Title

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Treatment Patterns and Clinical Outcomes for Central Retinal Vein Occlusion in the Antivascular Endothelial Growth Factor Era

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Abstract

Purpose: This article describes treatment patterns and visual outcomes for central retinal vein occlusion (CRVO) in the antivascular endothelial growth factor (anti-VEGF) era. **Methods:** A retrospective cohort study of eyes diagnosed with CRVO between 2009 and 2016 was conducted. Treatment history and visual acuity (VA) measurements were abstracted from medical records and analyzed. **Results:** A total of 476 eyes of 476 patients (median age 67 years, median follow-up 25.4 months) were included. Optical coherence tomography was obtained in 93.9% and fluorescein angiography in 80% of cases on presentation. Mean VA at presentation and final visit was 20/60 and 20/94, respectively, for eyes with nonischemic CRVO, whereas that of ischemic cases remained worse than 20/800 at final follow-up. Intravitreal bevacizumab was the most common first treatment (42.2%). Intravitreal steroid was the first treatment in 3.6% and ultimately administered in 11.3% of eyes. In the first year, an average of 5.2 ± 3.6 and 2.2 ± 3.4 anti-VEGF injections were given in treatment-naive and nontreatment-naive eyes, respectively. **Conclusions:** In our real-world cohort, anti-VEGF injection burden and frequency are lower than in published clinical trials. Visual outcomes in both ischemic and nonischemic eyes with CRVO are poorer than expected and worse than those recorded in controlled trial settings.

Keywords

antivascular endothelial growth factor (anti-VEGF), central retinal vein occlusion (CRVO), cystoid macular edema, treat-and-extend, treatment patterns

Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disease following diabetic retinopathy.[1] Central retinal vein occlusion (CRVO) is estimated to affect 2.5 million adults worldwide, with an estimated prevalence of 0.08% to 0.1%.[1-3] CRVO has historically been divided into ischemic and nonischemic types on the basis of capillary perfusion, as graded on fluorescein angiography (FA), and clinical features such as visual acuity (VA) and the presence of neovascular sequelae.[4,5] Recently, the ischemic index has been used to grade the perfusion status of CRVO using ultra-widefield angiography.[5] Whereas nonischemic CRVO is more common, eyes with ischemic CRVO have a substantially worse visual prognosis. A meta-analysis on the natural history of CRVO reported that eyes with ischemic CRVO not only present with worse VA but also experience an average decrease in 35 letters over time, in comparison with just 3 letters in untreated nonischemic CRVO cases.[6]

Increased expression of vascular endothelial growth factor (VEGF) due to CRVO may lead to increased vascular permeability and proliferation of new vessels, mediating sequelae of CRVO such as macular edema, neovascularization, and associated visual loss. In recent years, large, randomized, controlled trials of intravitreal anti-VEGF medications such as the CRUISE[7] investigation for ranibizumab and GALILEO[8] and COPERNICUS[9] studies for aflibercept have established the efficacy and safety of these agents in treating macular edema associated with CRVO. Patients who were administered monthly injections experienced significant and rapid improvement in VA at 6 months that was subsequently maintained with as-needed therapy in the clinical trial setting.[8,10]

Although the efficacy of anti-VEGF in the setting of randomized controlled trials is well established, there exists a need

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to also identify the real-world translation of practice patterns and efficacy. Studies have used claims data to examine treatment patterns of bevacizumab, ranibizumab, and aflibercept.[11,12] In addition, many international groups, such as those in Germany,[13] Denmark,[14] Portugal,[15] and the United Kingdom,[16] have studied the real-world practice and efficacy of anti-VEGF use in CRVO. A recent multicenter study in the United States of patients with acute RVO-associated macular edema reports that anti-VEGF injections given in clinical settings were administered less frequently and with less efficacy than in controlled trial settings.[17]

Although many international and domestic studies have examined the efficacy and usage pattern of specific treatments in CRVO, we seek to characterize all forms of treatment used within a large sample size in a tertiary care setting in the United States. This study uses real-world data in a large cohort of CRVO cases treated by 22 retina specialists at a single tertiary care institution to describe current patterns in workup and treatment as well as visual outcomes for patients diagnosed with CRVO in the anti-VEGF era.

Methods

This single-center, retrospective, longitudinal cohort study used data from a database created with approval from the Duke University Institutional Review Board. The study adhered to the tenets of the Declaration of Helsinki and complied with HIPAA, the Health Insurance Portability and Accountability Act.

Patient Selection

Patients presenting with CRVO between January 1, 2009 and July 1, 2016 at Duke Eye Center, Durham, North Carolina were identified by the Duke Enterprise Data Unified Content Explorer system using International Classification of Diseases-9 and -10 coding for CRVO. The entry point into the study was based on when spectral-domain optical coherence tomography (SD-OCT) was routinely available at our institution. Patients were excluded if their date of CRVO diagnosis or prior treatment history were unknown.

Review of Medical Records

Medical records were reviewed for demographic information such as age at CRVO diagnosis, sex, and race as well as smoking status, medication use, and concurrent diagnosis of hypertension, diabetes mellitus, hyperlipidemia, or glaucoma. Among patients with bilateral CRVO at presentation, the eye most recently diagnosed with CRVO was included in the analysis. In patients for whom the fellow eye developed a CRVO during the study period, this fellow eye was excluded from analysis.

Clinical notes were evaluated for characteristics of CRVO including duration of symptoms prior to presentation, eye laterality, perfusion status, lens status, and presence of a relative afferent pupillary defect (RAPD), neovascularization, or vitreous hemorrhage.

We considered whether a CRVO was ischemic or nonischemic. The degree of ischemia in CRVO on ultra-widefield FA has previously been correlated with the presence of intraocular neovascularization attributable to CRVO, or counting fingers or worse vision with a relative afferent pupillary defect confirmed by a physician;[5] because ultra-widefield FA was not available for many patients in this cohort, CRVO was therefore considered ischemic if it met either of these criteria.

Workup details such as whether SD-OCT, FA, or other tests were ordered, were abstracted, and treatment history was recorded. Treatments were defined as intravitreal injection of any anti-VEGF agent (bevacizumab, ranibizumab, and aflibercept) and intravitreal or periocular steroid injection. Further, documentation of gonioscopy and performance of panretinal laser photocoagulation (PRP) were collected, as well as whether patients underwent a workup for systemic risk factors of CRVO. In general, those patients without well-known risk factors for CRVO had a workup for other potential causes.

All patients were evaluated and treated at the same tertiary care institution by different providers within the retina service that share an overall similar approach to workup and treatment algorithms. Given the retrospective nature of this study, there were no predetermined criteria, and individual decisions were physician dependent.

The baseline visit was defined as the presenting visit for CRVO, whereas the final examination available for the affected eye was deemed the final visit. Optical coherence tomography (OCT) images at the baseline and final visits were graded for presence of cystoid macular edema (CME) or subretinal fluid, central subfield thickness, and subfoveal choroidal thickness, the latter of which was measured with the caliper tool using Spectralis software (Heidelberg Engineering). Corrected VA and intraocular pressure (IOP) in both the CRVO-affected and fellow unaffected eyes were recorded at the baseline and final visits. The final visit was used to calculate the time between initial presentation and final follow-up.

Statistical Analysis

Descriptive statistics were obtained for all variables as well as for a subset of subgroups including eyes with ischemic and nonischemic CRVO, eyes with each type of neovascularization, and treatment-naive and nontreatment-naive eyes. When data were not available, percentages were reported, where the denominator was the number of available data points. VA recorded in the form of Early Treatment of Diabetic Retinopathy Study (ETDRS) charts was converted to the logarithm of the minimum angle of resolution (logMAR) VA for the purpose of analysis. Analyses were performed using SAS 9.3 (SAS Institute Inc).

Results

Patient Characteristics

We identified 476 eyes of 476 patients diagnosed with CRVO. Median age at diagnosis was 67 years (interquartile range,

Table 1. Medical, Ocular, and Medication Use History of Patients.[a]

	n (%)	N
Medical and ocular history		
Hypertension	316 (79.0)	400
Diabetes	145 (38.6)	376
Current smoker	73 (18.0)	405
Glaucoma	160 (41.9)	382
Lens status at baseline		384
Phakic	257 (66.9)	
Pseudophakic	127 (33.1)	
Medication use		
ACE inhibitor	119 (34.4)	346
Beta blocker	123 (35.9)	343
Oral contraceptive	5 (1.2)	404
Hormone replacement therapy	12 (3.8)	320
Aspirin, 81 mg	151 (42.8)	353
Aspirin, 325 mg	21 (6.5)	323
Warfarin	21 (6.3)	333
Clopidogrel	25 (7.7)	325
Rivaroxaban	3 (0.9)	322
Apixaban	6 (1.9)	324
Dabigatran	3 (0.9)	322
Fish oil	25 (7.7)	325
Vitamin E	8 (2.5)	325
Other anticoagulants	7 (2.2)	321

Abbreviation: ACE, angiotensin-converting enzyme.
[a]The numbers reflect patient characteristics at the time of diagnosis with central retinal vein occlusion (CRVO); the number of patients included in each analysis varies based on whether this information was clearly available at the time of diagnosis of CRVO.

56.5-75 years). The median time to final follow-up was 25.38 months (interquartile range, 10.0-52.26 months). Slightly more than half (52.9%) of the patients were female. Caucasians (64.9%) and African Americans (21.9%) composed most of the cohort. The medical and ocular history as well as the patients' medication usage are displayed in Table 1. There were 143 eyes (30%) in this cohort that had been treated for CRVO prior to presentation at our institution (nontreatment naive).

Central Retinal Vein Occlusion Characteristics

Median duration of CRVO prior to presentation was 1 month for treatment-naive eyes and 10.5 months for nontreatment-naive eyes (2 months for all eyes). Roughly equal proportions of eyes had ischemic (45.2%) vs nonischemic (46.2%) CRVO, with 8.6% of eyes having CRVO of indeterminate perfusion status at presentation. Among treatment-naive eyes, 41.1% and 46.5% presented with ischemic and nonischemic CRVO, respectively. In nontreatment-naive eyes, 54.5% had ischemic CRVO and 45.5% had nonischemic CRVO.

At presentation, neovascularization of the iris, angle, disc, and elsewhere was found in 9.4%, 6.1%, 3.1%, and 4.4%, respectively, of treatment-naive eyes. Vitreous hemorrhage was discovered in 7.6% of eyes on presentation, whereas foveal intraretinal hemorrhage was noted in 39.5% of eyes. CME was detected in 72.6% of eyes on presentation and 45.9% of eyes at final follow-up. In 18.0% of cases, the fellow eye experienced

an RVO of any kind either before or after presentation to our institution for the study eye.

Treatment History of Nontreatment-Naive Eyes

Of the 143 nontreatment-naive eyes, the vast majority (91.9%) were treated with intravitreal anti-VEGF by other retina specialists prior to presentation at our institution. Bevacizumab was the most common anti-VEGF agent previously used (76.6%), followed by ranibizumab (30.0%) and aflibercept (11.1%). On average, the most recent anti-VEGF injection was administered 7.4 ± 14.1 weeks (range, 0-76 weeks) prior to presentation. The next most common treatments received were PRP (42.9%) and steroids (39.8%). Intravitreal triamcinolone (IVTA) was generally the steroid treatment of choice, administered in 81.0% of cases, whereas posterior subtenon triamcinolone (5.4%) and intravitreal dexamethasone (Ozurdex, Allergan) (2.7%) had been used less frequently. The last steroid treatment was administered an average of 8.64 ± 12.75 weeks (range, 0-48 weeks) prior to presentation.

Diagnostic Procedures

Details of the workup performed on presentation for all eyes—nontreatment-naive and treatment-naive—are shown in Table 2. Notably, laboratory evaluation of CRVO risk factors was obtained in 33.7% of nontreatment-naive eyes and 26.0% of treatment-naive eyes. In most of the cases (93.9%), OCT was obtained on presentation. FA was also commonly performed, in approximately 80% of eyes. In 24.1% of all eyes, additional FAs were produced during follow-up.

Treatment Practices and Patterns

Of all eyes, 53.5% received treatment of CRVO the day of presentation. A greater proportion of treatment-naive eyes (61.5%) than nontreatment-naive eyes (38.1%) was treated at the initial visit. Treatment patterns of CRVO following presentation are displayed in Table 3. Of note, the first treatment administered was most commonly intravitreal bevacizumab (42.2%) followed by intravitreal ranibizumab (20.4%). Of all eyes, 32 (11.3%) received intravitreal steroid during their treatment course (30 eyes received IVTA and 2 eyes received Ozurdex).

All (100%) nontreatment-naive eyes and 289 out of 333 (86.8%) treatment-naive eyes had 1 or more years of follow-up at our institution. Among eyes with 1 or more years of follow-up, treatment-naive eyes received a mean ± SD of 5.2 ± 3.6 anti-VEGF injections in the first year after presentation compared with 2.2 ± 3.4 anti-VEGF injections for nontreatment-naive eyes. In treatment-naive eyes, PRP was the first treatment in 2.4% and was ultimately administered in 30.4% of these eyes.

Visual Outcomes

VA and IOP information is displayed in Table 4. Mean ± SD logMAR VA for all eyes was 1.02 ± 0.83 (Snellen equivalent, 20/209) at presentation and 1.15 ± 0.91 (Snellen, 20/283) at the

Table 2. Diagnostic Procedures Performed.[a]

	All Eyes		Nontreatment-Naive Eyes		Treatment-Naive Eyes	
	n (%)	N	n (%)	N	n (%)	N
Workup for etiology of CRVO[b]	85 (28.3)	300	31 (33.7)	92	54 (26.0)	208
Gonioscopy performed on presentation	47 (15.7)	299	11 (12.4)	89	36 (17.1)	210
FA obtained on presentation		299		96		203
Yes	239 (79.9)		75 (78.1)		164 (80.8)	
30-degree without sweeps	106 (35)		35 (36.5)		71 (35.0)	
30-degree with sweeps	35 (11.7)		4 (4.2)		31 (15.3)	
UWF	98 (32.8)		36 (37.5)		62 (30.5)	
Additional FA obtained during follow-up	61 (24.1)	253	13 (15.9)	82	48 (28.1)	171
OCT obtained on presentation	308 (93.9)	328	104 (94.6)	110	204 (93.6)	218

Abbreviations: CRVO, central retinal vein occlusion; FA, fluorescein angiography; OCT, optical coherence tomography; UWF, ultra-widefield (200 degree).
[a]The "n" for each comparison was determined based on availability of data for the specific variable in question.
[b]In addition to testing for traditional risk factors, patients were tested with a hypercoagulability panel and for underlying retinal vasculitis when clinical suspicion was high.

Table 3. Treatment Received for Central Retinal Vein Occlusion.

	All Eyes	Nontreatment-Naive Eyes	Treatment-Naive Eyes
		n (%)[a]	
First treatment administered			
IVB	201 (42.2)	27 (18.8)	174 (52.3)
IVR	97 (20.4)	14 (9.7)	83 (24.9)
IVA	34 (7.1)	7 (4.9)	27 (8.1)
IVTA	17 (3.6)	3 (2.1)	14 (4.2)
PRP	9 (2.1)	1 (0.7)	8 (2.4)
PST	5 (1.1)	1 (0.7)	4 (1.2)
FAI	1 (0.2)	1 (0.7)	0 (0)
No intervention	110 (21)	89 (62.2)	21 (6.3)
First intravitreal anti-VEGF administered	N = 360	N = 48	N = 312
IVB	221 (61.4)	27 (56.3)	194 (62.2)
IVR	101 (28.1)	14 (29.2)	87 (27.9)
IVA	38 (10.6)	7 (14.6)	31 (9.9)
PRP administered	92 (28.7)	23 (24.5)	69 (30.4)
Intravitreal steroid administered	32 (11.3)	6 (7.1)	26 (13.1)
Pentoxifylline initiated	15 (2.5)	6 (4.2)	9 (4.5)
		Mean ± SD (range)	
Total number of PST treatments	0.03 ± 0.16 (0-1)	0.04 ± 0.2 (0-1)	0.02 ± 0.1 (0-1)
Total number of IVTA treatments	0.25 ± 0.96 (0-9)	0.14 ± 0.6 (0-4)	0.21 ± 0.8 (0-8)
Total number of Ozurdex (intravitreal dexamethasone) treatments	0.01 ± 0.1 (0-1)	0.01 ± 0.1 (0-1)	0.005 ± 0.07 (0-1)
Total number of IVB treatments	4.1 ± 6.20 (0-55)	1.89 ± 4.6 (0-27)	5.1 ± 7.1 (0-55)
Total number of IVR treatments	2.3 ± 4.4 (0-34)	1.8 ± 4.9 (0-27)	2.4 ± 4 (0-34)
Total number of IVA treatments	1.8 ± 4.1 (0-31)	1.5 ± 3.2 (0-15)	1.8 ± 4.4 (0-31)
Total number of anti-VEGF injections at 1 year[b]	4.2 ± 3.7 (0-12)	2.2 ± 3.4 (0-12)	5.2 ± 3.6 (0-12)
Total number of anti-VEGF injections at final follow-up	6.8 ± 9 (0-63)	3.9 ± 6.7 (0-28)	8.1 ± 10.4 (0-63)

Abbreviations: anti-VEGF, anti–vascular endothelial growth factor; FAI, fluocinolone acetonide implant; IV, intravitreal; IVA, intravitreal aflibercept; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; IVTA, intravitreal triamcinolone; PRP, panretinal photocoagulation; PST, posterior subtenon triamcinolone.
[a]The "n" for each comparison was determined based on availability of data for the specific variable in question.
[b]Comparison includes only those with 1 or more years of follow-up.

final visit. In treatment-naive eyes only, mean ± SD logMAR VA was 1.03 ± 0.83 (Snellen, 20/214) and 1.10 ± 0.92 (Snellen, 20/252) at presentation and the final visit, respectively.

Mean ± SD logMAR VA for eyes with nonischemic CRVO was 0.48 ± 0.46 (Snellen, ∼20/60) at presentation and 0.67 ± 0.72 (Snellen, ∼20/94) at the final visit. For eyes with ischemic CRVO, logMAR VA on presentation was 1.61 ± 0.73 (Snellen, 20/815), whereas final logMAR VA was 1.65 ± 0.82 (Snellen, 20/893). When restricted to treatment-naive eyes, those with nonischemic CRVO had a similar VA course;

Table 4. Visual Acuity and Intraocular Pressure Outcomes of Central Retinal Vein Occlusion Eyes From Presentation to Final Visit.

	On Presentation		Final Visit		Mean # of Lines Gained[a]	% With Improved VA	% With Worsened VA
	logMAR VA	IOP	logMAR VA	IOP			
All eyes (N = 476)	1.02 ± 0.83	17.24 ± 6.95	1.15 ± 0.91	16.85 ± 6.84	−1.18	37.23	42.20
Nonischemic CRVO (n = 220)	0.48 ± 0.46	16.12 ± 5.44	0.67 ± 0.72	16.28 ± 5.74	−2.02	35.33	44.0
Ischemic CRVO (n = 215)	1.61 ± 0.73	18.44 ± 8.13	1.65 ± 0.82	17.40 ± 7.82	−0.23	39.39	40.15
Nontreatment-naive eyes (n = 143)	1.00 ± 0.83	17.51 ± 6.07	1.29 ± 0.88	16.61 ± 6.23	−1.77	28.05	45.12
Treatment-naive eyes (n = 333)	1.03 ± 0.83	17.08 ± 7.41	1.10 ± 0.92	16.93 ± 7.06	−0.94	41.0	41.0
Treatment-naive and nonischemic CRVO (n = 155)	0.52 ± 0.49	15.78 ± 7.66	0.68 ± 0.74	15.91 ± 7.85	−1.90	38.26	43.48
Treatment-naive and ischemic CRVO (n = 137)	1.67 ± 0.93	18.72 ± 10.97	1.61 ± 1.00	18.08 ± 10.66	−0.36	44.71	37.65

Abbreviations: CRVO, central retinal vein occlusion; IOP, intraocular pressure; logMAR, logarithm of the minimum angle of resolution; VA, visual acuity.
[a]Indicates mean number of lines gained from presentation to final visit for all eyes within each group.

however, eyes with ischemic CRVO appeared to experience a slight improvement rather than worsening in VA over time (Snellen, 20/935 to 20/814). The mean number of lines gained for each group as well as percentages of eyes that improved or worsened from presentation to the final visit are also displayed in Table 4.

Conclusions

This retrospective longitudinal analysis of CRVO cases treated by 22 retina specialists at a major academic institution from 2009 to 2016 offers real-world data to assess treatment patterns and visual outcomes in the anti-VEGF era. To our knowledge, our cohort includes more cases of CRVO than other studies in the literature to date since the Central Vein Occlusion Study.[7-9,18-23]

Our main findings are as follows: (1) The first treatment administered was most commonly intravitreal bevacizumab, which mirrors regional, national, and international trends[24]; (2) OCT was obtained in the majority of cases (93.9%) at presentation, whereas FA was ordered slightly less frequently (80%); (3) at 1 year after presentation, an average of 5.2 ± 3.6 and 2.2 ± 3.4 injections were administered for treatment-naive eyes and nontreatment-naive eyes, respectively; and (4) the average VA for eyes with nonischemic CRVO decreased over time, whereas eyes with ischemic CRVO presented with substantially worse vision than their perfused counterparts but decline in VA over time was less prominent.

Large randomized clinical trials such as GALILEO, COPERNICUS, and CRUISE generally followed a treatment protocol of monthly anti-VEGF injections for 6 months followed by monthly as-needed injections for macular edema associated with CRVO.[8,9,25,26] In this setting, an average of 8.2 to 9.5 injections were administered in the first year of treatment. Previous studies using claims data reported that an average of 3.1 to 3.5 anti-VEGF injections were administered from 2008 to 2010[11] and 4.7 to 4.8 from 2012 to 2014[12] for treatment of CRVO in the first year after presentation. These frequencies were lower than those seen in randomized clinical trials and were thought at the time to be attributable to lack of availability of randomized, controlled trial data; after such data were published, the lower frequencies were believed to be attributable to lag time in using this new treatment paradigm.[11,12]

As the major clinical trials on anti-VEGF agents were first published in 2010, our study spans from before the presence of randomized, controlled trial evidence to several years after its publication, allowing for substantial time for thorough incorporation of anti-VEGF agents into clinical practice and insurance coverage plans for CRVO. Despite this, we found that injection frequency in the real world is lower than that of clinical trials.

One explanation for the disparity in injection frequency may be the use of other treatment patterns such as a treat-and-extend (TAE) or as-needed approach with a shorter period of initial fixed monthly injections. The SCORE2 trial randomized eyes with CRVO or hemispheric RVO after monthly anti-VEGF injections for 6 months to monthly or TAE-scheduled injections and found no significant differences in change in VA at 12 months.[27] Eyes with macular edema secondary to CRVO that were treated with a TAE regimen without an initial monthly dosage period experienced improvement in VA from 20/302 at baseline to 20/142 at 12 months.[28] In addition, the TAE and as-needed approaches have been compared in eyes with all types of RVO, with no significant differences in VA found at 12 months.[29]

Although further research is necessary to draw conclusions on the comparative efficacy of these approaches, the 2015 American Society of Retina Specialists Preferences and Trends survey showed that TAE is the preferred choice of treatment (56.3%) for RVO among US retina specialists; as-needed treatments were the second choice (40.2%), and only 0.5% reported that they would treat with monthly injections.[30]

Guichard et al[29] compared the TAE and as-needed approaches, each initiated after 1 ranibizumab injection at baseline, in eyes with macular edema associated with any type of RVO and found that mean number of injections in the first 12 months was 9.6 ± 2.0 and 4.2 ± 1.8 for TAE and as-needed approaches, respectively. Other studies have found similar results, with 1-year injection counts of 8 to 10 for the TAE approach of CRVO.[28,31]

Subsequently, our finding that an average of 5.2 ± 3.6 anti-VEGF injections were administered in the first 12 months for treatment-naive eyes in our cohort suggests that real-world treatment practices in a tertiary care referral center do not follow that of clinical trials, perhaps in both indications for treatment and extensions of treatment intervals. Specifically, we found that eyes in this large cohort received fewer injections. Our results are in line with other real-world studies, domestic[17] and international,[14,16] that have reported an average of 4.2 to 7.1 injections in the first year of treatment. In a recent large meta-analysis, eyes in nonrandomized trials were found to receive significantly fewer injections in the first 12 months of treatment of CRVO (5.6 ± 2.3) when compared with eyes in randomized trials (8.6 ± 0.7).[32]

Prior to the advent of anti-VEGF treatments of CRVO, visual outcomes were generally poor. In 1997, the Central Vein Occlusion Study Group studied the natural history of 714 CRVO eyes and found that median VA at baseline was 20/80, with 29% of eyes having VA 20/40 or better, 43% of eyes with VA in the range of 20/50 to 20/200, and 28% of eyes with VA worse than 20/200.[18] More recently, a meta-analysis of natural history studies on CRVO published before 2008 reported that eyes with nonischemic CRVO experienced a decrease in VA from 31 letters (Snellen, 20/250) at baseline to 28 letters (Snellen, 20/320) at 1 year; eyes with ischemic CRVO had baseline VA of 9 letters (Snellen, 20/640) and a loss of 35 letters after 1 year (Snellen, < 20/800).[6]

Studies examining visual course in the anti-VEGF era, on the other hand, have reported improved outcomes. In large, randomized clinical trials such as COPERNICUS, GALILEO, and CRUISE, treatment-naive eyes with CRVO that received monthly intravitreal anti-VEGF injections for 6 months followed by as-needed monthly injections experienced excellent improvement in VA, with mean baseline VA around 20/100 and 12-month VA ranging from 20/40 to 20/63.[9,26,33]

However, corrected VA at both presentation (20/214) and final follow-up (20/252) were substantially worse for treatment-naive eyes in our cohort using ETDRS VA charts. There are several potential explanations for this disparity. First, this finding, coupled with our report of fewer injections administered in our cohort, suggests the presence of undertreatment

in the real-world setting. Although it is difficult to ascertain cause and effect in this retrospective study, there is a potential association between fewer injections and poorer visual outcomes in our cohort. In addition, our study comprises a greater proportion of ischemic CRVO cases, even among treatment-naive eyes (45.2% all eyes, 41.1% treatment-naive eyes) compared with GALILEO[34] (8.2%), COPERNICUS[25] (15.5%), and CRUISE[7] (0.6%), which may explain not only the worse presenting VA but also the lack of improvement in VA over time due to poorer visual potential.

Despite this, even eyes with nonischemic disease had poor visual outcomes in our study. With a median follow-up time of more than 2 years, final VA measured in our study is also likely not comparable to shorter-term VA outcomes from clinical trials. Iftikhar and colleagues[35] suggest that although improvement in VA in eyes with CRVO is more often noted after initiation of anti-VEGF treatment, subsequent loss of the visual gain may occur because of recurrent episodes of CME, and as such, long-term VA may not always be substantially improved in select eyes with CRVO. Our study results are in line with the finding of Iftikhar et al and may reflect the long-term visual outcome of select eyes with CRVO that are treated in real-world scenarios, particularly in the setting of undertreatment.

It is possible that CRVO eyes with chronic refractory disease are less likely to experience improvement in VA. Our study cohort contained a large proportion of previously treated eyes (30%) that may have been referred to our tertiary care institution because of poor response to treatment. In particular, recalcitrant macular edema, which is estimated to occur in 37% to 43.7% of cases,[36,37] may be even more prevalent in our cohort because of the large proportion of nontreatment-naive eyes and is perhaps partially responsible for the poorer visual outcomes that were observed (VA 20/200 on presentation, 20/390 at the final visit in nontreatment-naive eyes).

However, even including previously treated eyes, good visual outcomes have been shown. The SCORE2 randomized clinical trial, which included 35.2% nontreatment-naive eyes with CRVO, reported improvement in VA from 20/100 at baseline to 20/32 to 20/40 for eyes treated with monthly anti-VEGF injections for 6 months followed by TAE injections for 6 months.[22,27] Notably, however, the SCORE2 study likely had few eyes with ischemic CRVO because eyes deemed unlikely to benefit from resolution of macular edema were excluded from the study. Poorer visual outcomes in the present analyses may thus be explained by the undertreatment, and perhaps also the large proportion, of ischemic CRVO cases and longer follow-up time to final visit, and they may also reflect the potential for increased VA improvement with more frequent anti-VEGF injections, both in the treatment-naive and nontreatment-naive populations.

Other studies based on real-world data have also found suboptimal visual outcomes. Jumper et al[17] studied 70 CRVO eyes treated with anti-VEGF and found that after the first 16 injections, only 20.0% to 36.7% of patients achieved the primary endpoint of combined best-corrected VA of 20/40 or better and central retinal thickness of less than or equal to 250 μm on

time-domain OCT or less than or equal to 300 μm on SD-OCT. In addition, treatment of CRVO with anti-VEGF agents has been reported to produce greater gains in VA at 12 months in the randomized trial setting than in nonrandomized trials, with a strong correlation between VA improvement and number of injections given.[32] Thus, stricter treatment practice, such as monthly injections followed by close follow-up and as-needed treatment, that mirrors that of clinical trials may perhaps be considered to improve visual outcomes in CRVO in practice. Further inquiry is warranted.

We additionally report that PRP was administered at presentation in only 2.4% of treatment-naive eyes and ultimately administered in 30.4% of such eyes. These rates are substantially lower than those prior to the advent of anti-VEGF. A study published in 1989, for instance, reports that of 55 eyes with CRVO, all 35 ischemic cases (63.6%) were treated with PRP as initial therapy.[38] Anti-VEGF agent administration may have contributed to the reduced rate of PRP placement at presentation as well as overall.

This study has limitations inherent to its retrospective design. Because all study patients were from a single, tertiary care, referral- and university-based practice, our study results may not be widely generalizable although the patients in our study were treated at our institution by 22 retina specialists, most of whom had trained elsewhere. Despite overall similar practices in our group, there certainly remains attendant selection bias in the cohort.

Given the retrospective nature of this database, practice patterns are not standardized and thus it is difficult to ascertain the true effect of treatment decisions. In addition, not all study patients entered the study at a uniform point in their disease process. That is, not all patients included had acute, treatment-naive CRVO on presentation. Although not all study patients were treatment naive, we attempted to account for this by including only nontreatment-naive eyes that had detailed treatment data available from the referring physician.

In conclusion, we used real-world clinical data to characterize a large number of CRVO cases in the anti-VEGF era and describe the diagnostic and treatment patterns of CRVO, corroborating surveyed practice patterns nationally as well as internationally. We additionally highlight that anti-VEGF injection burden and frequency are lower and visual outcomes are poorer in the real-world, tertiary care academic practice setting than in clinical trials that evaluate the monthly administration of injections, which may reflect the presence of undertreatment outside the controlled trial setting. With anti-VEGF therapy, the visual outcome of eyes with nonischemic CRVO is better than prior to the advent of such agents, and treatment with intravitreal steroids and application of PRP has become less frequent.

Authors' Note

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