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# Outcomes of Combination Therapy Using Aflibercept and Dexamethasone Intravitreal Implant for Macular Edema Secondary to Retinal Vein Occlusion

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## Abstract

**Purpose:** To evaluate the efficacy of the combination therapy of intravitreal aflibercept 2 mg (Eylea®) and a sustained-release dexamethasone 0.7 mg intravitreal implant (Ozurdex®) in providing a prolonged effect in eyes with Macular Edema (ME) secondary to branch or Central Retinal Vein Occlusion (RVO).

**Methods:** In this interventional, prospective case series, 36 eyes of 36 patients with treatment-naive ME secondary to RVO were recruited between December 2016 and September 2017 and were studied over a 12-month follow-up period. Patients were included in analysis if they had a central macular thickness (CMT) >300 µm, and best-corrected visual acuity (BCVA) of 20/40 or worse. All patients were treated with an Eylea® injection followed 2 weeks later by an Ozurdex® injection. The same cycle was repeated if BCVA decreased by 6 or more Snellen letters from the best measurement and/or if CMT increased by >50 µm from the lowest measurement. Intraocular Pressure (IOP) was evaluated 2 and 4 weeks after each Eylea® injection. CMT, BCVA and IOP were measured 6 weeks after the beginning of each cycle and subsequently every 4 weeks until retreatment is needed. The primary outcome measure was the time to retreatment. The secondary outcome measures included CMT, BCVA and IOP.

**Results:** Seven patients (19.44%) needed no retreatment after one-year follow-up. Twenty-nine patients (80.56%) needed ≥ 1 retreatment, and the first reinjection was at 142.17 ± 39.13 days. There was a significant peak decrease in CMT from 482.44 ± 79.78 µm at baseline to 209.78 ± 13.14 µm (P<0.0001). In addition, mean BCVA improved from initially 0.706 ± 0.23 logarithm of the minimum angle of resolution (logMAR) units to a maximum of 0.336 ± 0.09 logMAR units during the study period (P<0.0001). An increase of IOP was seen in 7 patients out of 36 (19.44%) and was controlled by topical treatment.

**Conclusion:** Aflibercept with dexamethasone implants provided a predictable duration of effect with low intravitreal retreatment rates at first year, and achieved significant anatomical and visual outcomes in eyes with ME secondary to RVO.

**Keywords: Macular edema; Retinal vein occlusion; Aflibercept; Dexamethasone; Combination therapy**

## Introduction

Retinal Vein Occlusion (RVO) is the second leading cause of visual loss from retinal vascular disease after diabetic retinopathy [1]. Branch Retinal Vein Occlusion (BRVO) and Central Retinal Vein Occlusion (CRVO) are the two major anatomic types of RVO, with the BRVO being more common. In both types, loss of vision is mainly secondary to Macular Edema (ME), and in case of extensive ischemia, it may result from neovascular complications, including vitreous hemorrhage and neovascular glaucoma. The mechanisms underlying the formation of ME are complex and involve multiple factors. Increased intraluminal venous pressure behind the occlusion leads to an increased hydrostatic pressure, which can cause plasma transudation. In addition, decreased blood flow through the retinal vasculature after RVO results in ischemic injury to the capillaries, upregulation

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of Vascular Endothelial Growth Factor (VEGF) and overexpression of inflammatory mediators, leading to a breakdown of the blood-retinal barrier and increased retinal vasculature permeability [2]. These factors that play a role in the ME pathogenesis are behind its pharmacological treatment, with intravitreal anti-VEGF drugs being the first-line therapy and intravitreal corticosteroids coming in second-line.

However, none of these two modalities can be advantageous for all patients, and both treatments have their limitations. Beside the possible complications associated with intravitreal injections, including infectious endophthalmitis, retinal detachment and intraocular hemorrhage, drawbacks of anti-VEGF therapy include the need for multiple injections, while intravitreal corticosteroid implants are associated with higher risks of elevated Intraocular Pressure (IOP) and cataract formation.

The purpose of this study was to determine if the combination of intravitreal aflibercept 2 mg (Eylea®) and a sustained-release dexamethasone 0.7 mg intravitreal implant (Ozurdex®) can be synergistic, thereby increasing the duration of effects and minimizing intravitreal retreatment rates.

## Methods

In this multicenter, open-label, interventional, prospective case series, 36 eyes of 36 patients with RVO, 12 males and 24 females with a mean age of 70.19 years, were recruited between December 2016 and September 2017 and were studied over a 12-month follow-up period. Eleven patients presented with CRVO, 25 with BRVO. Diagnosis of CRVO/BRVO was carried out by performing fluorescein angiogram (Topcon TRC-50EX retinal camera) (Table 1).

Patients were eligible for enrollment if they were at least 18 years old, with baseline central macular thickness (CMT) >300 µm on the ZEISS Stratus OCT, Best-Corrected Visual Acuity (BCVA) of 20/40 or worse and a maximum duration of symptoms of 3 months. Exclusion criteria were: ischemic CRVO/BRVO, or evidence of neovascularization in the anterior or posterior segment, or a history of vitrectomy, elevated IOP, glaucoma or diabetes mellitus (Table 2).

Each treatment cycle included an Eylea® injection followed 2 weeks later with an Ozurdex® injection. The same cycle was repeated if patients were eligible for retreatment. Criteria for a retreatment were as follows: loss of BCVA by 6 or more Snellen letters from the best measurement and/or an increase in CMT by >50 µm from the lowest measurement. IOP was evaluated 2 and 4 weeks after each Eylea® injection. CMT, BCVA and IOP were measured 6 weeks after the beginning of each cycle and subsequently every 4 weeks until retreatment is needed (Figure 1).

The primary outcome measure was the time to retreatment. The secondary outcome measures included the peak changes in CMT, BCVA and the safety of the procedure.

## Statistical Analysis

The BCVA fractions were converted into Logarithm of the Minimum Angle of Resolution (logMAR) units. Analysis of Variance (ANOVA) and two-tailed t-tests were used to evaluate inter-treatment interval and changes from baseline in CMT and BCVA, respectively. Continuous variables were noted by means and their corresponding standard deviations. A p-value <0.01 was considered as statistically significant. Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 24).

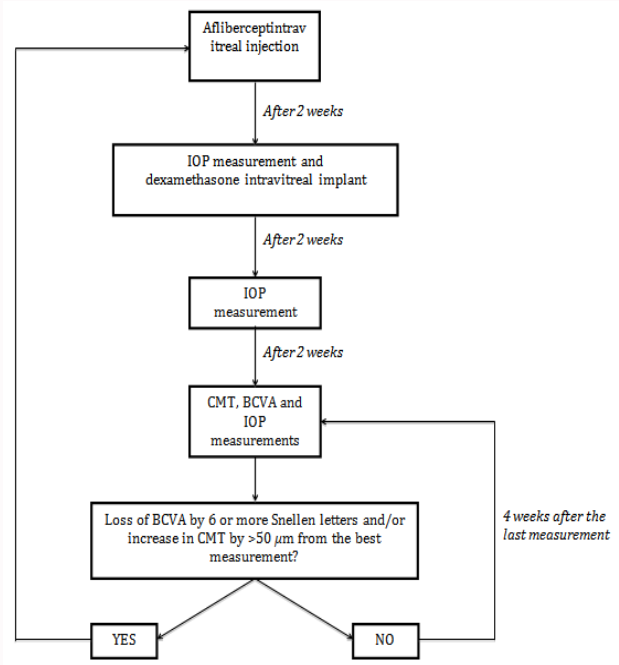


**Figure 1:** Treatment and retreatment protocol flow chart.
**Abbreviations**: BCVA: Best-Corrected Visual Acuity; CMT: Central Macular Thickness; IOP: Intraocular Pressure

**Table 1:** Baseline characteristics.

| Variables | All eyes (n=36) |
|---|---|
| Gender (Male:Female) | 12:24 |
| Age (years) | 70.19 ± 14.65 |
| RVO (central:branch) | 11:25 |
| BCVA (logMAR) | 0.706 ± 0.23 |
| CMT (µm) | 482.44 ± 79.78 |
| IOP (mmHg) | 16.05 |

**Abbreviations**: BCVA: Best-Corrected Visual Acuity; CMT: Central Macular Thickness; IOP: Intraocular Pressure; logMAR: Logarithm of Minimum Angle of Resolution; RVO: Retinal Vein Occlusion

## Results

### Time to retreatment

Seven patients (19.44%) needed no retreatment after 1-year follow-up. Twelve patients needed no retreatment for 6 months. The first retreatment was at 142.17 ± 39.13 days and it concerned 29 patients (80.55%). The second retreatment was 139.63 ± 34.96 days after the first retreatment and it concerned 22 patients (61.11%), meaning that 7 patients (19.44%) needed only one retreatment over one year of follow-up. The third retreatment was 131.16 ± 32.22 days after the second retreatment and it concerned 12 patients (33.33%), meaning that 10 patients (27.28%) needed only two retreatments. There was no statistically significant difference in mean intertreatment interval for up to 4 treatment cycles, and the mean intertreatment interval across all eyes was 139.19 ± 36.69 days (Table 3).

### Central macular thickness

At baseline, mean CMT was 482.44 ± 79.78 µm. CMT decreased to a minimum of 209.78 ± 13.14 µm across all treatment cycles (P<0.0001), and the mean peak decrease was 272.67 ± 82.35 µm.

**Table 2:** Inclusion and exclusion criteria.

| Inclusion criteria | Exclusion criteria |
|---|---|
| Adults ≥ 18 years of age | Ischemic CRVO/BRVO |
| CMT >300 μm | Glaucoma |
| BCVA of 20/40 or worse<br>Duration of symptoms ≤ 3 months<br>Patients are treatment-naïve<br>Patients were available for a follow-up of at least 1 year | Diabetes mellitus<br>History of elevated IOP<br>Previous vitrectomy<br>Neovascularization at the posterior or anterior segment of the eye |

**Abbreviations**: BCVA: Best-Corrected Visual Acuity; BRVO: Branch Retinal Vein Occlusion; CMT: Central Macular Thickness; CRVO: Central Retinal Vein Occlusion; IOP: Intraocular Pressure

### Best-corrected visual acuity

At baseline, mean BCVA was 0.706 ± 0.23 logMAR units. BCVA improved to a maximum of 0.336 ± 0.09 logMAR units across all treatment cycles (P<0.0001). Mean peak improvement in BCVA was 0.369 ± 0.22 logMAR units and 24 patients (66.67%) gained three or more lines of BCVA.

### Safety

Before initiation of treatment, IOP was within normal ranges in all patients, with a mean IOP of 16.05 mmHg. A relevant increase of IOP was defined as an increase of >5 mm Hg compared with baseline. During the 12-month follow-up, an increase of IOP was seen in 7 patients out of 36 (19.44%). The IOP increased above 35 mmHg in one patient and above 25 mmHg in 6 patients. IOP exceeding normal range was controlled by topical IOP-lowering medication.

No adverse events such as intravitreal hemorrhage, endophthalmitis, and retinal detachment were noted during this study.

**Table 3:** Number of retreatments in subjects who completed the study.

| Number of retreatments | Number of eyes (%) |
|---|---|
| 0 | 7 (19.44) |
| 1 | 7 (19.44) |
| 2 | 10 (27.78) |
| 3 | 12 (33.33) |

## Discussion

Until recently, treatment options for RVO therapy have been very limited. Starting the early 1980s, and based on the BVOS trial [3], the macular grid laser photocoagulation was the gold standard treatment for ME associated with BRVO. However, the Central Retinal Vein Occlusion study demonstrated that despite some reduction in macular edema from grid laser therapy, there was no visual benefit compared to observation in patients with CRVO [4].

Approximately 20 years later, the pharmacologic era began with the use of corticosteroid therapies and multiple formulations have been examined including triamcinolone and dexamethasone. Corticosteroids not only have an anti-inflammatory effect, but also indirectly inhibit the actions of VEGF [5]. Dexamethasone got FDA approved and was introduced in a sustained-release intravitreal implant (Ozurdex®; Allergan Inc., Irvine, CA, USA), while triamcinolone is being used as an off-label intravitreal injection by some physicians for RVO. The SCORE [6,7] trial showed that consideration of 1 mg intravitreal triamcinolone was recommended for ME secondary to CRVO, but there were no significant differences between triamcinolone and laser photocoagulation in improving ME secondary to BRVO. The use of 4 mg intravitreal triamcinolone was associated with a higher percentage of side effects including cataracts and increased IOP in comparison with the lower dosage. In the GENEVA study [8,9,] around 40% of patients with BRVO or CRVO showed a 15-letter improvement in BCVA when using a dexamethasone releasing implant (0.35 mg or 0.7 mg) in comparison with a sham group, and overall anatomic results showed a significant decrease in CMT.

More recently, anti-VEGF therapies have become one of the most frequently used therapeutics for ME associated with RVO because of their favorable side effect profile and tolerability when opposed to corticosteroids. Various anti-VEGF medications have been evaluated, including ranibizumab, aflibercept, bevacizumab and pegaptanib sodium. FDA approvals have included ranibizumab (Lucentis®; Genentech Inc., South San Francisco, CA, USA) which efficacy has been largely evaluated in both CRVO and BRVO. Campochiaro et al. [10] reported the results of the BRAVO trial showing that there was a significant improvement in visual acuity and CMT in patients receiving ranibizumab (0.3 mg or 0.5 mg) in comparison with sham patients with BRVO [11]. Furthermore, ranibizumab was studied by the CRUISE trial in the setting of CRVO. Brown et al. [12] reported the primary 6-month results, showing that 46% to 48% of patients receiving 0.3 mg and 0.5 mg respectively showed three lines of improvement of vision when compared to sham groups (17%). Campochiaro et al. [13] published the 12-month results showing that there was a significant improvement in VA and CMT in the ranibizumab group compared to sham in patients with CRVO. Scatter photocoagulation was added in order to reduce the anti-VEGF injections but the RELATE [14] study showed that adding a laser grid treatment had little effect on visual acuity and anatomical outcomes improvement or in reducing the frequency of intravitreal injections. While anti-VEGF monotherapy has been an effective first-line modality in this setting, RVO remains chronic by nature and necessitates a high treatment burden: 50% or more of patients still require ongoing anti-VEGF treatments 4 years after onset [15].

Additional anti-VEGFs approvals comprised Aflibercept (Eylea®; Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA). Previously known as VEGF Trap-Eye, aflibercept is a fusion protein consisting of portions of the VEGF human receptors 1 and 2, bound by the Fc domain of the human immunoglobulin IgG1, causing competitive inhibition of VEGF. Additionally, aflibercept blocks placental growth factor [16]. Consequently, three large prospective randomized controlled studies evaluating the efficacy and safety of aflibercept for ME associated with CRVO have been published. Both COPERNICUS and GALILEO trials studied the use of aflibercept in the setting of CRVO-related ME. Boyer et al. [17], Brown et al. [18] and Heier et al. [19] published the 6-month, 1-year and 2-year results of the COPERNICUS trial respectively, while Holz et al. [20] published the 6-month results of The GALILEO trial. Patients were randomized into intravitreal aflibercept and sham groups. Both studies yielded

similar results in terms of VA and CMT improvements and over 50% of treated patients compared with 12% of control patients gained three lines or more of vision. Additionally, studies showed that a delay in treatment results in a decrease in eventual visual improvement compared with early treatment. The VIBRANT [21] trial compared aflibercept to grid laser treatment for ME caused by BRVO. The overall results showed that 57% of patients treated with aflibercept gained three lines of vision. Also, after 6 months of regular monthly injections, less frequent rates could still maintain a good visual acuity [22].

Bevacizumab (Avastin®; Genentech Inc., South San Francisco, CA, USA) is being used as an off-label anti-VEGF, when the approved therapies are not available, and particularly for economical purposes since it is considered a cheaper alternative [23]. Multiple studies have evaluated the efficacy of bevacizumab for BRVO-related ME [24-28]. In a prospective randomized study of 30 patients with BRVO, Russo et al. [24] reported that the bevacizumab group had better BCVA and lower CMT numbers than the groups receiving grid photocoagulation. In addition, other trials have investigated the efficacy of bevacizumab for CRVO-related ME. Epstein et al. [29-30] reported the results of a prospective, sham-controlled, clinical trial and findings paralleled those of prior anti-VEGF studies [31-33].

Limited data are available on the use of intravitreal pegaptanib for ME associated with RVO, both CRVO [34] and BRVO [35].

In a systematic review, Semsiri et al. [23] aimed to study the efficacy among anti-VEGF drugs for the treatment of RVO-related ME by reviewing data from several published randomized controlled trials, since there is a lack of evidence for relative efficacy among anti-VEGFs. Although aflibercept was considered to be the most efficacious in terms of BCVA improvements and ranibizumab in CMT reduction, there were no significant differences between intravitreal aflibercept, ranibizumab and bevacizumab. Moreover, intravitreal aflibercept has a better binding affinity, which allows a longer treatment interval when opposed to monthly injections of intravitreal ranibizumab and bevacizumab.

Several surgical modalities (e.g.: radial optic neurotomy, vitrectomy, retino-choroidal anastomosis) were used but clinical trials lacked and some procedures have fallen out of favor in terms of safety and efficacy [36].

The emergence of pharmacological therapeutics, including intravitreal injections of corticosteroids and anti-VEGF drugs, was promising and gave patients with RVO better visual outcomes. However, despite its encouraging results found in numerous studies, monotherapy requires a considerable number of injections, which can be challenging for service supplies as well as treatment compliance. Therefore, considering the complexity of the disease's pathogenesis, seeking new treatment options such as combination therapy might be advantageous.

In the present study, patients were followed monthly and retreated with intravitreal aflibercept injection associated with dexamethasone implant based on their CMT and BCVA scores, allowing the retreatment period to vary according to each patient's needs. The study yielded considerable findings, most importantly a relatively fixed and longer intertreatment interval of 4 to 5 months in comparison to anti-VEGF monotherapy 10-13, knowing that dexamethasone implants monotherapy intertreatment interval isn't clearly established [37]. Additionally, crucial functional and anatomical improvements were recorded. One third of the patients needed no retreatment even after 6 months of their last injection, and were subsequently considered cured. Singer MA et al. [38] conducted two studies using bevacizumab or randomly chosen anti-VEGFs [39] along with dexamethasone implant, and found a mean intertreatment interval of 126 days and 134 days respectively, similar to that reported in the actual study. Having a constant intertreatment interval of 4 to 5 months implies that patients' BCVA and CMT values are slightly changing during this period. This may be helpful in reducing the frequency of the follow-up visits. Patients would then be more compliant and the treatment more cost-effective. Therefore, such outcome will have a major impact on the economical aspect of the disease.

In the present study, mean peak decrease in CFT (272.67 ± 82.35 μm) was similar to what was seen in a randomized controlled trial of dexamethasone implant in eyes with ME due to RVO (208 μm) [8,9] and in the trial combining dexamethasone and a randomly chosen anti-VEGF (219.2 μm for eyes with CRVO and 200.9 μm for eyes with BRVO) [39].

Mean improvement in BCVA was 0.369 ± 0.22 logMAR and 66.67% of eyes gained at least three lines of BCVA in this study. This percentage was similar to those seen in phase 3 trials for aflibercept (between 50% and 60%) [17,20,21] and in the interventional case series combining dexamethasone with a randomly chosen anti-VEGF (47.6%) [39], but higher than the 29.3% reported by the GENEVA study for dexamethasone implant monotherapy [8,9].

Concerning the safety profile, rates of IOP increases (19.44%) in the current study were similar to those seen in the GENEVA trial [9] (12.6 and 15.4% after the first and second treatments, respectively) and in a study evaluating the use of dexamethasone implants with a randomly chosen anti-VEGF in RVO (30.6%) [39]. IOP exceeding normal range was controlled by topical IOP-lowering medication.

Lately, the idea of associating both treatment modalities for RVO-related ME is being promoted by clinicians. However, studies concerning this matter are scant and additional trials are needed for definitive results.

In a prospective nonrandomized case series, Mayer et al. [40] compared three intravitreal bevacizumab injections followed by a dexamethasone implant versus dexamethasone implant monotherapy in eyes with ME secondary to RVO. This study found that dexamethasone implant monotherapy was associated with a better functional outcome in BRVO patients, whereas both treatment modalities showed no functional differences in CRVO patients. The initial treatment with an anti-VEGF drug was not effective in increasing the interval until the recurrence of ME. These results can be explained by the fact that there may be a difference in patients' baseline characteristics between this trial and ours.

Likewise, one prospective randomized trial reported that the addition of a dexamethasone implant 1 week following intravitreal bevacizumab increased the mean time to the first additional bevacizumab injection to 3 months *vs.* 1 month in the bevacizumab monotherapy group. However, the relatively short period of follow-up (6 months) constitutes one of the study's limitations [41].

Furthermore, in two studies by Singer et al. without a control group, patients receiving dexamethasone implants 2 weeks after anti-VEGF injections had a mean re-injection interval of 135 ± 36.439

days and 12938 days as well as improvements in visual acuity and central foveal thickness.

Moreover et al. [42] suggested the RandOL protocol (Ranibizumab and Ozurdex with Laser photocoagulation) as an individualized alternative for patients with ME due to RVO, in order to improve the short-term efficacy of intravitreal monotherapy and minimize the drug-related side effects. Although some patients had poor visual outcomes, the protocol achieved visual and anatomical results similar to those obtained with a single-agent therapy, and with less retreatment rates at 1 year. Despite these encouraging findings, randomized controlled studies are needed, especially to evaluate the role of laser on ischemic RVO.

In the TANZANITE study [43], Clearside Biomedical Inc. (Alpharetta, GA, USA) compared suprachoroidal triamcinolone acetonide (CLS-TA) plus intravitreal aflibercept versus aflibercept alone in patients with RVO. At three months, the combination arm showed an increase in visual acuity and improved OCT compared with the aflibercept-alone cohort. Concerning safety findings, the Tanzanite study suggests that suprachoroidal injection of CLS-TA is well tolerated. Suprachoroidal injection of CLS-TA does not alter choroidal thickness in eyes with macular edema due to RVO, but may result in expansion of the subchoroidal space [44]. Although the early results appear encouraging, solid conclusions cannot be made since this study is a phase 2 trial (46 patients; 3 months). In addition to that, cataract and increase in IOP need a chronic exposure to intraocular steroids in order to occur, therefore studies with larger samples and a longer follow-up period are needed.

That being said, associating anti-VEGF with dexamethasone implants, according to previous studies, showed encouraging results. The need to retreat patients by anti-VEGF injections is less frequent, while efficacy outcomes still meet those obtained with anti-VEGF monotherapy.

Despite being among the few trials to have investigated the efficacy of combining aflibercept and dexamethasone implants, this study has several limitations worth mentioning. In fact, having a small sample size and the absence of an anti-VEGF monotherapy control group are two major weaknesses. Therefore, the need of a large and comparative randomized clinical trial between combination and anti-VEGF monotherapy is of great value in order to be able to draw clear-cut conclusions.

On this basis, combining aflibercept intravitreal injections with dexamethasone implants after two weeks brought promising functional and anatomical improvements in ME related to RVO, along with a predictable 4 to 5 month retreatment interval during the first year of treatment. In conclusion, by improving vision and decreasing the number of needed treatments, combination therapy can alleviate the treatment burden. Everything considered, this treatment modality provided imperative results that meet the study's primary endpoint, making it a practical substitute that warrants a starting point for further research.

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