Loss of Peak Vision in Retinal Vein Occlusion Patients Treated for Macular Edema

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• PURPOSE: To evaluate long-term visual and anatomic outcomes in patients with retinal vein occlusion (RVO) treated with anti–vascular endothelial growth factor (VEGF) agents.
• DESIGN: Prospective, interventional case series.
• PARTICIPANTS: Patients with central RVO (CRVO) or branch RVO (BRVO).
• METHODS: Number of anti-VEGF injections and improvement from baseline best-corrected visual acuity (BCVA) and central subfield thickness (CST) were prospectively recorded in 40 eyes of 39 CRVO patients and 50 eyes of 47 BRVO patients.
• RESULTS: Mean follow-up was 58 months for BRVO and 78 months for CRVO. Within 6 months of last follow-up, 58% of BRVO patients and 75% of CRVO patients required anti-VEGF injections to control edema. Analysis of the course of each patient over time showed that for BRVO patients, BCVA letter score increased by a mean of 24, from baseline of 52 (20/100) to peak of 76 (20/32), and subsequently decreased by 13, to 63 (20/50), at final visit; and for CRVO patients, BCVA letter score increased by a mean of 26, from baseline of 48 (20/100) to peak of 74 (20/32), and subsequently decreased by 18, to 56 (20/80), at last follow-up. Loss from peak BCVA occurred primarily owing to persistent/recurrent edema and related foveal damage.
• CONCLUSIONS: Patients with RVO showed large improvements in BCVA after initiation of anti-VEGF injections, but in many patients some visual gains were lost over time owing to bouts of recurrent edema. Sustained suppression of VEGF may help to provide optimal outcomes in RVO and reduce treatment burden. (Am J Ophthalmol 2019;205:17–26. © 2019 Elsevier Inc. All rights reserved.)

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IN PATIENTS WITH CENTRAL RETINAL VEIN OCCLUSION (CRVO), thrombosis in the main outflow vessel of the retina results in a marked increase in resistance within the retinal circulation, compromising perfusion and leading to closure of retinal vessels. The amount of capillary closure that occurs early in the course varies among patients and likely depends upon the amount of pre-existent atherosclerosis in retinal arterioles. The reduced perfusion causes retinal ischemia and upregulation of hypoxia-regulated factors including vascular endothelial growth factor (VEGF). Leakage from retinal vessels causes macular edema, which decreases vision. Branch retinal vein occlusion (BRVO) occurs from thrombosis in a tributary of the central retinal vein, decreasing perfusion to less than half of the retina, resulting in similar, but on average less severe, consequences as those associated with CRVO.

A pilot trial testing ranibizumab, an anti-VEGF antigen-binding fragment, demonstrated that VEGF played a major role in the development of macular edema in patients with CRVO or BRVO.[1] This led to large multicenter trials that showed that monthly injections of ranibizumab improved macular edema and vision in patients with CRVO or BRVO[2,3] and also caused more rapid resolution of retinal hemorrhages,[4,5] slowed progression of retinal nonperfusion, and even caused improvement in retinal nonperfusion.[6] Studies using other anti-VEGF neutralizing proteins have confirmed the marked benefit of frequent anti-VEGF injections in retinal vein occlusions (RVO).[7–10]

Thrombotic occlusions elsewhere in the body may be compensated over time by lumen recanalization and collateral vessel formation, and it was thought that these same phenomena could provide resolution of retinal vein occlusions with good outcomes if edema and retinal nonperfusion were controlled by VEGF suppression during the acute phase of the disease. However, after 4 years of treatment, 54% of CRVO patients and 46% of BRVO patients still required anti-VEGF injections to control edema within 6 months of last follow-up.[11] In this study, we report additional follow-up and detailed analysis of best-corrected visual acuity (BCVA) over time for patients with CRVO and BRVO who participated in 1 or more of several clinical trials and subsequently received standard clinical care.

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METHODS

THE CONTINUING ASSESSMENT OF PATIENTS TREATED WITH ranibizUmab for REtinal Vein Occlusion (CAPTURE) Study (NCT01875770) was an observational study approved by the Johns Hopkins University Internal Review Board designed to assess the long-term outcomes of patients with CRVO or BRVO who had participated in RVO clinical trials (Appendix; Supplemental Material available at AJO.com), including: (1) A Pilot, Open-Label Study of the Safety, Tolerability, and Bioactivity of Multiple Intravitreal Injections of Ranibizumab in Subjects with Macular Edema Secondary to Vein Occlusions,[1,12] (2) A Study of the Efficacy and Safety of Ranibizumab Injection in Patients with Macular Edema Secondary to Central Retinal Vein Occlusion (CRUISE),[3,4] (3) A Study of the Efficacy and Safety of Ranibizumab Injection in Patients with Macular Edema Secondary to Branch Retinal Vein Occlusion (BRAVO),[2] (4) Extended Follow-up of Patients with Macular Edema Due to Retinal Vein Occlusion (HORIZON),[13] (5) Extended follow-up of patients with macular edema due to bRanch rETinal vein occlusion or centrAl retinal veIn occlusioN previously treated with intravitreal ranibizumab (RETAIN),[11] or (6) Ranibizumab DosE Comparison (0.5 mg and 2.0 mg) and the Role of LAser in the ManagemenT of REtinal Vein Occlusion - A Pharmacodynamic Approach (RELATE).[14] At completion of 1 of the above trials, patients were encouraged to enroll in CAPTURE to obtain prospective long-term follow-up by measuring BCVA using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol and assessing all clinical and imaging data whenever they returned for clinical care.

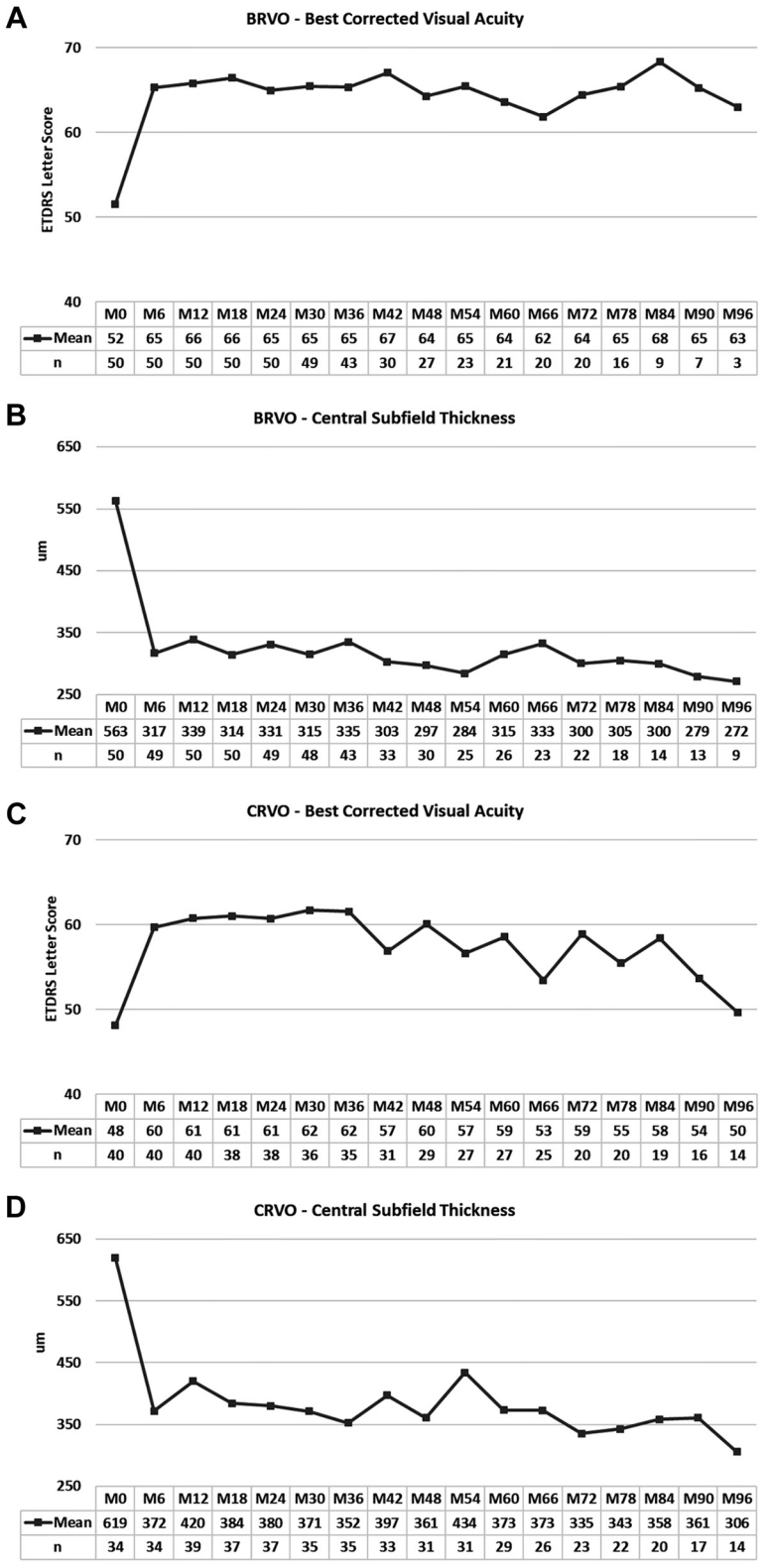
Visual outcome was categorized as good (≥20/40 Snellen equivalent), intermediate (<20/40 to ≥20/100), or poor (<20/100). Response to anti-VEGF treatment was categorized as good (minimal intraretinal or subretinal fluid in the macula with monthly or less frequent injections), suboptimal (moderate persistent/recurrent intraretinal or subretinal fluid in the macula despite monthly injections), or poor (severe persistent/recurrent intraretinal or subretinal fluid in the macula despite monthly injections). Resolution of edema was defined as no intraretinal or subretinal fluid in the macula for at least 6 months after the last anti-VEGF injection. The potential benefit of sustained VEGF suppression was judged based on high treatment burden, defined as (1) requiring 10 or more injections during the first year of treatment or (2) requiring regular injections for 2 or more years; and/or treatment fatigue, defined as (1) early termination from a study or loss to follow-up after study completion despite persistent disease or (2) poor follow-up, characterized by prolonged intervals between visits (owing to missed or rescheduled visits) despite persistent disease and frequent recurrences.

The primary outcome was change in BCVA from baseline (the first visit that the patient received an anti-VEGF injection) over time. Secondary outcomes included change in central subfield thickness (CST) from baseline over time, change from peak BCVA to that at the most recent follow-up visit and determination of the reason for that change, response to anti-VEGF treatment, resolution of edema, mean number of injections per year, evidence of treatment fatigue, and the potential role of sustained suppression of VEGF. The study was conducted in accordance with the Declaration of Helsinki.

RESULTS

OF 150 PATIENTS WITH CRVO OR BRVO WHO HAD PARTICIpated in single-center or multicenter interventional trials for RVO at the Wilmer Eye Institute, 90 patients (50 BRVO and 40 CRVO) participated in CAPTURE, in which they received standard care, but had measurement of BCVA using the ETDRS protocol at multiple clinic visits per year. Standard care consisted of a pro re nata regimen initially, but over time many patients transitioned to a treat-and-extend regimen. All imaging and treatment data were available for analysis.

• **CHANGE IN BEST-CORRECTED VISUAL ACUITY OVER TIME IN PATIENTS WITH BRANCH RETINAL VEIN OCCLUSION:** In patients with BRVO (n = 50), the mean duration of follow-up was 58 months, which includes time in 1 or more interventional trials and prospective follow-up while receiving standard care. The mean BCVA letter score at baseline was 52 (20/100 Snellen equivalent) and there was a mean improvement of 13 letters between baseline and month 6 that was maintained through month 36, when only 5 patients were lost to follow-up (Figure 1A). There was gradual attrition of patients after month 36, but through month 48 when more than half of the patients remained, mean BCVA was stable. The rapid improvement and subsequent stability in mean BCVA was accompanied by a rapid reduction in mean CST, from 563 μm at baseline to 317 μm at month 6, with little change thereafter (Figure 1B). These data suggest that patients with BRVO treated with anti-VEGF injections improved and remained stable thereafter; however, detailed analysis of BCVA over time for each patient showed that this was not the case (Table 1). Instead, patients often showed remarkably large improvements to excellent peak BCVA, followed by decline to final BCVA better than baseline, but substantially worse than peak BCVA. Mean BCVA letter score increased by 24, from a baseline of 52 (20/100) to a peak of 76 (20/32), and subsequently decreased by 13, to 63 letters (20/50) at last BCVA measurement. This remarkable swing in BCVA is not apparent from examination of the mean BCVA over time because the gains and losses of vision occur at different times in different patients, giving the impression of stable vision for the group as a whole.



	M0	M6	M12	M18	M24	M30	M36	M42	M48	M54	M60	M66	M72	M78	M84	M90	M96
Mean	52	65	66	66	65	65	65	67	64	65	64	62	64	65	68	65	63
n	50	50	50	50	50	49	43	30	27	23	21	20	20	16	9	7	3

	M0	M6	M12	M18	M24	M30	M36	M42	M48	M54	M60	M66	M72	M78	M84	M90	M96
Mean	563	317	339	314	331	315	335	303	297	284	315	333	300	305	300	279	272
n	50	49	50	50	49	48	43	33	30	25	26	23	22	18	14	13	9

	M0	M6	M12	M18	M24	M30	M36	M42	M48	M54	M60	M66	M72	M78	M84	M90	M96
Mean	48	60	61	61	61	62	62	57	60	57	59	53	59	55	58	54	50
n	40	40	40	38	38	36	35	31	29	27	27	25	20	20	19	16	14

	M0	M6	M12	M18	M24	M30	M36	M42	M48	M54	M60	M66	M72	M78	M84	M90	M96
Mean	619	372	420	384	380	371	352	397	361	434	373	373	335	343	358	361	306
n	34	34	39	37	37	35	35	33	31	31	29	26	23	22	20	17	14

FIGURE 1. Visual and anatomic outcomes in patients with retinal vein occlusion treated with intravitreous injections of agents that block vascular endothelial growth factor. (A) Mean best-corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Study (ETDRS) protocol letter score is plotted at 6-month intervals from first entry into a clinical trial for branch retinal vein occlusion (BRVO). (B) Mean central subfield thickness (CST) is plotted at 6-month intervals from first entry into a clinical trial for BRVO. (C) Mean BCVA is plotted at 6-month intervals from first entry into a clinical trial for central retinal vein occlusion (CRVO). (D) Mean central subfield thickness (CST) is plotted at 6-month intervals from first entry into a clinical trial for CRVO patients.

TABLE 1. Visual Outcomes of Patients With Retinal Vein Occlusion Treated With Intravitreal Anti–Vascular Endothelial Growth Factor

	BRVO Patients (N = 50)	CRVO Patients (N = 40)
Mean baseline BCVA	52 letters (20/100)	48 letters (20/100)
Mean peak BCVA	76 letters (20/32)	74 letters (20/32)
Mean final BCVA	63 letters (20/50)	56 letters (20/80)
Mean BCVA loss (peak – final)	13 letters	22 letters

BCVA = best-corrected visual acuity; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion.

Ten patients with BRVO (20%) lost <5 letters from peak BCVA, 20 (40%) lost between 5 and 9 letters, 10 (20%) lost between 10 and 14 letters, and 10 (20%) lost ≥15 letters (Table 2).

• **CHANGE IN BEST-CORRECTED VISUAL ACUITY OVER TIME IN PATIENTS WITH CENTRAL RETINAL VEIN OCCLUSION:** In patients with CRVO (n = 40), the mean duration of prospective follow-up was 78 months. The mean BCVA letter score at baseline was 48 (20/100), improved 12 letters between baseline and month 6, and was maintained through month 36, when only 5 patients (13%) were lost to follow-up (Figure 1C). With follow-up for 73% of patients through month 48 and 50% through month 72, there was mean improvement of 12 and 11 letters from baseline BCVA, respectively. There was a large reduction in mean CST, from 619 μm at baseline to 372 μm at month 6; but unlike the situation in the BRVO group, in which mean CST was ≤350 μm at all time points after baseline, in the CRVO group mean CST was in the 350-450 μm range between months 6 and 66, indicating that on average, there was relatively more persistent edema (Figure 1D). These aggregate data for CRVO, like those for BRVO, give the impression of improvement followed by relative stability. However, detailed analysis of BCVA over time for each patient painted a different picture. Mean BCVA letter score increased by 26, from a baseline of 48 (20/100) to a peak of 74 (20/32), and subsequently decreased by 18, to 56 (20/80) at last BCVA measurement (Table 1). Thus, the swing in BCVA was even more dramatic for the CRVO group than the BRVO group, because while the increase from baseline to peak vision was similar (approximately 5 lines), the reduction from peak vision was larger. Eight patients with CRVO (20%) lost <5 letters from peak BCVA at last follow-up, 9 (23%) lost between 5 and 9 letters, 6 (15%) lost between 10 and 14 letters, and 17 (43%) lost ≥15 letters (Table 2).

• **CHANGE IN BEST-CORRECTED VISUAL ACUITY OVER TIME AS A FUNCTION OF VISUAL OUTCOME:** To further assess the relationship between peak BCVA and final BCVA, patients were divided into those with good (≥20/40 Snellen equivalent), intermediate (<20/40 to ≥20/100), or poor (<20/100) BCVA outcomes. Patients with BRVO who had a good outcome showed a very large improvement from baseline to peak BCVA, followed by a substantially smaller reduction to final BCVA (Figure 2A). Mean baseline, peak, and final BCVA letter score was 60, 86, and 80, respectively. Patients with intermediate outcomes showed a similar pattern, but the range of baseline BCVA measures were lower, with many more patients <40 letters, and the decline between peak and final BCVA tended to be larger (Figure 2B). Mean baseline, peak, and final BCVA score was 48, 72, and 61, respectively. Patients with poor outcomes showed a different pattern, because while many patients showed a substantial improvement from baseline to peak BCVA, most showed a greater reduction between peak and final BCVA than their initial rise (Figure 2C). Mean baseline, peak, and final BCVA score was 39, 61, and 27, respectively.

Results were very similar in patients with CRVO. Patients with good outcome showed a very large improvement from baseline to peak BCVA, followed by a substantially smaller reduction to final BCVA (Figure 2D). Mean baseline, peak, and final BCVA letter score was 56, 85, and 80, respectively. Patients with intermediate outcomes had a wider range of baseline BCVA measurements and showed a similar pattern, but the decline between peak and final BCVA tended to be larger (Figure 2E). Mean baseline, peak, and final BCVA score was 45, 75, and 62, respectively. Patients with poor outcomes showed a different pattern, with many patients showing a substantial improvement from baseline to peak BCVA, but almost all showing a greater reduction between peak and final BCVA than their initial rise (Figure 2F). Mean baseline, peak, and final BCVA score was 42, 61, and 22, respectively. Thus, patients with BRVO or CRVO who have a poor visual outcome provide the largest contribution to the reduction in BCVA from peak levels seen in the entire groups, but the phenomenon of initial BCVA improvement followed by loss of some of that gain is universal, with the magnitude of the loss an important determinant of final visual outcome.

Baseline BCVA is positively associated with final visual outcome in interventional trials for RVO. We sought to determine if there was any association between baseline BCVA and peak vision and likelihood or magnitude of loss of BCVA from peak level. There was good correlation between baseline and peak BCVA (BRVO: $r = 0.636$; $P < .001$ and CRVO: $r = 0.541$; $P < .001$) and peak and final BCVA (BRVO: $r = 0.833$; $P < .001$ and CRVO: $r = 0.874$; $P < .001$, Figure 3).

• **RESPONSE TO ANTI–VASCULAR ENDOTHELIAL GROWTH FACTOR INJECTIONS:** Patients were categorized with regard to their response to anti-VEGF treatment based on the amount of residual edema while receiving monthly injections: (1) good if they had no or minimal edema; (2)

TABLE 2. Characteristics of Patients With Retinal Vein Occlusion Treated With Intravitreal Anti–Vascular Endothelial Growth Factor

	Letters Lost From Peak BCVA							
	BRVO Patients (N = 50)				CRVO Patients (N = 40)			
	<5	5-9	10-14	≥15	<5	5-9	10-14	≥15
Patients who lost letters from peak BCVA, n (%)	10 (20%)	20 (40%)	10 (20%)	10 (20%)	8 (20%)	9 (23%)	6 (15%)	17 (43%)
Mean total injections	26	23	20	26	25	22	38	37
Mean injections per year	3.5	4.2	3.6	5.0	4.2	4.1	5.5	4.2
Response to anti-VEGF								
Good	9 (90%)	19 (95%)	8 (80%)	9 (90%)	8 (100%)	9 (100%)	5 (83%)	12 (71%)
Suboptimal	1 (10%)	0 (0%)	1 (10%)	1 (10%)	0 (0%)	0 (0%)	1 (17%)	2 (12%)
Poor	0 (0%)	1 (5%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (18%)
Mechanism of vision loss								
Persistent/recurrent edema								
- Sole cause			3 (30%)	3 (30%)			0 (0%)	7 (41%)
- Partial cause			1 (10%)	1 (10%)			1 (17%)	1 (6%)
Atrophy								
- Chronic recurrent edema			0 (0%)	1 (10%)			2 (33%)	5 (29%)
- Progressive nonperfusion			0(0%)	1 (10%)			0 (0%)	1 (6%)
Other[a]			6 (60%)	4 (40%)			3 (50%)	3 (18%)

BCVA = best-corrected visual acuity; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; VEGF = vascular endothelial growth factor.

[a]Includes cataract, corneal disease, etc.

suboptimal if they had moderate reduction from baseline levels, but still had substantial edema; or (3) poor if they had minimal reduction from baseline levels. Using these criteria, a good response to anti-VEGF injections was seen in 45 (90%) patients with BRVO and 34 (85%) patients with CRVO (Table 2). A poor response was seen in only 2 patients with BRVO and 3 patients with CRVO.

• **MEAN NUMBER OF ANTI–VASCULAR ENDOTHELIAL GROWTH FACTOR INJECTIONS OVER TIME:** Within 6 months of last follow-up, 58% of BRVO patients and 75% of CRVO patients required anti-VEGF injections to control edema. The mean number of anti-VEGF injections received by BRVO patients was 23.3, for a rate of 4.1 per year, and the mean total number received by CRVO patients was 31.6, for a rate of 4.4 per year (Table 3). For BRVO patients the number of injections per year decreased from 8 in year 1 to 2 in year 4 and remained at that level through year 6, when 72% of patients still remained in the study (Figure 4). For CRVO patients, the number of injections per year decreased from 9 in year 1 to 3 in year 6, when 78% of patients remained. While approximately 80% of BRVO and CRVO patients tolerated this prolonged need for injections well, 20% may have exhibited treatment fatigue, as suggested by early termination or poor follow-up (Table 3). Based on treatment fatigue or high treatment burden, it was judged that 86% of patients with BRVO and 80% of patients with CRVO would benefit from a treatment that provided sustained suppression of VEGF for long duration (Table 3).

• **MECHANISMS BY WHICH PEAK VISION WAS LOST:** It is important to know why patients fail to maintain peak BCVA. In order to investigate this issue, every spectral-domain optical coherence tomography image of each patient was evaluated and the reason for loss was assessed in patients with loss ≥10 letters (because a loss ≥10 letters is unlikely to be due to chance) (Table 2). In 6 patients with BRVO and 7 with CRVO, the loss of peak vision could be attributed to persistent/recurrent edema at 1 or all of the last 3 visits that was greater than the amount of edema at time of peak vision and appeared consistent with the magnitude of BCVA reduction (Table 2, Supplemental Figures 1-5; Supplemental Material available at AJO.com). The mean change in CST from time of peak BCVA to time of final BCVA in these patients was +243 μm (range: 63-621 μm) and the mean number of anti-VEGF injections was 39 during mean follow-up of 76 months, with a mean of 3.7 injections during the last year of follow-up. Four patients (2 BRVO and 2 CRVO) had persistent/recurrent edema that did not fully account for their loss of peak vision and were felt to have a component of permanent vision loss from edema-related foveal photoreceptor disruption seen on spectral-domain optical coherence tomography (Supplemental Figures 6 and 7; Supplemental Material available at AJO.com). Loss of

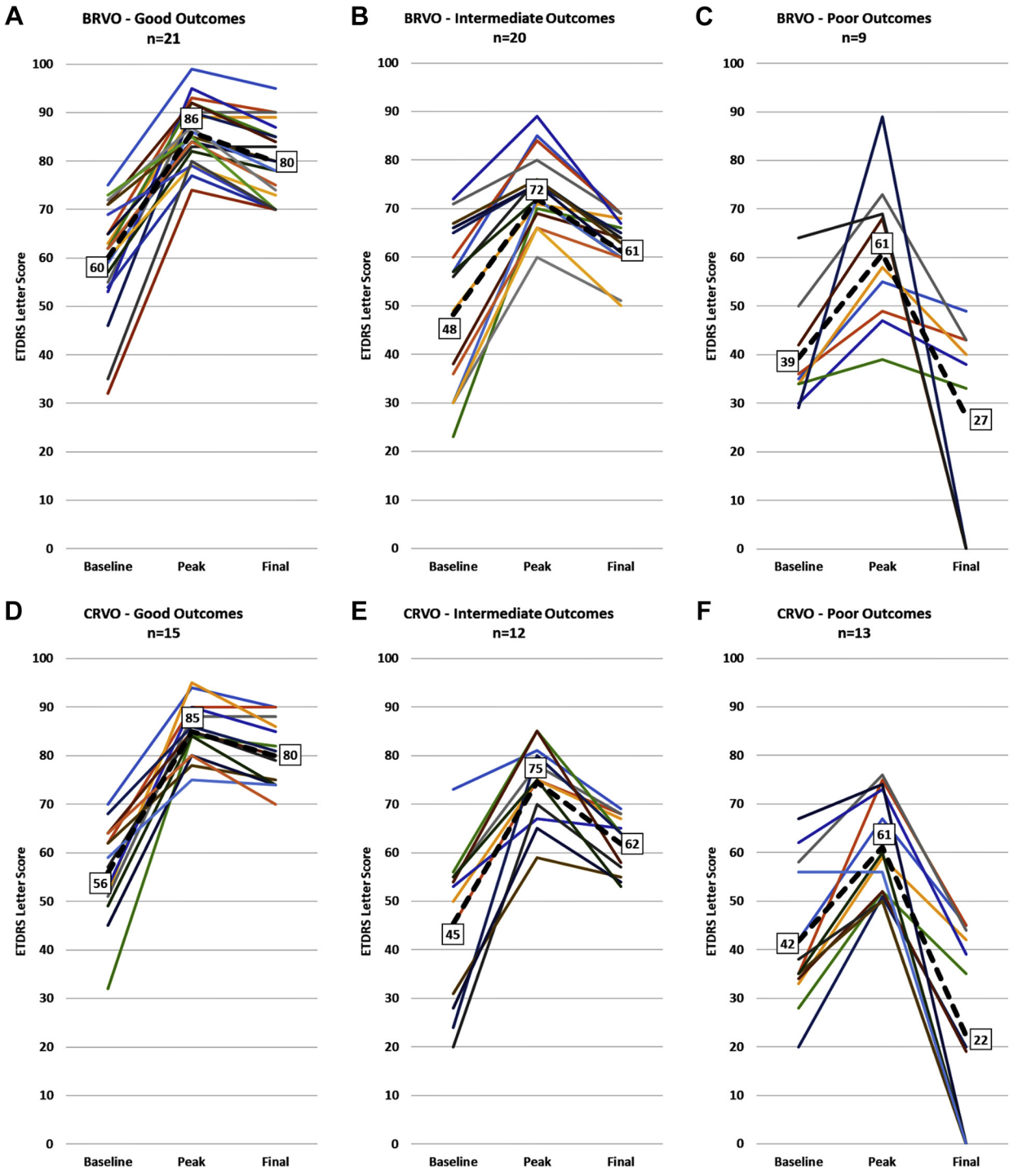


FIGURE 2. Plots of baseline, peak, and final best-corrected visual acuity (BCVA) in patients with retinal vein occlusion (RVO) treated with intravitreous injections of agents that block vascular endothelial growth factor. Baseline, peak, and final BCVA in Early Treatment Diabetic Retinopathy Study (ETDRS) letter score was plotted for each patient with (A-C) branch RVO (BRVO) or (D,E,F) central RVO (CRVO), with final BCVA in Snellen equivalent ≥20/40 (A and D), <20/40 to ≥20/100 (B and E), or <20/100 (C and F).

peak vision was judged to be due to foveal damage with no residual edema in 2 BRVO and 8 CRVO patients (Supplemental Figure 8; Supplemental Material available at AJO.com). In 8 of these 10 patients, drops in BCVA that never recovered coincided with 1 or more periods of persistent/recurrent edema, suggesting that foveal damage

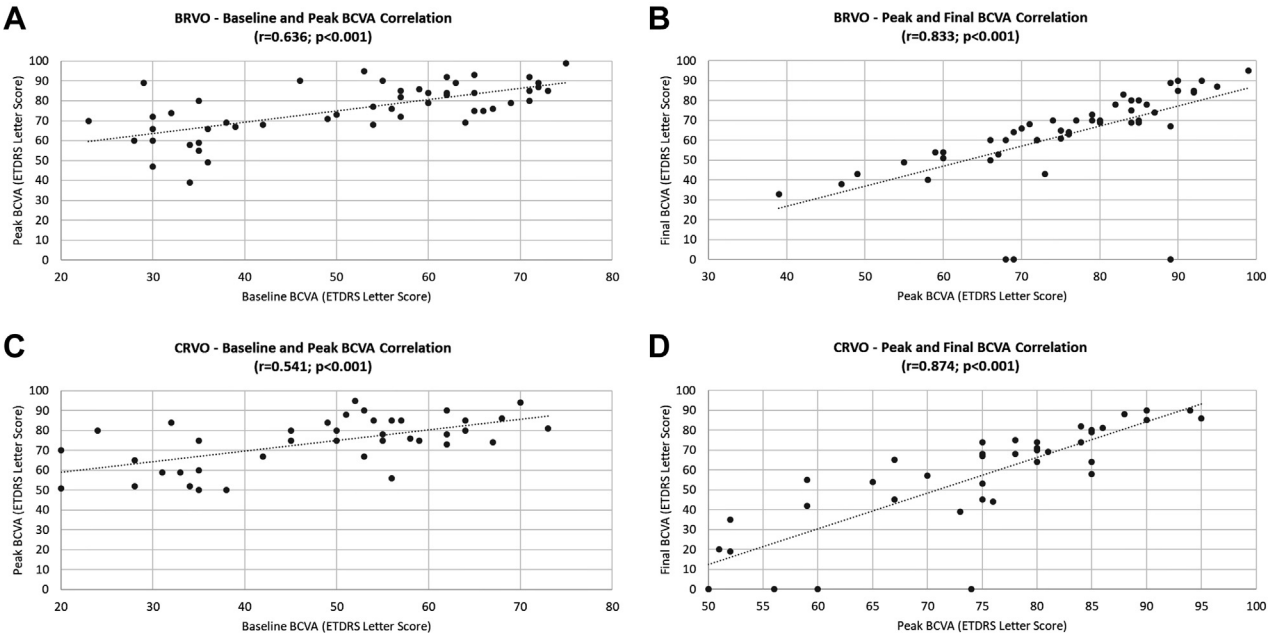


FIGURE 3. Correlation between baseline and peak best-corrected visual acuity (BCVA) and between peak and final BCVA. Peak BCVA in Early Treatment Diabetic Retinopathy Study (ETDRS) letter score is plotted against baseline BCVA for (A) branch retinal vein occlusion (BRVO) or (B) central retinal vein occlusion (CRVO) patients. Final BCVA is plotted against peak BCVA for (C) BRVO patients or (D) CRVO patients.

from edema was responsible. In the other 2 patients, fluorescein angiograms showed progression of central retinal nonperfusion with loss of all perifoveal capillaries. Loss of peak vision ≥10 letters was judged to be due to another ocular disease unrelated to retinal vein occlusion in 10 patients with BRVO and 6 with CRVO.

A number of patients had minimal or no reduction between peak and final vision. In rare instances this was owing to permanent resolution of edema after a period of VEGF suppression (Supplemental Figure 9; Supplemental Material available at AJO.com). In most instances it occurred in patients who required continued injections over a prolonged period of time but achieved stability on a treat-and-extend regimen (Supplemental Figures 10-12; Supplemental Material available at AJO.com).

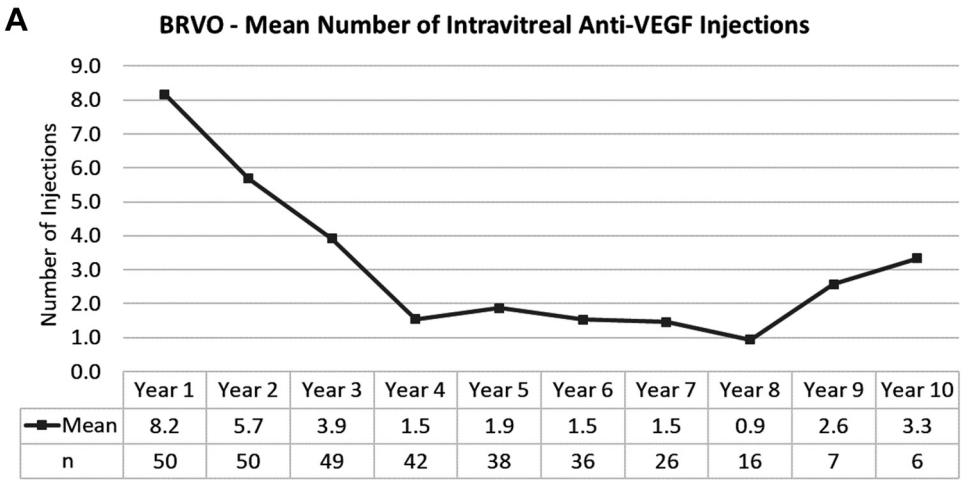
TABLE 3. Treatment Fatigue and Role of Sustained-Release Therapy in Patients With Retinal Vein Occlusion Treated With Intravitreal Anti–Vascular Endothelial Growth Factor

	BRVO Patients (N = 50)	CRVO Patients (N = 40)
Mean total injections	23.3	31.6
Mean injections per year	4.1	4.4
Treatment fatigue		
Not identified	41 (82%)	33 (83%)
Early termination	4 (8%)	3 (8%)
Poor follow-up	5 (10%)	4 (10%)
Sustained-release therapy		
Likely benefit	43 (86%)	32 (80%)
Unlikely benefit	7 (14%)	8 (20%)

BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; VEGF = vascular endothelial growth factor.

DISCUSSION

MACULAR EDEMA DUE TO BRVO OR CRVO IS HIGHLY responsive to suppression of VEGF. Mean improvement from baseline BCVA with frequent 0.5 mg ranibizumab injections for 1 year was 18.3 letters in patients with BRVO[5] and 13.9 letters in patients with CRVO.[4] Mean improvement from baseline BCVA with frequent 2.0 mg aflibercept injections for 1 year in patients with CRVO was 16.9 letters in 1 study[15] and 16.2 letters in another.[7] In this study, we found that patients with BRVO showed an improvement of 24 letters, from 20/80 mean baseline BCVA to mean peak BCVA of 20/32, which subsequently decreased by 13 letters, to mean final BCVA of 20/50, with mean follow-up of 58 months. Patients with CRVO showed a mean improvement of 26 letters, from 20/100 mean baseline BCVA to mean peak BCVA of 20/32, and subsequently decreased by 18 letters, to final BCVA of 20/80, with mean follow-up of 78 months. Interestingly, loss of peak vision occurred in almost all patients and while it



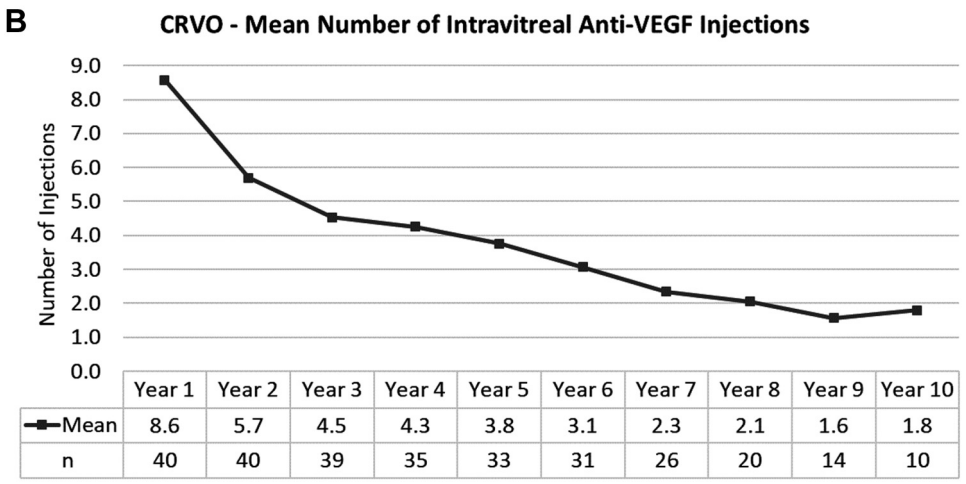


FIGURE 4. Mean number of anti-vascular endothelial growth factor (VEGF) injections per year in patients with (A) branch retinal vein occlusion (BRVO) or (B) central retinal vein occlusion (CRVO).

was greater in patients with poor visual outcome, it also occurred in patients with good visual outcome (Figure 2). The mean peak BCVA of 20/32 is surprisingly good, particularly in patients with CRVO, and begs the questions: What are the causes of loss of peak vision, and in what percentage of patients would it be possible to avoid the loss? In patients with BRVO or CRVO who lost ≥10 letters from peak BCVA, 85% and 74%, respectively, showed elimination of edema during at least 1 period of frequent anti-VEGF injections. Based on this observation, one might predict that with continued strong suppression of VEGF, a maximum of 15% of patients with BRVO and 26% of patients with CRVO would have vision decline related to RVO; however, 45% of BRVO patients and 70% of CRVO patients who lost ≥10 letters from peak BCVA had reduced BCVA judged to be due to persistent/recurrent edema and/or foveal disruption related to persistent/recurrent edema, which in theory should be preventable. All of these patients went through a prolonged period of pro re nata treatment with an anti-VEGF agent before transitioning to a treat-and-extend protocol. Whenever patients were seen to have recurrent edema, they received an anti-VEGF injection (or a dexamethasone implant, in patients who showed poor responsiveness to anti-VEGF injections). In many instances, declines in BCVA that were never recovered occurred during and after recurrent edema. Some patients missed visits and may have had prolonged periods of recurrent edema. It is possible that outcomes would have been better if patients were managed with a treat-and-extend protocol that minimized recurrent edema throughout their entire course, but this determination cannot be made from the available data. Even after transitioning to treat-and-extend, patients sometimes missed or delayed visits and returned with recurrent edema, and other patients had recurrent edema without missing an appointment.

While it did not contribute to undertreatment in the current study, concern over potentially causing retinal damage

and atrophy from aggressive suppression of VEGF may be 1 of the factors contributing to undertreatment throughout the retinal community. The choriocapillaris depends on paracrine signaling from retinal pigment epithelium (RPE)-derived VEGF, because complete elimination of VEGF in the RPE by genetic engineering causes rapid regression of the choriocapillaris and atrophy of the overlying retina,[16] but transgenic expression of high levels of a potent VEGF-neutralizing protein for up to 7 months had no effect on the choriocapillaris or the retina,[17] suggesting that it is unlikely that aggressive administration of biologics or drugs that block VEGF signaling can disrupt paracrine delivery of VEGF between the RPE and choriocapillaris. Furthermore, despite the surprising suggestion that systemic injection of an adenoviral vector expressing soluble VEGFR1 caused photoreceptor degeneration,[18] there is compelling evidence that VEGF is not a survival factor for photoreceptors and blocking VEGF has no adverse effect on photoreceptors.[19] While retinal atrophy is seen in patients with neovascular age-related macular degeneration treated with anti-VEGF agents because it is part of the natural history of the disease, it is not seen in patients with RVO who are treated with frequent injections of an anti-VEGF agent, as long as they do not have some other cause for retinal damage, such as severe recurrent bouts of edema or severe nonperfusion of perifoveal capillaries.

A weakness of this study, which is true of all long-term follow-up studies, is the loss of subjects over time. It is possible that patients who were doing particularly well or particularly poorly were more likely to withdraw or be lost to follow-up. This would influence the aggregate data but would not change the main conclusions of the study, which are based on detailed observations made in each patient over time.

An alternative approach to frequent injections to attempt to avoid recurrent edema is sustained suppression of VEGF. Several strategies aimed at achieving sustained suppression of VEGF are being tested in patients with neovascular age-related macular degeneration (NVAMD) including gene transfer of VEGF-neutralizing proteins[20,21] (ClinicalTrials.gov NCT03066258), surgical insertion of a refillable reservoir that slowly releases ranibizumab into the eye (ClinicalTrials.gov NCT02510794), and intravitreous injection of microparticles that provide sustained release of sunitinib, a VEGF receptor tyrosine kinase inhibitor (ClinicalTrials.gov NCT03249740). It is widely accepted that NVAMD is a chronic disease that requires prolonged anti-VEGF injections. In this study, we have shown that both BRVO and CRVO are chronic diseases that require many years of injections in most patients. Mean follow-up was long in this study, 58 months for BRVO and 78 months for CRVO; but despite this long follow-up, 58% of BRVO patients and 75% of CRVO patients required an anti-VEGF injection to control edema within 6 months of their last visit, indicating that they were not yet stable. The average number of injections required was 23.3 for patients with BRVO and 31.6 for patients with CRVO. Judging from this high treatment burden and evidence of treatment fatigue, the vast majority of patients with RVO would benefit from a durable, sustained delivery treatment, because only 14% of BRVO patients and 20% of CRVO patients had edema resolution without a large number of injections. Therefore, after proof-of-concept is obtained for new treatments that provide sustained suppression of VEGF in patients with NVAMD, it would be reasonable to test them in patients with RVO.

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