

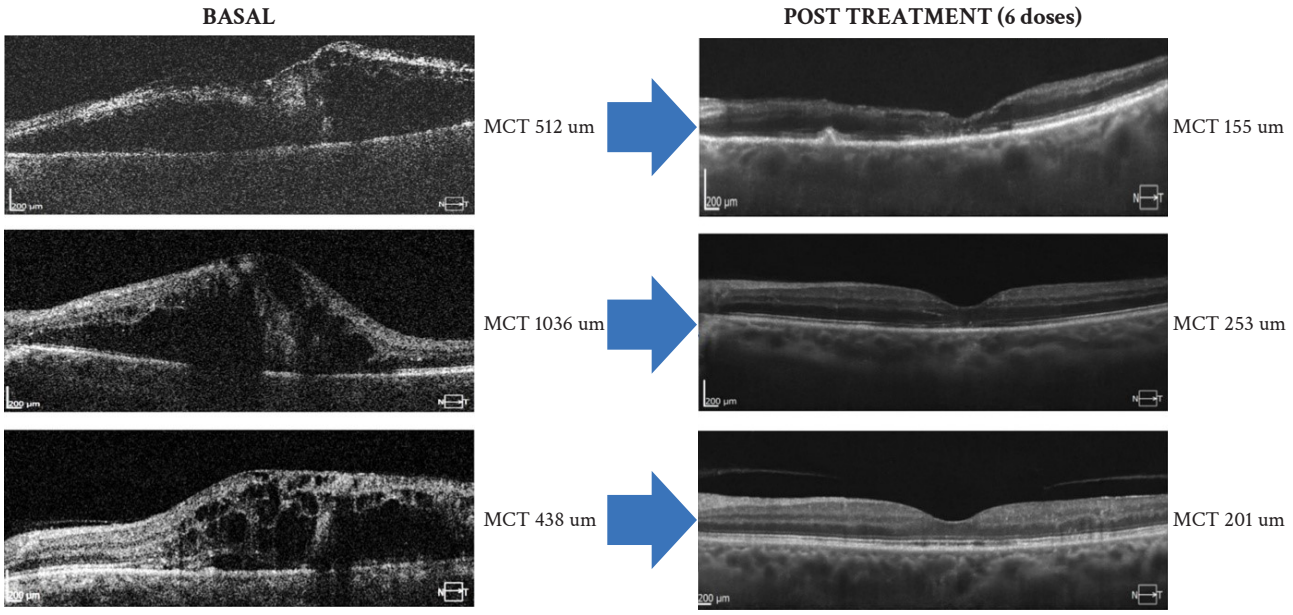


Figure 1. Tomography of the macula showing the anatomical and tomographic changes after treatment with intravitreal Ziv-Aflibercept.

DISCUSSION

This study aimed to evaluate the short-term efficacy of Ziv-Aflibercept in treating macular edema secondary to retinal vein occlusion (RVO), focusing not only on functional outcomes (e.g., BCVA) but also on anatomical changes through advanced OCT biomarkers. By incorporating these biomarkers, we sought to provide a more comprehensive understanding of treatment response compared to studies that rely solely on central macular thickness (CMT) and visual acuity. We saw it necessary to include tomographic biomarkers such as state of the EZ/ELM layer, presence of DRIL, cyst size, subretinal fluid, hyper-reflective foci, vitreomacular relationship, which will aid us in learning the anatomical and visual prognosis of our patients. [20]

Regarding functional Outcomes, it was shown significant improvement in BCVA was observed, with a reduction from LogMAR 2 pre-treatment to LogMAR 1 post-treatment ($p < 0.01$). This improvement aligns with prior reports of anti-VEGF efficacy in RVO [3,10]. In relation to the anatomical Outcomes: marked reductions were noted in CMT (671 μm pre-treatment vs. 207 μm post-treatment; $p < 0.01$) and MCV (14.1 mm^3 pre-treatment vs. 7.7 mm^3 post-treatment; $p < 0.01$). Additionally, intraretinal cyst size decreased (84.6% severe cysts pre-treatment vs. 61.5% absence of cysts post-treatment), and DRIL improved significantly (96.2% pre-treatment vs. 69.2% absence post-treatment), the presence of SRF was reduced from 80.8% pre-treatment to absence of the same in 100% post-treatment.

Poor response to treatment was associated with older age, higher baseline CMT (>900 μm), and disruption of key retinal structures (e.g., EZ/ELM, DRIL). These findings suggest that ischemia-induced damage to the outer blood-retina barrier may limit the efficacy of anti-VEGF therapies in MES, which coincides with the study by Sen et al[3][7]. Other factors were associated to poor anatomical and functional responses to treatment such as the disruption of EZ/ELM, the presence of hyperreflective foci, the presence of DRIL, and having vitreomacular traction syndrome. In contrast to diabetic macular edema, which primarily affects the inner blood-retina barrier, RVO-related edema often involves both inner and outer barriers due to ischemic damage. This dual involvement may explain the variability in treatment response observed in our study. [20]

In the anatomical aspect of our study, the response to treatment was very good, however not so in the functional aspect. Although functional improvements were modest, future research should explore potential benefits such as increased contrast sensitivity, which may further enhance patient outcomes. [21]

Ziv-Aflibercept is an isomer of Aflibercept with a difference in its composition associated tamponades, which elevates its osmolarity to 1000 mOsm. Despite its elevated osmolarity (1000 mOsm), IV-ZA demonstrated a favorable safety profile, consistent with prior studies [4,5,22]. The lack of severe adverse events in our cohort supports its potential as a safe alternative to FDA-approved anti-VEGF agents. With a cost of 30–50perdose, Ziv–Aflibercept offers a cost–effective alternative to Aflibercept (2,000 per dose) while providing comparable anatomical and functional outcomes. This affordability could enhance treatment accessibility, particularly in resource-limited settings. [4,5,22]

Even though it is not authorized by the FDA for ophthalmologic use, IV-ZA has been demonstrated to be effective for the use of diverse macular pathologies such as diabetic macular edema, treatment of diverse neovascular membranes (age-related macular degeneration, myopic maculopathy), and macular edema secondary to retinal vein occlusion. [2–4]

We rely on evidence that IV-ZA is a safe drug. Diverse studies have reported using 6 to 12 monthly doses for the treatment of macular edema secondary to vein occlusions with no adverse effects. Although there are many studies that support its safety and effectiveness, we still require an even greater number of studies to obtain more solid conclusions. In our study, severe adverse effects were not reported with the use of intravitreal Ziv-Aflibercept. [2,4,5,7,23]

Limitations of this study include the small sample size and observational design, which preclude definitive conclusions about causality. Future randomized controlled trials with larger cohorts are needed to validate our findings and explore long-term outcomes. [3,4,10]

In conclusion, six-monthly doses of Ziv-Aflibercept demonstrated short-term efficacy in treating RVO-related macular edema, with significant improvements in both anatomical and functional outcomes. Given its safety, efficacy, and cost-effectiveness, Ziv-Aflibercept represents a promising alternative to FDA-approved anti-VEGF agents, particularly in resource-constrained settings.

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