

## Neovascular Events in Eyes with Central Retinal Vein Occlusion Undergoing Serial Bevacizumab or Ranibizumab Intravitreal Injections: A Retrospective Review

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### Abstract

**Purpose:** To characterize the onset and type of neovascular events in eyes with central retinal vein occlusion (CRVO) undergoing serial anti-VEGF therapy.

**Methods:** Consecutive eyes undergoing serial intravitreal bevacizumab or ranibizumab injections for treatment of CME secondary to CRVO were identified. Pertinent data was retrospectively collected and included type and onset of the neovascular event, and the treatment free interval from last injection until the neovascular event. Kaplan–Meier life table analysis was performed to determine the differential effects of baseline perfusion status, early initiation of anti-VEGF treatment (within 3 months of CRVO onset) versus later treatment, and continuous (1-month±2 weeks) versus discontinuous treatment interval (>1.5 months) on time until neovascular event.

**Results:** Of 31 eligible eyes, 12 (39%) and 19 (61%) presented with perfused and ischemic CRVO, respectively. The mean duration from CRVO until the onset of any neovascular event was 17.0±10.3 months. The mean treatment-free interval prior to any neovascular event was 6.2±7.3 months. On average, 5.3±3.2 anti-VEGF injections were given prior to any neovascular event. Neovascularization of the iris or angle occurred in 18 eyes (58%), vitreous hemorrhage associated with neovascularization was observed in 9 eyes (29%) and neovascularization of the disc developed in 5 eyes (16%). Neovascular events showed a trend towards occurring later in eyes with perfused CRVO at baseline (log rank test,  $P=0.07$ ).

**Conclusion:** Neovascular events occur in eyes with CRVO undergoing serial anti-VEGF therapy, and these events may be delayed compared to the natural history of CRVO-associated neovascularization. Iris neovascularization occurred most frequently.

**Keywords:** Bevacizumab; Central Retinal Vein Occlusion; Intravitreal; Neovascularization; Ranibizumab

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### INTRODUCTION

A variety of neovascular events can occur in eyes with central retinal vein occlusion (CRVO) including iris neovascularization, angle neovascularization, disc neovascularization, neovascularization elsewhere, neovascular glaucoma (NVG) and vitreous hemorrhage.<sup>[1]</sup> These last two events can lead to

substantial visual morbidity. The frequency of ocular neovascularization is inversely proportional to the degree of retinal perfusion.<sup>[2,3]</sup> To this end, CRVO is stratified into perfused and ischemic categories based on the quantity of capillary non perfusion observed on fluorescein angiography.<sup>[2]</sup> Though the ischemic subtype

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of CRVO accounts for about only 20% of all CRVO cases, the majority of neovascular events occur in eyes with this subtype of the condition.<sup>[1]</sup> In one study for example, iris neovascularization occurred in 125 of 239 (52.3%) eyes with ischemic CRVO at baseline compared to only 6 of 673 (0.9%) eyes with perfused CRVO at baseline.<sup>[3]</sup>

The vascular endothelial growth factor (VEGF) plays a prominent role in the development of neovascularization in eyes with CRVO,<sup>[4-6]</sup> and this molecule has been found in higher intraocular concentrations in eyes with CRVO as compared to eyes with other retinal vascular diseases.<sup>[7]</sup> In primate models, intraocular VEGF injection produced iris neovascularization and neovascular glaucoma,<sup>[8]</sup> and conversely VEGF inhibition prevented ischemia-associated ocular neovascularization.<sup>[9]</sup>

VEGF inhibition through intravitreal anti-VEGF injection is a frequent treatment modality for macular edema secondary to CRVO; however, the effect of this method of VEGF suppression on subsequent ocular neovascular events is not well understood. Though neovascularization is promoted in part by VEGF, neutralizing this growth factor with serial anti-VEGF injections does not always completely prevent neovascular events in eyes with CRVO. Clinically, VEGF inhibition may delay the onset of neovascular events in some eyes with CRVO as compared to the natural history of the disease. In the natural history subgroup of the landmark central vein occlusion study (CVOS), the vast majority of eyes that developed neovascularization did so within 6 months of study entry.<sup>[2]</sup> However, the CVOS was performed before the widespread administration of anti-VEGF agents to eyes with CRVO as treatment for macular edema.

More recently, serial intravitreal ranibizumab injections during pivotal phase III trials did not completely eliminate neovascular events in eyes with macular edema secondary to CRVO. In the Central Retinal Vein Occlusion study (CRUISE) trial that studied the effect of serial intravitreal ranibizumab therapy in eyes with CRVO, 7% of sham injection treated eyes developed iris neovascularization compared to only 0.8% of ranibizumab treated eyes at 6 months. Subsequently at 12 months, 3.9% of eyes treated monthly for 6 months followed by as needed ranibizumab dosing developed iris neovascularization.<sup>[10]</sup> Longer term neovascularization frequencies were not reported within the 24 months extension study results from the CRUISE trial.<sup>[11]</sup> Also, the CRUISE trial design excluded eyes with worse than 20/320 vision or with an obvious afferent pupillary defect, making inclusion of eyes with baseline ischemic CRVO less likely.<sup>[10]</sup> Despite being monthly followed by as needed VEGF suppression with ranibizumab in eyes with likely perfused CRVOs at baseline, neovascular events still occurred at a low frequency. However, it is not known if this frequency would increase with prolonged follow up, less frequent

anti-VEGF dosing, or in eyes with ischemic CRVO at baseline. In routine clinical practice, all of these scenarios become more relevant.

Similarly, a marked paucity of data limits better understanding of neovascular events in eyes undergoing serial bevacizumab treatment for macular edema secondary to CRVO. While the CRUISE trial enrolled 392 patients, no comparable large series exists to characterize neovascular events following bevacizumab treatment for macular edema secondary to CRVO. Several smaller series interestingly report a 0% incidence of neovascular events during bevacizumab treatment for CRVO including a report of 45 patients followed prospectively for 18 months,<sup>[12]</sup> a series of 61 patients followed for a mean of 60 weeks,<sup>[13]</sup> and others.<sup>[14-16]</sup> Similarly, little is known about neovascular events in the context of aflibercept treatment for CME secondary to CRVO. After 6 months of follow up in the COPERNICUS (vascular endothelial growth factor trap-eye: Investigation of efficacy and safety in central retinal vein occlusion) study, neovascular events were reported in 0% of eyes undergoing treatment with aflibercept compared to 6.8% of eyes in the sham injection group.<sup>[17]</sup> All in all, it is unlikely that serial treatment with any intravitreal anti-VEGF completely prevents neovascular events in all eyes with CRVO. Instead, it is possible that the series in the literature are either underpowered or lack sufficient follow up duration to detect infrequent but visually debilitating neovascular events that affect eyes with CRVO undergoing serial anti-VEGF treatment for macular edema.

The purpose of this study is to characterize neovascular events that occurred in eyes receiving serial intravitreal bevacizumab or ranibizumab treatment for macular edema secondary to CRVO. The primary outcome is to identify the duration between CRVO and first neovascular event, and secondary outcomes include reporting the treatment-free interval from last anti-VEGF injection until a neovascular event. This is particularly salient since in clinical practice intravitreal anti-VEGF therapy for CRVO may deviate from the dosing intervals utilized in phase III prospective clinical trials.<sup>[18]</sup> Intravitreal anti-VEGF therapy may not be administered indefinitely, and instead may be either extended or discontinued after sustained resolution of macular edema, after poor response to therapy, or due to patient related factors such as failure to follow up or financial considerations.

## METHODS

### Patients

Following IRB approval at Wills Eye Institute and Duke Eye Center and in accordance with the declaration of Helsinki, a retrospective consecutive case review was

performed for subjects who developed neovascular events while receiving intravitreal bevacizumab or ranibizumab for treatment of CME secondary to CRVO between December 2005 and November 2011. No patients receiving aflibercept for CRVO were available for review at the time of the study data collection. Inclusion criteria included age greater than 18 years, at least two prior intravitreal anti-VEGF treatments for CME secondary to CRVO, and any neovascular event defined as iris neovascularization, angle neovascularization, disc neovascularization, neovascularization elsewhere, neovascular glaucoma (NVG) and vitreous hemorrhage. Exclusion criteria included previous vitrectomy, history of prior neovascularization, or history of prior laser photocoagulation.

The patients were evaluated prior to first injection with a detailed history and ophthalmic examination, color fundus photographs, optical coherence tomography (OCT), and fluorescein angiography (FA). Visual acuity was determined using either best corrected Snellen (Longlife POC, Reichert Technologies, Depew, New York, USA) or Early Treatment of Diabetic Retinopathy Study (ETDRS, Lifehouse, New York, NY, USA) charts and converted to logarithm of the minimum angle of resolution (logMAR) acuity for further analysis. A standardized refraction was not performed prior to acuity measurement on the ETDRS chart. Eyes demonstrating less than 10 disc areas of capillary non perfusion on FA were considered as perfused CRVO. The remaining eyes were considered ischemic unless sufficient intraretinal hemorrhage existed to prevent classification, in which case the eyes were termed indeterminate.<sup>[19]</sup> Of note, the date of onset of CRVO was based on patient recall of symptom commencement. Other clinical information of interest included visual acuity at each visit, intraocular pressure, gonioscopy, laser treatment for neovascularization, subsequent anti-VEGF injection after a neovascular event, need for glaucoma surgery, need for vitrectomy, and postinjection complications.

### Subgroup Analysis

Subgroup analyses were performed to determine associations between baseline factors or treatment course and onset of any neovascular event. Eyes were divided by baseline perfusion status to determine differential onset of any neovascular event. For the same purpose, eyes were also divided into early initial and late initial treatment categories determined by the duration between CRVO onset until initiation of anti-VEGF treatment. Late initial treatment was defined as first anti-VEGF treatment more than 3 months after onset of CRVO, and the early initial treatment subgroup included all other eyes. Finally, comparison was performed between eyes receiving

continuous anti-VEGF treatment and those receiving discontinuous treatment. Continuous treatment was defined as approximately monthly injections (1-month $\pm$ 2 weeks) on average from first anti-VEGF until onset of neovascularization. Discontinuous treatment was defined as a mean interval between anti-VEGF injections greater than 1.5 months.

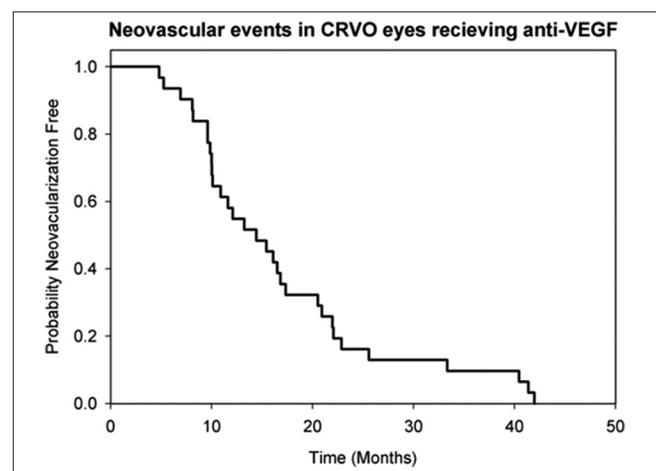
### Statistical Analysis

Wilcoxon signed rank test of median change was used to compare changes in visual acuity relative to baseline. The Kaplan–Meier life table analysis method was used to create time to first neovascular event curves. Differences in temporal onset of neovascularization were evaluated with the log rank test. Statistical analysis was performed using SAS Enterprise Guide Version 4.3 (SAS Institute, Cary, North Carolina).  $P=0.05$  or less were considered as statistically significant.

## RESULTS

Thirty-one consecutive eyes of 31 patients underwent serial intravitreal bevacizumab or ranibizumab for CME secondary to CRVO prior to experiencing a neovascular event. Patients ranged in age from 40 to 90 years (mean=73.9, SD=11.2). Of these eyes, 12 (39%) presented with perfused CRVO and 19 (61%) with ischemic CRVO while none had indeterminate CRVO. Other demographic variables of interest are described in Table 1 including past medical history, anticoagulation, and prior interventions. Of note, one eye received intravitreal triamcinolone approximately 2 months prior to initial anti-VEGF treatment and two other eyes received intravitreal triamcinolone 3 months or more prior to anti-VEGF treatment.

The mean duration from CRVO onset until any neovascular event was 17.0 $\pm$ 10.3 months [Figure 1]. The



**Figure 1.** Kaplan–Meier time to first neovascular event analysis for eyes undergoing serial anti-VEGF treatment for macular edema secondary to central retinal vein occlusion. CRVO, central retinal vein occlusion; VEGF, vascular endothelial growth factor.

mean treatment-free interval prior to any neovascular event was  $6.2 \pm 7.3$  months. The mean number of injections prior to any neovascular event was  $5.3 \pm 3.2$  injections.

The mean follow-up time from initial visit to final visit was  $27.9 \pm 14.1$  months for the 31 eyes in this series. The interval from onset of CRVO to initial presentation in the clinic averaged  $3.0 \pm 3.6$  months. The mean time from onset of CRVO to initial anti-VEGF treatment was  $3.8 \pm 4.0$  months. The mean duration from the first anti-VEGF injection until any neovascular event was  $13.2 \pm 9.7$  months. The subtype of the neovascular event and subsequent treatments are summarized in Table 2.

Baseline and final mean best corrected visual acuity (BCVA) were  $1.4 \pm 0.7$  logMAR (Snellen equivalent=20/502) and  $2.1 \pm 0.9$  logMAR (Snellen equivalent=20/2518), respectively ( $P=0.002$ ). Other visual acuity outcomes are detailed in Table 2. No eyes required vitrectomy and no injection-related complications were noted.

### Subgroup Analyses

Eyes with perfused CRVO at baseline experienced a neovascular event on average at  $21.5 \pm 11.8$  months as

**Table 1. Demographics and baseline factors of eyes undergoing serial intravitreal anti-VEGF injections for macular edema due to CRVO**

	(%)
Mean age (years, SD)	73.9 (11.2)
Gender (number, percentage)	
Male	14 (45)
Female	17 (55)
Eye (number, percentage)	
Right eye	18 (58)
Left eye	13 (42)
Perfusion status (number, percentage)	
Perfused	12 (39)
Ischemic	19 (61)
Indeterminate	0 (0)
Any macular ischemia	19 (61)
Patient past medical history (number, percentage)	
Hypertension	20 (65)
POAG	11 (35)
Diabetes mellitus	9 (29)
Prior MI	6 (19)
Prior CVA	4 (13)
Anticoagulation	10 (32)
Fellow eye occlusion	2 (6)
Prior therapy (number, percentage)	
Intravitreal triamcinolone	3 (10)
Grid pattern laser	0 (0)
Intravitreal anti-VEGF therapy	0 (0)

SD, standard deviation; VEGF, vascular endothelial growth factor; CRVO, central retinal vein occlusion; POAG, primary open angle glaucoma; MI, myocardial infarction; CVA, cerebrovascular accident

compared to  $14.2 \pm 8.4$  months for eyes with ischemic CRVO at baseline. Neovascular events showed a trend towards occurring later in eyes with perfused CRVO compared to eyes with ischemic CRVO at baseline (log rank  $P=0.07$ ) [Figure 2]. Eyes with perfused and ischemic CRVO at baseline received anti-VEGF injections at  $3.2 \pm 1.6$  and  $2.5 \pm 1.7$  months intervals on average, respectively.

Eyes with the early initial treatment (first anti-VEGF treatment within 3 months of CRVO onset) experienced a neovascular event at  $14.7 \pm 10.4$  months compared to  $20.8 \pm 9.4$  months in eyes with delayed initial treatment (more than 3 months after CRVO onset). Eyes undergoing early versus late initial treatment for macular edema secondary to CRVO received anti-VEGF injections at  $2.7 \pm 1.7$  and  $2.9 \pm 1.6$  months intervals, respectively. Eyes in the early and late initial treatment groups presented with perfused CRVO at baseline in 28% and 64% of cases, respectively. The time course of neovascular events in eyes receiving early versus late

**Table 2. Treatment course, neovascular events and subsequent management of eyes undergoing serial intravitreal anti-VEGF injections for macular edema CRVO**

	(%)
Mean onset of CRVO prior to neovascular event (months, SD)	17.0 (10.3)
Mean duration treatment free until first neovascular event (months, SD)	6.2 (7.3)
Mean onset of CRVO prior to initial presentation (months, SD)	3.0 (3.6)
Mean onset of CRVO prior to 1 <sup>st</sup> anti-VEGF treatment (months, SD)	3.8 (4.0)
Mean duration between 1 <sup>st</sup> anti-VEGF and neovascular event (months, SD)	13.2 (9.7)
Mean number of injections until 1 <sup>st</sup> neovascular event (injections, SD)	5.3 (3.2)
Neovascular event (number of eyes, percentage)	
Disc neovascularization	5 (16)
Iris/angle neovascularization/neovascular glaucoma	18 (58)
Vitreous hemorrhage associated with neovascularization	9 (29)
Management of neovascular event (number of eyes, percentage)	
Panretinal photocoagulation	31 (100)
Glaucoma surgery	6 (19)
Anti-VEGF injection	22 (71)
Best corrected visual acuity outcomes	
Mean baseline visual acuity (snellen equivalent)	20/502
Mean final visual acuity (snellen equivalent)	20/2581
Number of eyes with final acuity worse than 20/400 (number of eyes, percentage)	20 (74)
Number of eyes with final acuity=No light perception (number of eyes, percentage)	5 (16)

SD, standard deviation; CRVO, central retinal vein occlusion; VEGF, vascular endothelial growth factor

initial treatment was not different (log rank  $P=0.18$ ) [Figure 3].

Eyes undergoing continuous anti-VEGF treatment (mean treatment interval of 1-month $\pm$ 2 weeks) experienced a neovascular event on average at 12.1 $\pm$ 6.3 months as compared to 18.5 $\pm$ 10.9 months in eyes undergoing discontinuous treatment (mean treatment interval greater than 1.5 months). Eyes in the continuous and discontinuous treatment groups received anti-VEGF injections at 1.3 $\pm$ 0.1 and 3.2 $\pm$ 1.6 months intervals, respectively. Eyes in the continuous and discontinuous treatment group presented with perfused CRVO at baseline in 14% and 46% of cases, respectively. The time course of neovascular events in eyes undergoing discontinuous treatment for CRVO was not different from eyes undergoing continuous treatment (log rank  $P=0.14$ ) [Figure 4].

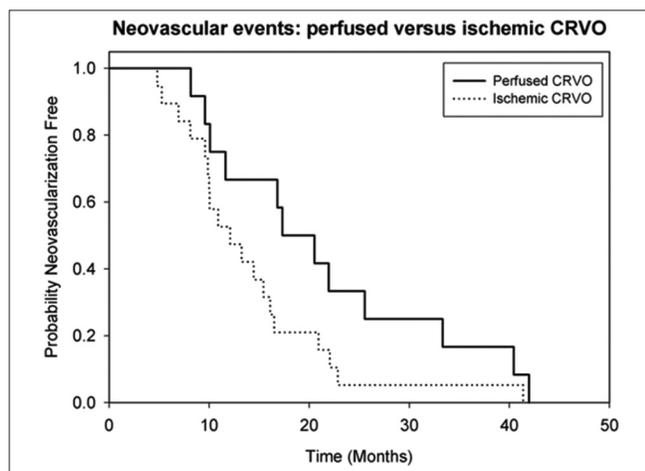
## DISCUSSION

Serial anti-VEGF therapy for CME secondary to CRVO reduces the frequency of neovascular events when compared to natural history of CRVO-associated neovascularization.<sup>[2,3,10,16,17]</sup> Several series report neovascularization rates between 14% and 50% for untreated CRVO,<sup>[1-3]</sup> compared to the rates between 0–4% reported for eyes with CRVO undergoing serial anti-VEGF therapy.<sup>[10,17]</sup> In the present study, we noted that neovascular events occurred on average at 17.0 months after CRVO onset, and this time interval was much longer than the approximately 6 months duration reported between CRVO onset and neovascular events described previously in CRVO natural history studies.<sup>[2,3]</sup> Serial anti-VEGF therapy for CME secondary to CRVO may delay, rather than completely eliminate neovascular

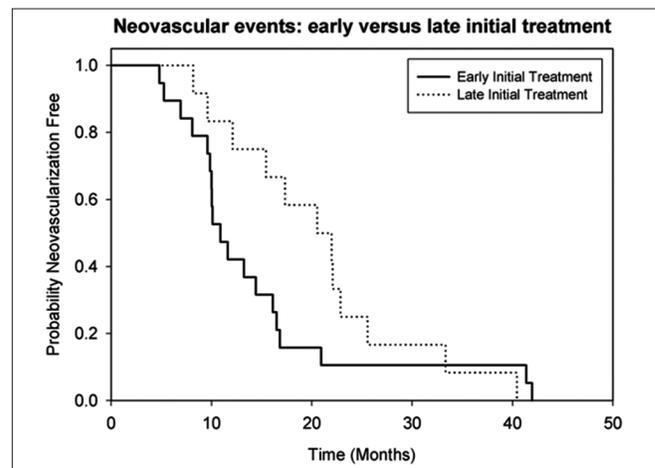
events as compared to the natural history of CRVO-associated neovascularization.

Some debate exists regarding the time course of neovascular events after the onset of a vein occlusion. In the CVOS, iris or angle neovascularization occurred in the vast majority of eyes within 6 months of study enrollment. Iris or angle neovascularization developed in 117 (16%) of the 714 eyes during a follow up period as long as 56 months in some patients in the CVOS. Despite the impressive sample size and lengthy follow up, extrapolating the time course of neovascular events from the CVOS is not without limitations. In particular, the natural history cohort from the CVOS consisted of eyes with CRVO of varying duration aggregated together. Specifically, the CVOS pooled 714 eyes enrolled within 1-year of CRVO onset, of which 187 eyes were included within 1-month of CRVO onset.<sup>[2]</sup> While the CVOS reported the onset of a subset of neovascular events from trial initiation, the CVOS did not additionally report the mean time interval between CRVO onset and first neovascular event.<sup>[20]</sup> Reporting this interval would facilitate more meaningful comparison to other studies.

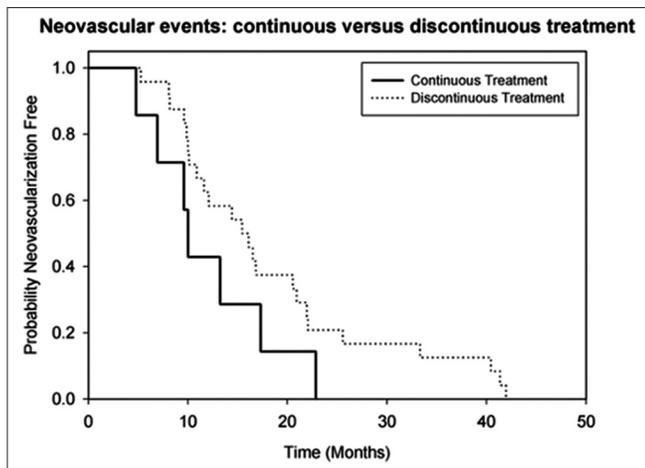
However, data from more recent studies similarly does not completely elucidate the natural history time course between CRVO onset and neovascular event. Direct comparison among these studies is difficult due to differences in sample size, composition of patient population, and follow-up duration. Moreover, the methodology for stratifying perfused versus ischemic CRVO varied widely from study to study yielding inconsistent results. For example, in a meta-analysis of 18 studies, numbers ranged widely regarding the incidence and time course of CRVO. In one study where perfusion status of CRVO was not defined, the incidence



**Figure 2.** Comparison of time to any neovascular event between eyes with perfused central retinal vein occlusion (CRVO) at baseline versus ischemic CRVO at baseline. All eyes were receiving serial anti-vascular endothelial growth factor therapy (log rank  $P=0.07$ ).



**Figure 3.** Comparison of time to any neovascular event between eyes undergoing early initial anti-vascular endothelial growth factor (VEGF) treatment (within 3 months of central retinal vein occlusion (CRVO) onset) for macular edema secondary to CRVO versus eyes undergoing late initial anti-VEGF treatment (3 months or more after CRVO onset) (log rank  $P=0.18$ ).



**Figure 4.** Comparison of time to any neovascular event between eyes undergoing continuous anti-vascular endothelial growth factor (VEGF) treatment (treatment interval of 1-month $\pm$ 2 weeks) for macular edema secondary to central retinal vein occlusion versus eyes undergoing discontinuous anti-VEGF treatment (treatment interval >1.5 months) (log rank  $P=0.14$ ).

of neovascular events was reported as high as 50% at 6 months. In contrast, for another series describing ischemic CRVO only, the incidence of neovascularization was much less frequent, reported as less than 20% after 8–9 months.<sup>[1]</sup>

A recent series of 239 eyes with ischemic CRVO prospectively followed for a mean of 36.2 months is very helpful in better delineating the natural history of neovascular events in eyes with CRVO. This study stratified neovascular events into iris neovascularization, angle neovascularization, neovascular glaucoma, disc neovascularization, and neovascularization elsewhere. This work did not specifically reports rates of vitreous hemorrhage. In all types of anterior segment neovascularization, the vast majority of eyes (74–78%) that would go on to develop a particular type of anterior segment neovascularization did so by 6 months. Posterior pole neovascularization occurred in the majority of eyes in this series at more delayed intervals, around 9 months for disc neovascularization and 18 months for neovascularization elsewhere. Also, this series followed 673 eyes with perfused CRVO at baseline and noted only nine cases with any neovascular event over a mean follow up of 18.5 months. Of note, this series rigorously differentiated ischemic from perfused CRVO using six tests including relative afferent pupillary defect, Goldmann visual fields, electroretinography, and fluorescein angiography.<sup>[3]</sup>

The present study differentiated perfused versus ischemic CRVO using fluorescein angiography. Our subgroup analysis suggested that neovascular events in eyes with perfused CRVO at baseline undergoing serial anti-VEGF therapy may occur later than their counterparts with ischemic CRVO at baseline. It is

reasonable to conclude that this potential delay in onset of neovascularization may in part be due to the time required for conversion from perfused to ischemic CRVO in some eyes, as eyes with perfused CRVO typically do not develop neovascularization. Subsequent fluorescein angiography, however, was not performed to verify conversion to ischemic CRVO in the present study. Also, serial fluorescein angiography would be helpful in assessing whether repeated anti-VEGF treatment actually delays conversion from perfused to ischemic CRVO. Since high levels of VEGF exacerbate capillary nonperfusion,<sup>[18]</sup> it is possible that serial VEGF inhibition may postpone ischemic progression. For comparison, the CVOS natural history cohort reported that 15% and 34% of eyes with perfused CRVO at baseline converted to ischemic CRVO at 4 months and 36 months respectively.

Early compared to late initial anti-VEGF treatment did not demonstrate a differential effect on the onset of neovascular events. Since neovascular events in eyes with CRVO may be protracted for months to years after initiation of anti-VEGF therapy, it may be that starting anti-VEGF therapy within 3 months of CRVO onset does not substantially alter the temporal course of neovascular complications when compared to later initiation of therapy. Another reason that any difference in the temporal course of neovascular events was not detected may be due to the increased proportion of eyes with perfused CRVO at baseline receiving late initial treatment compared to early treatment (64% vs. 28%). This imbalance in perfusion status may have masked the effect of earlier treatment initiation.

The onset of neovascular events in eyes undergoing continuous therapy was not different from eyes undergoing discontinuous therapy. Interestingly, the mean onset of neovascular events in eyes undergoing discontinuous anti-VEGF therapy occurred later than eyes undergoing continuous therapy. This is counterintuitive as one would expect more frequent anti-VEGF administration to delay neovascularization by inhibiting the effect of VEGF on neovascular progression as well as ameliorating VEGF exacerbated capillary nonperfusion as mentioned previously. This may be in part due to lack of balance in baseline factors between the two subgroups, in particular the increased number of eyes with perfused CRVO at baseline in the discontinuous group compared to the continuous group (46% vs. 14%). Again, this imbalance in perfusion status may have masked the effect of continuous treatment.

Another consideration is this stratification of therapy into continuous and discontinuous groups may have identified two discrete neovascular responses to serial anti-VEGF for macular edema secondary to CRVO that the present study was underpowered to differentiate. One subset of CRVO eyes may have had more severe disease. These eyes may develop “breakthrough” neovascularization despite approximately monthly

serial anti-VEGF injections as noted during the CRUISE study and within our continuous subgroup. This breakthrough neovascularization subtype may suggest more aggressive progression of ischemia in addition to more ischemia at baseline and possibly an increased propensity towards neovascular events. One possible mechanism for breakthrough neovascularization may be higher levels of intraocular VEGF when compared to other CRVO eyes that develop neovascularization at more protracted treatment intervals. Other systemic vascular factors could also increase the propensity towards ischemic progression such as poor blood pressure control, severe dyslipidemia, or increased pack years of smoking. In contrast, another subgroup of CRVO eyes may not develop neovascularization during continuous treatment, but may develop neovascularization in a more indolent fashion due to less ischemia at baseline and slower ischemic progression as treatment intervals extend due to a variety of reasons such as physician discretion, patient fatigue, or loss to follow up. The slower ischemic progression may be due to relatively lower levels of ocular VEGF than CRVO eyes with breakthrough neovascularization, as well as better control of vascular systemic risk factors.

Several prospective trials such as CRUISE,<sup>[10]</sup> COPERNICUS,<sup>[17]</sup> and others<sup>[16]</sup> demonstrate the benefit of continuous serial anti-VEGF dosing once monthly for at least 6 months to treat CRVO-related macular edema. In the present study, eyes received injections on average every 2.7 months prior to demonstrating a neovascular event. Furthermore, in the present series, a lengthy average treatment free interval of 6.2 months was noted prior to the onset of any neovascular event. Though, for these reasons, the data from the present study cannot be directly compared to the pivotal phase III trials of anti-VEGF for macular edema associated with CRVO, our data well represents a snapshot of clinical realities for managing eyes with a chronic retinal vascular disease over multi-year durations.<sup>[18]</sup> In day to day clinical practice, clinicians not infrequently treat eyes with ischemic CRVO, attempt to manage patient fatigue by extending treatment interval, and respond to a certain proportion of patients being lost to follow up.

It is also important to recall that neovascular events can occur despite ongoing serial monthly anti-VEGF therapy. This is not surprising as three eyes in the CRUISE treatment group receiving serial monthly intravitreal ranibizumab injections still developed iris neovascularization. This is particularly remarkable as the CRUISE trial sought to exclude eyes with baseline ischemic CRVO by screening for a relative afferent pupillary defect in addition to more standard fluorescein angiographic-based criteria.<sup>[10]</sup> Interestingly, in the COPERNICUS trial, none of the 114 eyes treated with intravitreal aflibercept developed any neovascularization at 12 months of follow up. It is unknown whether

theoretical differences in the binding affinity of aflibercept relative to ranibizumab or bevacizumab<sup>[21]</sup> may decrease the incidence of or delay onset of neovascular events. Perhaps most noteworthy, it is important for the clinician to be mindful that neovascular events can still occur during serial anti-VEGF treatment as no intravitreal anti-VEGF agent addresses the underlying pathobiology of CRVO, i.e. venous stasis due to occlusion.

In eyes experiencing neovascular events from CRVO despite serial anti-VEGF therapy, the visual outcome is guarded. Over the duration of follow-up, patients demonstrated a profound visual decline in the affected eye from a mean baseline acuity of 20/502 to final mean acuity of 20/2518 over a mean follow up of 27.9 months. While poor visual outcomes are more common in eyes with baseline ischemic CRVO and worse visual acuity,<sup>[22]</sup> our series included nearly 40% perfused CRVO at baseline. When counseling patients with breakthrough neovascular events, it may be appropriate to emphasize a guarded visual prognosis despite aggressive intervention with panretinal photocoagulation, glaucoma surgery, or subsequent anti-VEGF injection. It is interesting that some studies suggest the utility of anti-VEGF for treatment of neovascular events secondary to CRVO. However laser treatment remains the standard of care for these events.<sup>[23-25]</sup>

These data must be interpreted in the context of several limitations. This work is a retrospective, multicenter study that did not include a sham group for direct comparison to natural history. Likewise, due to lack of randomization, the subgroups analyzed were not completely balanced as detailed above. Next, onset of CRVO symptoms was based on patient self-reporting, which potentially reduces accuracy. Finally, the serial anti-VEGF regimen did not follow a strict algorithm, but instead was based on the aggregated clinical practices of nearly two dozen retina specialists over a duration of 7 years. Despite these limitations, this series remains one of the largest to characterize neovascular events that have occurred in the context of serial anti-VEGF treatments for macular edema secondary to CRVO, and one of the first to investigate the differential effects of baseline perfusion status, time to initial treatment, and treatment interval with respect to these neovascular events.

Neovascular events occur in eyes undergoing serial anti-VEGF therapy, and these events may be delayed compared to the natural history of CRVO-associated neovascularization. Iris or angle neovascularization occurred most frequently. Neovascular events may occur later in eyes with perfused CRVO at baseline, and poor visual acuity outcomes were associated with neovascular events in the context of serial anti-VEGF therapy. Our data suggests that clinicians should be vigilant for the onset of neovascular events even months to years after initiation of anti-VEGF therapy for CME secondary to CRVO.

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