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ORIGINAL PAPER

Five-year outcomes after intravitreal bevacizumab of treatment-naive eyes with macular edema secondary to CRVO in routine clinical practice: Results of the Pan-American Collaborative Retina Study (PACORES) group

Lihteh Wu · Dhariana Acon · Maria H. Berrocal · Roberto Gallego-Pinazo · Rosa Dolz-Marco · Jose A. Roca · Mauricio Maia · Sergio Rojas · Marcelo Zas · J. F. Arevalo · Jay Chhablani

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Abstract

Purpose The purpose of this study was to report the 5-year outcomes of treatment-naive eyes with cystoid macular edema secondary to central retinal vein occlusion treated with intravitreal bevacizumab in routine clinical practice.

Methods We conducted multicenter retrospective non-comparative case series of 102 eyes. The main outcome measured was the change in best-corrected visual acuity (BCVA) at 5 years. Secondary outcomes included the number of injections and the change in CMT at 5 years.

Results At 5 years, the mean BCVA improved from 1.22 ± 0.58 (Snellen 20/428) at baseline to 1.00 ± 0.68 logMAR (Snellen 20/200; $p < 0.0001$). At 5 years, 48 (47%) eyes had a gain of ≥ 3 lines, 41 (40.2%) eyes remained within 3 lines and 13 (12.7%) eyes had a loss of ≥ 3 lines of BCVA. The CMT improved from 740 ± 243 to 322 ± 179 µm ($p < 0.0001$). At 5 years, 59 (57.8%) eyes had a completely dry SD-OCT. Patients received a total of 10.6 ± 6.1 (range 6–27) injections. Baseline BCVA ($p < 0.0001$) and the duration of symptoms prior to

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L. Wu (✉) · D. Acon
Asociados de Macula Vitreo y Retina de Costa Rica, Primer Piso, Torre Mercedes, Paseo Colón, San José, Costa Rica
e-mail: LW65@cornell.edu

L. Wu
Department of Ophthalmology, Illinois Eye and Ear Infirmary, University of Illinois Chicago School of Medicine, Chicago, IL, USA

M. H. Berrocal
Department of Ophthalmology, University of Puerto Rico, San Juan, Puerto Rico

R. Gallego-Pinazo · R. Dolz-Marco
Oftalvist Clinic, Valencia, Spain

J. A. Roca
Oftalmologos Contreras, Lima, Peru

M. Maia
Department of Ophthalmology, Vision Institute, Federal University of Sao Paulo, Sao Paulo, Brazil

S. Rojas
Fundación Hospital Nuestra Señora de la Luz, Mexico City, Mexico

M. Zas
Department of Ophthalmology, University of Buenos Aires, Buenos Aires, Argentina

J. F. Arevalo
Wilmer Eye Institute, Johns Hopkins University, Baltimore, MD, USA

initial anti-VEGF injection ($p = 0.0274$) were the only predictive factors for BCVA at 5 years.

Conclusions After 5 years with an average of 10.6 injections, there was a mean gain of 0.22 logMAR. In addition, more eyes achieved a BCVA of $\geq$ 20/40, gained $\geq$ 3 lines and less patients had a BCVA $\leq$ 20/200. Eyes with a better baseline BCVA and a shorter duration of symptoms were more likely to achieve better BCVA at 5 years.

Keywords Central retinal vein occlusion · Macular edema · VEGF · Bevacizumab · Ranibizumab · Aflibercept · Real world · Routine clinical practice

Introduction

Over the past two decades, experimental and clinical studies have demonstrated the key role that vascular endothelial growth factor (VEGF) plays in central retinal vein occlusions (CRVO) [1, 2]. Patients with CRVO have elevated aqueous VEGF levels [3]. The degree of cystoid macular edema (CME) and retinal ischemia correlates with the VEGF levels [4]. When VEGF is injected serially into a non-human non-diseased primate eye, the retinal vessels become dilated and tortuous. Intraretinal hemorrhages appear and retinal capillary non-perfusion is documented on fluorescein angiography (FA) [5]. Electron microscopy revealed that VEGF induces retinal endothelial cell hypertrophy [6]. The hypertrophied retinal endothelial cells impinge on the capillary lumen narrowing it and in some cases obliterating it. Several clinical trials demonstrated the effectiveness of VEGF inhibitors in improving visual acuity in eyes with CME [7–10].

Both ranibizumab and aflibercept have been approved for the treatment of CME secondary to CRVO. In places where cost is an issue, bevacizumab has been widely used off-label with success [11–15]. Our group has previously reported on the beneficial effects of bevacizumab with up to 24 months of follow-up [16]. Bevacizumab compared favorably with aflibercept in the SCORE-2 trial [17, 18]. There is little information regarding the long-term outcomes of these eyes treated with anti-VEGF agents. The purpose of the current study is to report the real-life five-year anatomical and functional outcomes of treatment-naive eyes with CME secondary to CRVO treated with bevacizumab.

J. Chhablani
L.V.Prasad Eye Institute, Hyderabad, India

J. Chhablani
Department of Ophthalmology, University of Pittsburgh, Pittsburgh, PA, USA

Methods

We conducted a multicenter retrospective study of 102 eyes with treatment-naive CME secondary to CRVO that were treated with at least three consecutive monthly intravitreal injections of 1.25 mg of bevacizumab. These patients had their initial injection with bevacizumab between September 2009 and July 2015. We reviewed the clinical records of 102 consecutive patients. The off-label use of bevacizumab and its potential risks and benefits were discussed with all patients. The tenets of the Declaration of Helsinki were adhered to. Institutional review board approval was obtained at all centers.

Patient eligibility and exclusion criteria

All patients with CME secondary to CRVO were included in the study if they had decreased visual acuity and met the following criteria: (1) no other possible causes for visual loss; (2) treatment naive at baseline; (3) no vitreomacular traction on OCT; (4) minimal follow-up of 5 years; and (5) no cataract surgery within the past 3 months.

Examination and treatment procedures

At baseline, each patient underwent a complete ophthalmic examination and spectral domain optical coherence tomography (SD-OCT). A volume scan centered on the fovea was performed. The scans were reviewed and manual corrections were performed in case of segmentation errors. FA was done at the discretion of the treating physician.

Patients were injected with 1.25 mg of bevacizumab through the pars plana after standard preparation with topical anesthesia and 5% povidone iodine. No antibiotics drops were used pre- or post-injection.

Patients were seen and treated monthly for the first 3 months or until the edema stabilized. All ophthalmologic examination visits included SD-OCT. Patients were re-injected if recurrence of CME or loss of visual acuity occurred. Usually, if there was no reduction in the edema or improvement in BCVA after at least three consecutive monthly injections, alternative treatments, including other anti-VEGF agents, intravitreal triamcinolone, intravitreal dexamethasone implant, macular laser photocoagulation (MLP), pars plana vitrectomy (PPV), subthreshold macular laser or fluorescein-guided photocoagulation to ischemic retinal areas, were offered. The choice of the alternative treatment was left to the discretion of the treating physician and the patient.

Statistical analysis

Conversion of BCVA to a logMAR scale was performed to facilitate statistical analysis of the data. Statistical analysis was performed using GraphPad Prism ® (version 8.0 for the Macintosh OSX, GraphPad Software, San Diego, California, USA). Descriptive statistics including mean and standard deviation (SD) were calculated. The Fisher exact test and the nonparametric ANOVA with Mann–Whitney test were calculated. A p value of < 0.05 was considered significant.

The main outcome measured was the change in BCVA from baseline to year 5. Secondary outcomes measured included change from baseline in central macular thickness (CMT) and total number of injections at year 5. SD-OCTs were evaluated for quantitative data (CMT) and qualitative data (presence or absence of cystoid spaces in the different retinal layers, subretinal fluid (SRF) and disruption of the outer retina).

Results

Baseline characteristics

A total of 102 eyes from 102 patients were included. The mean time of duration of symptoms prior to consultation was 4.5 months ± 5.2 months. The mean age of this cohort was 72.2 ± 11 years and included 62 male patients. Patients had a mean follow-up of 61 ± 6.8 months. At baseline, 20 patients had primary open angle glaucoma, 75 had systemic hypertension, 32 were diabetic, 5 had a prior stroke and 9 had a prior myocardial infarction (MI).

Visual acuity outcomes

At 5 years, the mean BCVA improved from 1.22 ± 0.58 logMAR (Snellen 20/332) at baseline to logMAR 1.00 ± 0.68 (Snellen 20/200) ($p < 0.0001$; Wilcoxon matched-pairs signed-ranks test) at 5 years of follow-up. At baseline, 5 eyes had a BCVA of ≥ 20/40, 20 eyes between < 20/40 and > 20/200 and 77 eyes ≤ 20/200. At 5 years, 20 eyes had ≥ 20/40, 32 eyes between < 20/40 and > 20/200 and 50 eyes ≤ 20/200 ($p = 0.000195$; Chi-square). At 5 years, 48 (47%) eyes had a gain of ≥ 3 lines, 41 (40.2%) eyes remained within 3 lines and 13 (12.7%) eyes had a loss of ≥ 3 lines of BCVA. The BCVA at different time points is summarized in Table 1. The difference in BCVA was statistically significant between baseline and all time points ($p < 0.0001$; Friedman test), but not between years 1, 2, 3, 4 and 5.

Imaging outcomes

The mean CMT improved from 740 ± 243 to 322 ± 179 µm ($p < 0.0001$). The CMT at different time points is summarized in Table 1. Foveal cuts of the OCT were analyzed. At baseline, 12.7% (13/102) of eyes had an epiretinal membrane (ERM), 42.2% (43/102) of eyes had SRF, 56.9% (58/102) of eyes had disruption of either the ellipsoid and/or the external limiting membrane (ELM), 78.4% (80/102) of eyes

Table 1 BCVA, CMT and number of intravitreal bevacizumab injections at different time points

	BCVA (logMAR)	CMT (µm)	# Injections
Baseline	1.22 ± 0.58	740 ± 243	
12 months	0.86 ± 0.57	304 ± 110	4.6 ± 2.3
24 months	0.93 ± 0.64	304 ± 113	2.1 ± 1.8
36 months	0.94 ± 0.66	305 ± 114	1.1 ± 1.5
48 months	0.99 ± 0.69	304 ± 114	0.8 ± 1.3
60 months	1.00 ± 0.68	322 ± 179	0.5 ± 1.1

BCVA, best-corrected visual acuity; CMT, central macular thickness; logMAR, logarithm of the minimal angle of resolution; µm, microns

had cystoid spaces in the outer nuclear layer (ONL), 73.5% (75/102) of eyes had cystoid spaces in the outer plexiform layer (OPL), 79.4% (81/102) of eyes had cystoid spaces in the inner nuclear layer (INL), 71.6% (73/102) of eyes had cystoid spaces in the inner plexiform layer (IPL), 51% (52/102) of eyes had cystoid spaces in the ganglion cell layer (GCL) and 39.2% (40/102) had cystoid spaces in the nerve fiber layer (NFL). At 5 years of follow-up, only 6.9% (7/102) of eyes remained with SRF, 39.2% (40/102) of eyes had disruption of either the ellipsoid and/or the ELM, 33.3% (34/102) of eyes had cystoid spaces in the ONL, 25.5% (26/102) of eyes had cystoid spaces in the OPL, 22.5% (23/102) had cystoid spaces in the INL, 25.5% (26/102) of eyes had cystoid spaces in the IPL, 13.7% (14/102) of eyes had cystoid spaces in the GCL and 7.8% (8/102) of eyes had cystoid spaces in the NFL. The prevalence of ERM on the other hand increased to 39.2% (40/102) of eyes. The prevalence of OCT abnormalities was statistically significantly less at 5 years of follow-up when compared to baseline for all the variables ($p < 0.0001$; Chi-square). However, differentiating the presence of fluid at baseline in any of the different anatomic compartments did not predict BCVA at 5 years. The disruption of either the ELM or the ellipsoid and presence of ERM at baseline also did not predict visual outcomes in this cohort (two-sided Fisher's exact test).

At 5 years, 59 (57.8%) eyes had a completely dry SD-OCT. At 5 years of follow-up, the BCVA in eyes with a completely dry SD-OCT improved from 1.22 ± 0.57 logMAR at baseline to 0.90 ± 0.71 logMAR ($p = 0.0002$; Wilcoxon matched-pairs signed-rank test). In eyes with residual fluid, the BCVA at 5 years improved from 1.30 ± 0.60 logMAR at baseline to 1.07 ± 0.60 logMAR ($p = 0.0190$; Wilcoxon matched-pairs signed-rank test). The CMT decreased from 633 ± 231 at baseline to 385 ± 119 μm in eyes with residual fluid on SD-OCT ($p < 0.0001$; paired t test). The CMT decreased from 609 ± 232 at baseline to 236 ± 49 μm in eyes with completely dry SD-OCT ($p < 0.0001$; paired t test). Only 7% (3/43) of eyes with residual CME achieved a BCVA of $\geq$ 20/40 compared to 28.8% (17/59) of eyes without CME ($p = 0.0087$; Fisher's exact test) and 54.2% (32/59) of eyes without CME achieved a gain of $\geq$ 3 lines BCVA from baseline compared to 37.2% (16/43) of eyes with residual CME ($p = 0.0651$; Fisher's exact test).

At 5 years, a total of 29 (28.4%) eyes had a CMT $\leq$ 225 μm. In this group of eyes, the baseline BCVA improved from 1.36 ± 0.72 (Snellen 20/448) to 1.17 ± 0.72 (20/296) logMAR. Only 6.9% (2/29) of eyes achieved a BCVA $\geq$ 20/40 and 31% (9/29) of eyes gained $\geq$ 3 lines of BCVA. A total of 33 eyes had a CMT between 226 and 299 μm at 5 years. The baseline BCVA improved from 1.15 ± 0.49 (Snellen 20/282) to 0.73 ± 0.61 (Snellen 20/107) logMAR at 5 years. Forty-two percent (14/33) of eyes achieved a BCVA $\geq$ 20/40 and 72.7% (24/33) of eyes gained $\geq$ 3 lines of BCVA. A total of 40 eyes had a CMT $\geq$ 300 μm at 5 years of follow-up. The baseline BCVA improved from 1.24 ± 0.58 (Snellen 20/348) to 1.03 ± 0.64 (Snellen 20/214) logMAR at 5 years. Only 10% (4/40) of eyes achieved a BCVA $\geq$ 20/40 and 37.5% (15/40) of eyes gained $\geq$ 3 lines of BCVA.

Injections outcomes

Patients received a total of 10.6 ± 6.1 (range 6–27) injections. On average, patients were injected 4.6 ± 2.3 (range 1–12) times in the first year, 2.1 ± 1.8 (range 0–9) in the second year, 1.1 ± 1.5 (range 0–8) in the third year, 0.8 ± 1.3 (range 0–5) in the fourth year and 0.5 ± 1.1 (range 0–5) in the fifth year.

Adjunctive therapy

A total of 39 (38.2%) eyes received some type of adjunctive therapy during the study period. In 11.8% (12/102) of eyes, intravitreal triamcinolone was injected. In 5.9% (6/102) of eyes, MLP was delivered. In 5.9% (6/102) of eyes, PPV was undertaken. In 5.9% (6/102) of eyes, sub-threshold macular laser was performed. Six (5.9%) eyes received another anti-VEGF agent (four ranibizumab and two aflibercept). Three (2.9%) eyes were injected with a dexamethasone implant. In addition, FA-guided laser to ischemic retinal areas was performed in 27.4% (28/102) of eyes. Eyes with adjunctive therapy did not do as well as the eyes that did not receive adjunctive therapy. The BCVA at 5 years of log MAR 1.22 was not statistically different from the baseline BCVA of log MAR 1.42 ($p = 0.1615$; Wilcoxon matched-pairs signed-ranks test). In comparison, eyes that did not receive adjunctive therapy had an improvement of BCVA from 1.12 logMAR at baseline to 0.75 logMAR at

Table 2 Comparison of outcomes of eyes that received adjunctive therapy and those that did not

	No. adjunctive therapy ($N = 48$)	Adjunctive therapy ($N = 29$)	p value
Baseline BCVA	1.18 log MAR	1.57 log MAR	0.01
Baseline CMT	603 microns	630 microns	0.8955
Duration of symptoms	2.7 months	6.7 months	0.0002
Total number of injections	13.3	6.2	0.0069
BCVA 5 years	0.81 log MAR	1.33 log MAR	0.0015
CMT 5 years	303 microns	303 microns	0.6511

BCVA, best-corrected visual acuity; CMT, central macular thickness; logMAR, logarithm of the minimal angle of resolution

5 years ($p < 0.0001$; Wilcoxon matched-pairs signed-ranks test). Eyes without adjunctive therapy also received more injections than those without adjunctive therapy (13.4 vs. 6; $p = 0.0069$). Table 2 summarizes these results.

Prognostic analysis of baseline characteristics

Univariate analysis identified baseline CMT ($p = 0.0048$), baseline BCVA ($p < 0.0001$) and duration of symptoms prior to initial injection ($p = 0.0232$) as predictive factors for BCVA at 5 years. Following multiple linear regression analysis only, baseline BCVA ($p = 0.0002$) and the duration of symptoms prior to initial anti-VEGF injection ($p = 0.0381$) remained as the only predictive factors for BCVA at 5 years.

Adverse events

None of the eyes developed endophthalmitis, retinal detachment or uveitis. Neovascular glaucoma developed in 5 (4.9%) eyes. Two patients developed a stroke, three developed a MI and one patient died.

Discussion

Several clinical trials have demonstrated the short-term efficacy of VEGF suppression in the treatment of CME secondary to CRVO [19–21]. A meta-analysis that included more than 1800 eyes that were treated with anti-VEGF drugs reported that at 12 months the average visual gain was of almost 3 lines. The improvement in visual acuity was directly correlated with the number of injections [22]. Despite the availability of approved medications for CME secondary to CRVO like ranibizumab and aflibercept, there is still widespread use of off-label bevacizumab throughout the world. Bevacizumab's lower cost, perceived effectiveness and relative safety make it a popular choice, particularly in the developing world [11, 12]. A recent analysis concluded that bevacizumab yielded the best cost utility among anti-VEGF drugs when modeled to treat CME secondary to CRVO [23].

It remains unclear whether there is any advantage in choosing one anti-VEGF over the others [17, 24]. Recently, the SCORE-2 trial compared the outcomes of aflibercept and bevacizumab [17]. In this clinical trial, eyes with CME secondary to non-ischemic CRVO or HRVO were randomized to six consecutive monthly injections of either aflibercept or bevacizumab. At 6 months, treatment of eyes with bevacizumab was non-inferior to treatment with aflibercept. In contrast, in the LEAVO trial, which included eyes with ischemic and non-ischemic CRVO, eyes received four consecutive monthly injections of ranibizumab, aflibercept or bevacizumab. Ranibizumab and aflibercept were non-inferior, but bevacizumab was not non-inferior to aflibercept or ranibizumab at 24 months. Interestingly, in this trial, at all time points it appeared that there was not much of a difference between the three drugs except at the primary outcome of 24 months. It would have been revealing to see what the comparison of the area under the curve for the three drugs as a function of time yielded. Unfortunately, these data are not available [24]. The different outcomes of these two trials can be attributed to different inclusion criteria and trial designs.

Several randomized clinical trials have shown that after a loading dose of six mandatory monthly injections followed by monthly monitoring with prn injections until month 12, visual gains were obtained. Thereafter, patients were followed on a mandatory quarterly basis for 12 months and re-injected as needed. During the second year, the BCVA gains obtained during the first 12 months were not sustained. Less intensive monitoring with fewer injections compromised the possible visual gains from anti-VEGF therapy. In a few eyes, stabilization may occur after a few consecutive monthly injections and require a few injections thereafter but the vast majority require more frequent monitoring and many more injections to control CME [9, 19, 20, 25, 26]. Similarly, in our study the best BCVA was seen at 12 months of follow-up when the number of injections given was the highest. As time progressed with less injections, the visual gain started to slowly decline.

The RETAIN-CRVO study was an extension of the HORIZON and CRUISE studies which unlike our cohort excluded eyes with an afferent pupillary defect or BCVA $\leq$ 20/320. Only 32 patients of the original 392 patients treated with ranibizumab were followed for a mean of 4 years. The functional results demonstrated that 44% of eyes had a BCVA $\geq$ 20/40, 53% had an improvement of $\geq$ 3 lines from the CRUISE trial baseline and resolution of CME was observed in 44% of eyes. In the RETAIN-CRVO study, eyes without CME fared better than those with persistent CME. In eyes where the CME had resolved, a gain in BCVA of 25.2 letters compared to 4.3 letters was reported. In addition, a greater proportion of eyes (64.3% vs. 27.8%) achieved a BCVA $\geq$ 20/40 as compared to those eyes without CME resolution [27]. In comparison, in our cohort at 5 years, only 18% had a BCVA $\geq$ 20/40, 47% had a gain of $\geq$ 3 lines and 58% of eyes had complete resolution of CME. Similarly in our study, resolution of CME was associated with a greater chance of achieving a BCVA of $\geq$ 20/40. Nevertheless, more than 70% of eyes without CME failed to achieve a BCVA of $\geq$ 20/40. It is plausible that some of these eyes that failed to improve despite the resolution of CME may have sustained photoreceptor and or neuroretinal damage from recurrent CME, a large ischemic insult that infarcted the macula or both thus limiting the visual recovery [27, 28]. In these cases, the CMT was usually $\leq$ 225 μm and may represent neuroretinal atrophy.

There are a handful of reports of long-term outcomes of bevacizumab for CME secondary to CRVO. The BERVOLT study, a retrospective non-comparative case series of 65 patients, reported that after a mean follow-up of 26.1 months, eyes suffered a mean loss of 0.118 log MAR units following treatment with bevacizumab [29]. Similar to our current study, the baseline BCVA was identified as a prognostic factor in the BERVOLT study. Eyes with a baseline BCVA $\leq$ 20/356 had a worse outcome. In contrast, the visual outcomes of Bajric and Bakri's [30] study of 51 eyes that were treated with intravitreal bevacizumab and followed for a mean of 2 years were much better. In this study, the mean BCVA at baseline improved from 20/214 to 20/107 at 1 year of follow-up. This improvement was maintained clinically at 4 years [30]. Spooner et al. [31] reported the 5-year outcomes of 35 eyes with CRVO and 2 eyes with HRVO. These eyes had a baseline visual acuity of 54.1 letters. At 5 years of follow-up, there was a mean gain of 11.1 letters. These patients had a mean of 7.3 injections in the first year and then 5.5 per year thereafter. On average, patients received 29.5 injections over 5 years. Similar to our study, eyes that were switched to another treatment had a worse outcome [31]. In one of the largest studies, Gale et al. [32] used an electronic medical database from the UK to report the outcomes of 3577 patients that underwent anti-VEGF treatment for CME secondary to CRVO. At 3 years of follow-up, the mean gain from baseline was 11.5 letters. This was achieved with an average of 7.06 treatments.

The number of injections that our patients received was considerable lower than in the clinical trials. In our current study, the annual mean number of bevacizumab injections per patient was 4.6 in the first year and then progressively declined to 0.5 injections per patient in the fifth year. Similar rate of injections findings was reported by Bajric and Bakri [30]. We can only speculate as to why the injections became less frequent with time. It may well be that eyes were improving and required less injections. Alternatively, the eyes were not doing well and treatment was stopped because of futility. Finances may also have played a role as the vast majority of our patients did not have medical insurance and had to finance their own medical treatment.

About a third of our patients received adjunctive therapy, which usually indicated that either the doctor or the patient or both perceived that bevacizumab monotherapy was not working to their satisfaction. In the SCORE-2 trial after six consecutive monthly injections of bevacizumab, only 22% of eyes had a poor response [33]. In the current study, the mean number of injections in the first year was only 4.6, so the decision to switch to an alternative therapy was made in most cases with less than six consecutive injections. It is possible that if these eyes had stayed the course, a percentage of them would have had a better outcome. In the SCORE-2 trial, the 22% of eyes that had a poor response were injected with aflibercept [33]. In contrast, in our cohort less than 6% were switched to a different VEGF inhibitor. In the current study, the eyes that had alternative treatments did not fare as well as the eyes that did not have alternative treatments. The 5-year BCVA was not statistically significantly different from the baseline BCVA. In addition these eyes also were injected less frequently.

There has been a recent interest in "real-world" data since it better reflects the experience of everyday clinical practice. We believe that the results of this study may be clinically useful and can offer some valuable and preliminary data on this subject despite the limitations of our study which includes its retrospective nature, the small number of patients and the lack of a control group. It also remains unclear whether a more intensive VEGF inhibition or a switch to another anti-VEGF would have improved the current outcomes. The current study provides additional information to the limited long-term data currently available.

In summary, after 5 years of monitoring and treatment in routine clinical practice, bevacizumab appears to be effective in reducing CME and improving BCVA in eyes with CME secondary to CRVO. Following an average of 10.6 injections, there was a mean gain of 0.22 logMAR from baseline. In addition, more eyes achieved a BCVA of $\geq$ 20/40, gained $\geq$ 3 lines and less patients had a BCVA $\leq$ 20/200. More than 40% of eyes had persistent CME at 5 years. Eyes with a better baseline BCVA and shorter duration of symptoms were more likely to achieve better BCVA at 5 years.

Author contributions All authors contributed to the study conception and design. Material preparation and data collection were performed by all the authors. Data analysis was performed by LW and DA. The first draft of the manuscript was written by DA, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The data have not been shared on a repository.

Declarations

Conflict of interest Dhariana Acon, Mauricio Maia, Jose A Roca, Sergio Rojas, Roberto Gallego-Pinazo and Jay Chhablani declare that they do not have conflict of interest. Dr. Lihteh Wu has received lecture fees from Bayer and Quantel Medical. Dr. Rosa Dolz-Marco has received lecture fees from Heidelberg Engineering. Dr. Maria H Berrocal and Dr Marcelo Zas have received lecture fees from ALCON. Dr. J Fernando Arevalo Abbvie: Consultant/Advisor; GENENTECH: Consultant/Advisor; Springer SBM LLC: Patents/Royalty; THEA Laboratories: Consultant/Advisor; Topcon Medical Systems Inc.: Grant Support.

Consent to participate Exemption of informed consent was obtained by being a retrospective case series that used de-identified patient data. IRB approval was obtained at all centers.

Consent to publish Exemption of informed consent was obtained by being a retrospective case series that used de-identified patient data.

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