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Current Management of Macular Edema Associated with Central and Branch Retinal Vein Occlusion

By Radha P. Kohly, MD, PhD, FRCSC, and Rajeev H. Muni, MD, MSc (Clin Epi), FRCSC

With an estimated prevalence of 1%–2% in the general population ≥40 years of age, retinal vein occlusion (RVO) is an important cause of significantly impaired vision. The landmark Branch Vein Occlusion and Central Vein Occlusion studies dominated clinical management of RVO for several years; however, evidence is emerging to support alternative therapeutic options, including intravitreal corticosteroids and vascular endothelial growth factor inhibitors. This issue of *Ophthalmology Rounds* presents the most recent data on these promising therapies.

Retinal vein occlusions (RVOs) are a common presentation of retinal vascular disease, second in incidence and prevalence only to diabetic retinopathy. Vision loss most commonly occurs secondary to macular edema (ME), although patients may also lose vision as a result of neovascular complications. Central RVO (CRVO), characterized by retinal hemorrhages in all 4 quadrants of the retina, with associated tortuosity of the retinal veins, has an estimated prevalence of 1.6% in individuals ≥49 years,[1] and a 15-year cumulative incidence of 2.3%.[2] ME secondary to CRVO (MECRVO) can result in significant visual loss and usually carries a poor prognosis. More than half of CRVO patients had worse than 20/100 vision at 3 years.[3]

Treatment for ME associated with branch RVO (BRVO) and CRVO has been the subject of intense clinical study in the past 10 years. Prior to recent studies demonstrating a role of intravitreal inhibitors of vascular endothelial growth factor (VEGF) and intravitreal corticosteroids, observation and macular laser photocoagulation dominated the armamentarium for MECRVO and MEBRVO, respectively.

The pivotal Branch Vein Occlusion Study (BVOS)[4,5] and Central Vein Occlusion Study (CVOS),[6] conducted more than 20 years ago, established a standard of care for the treatment of ME associated with RVO that was only recently challenged. The BVOS, which followed 139 eyes randomly assigned to argon laser photocoagulation or no treatment for a mean of 3.1 years, clearly demonstrated that laser photocoagulation was beneficial in the treatment of eyes with MEBRVO that reduced vision to 20/40 or worse. Significantly more laser-treated eyes maintained a gain from baseline of ≥2 Early Treatment Diabetic Retinopathy Study (ETDRS) lines over 2 consecutive visits (P=0.0005) than controls. The CVOS, which followed 155 eyes treated with either macular grid photocoagulation or no treatment for 3 years or until the study end, concluded that laser photocoagulation reduced the extent of MECRVO, but it did not result in a statistically significant gain in visual acuity (VA). The BVOS and CVOS also established the role of sectoral and full-field panretinal photocoagulation for neovascularization associated with BRVO and CRVO, respectively. Based on the results of the BVOS, it was recommended to obtain fluorescein angiography in patients whose vision was reduced to 20/40 or worse to determine if the vision loss was attributable to macular ischemia versus ME. If macular ischemia was thought to be the cause of the vision loss, it was recommended that no treatment be offered. However, if the vision loss was attributable to ME, macular argon grid laser photocoagulation was recommended if the edema persisted after a 3-month observation period.

Although several alternative medical and surgical treatments were proposed for BRVO and CRVO, none of these options are supported by level 1 evidence. These treatments include laser chorioretinal anastamosis and radial optic neurotomy for CRVO and sheathotomy for BRVO. Other proposed treatments include anticoagulants, fibrinolytics, acetozolamide, isovolemic

Ophthalmology & Vision Sciences
UNIVERSITY OF TORONTO

Department of Ophthalmology and Vision Sciences, Faculty of Medicine, University of Toronto,
60 Murray St.
Suite 1-003
Toronto, ON M5G 1X5

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hemodilution,[7] surgically induced retinochoroidal anastomoses,[8] vitrectomy with or without peeling of the internal limiting membrane,[9,10] and intravitreal bevacizumab. The variation in treatment of MECRVO was highlighted in a recent survey of the German Retina Society,[11] which revealed the following levels of recommendation by retina specialists despite the lack of firm evidence for any of these treatment modalities: isovolemic hemodilution (64%), pentoxifylline infusions (32%), radial optic neurotomy (43%), intravitreal triamcinolone (IVT; 58%), and intravitreal bevacizumab (72%).

Over the past few years, several Phase III trials have presented important supporting evidence for new therapeutic options in the management of BRVO and CRVO, particularly intravitreal corticosteroids and anti-VEGF agents.

Intravitreal Corticosteroids

IVT is a synthetic corticosteroid that has long been studied for use in the eye.[12,13] It has been used to treat ME secondary to numerous etiologies including age-related macular degeneration, diabetic retinopathy, BRVO, and juxtafoveal telangiectasis. IVT was first reported to be used for ME secondary to CRVO by Greenberg et al.[14] Since this initial case report, numerous other published case series have provided promising visual[15-17] and anatomic[18,19] results on optical coherence tomography (OCT) for the treatment of MECRVO with IVT.

Despite the apparent benefits of IVT, other studies have found the anatomic and functional gains to be temporary.[20-23] Furthermore, IVT was found to be less beneficial with ischemic CRVO[18,24,25] and in studies where cases with severe vision loss from old CRVOs were included.[26] Ozdek et al[27] found that both ischemic and nonischemic CRVOs had a similar anatomic improvement on OCT; however, as expected, the functional outcomes were better with nonischemic CRVOs. Potential risks of IVT include a 20%–50% chance of increased intraocular pressure (IOP),[17,26,28] requiring medications and a small chance of requiring filtering surgery for persistent elevations in IOP despite maximal tolerated medical therapy. Furthermore, patients receiving IVT are at increased risk of developing sterile or infectious endophthalmitis, retinal detachment or vitreous hemorrhage, as are all patients receiving intraocular injections.

The multicentre, randomized Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study compared the safety and efficacy of 2 doses (1 mg and 4 mg) of preservative-free IVT to standard care in the management of ME associated with CRVO and BRVO. In SCORE-CRVO,[29] 271 patients with centre-involved ME secondary to CRVO, a best corrected VA (BCVA) score of 19–73 (approximately 20/40 to 20/400 Snellen acuity), and a mean central subfield retinal thickness of ≥250 µm were randomized to the 3 treatment groups. The primary outcome measure – gain of ≥15 ETDRS letters of BCVA from baseline to 12 months – was achieved by 6.8%, 26.5%, and 25.6% of participants in the observation, 1-mg IVT and 4-mg IVT groups, respectively (Table 1). Patients in either IVT group had 5 times the odds of achieving a 15-letter improvement in BCVA compared to patients in the observation group (P=0.001), after adjusting for baseline vision. There was no statistically significant difference in BCVA improvement between the 1-mg and 4-mg IVT groups. In terms of safety, no cases of infectious or noninfectious endophthalmitis or retinal detachment were observed in any of the groups at 12 months. Overall, adverse events were comparable between the 1-mg IVT and observation groups. Four cataract surgeries were performed in patients in the 4-mg IVT group, and none in the 1-mg IVT or observational groups. The frequency of prescription of IOP-lowering therapy was dose dependent (35% of patients in the 4-mg group, 20% in the 1-mg group, and 8% in the observation group; P=0.02 for 1-mg group versus observation and for 1-mg versus 4-mg groups, and P<0.001 for 4-mg group versus observation); however, no study participants received filtration surgery during the 12-month study period.

In SCORE-BRVO,[30] the 2 doses of IVT were compared with standard care (ie, grid photocoagulation) in 411 patients (same inclusion criteria as SCORE-CRVO). There was no significant difference in the primary outcome between any of the groups: ≥15-letter gains were achieved by 28.9%, 25.6%, and 27.2% of participants receiving photocoagulation, and 1 mg and 4 mg of IVT, respectively (Table 2). IOP-lowering treatment was initiated in 41% of the 4 mg IVT group compared with 7% of the IVT 1 mg group and 2% of the photocoagulation group (P=0.03 for 1-mg group versus standard care, and P<0.001 for 4-mg group versus standard care and 1-mg group).

SCORE-CRVO is the first published study to report a VA benefit for any treatment for perfused CRVO. Although 4 mg IVT has been widely used in clinical practice for CRVO since its original description by Greenberg et al,[14] this study provides conclusive evidence to support the use of 1-mg sterile, preservative-free, single-use IVT. The authors also recommend using a luer cone needle design instead of a staked-on needle design to reduce the risk of silicone oil droplets in the vitreous cavity following treatment.

Other methods of delivering corticosteroids to the eye have also been assessed. Studies using posterior subtenon steroids have found promising results in terms of vision gains and reduction of OCT central retinal thickness measurements.[31] Ramchandran et al[32] recently published 12-month results from a 3-year prospective case series involving a fluocinolone acetonide sustained drug delivery device for chronic CRVO. They reported an improvement in vision (20/126 to 20/80) and mean central retinal thickness measurements on OCT (622 µm to 307 µm) at 12 months. In this study, all phakic patients developed a cataract and 13 of 14 patients required medical or surgical management for IOP elevations.

The Global Evaluation of Implantable Dexamethasone in Retinal Vein Occlusion With Macular Edema (GENEVA) study[33] was a multicentre, blinded, randomized, sham-controlled evaluation of an intravitreal dexamethasone implant (0.35 mg and 0.7 mg) in 1267 patients with BRVO- and CRVO-associated ME. Data from the 2 individual 6-month studies (ie, BRVO and CRVO) were pooled and the primary outcome measure was time to achieve a ≥15-letter improvement in BCVA. Both the time to this improvement

Table 1: 12-month VA outcomes of SCORE-CRVO[29]

	IVT, 1 mg (n=83)	IVT, 4 mg (n=82)	Observation (n=73)
≥15-letter gain (%)	26.5	25.6	6.8
≥15-letter loss (%)	25.3	25.6	43.8
Mean change from baseline (letters)[a]	-1.2	-1.2	-12.1
Odds of achieving the primary outcome (vs observation)[b]	5.0	5.0	–

[a] Change in Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity (VA) letter score; IVT 1 mg and 4 mg vs observation: *P*=0.004.
[b] Odds ratio (OR) of IVT 1 mg vs observation: 5.0; 95% confidence interval (CI) 1.8–14.1; *P*=0.001; OR of IVT 4 mg vs observation: 5.0; 95% CI 1.8–14.4; *P*=0.001

SCORE-CRVO = Standard Care vs Corticosteroid for Retinal Vein Occlusion – Central Retinal Vein Occlusion; IVT = intravitreal triamcinolone

and the percentage of eyes that achieved it at 30 and 90 days were significantly greater in both implant groups than control ($P<0.001$ for both measures). As well, mean improvement in BCVA was significantly better with an implant than sham injection ($P\leq0.006$). However, there was no marked improvement with the implants over control by day 180. In terms of safety, IOP increases of ≥25 mm Hg were greatest (16%) at day 60 for both dexamethasone doses, and returned to control levels by day 180.

VEGF Inhibitors

Bevacizumab

As alluded to previously, bevacizumab has been studied for the treatment of MECRVO and MEBRVO in several small trials. Rosenfeld et al[34] found that a single injection (1.0 mg) improved VA from 20/200 to 20/50 and OCT showed resolution of the cystic maculopathy that persisted for at least 4 weeks. Similar benefit was seen with repeat injections over 3–12 months,[35-39] and a recent meta-analysis by Zhu et al[40] concluded that VA and central macular thickness were markedly improved with bevacizumab in BRVO patients.

Bevacizumab, however, has not been approved by Health Canada for this indication.

Ranibizumab

CRUISE[41] (A Study of the Efficacy and Safety of Ranibizumab Injection in Patients With Macular Edema Secondary to Central Retinal Vein Occlusion; N=392) and BRAVO[42] (Ranibizumab for the Treatment of Macular Edema Following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety; N=397) were prospective, multicentre, randomized, controlled studies comparing 0.3 mg and 0.5 mg of ranibizumab with sham injection in patients with ME secondary to CRVO and BRVO, respectively. In both studies, subjects received treatment for 6 months, followed by 6 months of observation, during which patients were eligible to receive

Table 2: 12-month VA outcomes of SCORE-BRVO[30]

	IVT, 1 mg (n=121)	IVT, 4 mg (n=125)	Standard care (n=121)
≥15-letter gain (%)	25.6	27.2	28.9
≥15-letter loss (%)	11.6	12.0	14.9
Mean change from baseline (letters)[a]	5.7	4.0	4.2

[a] Change in ETDRS VA letter score

SCORE-BRVO = Standard Care vs Corticosteroid for Retinal Vein Occlusion – Branch Retinal Vein Occlusion

monthly as-needed (prn) ranibizumab treatment, and/or a single grid laser photocoagulation in the case of BRAVO, if they met prespecified criteria. The primary outcome measure for these studies was mean change from baseline BCVA letter score at 6 months.

In CRUISE, the mean changes from baseline BCVA letter score at 6 months were 12.7 and 14.9 in the 0.3 mg and 0.5 mg ranibizumab groups, respectively, versus 0.8 in the sham group ($P<0.0001$ for both ranibizumab groups versus sham; Table 3). Improvements of ≥15 ETDRS letters were seen in 46.2%, 47.7%, and 16.9% of patients in the 0.3-mg ranibizumab, 0.5-mg ranibizumab, and sham injection groups, respectively. Anatomic outcomes, specifically improvements in central foveal thickness (CFT) of OCT, were also rapidly reduced, concomitant with the improvements in VA. The 12-month results demonstrated a sustained benefit of intravitreal ranibizumab.[43] Mean (95% confidence interval) change from baseline BCVA letter score at month 12 was 13.9 (11.2–16.5) and 13.9 (11.5–16.4) in the 0.3-mg and 0.5-mg groups, respectively, and 7.3 (4.5–10.0) in the sham/0.5-mg group ($P<0.001$ for each ranibizumab group vs. sham/0.5 mg). It was determined during the follow-up study that patients in the ranibizumab arms receiving prn treatment maintained their VA benefit. It was interesting that VA results in the sham group were similar to the natural history cohort in the CVOS trial, and it should be noted that, in receiving prn ranibizumab in the second 6 months, the sham group gained in VA; however, VA did not reach the same level as in the ranibizumab groups. Patients in the sham/0.5 mg group also experienced similar reductions in CFT after the first prn injection as the ranibizumab groups. There were no significant differences in the rates of ocular or systemic adverse events between the 3 groups.

In BRAVO, the primary outcome measure (ie, mean change from baseline BCVA letter score at 6 months) was 16.6 and 18.3 letters in the 0.3-mg and 0.5-mg ranibizumab groups, respectively, compared with 7.3 letters in the sham group ($P<0.0001$ for both ranibizumab groups versus sham; Table 4). These benefits were maintained at 12 months with both the 0.3-mg and 0.5-mg doses (16.4 and 18.3, respectively) and was 12.1 in the sham/0.5 mg injection group ($P<0.01$ for both ranibizumab groups versus sham/0.5 mg).[43] The percentage of patients who gained ≥15 letters from baseline BCVA at month 6 was 55.2% (0.3 mg) and 61.1%

Table 3: 6-month VA outcomes of CRUISE[41]

	Ranibizumab, 0.3 mg (n=132)	Ranibizumab, 0.5 mg (n=130)	Sham (n=130)
≥15-letter gain (%)	46.2	47.7	16.9
≥15-letter loss (%)	3.8	1.5	15.4
Mean change from baseline (letters)[a]	12.7	14.9	0.8

[a] 95% CIs: 9.9–15.4 (ranibizumab 0.3 mg), 12.6–17.2 (ranibizumab 0.5 mg), -2.0–3.6 (sham); difference in means: 11.9 (ranibizumab 0.3 mg vs sham), *P*<0.0001; 14.1 (ranibizumab 0.5 mg vs sham), *P*<0.0001.

CRUISE = A Study of the Efficacy and Safety of Ranibizumab Injection in Patients With Macular Edema Secondary to Central Retinal Vein Occlusion

Table 4: 6-month VA outcomes of BRAVO[42]

	Ranibizumab, 0.3 mg (n=134)	Ranibizumab, 0.5 mg (n=131)	Sham (n=132)
≥15-letter gain (%)	55.2	61.1	28.8
≥15-letter loss (%)	0	1.5	4.5
Mean change from baseline (letters)[a]	16.6	18.3	7.3

[a] 95% CIs: 14.7–18.5 (ranibizumab 0.3 mg), 16.0–20.6 (ranibizumab 0.5 mg), 5.1–9.5 (sham); difference in means: 9.3 (ranibizumab 0.3 mg vs sham), *P*<0.0001; 11.0 (ranibizumab 0.5 mg vs sham), *P*<0.0001.

BRAVO = Ranibizumab for the Treatment of Macular Edema Following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety

(0.5 mg) and 28.8% in the sham group; 12-month percentages were 56.0%, 60.3%, and 43.9%, respectively. Despite prn treatment in the second 6 months, the sham/0.5 mg group remained inferior to the ranibizumab arms in terms of vision and CFT measurements. No new ocular or nonocular safety events were identified. It was also interesting that in the BRAVO study patients in the ranibizumab arms experienced a faster clearing of the intraretinal hemorrhages. Anatomical and quality of life improvements, as measured with the OCT and the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ25), mirrored VA results.

Despite the results of these studies, we must be cautious about the repeated and potentially long-term VEGF suppression in vasculopathic patients. The fact that repeated injections were needed even after 6 monthly ranibizumab injections suggests that the drug does not alter the underlying pathophysiological process but rather controls the end result; ie, edema. Other treatment approaches will be required to alter the pathophysiology of the persistent and recurrent edema. The blockage in the retinal vein may lead to reduced arterial perfusion with subsequent ischemia and VEGF production. A recent case series (N=20 eyes) was presented at the 2012 annual meeting of the American Society of Retina Specialists,[44] where ranibizumab-resistant patients underwent several surgically induced chorioretinal anastomoses with good anatomic results.

Furthermore, the durability of this treatment effect and injection frequency are still being established. HORIZON, a 12-month open-label extension of CRUISE and BRAVO (N=608; 304 patients from each study)[45] found that the mean numbers of injections of 0.5 mg ranibizumab over the study period were 2.1 and 3.5 in BRVO and CRVO groups, respectively. Mean changes from baseline BCVA letter scores with 0.5 mg ranibizumab injections to the end of 12 months (ie, 2 years of treatment) were -0.7 for BRVO and -4.1 for CRVO.

Aflibercept

The multicentre, randomized, prospective Controlled Phase 3 Evaluation of Repeated Intravitreal Administration of VEGF Trap-Eye in Central Retinal Vein Occlusion: Utility and Safety (COPERNICUS) study[46] evaluated 6 monthly injections of aflibercept 2 mg against sham injection in 189 eyes with MECRVO. The primary endpoint – proportion of eyes with a ≥15-letter gain in BCVA at week 24 – was achieved by a significantly greater percentage of eyes treated with aflibercept than controls (56.1% versus 12.3%; *P*<0.001). Aflibercept was also superior in mean letters gained (17.3 versus -4.0; *P*<0.001) and decrease of central retinal thickness (-457.2 µm versus -144.8 µm; *P*<0.001). Serious ocular adverse events were more common with sham injection (13.5%) than aflibercept (3.5%) and nonocular serious adverse events were equivalent in the 2 groups (Table 5).

In the 1-year extension to COPERNICUS,[47] all patients were eligible to receive prn aflibercept (2 mg), according to retreatment criteria. The percentages of subjects gaining ≥15 letters and mean letter gain from baseline remained significantly higher with aflibercept (55.3% versus 30.1% and 16.2 versus 3.8 letters, respectively; *P*<0.001 for each; Table 5).

Although approved in the United States by the Food and Drug Administration for MECRVO, aflibercept has not received Health Canada approval at the time of this publication.

Combination Therapy

It is understandable that the SCORE study did not include an anti-VEGF arm, and vice versa for the CRUISE or COPERNICUS studies, as none of the active agents in these studies had been shown to be

superior to observation or sham at the time these studies were designed. However, the results of the CRUISE and COPERNICUS studies highlight the potential promise of anti-VEGF agents in the management of MECRVO. Head-to-head studies among these agents will be required. Several small studies[48-50] comparing IVT and bevacizumab found that both agents significantly improved BCVA, with no marked difference between them. Although there is likely some overlap in mechanism of action, combining IVT and an anti-VEGF agent seems reasonable from the results of these recently completed clinical trials and further studies will be required to investigate this possibility.

It is also possible that the combination of an anti-VEGF agent with laser may be superior to either treatment alone. Perhaps the anti-VEGF agent would allow for a faster clearing of the intraretinal hemorrhage, which would then allow for an earlier and more precise laser treatment.

Conclusion

Several recent Phase III trials, notably SCORE, CRUISE, BRAVO, and COPERNICUS, have shown promising results in the management of MECRVO and MEBRVO. VA benefit was achieved without high incidence of serious adverse events. Additional research is required to confirm the long-term effectiveness of these agents, to establish optimal timing and duration of treatment, to compare these therapies in well-designed head-to-head studies, and to investigate the potential usefulness of combination therapies.

Table 5: 6- and 12-month VA outcomes of COPERNICUS[46,47]

	6 months		12 months	
	Aflibercept, 2 mg (n=114)	Sham (n=73)	Aflibercept, 2 mg (n=114)	Sham[a] (n=73)
≥15-letter gain (%)[b]	56.1	12.3	55.3	30.1
≥15-letter loss (%)	1.8	27.4	5.3	15.1
Mean change from baseline (letters)[c]	17.3	-4.0	16.2	3.8

[a] Patients in the sham-treatment group were eligible to receive as-needed aflibercept if they met protocol-specified criteria on monthly evaluation;
[b] P<0.001 for aflibercept vs sham in both 6- and 12-month data; [c] 6-month data: P<0.001; standard deviations aflibercept ±12.8 letters, sham ±18.0 letters. 12-month data: P<0.001.

COPERNICUS = Controlled Phase 3 Evaluation of Repeated Intravitreal Administration of VEGF Trap-Eye in Central Retinal Vein Occlusion: Utility and Safety

Dr. Muni is an Assistant Professor, Department of Ophthalmology and Vision Sciences, University of Toronto, and St. Michael's Hospital, Toronto, Ontario.
Dr. Kohly is an Assistant Professor, Department of Ophthalmology and Vision Sciences, University of Toronto, and Sunnybrook Health Sciences Centre, Toronto, Ontario.

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