Aflibercept Versus Bevacizumab and/or Ranibizumab for Recurrent Macular Edema Secondary to Central Retinal Vein Occlusion

Cem Ozgonul, MD,¹ Vaidehi S. Dedania, MD,² and Cagri G. Besirli, MD, PhD²

Abstract

Purpose: To compare functional and anatomic outcomes of treatment with intravitreal aflibercept versus bevacizumab and/or ranibizumab in patients with recurrent macular edema (ME) secondary to central retinal vein occlusion (CRVO).

Methods: Retrospective, comparative case series of patients with recurrent ME in the setting of CRVO. Patients with recurrent ME received treatment with aflibercept (Group 1, G1) or bevacizumab and/or ranibizumab (Group 2, G2). Primary outcome measures were best-corrected visual acuity (BCVA) and central foveal thickness (CFT).

Results: Of the 20 eyes (20 patients) with recurrent ME included in the study, 9 received aflibercept (G1) and 11 received bevacizumab and/or ranibizumab (G2). Median BCVA at recurrence of ME and at most recent follow-up was 20/60 (G1) and 20/80 (G2) and 20/40 (G1) and 20/50 (G2, $P > 0.05$ for all comparisons), respectively. Median CFT at recurrence of ME and at most recent follow-up was 492 μm (G1) and 448 μm (G2) and 291 μm (G1) and 295 μm (G2, $P > 0.05$ for all comparisons), respectively. Complete resolution of ME for at least 4 months was found in 78% (G1) and 55% (G2) of patients with a median injection free interval of 11 (G1) and 13 (G2) months ($P > 0.05$).

Conclusions: In patients with recurrent ME secondary to CRVO, there was improvement in BCVA and CFT in all groups, although patients treated with aflibercept showed a trend toward better anatomical outcomes decreased need for recurrent injections.

Keywords: aflibercept, bevacizumab, central retinal vein occlusion, macular edema, ranibizumab, recurrent

Introduction

CENTRAL RETINAL VEIN OCCLUSION (CRVO) is a common cause of visual morbidity across the world.¹ Clinical findings include diffuse intraretinal hemorrhages, tortuous and dilated vessels, cotton-wool spots, and macular edema (ME). ME is the most frequent cause of vision loss in CRVO and is present at the time of initial presentation in many patients.^{2–4} The pathophysiologic process underlying development of ME is likely secondary to a combination of mechanical and chemical changes. There is increased extravasation of fluid and protein secondary to elevated intraluminal pressure caused by central retinal vein thrombosis.³ This further promotes retinal edema, as the interstitial oncotic pressure is increased, ultimately resulting in microvascular

ischemia.³ In addition, tissue hypoxia results in elevated levels of vitreous and aqueous cytokines, including vascular endothelial growth factor (VEGF), that stimulate angiogenesis and vascular permeability.^{3,5–7} Antagonism of VEGF has emerged as the leading treatment strategy for ME in CRVO and several studies have reported success with intravitreal anti-VEGF agent use.^{8–11}

Numerous studies have demonstrated the efficacy of intravitreal bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA) and ranibizumab (Lucentis; Genentech, Inc.) for the treatment of ME in patients with CRVO. Epstein et al.⁸ showed a gain of ≥ 15 letters in BCVA in 60% (18/30) of patients treated with intravitreal bevacizumab compared with 20% (6/30) in the observation only group ($P < 0.003$). Similarly, in the CRUISE study, mean change in BCVA

¹Gulhane Training and Research Hospital, Department of Ophthalmology, Ankara, Turkey.

²Department of Ophthalmology and Visual Sciences, Kellogg Eye Center, University of Michigan, Ann Arbor, Michigan.

from baseline was significantly greater in the ranibizumab groups compared with the sham group ($P < 0.0001$ for both ranibizumab groups).⁹ In addition, there was a greater decrease in mean central foveal thickness (CFT) in the ranibizumab groups when compared with the sham groups ($P < 0.001$ for both ranibizumab groups).⁹ The most recent Food and Drug Administration (FDA)-approved intravitreal anti-VEGF agent, aflibercept (Eylea; Regeneron, Tarrytown, NY), is also effective for the treatment of ME resulting from CRVO. The COPERNICUS and GALILEO studies evaluated the efficacy and safety of intravitreal aflibercept and found significant improvement in both BCVA and CFT.^{10–12}

Despite the efficacy of intravitreal anti-VEGF agents, recurrent ME is common in CRVO. Ach et al.¹³ and Hoeh et al.¹⁴ found that 43.7% and 37% of patients, respectively, treated with bevacizumab had recurrence of ME. Reports evaluating the treatment of recurrent ME secondary to CRVO are limited and many studies evaluate treatment for persistent ME, not recurrent ME.¹⁵ One study reported a beneficial effect on anatomic and VA outcomes in patients with recalcitrant ME switched from bevacizumab and ranibizumab to aflibercept, while another study found decreased exudation in patients treated with aflibercept, but no corresponding improvement in VA.^{16,17} The results of these studies are promising for aflibercept as a treatment option for recalcitrant, and possibly recurrent, ME, although they do not compare outcomes in patients on aflibercept with those continuing treatment with bevacizumab and/or ranibizumab.¹⁸

The goal of this study was to compare functional and anatomic outcomes of intravitreal aflibercept and bevacizumab and/or ranibizumab in patients with recurrent ME in the setting of a CRVO.

Methods

The study protocol was approved by the Institutional Review Board of the University of Michigan Medical School and follows the tenets set forth by the Declaration of Helsinki. This is a retrospective, interventional, comparative case series of patients with recurrent ME secondary to CRVO at the W. K. Kellogg Eye Center/University of Michigan Hospitals from January 1, 2012 to July 31, 2016.

Cases of ME secondary to CRVO were identified by using International Classification of Diseases-9 and -10 (ICD-9 and -10) and Current Procedural Terminology codes. A total of 160 patients were identified and patients were included and excluded based on the below described criteria. Patients were included if they had recurrent ME and were treated with bevacizumab and/or ranibizumab and aflibercept. Recurrent ME was defined as ME that recurred after complete resolution for a period of at least 4 months. A period of 4 months was chosen as studies have demonstrated that intravitreal anti-VEGF agents are cleared from the vitreous by this time.¹⁹ Exclusion criteria included patients with concomitant ocular diseases (such as diabetic retinopathy, age-related macular degeneration, and glaucoma), insufficient medical records, history of vitreoretinal surgery, focal or grid laser photocoagulation, and history of intravitreal steroid injection.

In addition to the treatment schedule and frequency of follow-up, data collected at each visit included: age, gender, injected medication, injection interval, best-corrected visual

acuity (BCVA), dilated fundus examination, and spectral-domain optical coherence tomography (Heidelberg Spectralis SD-OCT; Heidelberg Engineering, Inc., Heidelberg, Germany) findings, including CFT and the presence or absence of intraretinal and/or subretinal fluid.

Patients underwent dilated fundus examination and SD-OCT at each monthly visit. Fluorescein angiography was performed at the discretion of each retina specialist. All patients were treated with intravitreal bevacizumab (1.25 mg/0.05 mL) and/or ranibizumab (0.5 mg/0.05 mL) monthly until there was complete resolution of intraretinal and/or subretinal fluid in the macula on SD-OCT. A pro re nata (PRN) or treat-and-extend treatment approach was applied to extend the injection interval. Patients reverted to monthly intravitreal injections if ME was visualized on SD-OCT. After recurrence of ME, patients were treated with intravitreal aflibercept (2.0 mg/0.05 mL) (Group 1) or bevacizumab and/or ranibizumab (Group 2). Resolution of ME for at least 4 months was defined as success in each group.

Statistical analyses were performed with Social Science v.22.0 (SPSS 22.0, Chicago, IL). Statistical comparisons were performed using the Mann-Whitney U test and Chi-squared test. For all comparisons, statistical significance was $P < 0.05$. Median values were calculated and reported for BCVA and CFT due to small sample size.

Results

Demographics

Twenty eyes of 20 patients with recurrent ME secondary to CRVO were included in the study. There were 9 patients in Group 1, 44% ($n = 4$) female and 56% ($n = 5$) male, and 11 patients in Group 2, 64% ($n = 7$) female and 36% ($n = 4$) male. Mean age $\pm$ standard deviation at diagnosis of recurrent ME was 78 ± 10 years (Group 1) and 72 ± 11 years (Group 2, Table 1). Median number of injections of bevacizumab and/or ranibizumab after initial diagnosis of ME, before recurrence, was 3 (range 1–15) in Group 1 and 4 (2–8) in Group 2.

Treatment

At the visit before recurrence, last follow-up visit with remission of ME, median BCVA in Group 1 was 20/50 (20/25–20/70) and 20/40 (20/25–20/160) in Group 2 ($P > 0.05$). Median CFT was 269 μ m (243–356) and 248 μ m (221–361) in Groups 1 and 2, respectively ($P > 0.05$, Fig. 1). Mean number of injections before the recurrence of ME for Groups 1 and 2 was 3 (1–15) and 4 (2–8), respectively. At the time of recurrence of ME, median BCVA was 20/60 (20/30–20/800) in Group 1 and 20/80 (20/25–20/800) in Group 2 ($P > 0.05$), and median CFT was 492 μ m (432–927) in Group 1 and 448 μ m (286–822) in Group 2 ($P > 0.05$).

At most recent follow-up, after treatment for recurrent ME, median BCVA was 20/40 (20/25–20/125) and 20/50 (20/25–20/600) in Groups 1 and 2, respectively ($P > 0.05$), and median CFT in Group 1 was 291 μ m (197–721) and 295 μ m (217–736) in Group 2 ($P > 0.05$). The median decrease in CFT for Groups 1 and 2 was 201 μ m (41%) and 153 μ m (34%), respectively ($P > 0.05$).

In patients with successful treatment of recurrent ME, median injection-free interval at the last follow-up was 11 months (4–21) and 13 months (4–28) in Groups 1 and 2,

TABLE 1. CHARACTERISTICS AND CLINICAL FEATURES OF PATIENTS IN GROUPS 1 AND 2

Variable	Group 1 (n=9)	Group 2 (n=11)
Age (years)	78 ± 10	72 ± 11
Gender (male/female)	5/4	4/7
BCVA ^a		
Baseline	20/50 (20/25–20/70)	20/40 (20/25–20/160)
At recurrence of ME	20/60 (20/30–20/800)	20/80 (20/25–20/800)
After treatment	20/40 (20/25–20/125)	20/50 (20/25–20/600)
CFT (μm)		
Baseline	269 (243–356)	248 (221–361)
At recurrence of ME	492 (432–927)	448 (286–822)
After treatment	291 (197–721)	295 (217–736)
Months without recurrence ^b	11 (4–21)	13 (4–28)
Number of injections after recurrence	3 (1–7)	3 (1–8)
Complete resolution of ME (%)	78	55

Data are expressed as the mean ± SD, median (range) or percentage of cases as appropriate.

^aSnellen BCVA.

^bAfter treatment with aflibercept or bevacizumab and/or ranibizumab at most recent follow-up.

BCVA, best-corrected visual acuity; CFT, central foveal thickness; ME, macular edema; n, number of patients.

respectively ($P > 0.05$, Fig. 2). The rate of successful treatment of recurrent ME was 78% (7/9) in Group 1 and 55% (6/11) in Group 2 ($P > 0.05$). Two of 9 patients (22%) in Group 1 and 5 of 11 patients (45%) in Group 2 had persistent ME and continued to receive intravitreal anti-VEGF injections (Fig. 3). Median number of injections after recurrence of ME was 3 (1–7) and 3 (1–8) in Groups 1 and 2, respectively ($P > 0.05$). Unsuccessful patients received a median of 2 injections over a 4 month follow-up period for Group 1 (2–4) and 3 injections (2–4) over a 7 month follow-up period in Group 2. There were 2 patients with a partial response, both in Group 2. One patient received 3 bevacizumab injections after recurrence over a 5 month follow-up period and demonstrated an improvement in CFT from 822 to 541 μm. The second patient received 2 injections of ranibizumab after recurrence, with an improvement in CFT from 448 to 345 μm.

Adverse events

There were no adverse events in any patients related to intravitreal injection or medication.

Discussion

Aflibercept has become an essential option in the armamentarium against numerous retinal diseases, including CRVO, since its FDA approval in 2011. Studies have shown that aflibercept is an effective initial treatment for ME in the setting of a CRVO and provides additional benefit in select cases resistant or partially responsive to treatment with bevacizumab and/or ranibizumab.^{10,11,16,17} In this study, we compared functional and anatomic outcomes in patients with recurrent ME treated with bevacizumab and/or ranibizumab to those switched to treatment with aflibercept. We

FIG. 1. BCVA and CFT in Groups 1 and 2. (A) There was a decline in BCVA in both groups at the time of recurrence, but improvement after treatment with aflibercept (Group 1) or bevacizumab and/or ranibizumab (Group 2). (B) CFT increased at the time of recurrence of ME and decreased after treatment with aflibercept (Group 1) and bevacizumab and/or ranibizumab (Group 2). BCVA, best-corrected visual acuity; CFT, central foveal thickness; Final, after treatment with aflibercept or bevacizumab and/or ranibizumab; Post, after initial treatment with bevacizumab and/or ranibizumab; Recurrence, at recurrence of ME; ME, macular edema.

FIG. 2. Spectral-domain optical coherence tomography of a patient in Group 1. A 72-year-old man with (A) complete resolution of ME after 3 injections of bevacizumab (BCVA 20/30, CFT 297 μm), (B) recurrence of ME after 6 months (BCVA 20/50, CFT 551 μm) and (C) complete resolution of ME after 4 monthly injections of aflibercept without recurrence 21 months after the last aflibercept injection (BCVA 20/25, CFT 289 μm).

found no significant difference in BCVA or CFT the groups, although 78% of patients treated with aflibercept had complete resolution of ME compared with 55% in patients treated with bevacizumab and/or ranibizumab. Our findings demonstrate a trend toward improved response to aflibercept, compared with bevacizumab and/or ranibizumab, in patients with recurrent ME secondary to CRVO.

COPERNICUS and GALILEO were large, randomized, sham-controlled studies evaluating aflibercept for the treatment of ME in CRVO.^{10–12} COPERNICUS found a gain of ≥ 15 letters in BCVA in 56.1% versus 12.3% ($P < 0.001$) of patients at week 24 in the aflibercept and sham groups, respectively, compared to 55.3% and 49.1% versus 30.1% and 23.3% ($P < 0.001$ for both) of patients at week 52 and 100 in the aflibercept and sham groups, respectively.¹⁰ In this study, patients in the sham group received intravitreal aflibercept on an as-needed, or PRN, basis after 24 weeks.¹⁰ The results of GALILEO showed a gain of ≥ 15 letters in BCVA of 60.2% and 22.1% at week 24 in the aflibercept and sham groups ($P < 0.0001$), respectively, and a decrease

FIG. 3. Spectral-domain optical coherence tomography of a patient in Group 2. A 75-year-old woman with (A) complete resolution of ME after 4 injections of bevacizumab (BCVA 20/150, CFT 324 μm), (B) recurrence of ME after 6 months (BCVA 20/800, CFT 758 μm), and (C) persistent ME despite treatment with 8 bevacizumab injections (BCVA 20/600, CFT 736 μm).

in CFT of 448.6 μm compared with 169.3 μm ($P < 0.0001$) in the aflibercept and sham groups, respectively.¹¹ Both studies showed efficacy of aflibercept in the treatment of ME secondary to CRVO, but they also demonstrated that long-term antagonism of VEGF was necessary to control ME in many patients with CRVO. This may be due to the continued ischemia characteristic of CRVO and thus continued production of VEGF, which may be the mechanism for persistent and/or recurrent ME in a large proportion of patients.

Matsumoto et al.²⁰ reported 3 cases of ME in patients with retinal vein occlusion with a more pronounced ME at recurrence than at initial presentation and speculated that this rebound ME may be secondary to upregulation of

retinal VEGF receptors. This in turn could result in a greater sensitivity and response to VEGF. Several studies have demonstrated the efficacy of aflibercept for recalcitrant cases of ME in CRVO and the results are encouraging for switching therapy from bevacizumab and/or ranibizumab to aflibercept.^{16–18} Cohen et al.¹⁶ reported on 17 cases with persistent ME secondary to CRVO switched to aflibercept after treatment with a mean of 12.9 injections of bevacizumab and/or ranibizumab. After switching to aflibercept, with a mean of 4 injections, 35.2% of patients gained ≥ 3 lines in VA, and 29% of patients had complete resolution of ME.¹⁶ Lehmann-Clarke et al.²¹ described 5 cases of ME secondary to CRVO refractory to treatment with ranibizumab with a mean improvement of 9.2 ± 9.5 ETDRS letters and decrease of $248 \pm 248.7 \mu\text{m}$ after switching to aflibercept. They also described increased interval between injections in patients treated with aflibercept. Similarly, Pfau et al.²² reported a mean injection interval increase of 0.51 months ($P=0.023$) and relapse-free interval increase by 3.02 weeks ($P=0.003$) at 1 year in 13 eyes with insufficient response to bevacizumab and/or ranibizumab switched to aflibercept.

Results of the largest retrospective study evaluating patients with ME switched from bevacizumab and/or ranibizumab to aflibercept were reported by Papakostas et al.¹⁸ in 42 patients with persistent or recurrent ME. For the entire cohort of patients, the median VA before switching to aflibercept was 20/126, 1 month after the first injection of aflibercept was 20/89 ($P=0.0191$), and at the end of the follow-up was 20/100 ($P=0.272$). The median central retinal thickness (CRT) was $536 \mu\text{m}$, $293.5 \mu\text{m}$ ($P=0.0038$), and $279 \mu\text{m}$ ($P=0.0013$) before switching to aflibercept, 1 month after the first injection of aflibercept and at the end of follow-up, respectively. Of the 42 patients in this study, only 8 had recurrent ME with an unspecified injection-free interval before recurrence. In addition, despite the overall improvement in VA and CRT with aflibercept injections, 45% (19) of eyes had persistent intraretinal and/or subretinal fluid at the end of the follow-up period.¹⁸

In our study, BCVA and CFT improved in both groups from the time of recurrence of ME to final follow-up. Our statistical analyses showed similar outcomes in both treatment groups with a trend toward improved and more rapid response with aflibercept. Although the baseline BCVA differed slightly between Groups 1 and 2, the BCVA at recurrence, before switching to aflibercept was similar. The impact of the baseline BCVA on the final BCVA, after treatment with aflibercept, is unclear. Larger, randomized-controlled studies will be needed to better investigate the use of bevacizumab, ranibizumab, and aflibercept for recurrent ME secondary to RVO. ME secondary to CRVO can be recalcitrant to any of these medications and some patients may still have limited functional and anatomical improvement.

The main limitations of this study include retrospective design and small study population. Although this is the largest comparative, interventional study investigating treatment for recurrent ME in the setting of CRVO, the study size may not be adequately powered to detect infrequent events. However, our results are encouraging for the use of aflibercept as an alternative to bevacizumab and/or ranibizumab, in cases of CRVO with recurrent ME.

In summary, we found that for the treatment of recurrent ME in the setting of a CRVO, aflibercept led to more complete resolution of intraretinal and/or subretinal fluid than bevacizumab and/or ranibizumab. Larger studies comparing bevacizumab and/or ranibizumab to aflibercept will help us better elucidate the role of aflibercept in the treatment of ME secondary to CRVO.

Author Disclosure Statement

No competing financial interests exist.

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Received: July 3, 2017

Accepted: December 4, 2017

Address correspondence to:

Dr. Cagri G. Besirli

Department of Ophthalmology and Visual Sciences

Kellogg Eye Center

University of Michigan

Ann Arbor, MI 48105

E-mail: cbesirli@med.umich.edu