CLINICAL INVESTIGATION

Ranibizumab for the treatment of macular edema following retinal vein occlusion

Clin. Invest. (2011) 1(9), xxx–xxx

Retinal vein occlusions (RVOs) are the second most common form of retinal vascular disease. The Beaver Dam Study estimated the 15 year cumulative incidence of RVOs at 2.3%. The predominant causes for vision loss from RVOs include macular edema and macular ischemia. Data from historic studies recommended focal macular laser only for branch vein occlusion patients with macular edema and >20/40 vision within 3–18 months of onset and without significant retinal hemorrhages. No treatment for macular edema was recommended for central vein occlusion patients. For years, the standard of care has been extrapolated from these historic studies. However, exciting new data from two multicenter randomized controlled studies using ranibizumab for the treatment of macular edema in vein occlusions have yielded impressive results, reshaping the management of RVO.

Keywords: ETDRS • focal macular laser • hyaloid • lamina cribosa • macular • macular edema • macular ischemia

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Retinal vein occlusions

There are two major types of retinal vein occlusions (RVOs): central and branch RVO. Histopathologic studies show that central RVO (CRVOs) occur when there is obstruction to blood flow in the central retinal vein at the lamina cribosa, or just proximal to it [1]. Branch RVO (BRVOs) usually occur where a branch retinal vein crosses under a branch retinal artery [2–6]. The perfusion of the retina and pathophysiology of retinal vein occlusions will be reviewed in this section.

■ Perfusion of the retina

The inner two-thirds of the retina is supplied by the retinal vasculature, whereas the outer third is supplied by the choroidal circulation. The retinal vasculature originates at the central retinal artery, which branches into tributaries either just before or shortly after it exits the optic nerve head. These tributaries run over the surface of the retina and further branch into smaller arterioles extending into the periphery. Penetrating branches dive into the retinal tissue forming a capillary network that drains into small venules collecting into larger and larger veins, which coalesce at the optic nerve head into the central retinal vein.

■ Pathophysiology of retinal vein occlusions

The central retinal vein and artery run parallel to one another within the retro-orbital optic nerve. There is a natural compression of the central retinal vein and artery as they pass through the sieve-like openings of the lamina cribosa. It is postulated that this narrowed site is predisposed to hemodynamic alterations that can cause an occlusion in the central retinal vein. Alterations in blood flow due to systemic vascular disease, elevated intraocular pressure and glaucoma, increased blood

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viscosity, inflammatory vasculitis, or compression have all been associated with an increased risk for CRVO. Typically, older patients with CRVO usually have glaucoma or concurrent systemic vascular disease such as hypertension or diabetes whereas younger patients with CRVO may have an underlying hypercoagulopathy, inflammatory disease or compressive lesion. Patients with CRVO can be further divided into ischemic versus nonischemic CRVOs [7,8]. Ischemic CRVOs have greater than ten disc areas in diameter of retinal capillary nonperfusion on angiography and have greater amounts of intraretinal hemorrhage. Nonischemic CRVOs have fewer than ten disc areas of retinal capillary nonperfusion and have less intraretinal hemorrhage on presentation. Patients with the nonischemic form have a better visual prognosis.

Most BRVOs occur where a retinal artery crosses anterior to a retinal vein [5,6]. At these crossings, the artery and vein share a common adventitial sheath and compression of the more compliant retinal vein may occur when there is thickening of the adjacent retinal artery. Systemic vascular disease such as hypertension and arteriosclerosis are risk factors for BRVO, probably because they lead to thickening of the retinal artery [2,6]. Other risk factors for BRVOs include diabetes, smoking, hyperlipidemia, glaucoma and ocular inflammatory disease [9].

Occlusion of retinal veins causes stagnation of blood flow in the areas of the retina drained by the blocked vein. This in turn impedes arterial flow, leading to ischemia, edema and local intraretinal hemorrhages. If the central retinal vein is affected, the entire retina will exhibit these clinical findings. If a branch retinal vein is affected, only the areas drained by the vein will be affected. Vision loss from retinal vein occlusions are typically due to macular ischemia, macular edema or complications from neovascular disease.

■ Pathophysiology of macular edema in vein occlusions

Macular edema is a leading cause of vision loss in patients with BRVOs and nonischemic CRVOs. Macular edema results from increased vascular permeability as a response to retinal nonperfusion. In patients with RVOs, retinal ischemia leads to the secretion of VEGF, which leads to increased vascular permeability [10,11]. VEGF was initially purified as a tumor-secreted factor in the 1980s, using an assay measuring the extravasation of dye [12]. VEGF acts by binding to one of two VEGF receptors in humans. Activation of VEGF receptors causes homo- or hetero-dimerization and activation of tyrosine kinase activity with subsequent recruitment of SH2 domain-binding proteins. Activation of these SH2-binding proteins causes increased vascular permeability, vasodilation, migration of endothelial cells and neovascularization [13]. Increased vascular permeability and perhaps vasodilation leads to retinal edema.

■ Historic treatments for vein occlusions

Two landmark studies, BVOS and CVOS, evaluated the use of macular grid laser photocoagulation for the treatment of macular edema after RVOs. The BVOS demonstrated that laser therapy was successful in improving visual outcomes and reducing macular edema in patients with BRVO. However, the CVOS did not show any benefits in patients with CRVO, despite a reduction in macular edema.

BVOS

The BVOS was designed to address two major complications from BRVO, neovascular disease and macular edema [14]. Patients were split into four separate subgroups. Group I and II patients were randomized to receive scatter laser photocoagulation or no treatment to determine if scatter laser reduced the chance of neovascular complications. Group I patients did not have neovascular disease at the time of enrollment and group II patients did. Group X patients were at high risk for developing neovascularization and were used for the natural history study as well as to maintain a pool of patients who would likely qualify for group II.

Group III patients had vision worse than 20/40 and macular edema verified by fluorescein angiography. A total of 139 group III eyes were randomized to receive either macular grid laser or no treatment. The results for group III were published in 1984. Patients with insufficient clearance of intraretinal hemorrhages to permit adequate angiography and safe application of laser photocoagulation were excluded. Patients with BRVO of less than 3 months duration, or vision loss due to other causes were also excluded. A total of 71 eyes were enrolled in the treatment group and 68 eyes in the control group. At the end of the 3 year study, 68% attained at least a two line gain in visual acuity in the treatment group compared with 37% in the control group ($p = 0.00049$). The average lines gained in the treatment group was 1.33 compare with 0.23 in the control group ($p < 0.0001$). A total of 17% of the control group eyes lost two lines of vision compared with 12% in the treatment group, however this difference was not statistically significant. As a result of the BVOS, macular grid laser is recommended for patients with macular edema from BRVO, vision worse than 20/40, and the absence of intraretinal hemorrhage affecting treatment or macular ischemia.

CVOS-group M

The CVOS was a parallel study to the BVOS, for patients with CRVO. The CVOS patients were divided

into four separate subgroups. Two subgroups, group P and I, were used to study the natural history of the disease. Group P included eyes with good perfusion and group I included eyes with indeterminate perfusion status. The two remaining subgroups, group N and M, were interventional study groups. Group N included eyes with over ten disc areas of nonperfusion, and were randomized to receive either scatter panretinal photocoagulation to prevent neovascular disease or no treatment.

Group M included eyes with vision loss ascribable to macular edema. The Group M report was published in 1995 [15]. A total of 155 eyes in 155 patients with macula edema and CRVO were randomized to receive either macular grid laser or no treatment. Patients with macular edema and CRVO with visual acuity between 5/200 and 20/50 and without macular ischemia on fluorescein angiography were included. Patients with concurrent ocular disease, which was likely to affect visual acuity, and new-onset CRVO of less than 3 month's duration were excluded. A total of 77 eyes were enrolled into the treatment group and 78 eyes in the control group. There was no difference in visual acuity or change in visual acuity between the two groups throughout the entire study duration, despite a significant difference in angiographic macular edema. The treated group showed an average improvement of 4 Early Treatment in Diabetic Retinopathy Study (ETDRS) letters and the untreated group 3 ETDRS letters. The median disc areas of macular edema in the treated group was zero compared with three in the untreated group. The baseline median disc areas of macular edema were 5.5 and 5.0 in the treated versus untreated group, respectively. As a result of the group M CVOS report, most practitioners do not treat patients with CRVO and macular edema with grid laser photocoagulation.

No serious complications were reported in the BVOS and CVOS. However, in theory, laser photocoagulation may worsen macular ischemia, create scotomas, induce tractional detachment of the retina, and hasten cataract formation.

Other treatments

The most influential studies that have shaped the way ophthalmologists treat patients with macular edema from RVOs were the BVOS and CVOS. However, several other approaches have been described in the literature with variable success.

■ Laser-induced chorioretinal venous anastamosis for CRVO

Recently, a prospective, randomized, controlled study describing chorioretinal venous anastamosis for the treatment of nonischemic CRVO was completed [16]. A total of 113 patients were randomized to laser-induced chorioretinal venous anastamosis (L-CRA) or sham laser. The treatment group received a very strong (3.5–6 W) green argon laser treatment adjacent to a major tributary of the central retinal vein. A second laser application with either the argon or a neodymium:yttrium aluminum garnet laser followed at the edge of the targeted vein to rupture the vessel wall. Of the 55 treatment group patients, 42 (76.4%) successfully developed an L-CRA. After 18 months of follow-up, the L-CRA group gained an average of 0.2 ETDRS letters compared with losing 8.1 letters for the control group ($p = 0.03$). By forming a chorioretinal venous anastamosis, the blood flow would hypothetically be restored, thus reducing retinal ischemia and subsequent macular edema.

■ Radial optic neurotomy for CRVO

Radial optic neurotomy has been described for the treatment of CRVO. After pars plana vitrectomy, radial incisions at the nasal edge of the optic nerve are made, in theory to release the compression of the central retinal vein at the lamina cribosa. Lack of large prospective randomized controlled studies and variable results from published reports [17–20] limit its utility by most retina specialists.

■ Sheathotomy & vitrectomy for BRVO

Based on the pathophysiology of BRVOs, surgical dissection of the adventitial sheath and separation of the branch retinal artery from the vein at the occlusion site has been shown to reduce macular edema and improve vision in prospective controlled studies [21,22]. However, since sheathotomy is performed after pars plana vitrectomy and hyaloidal separation, it is unclear whether improvement of macular edema can be attributed to sheathotomy or vitrectomy alone. Vitrectomy has been reported to reduce macular edema [23,24] either by relieving macular traction or by improving oxygen exposure of the inner retina. Although many trials suggested an improvement in macular edema after sheathotomy, it was unclear whether vitrectomy alone provided the same visual benefit [24–26]. Due to the risk of intraoperative complications and the availability of less invasive alternatives, vitrectomy with or without sheathotomy has limited clinical use as a first-line therapy.

■ Intravitreal steroids for RVO

Many case series have demonstrated the effectiveness of intravitreal triamcinolone acetate (IVTA) in treating macular edema in patients with RVOs. The rationale behind the use of triamcinolone is based on the observation that macular edema results from the increased permeability mediated, at least in part, by an increase in VEGF [10,11]. Corticosteroids have been shown to

inhibit the expression of VEGF and therefore reduce macular edema in animal models [27,28]. Furthermore, the anti-inflammatory effects of corticosteroids may further potentiate the anti-VEGF affects and help attenuate the disease process. Recently, two randomized controlled trials evaluating the effectiveness and safety of IVTA were completed. In the SCORE-BRVO trial, 411 patients with macular edema and BRVO were randomized to receive macular grid laser, IVTA 1 mg, or IVTA 4 mg. There was no significant difference in vision or the reduction of macular edema measured by OCT at the end of 12 months [29]. In the SCORE-CRVO study, 271 patients with macular edema and CRVO were randomized to observation, IVTA 1 mg, or IVTA 4 mg. Although there was no significant difference in the reduction in macular edema measured by OCT, patients in both IVTA groups had a significant improvement in vision compared with the control group [30]. Although both SCORE trials showed a benefit of IVTA in the treatment of macular edema from RVOs, there were also significant side effects from IVTA, including visually significant cataract formation and elevation of intraocular pressure requiring treatment. As a result of these studies, IVTA is not recommended as first-line therapy for macular edema in BRVO, but the lower 1 mg dose may be used in CRVO.

Recently, the GENEVA study, which evaluated a dexamethsone intravitreal implant (Ozurdex®) for the treatment of macular edema in CRVO and BRVO patients, was completed [31]. Ozurdex is a biodegradable copolymer containing micronized dexamethasone. It is inserted intravitreally through a pars plana route using a custom injector, and it gradually releases the total dose of dexamethasone over several months. In this multicenter, randomized, controlled study, an increase in best corrected visual acuity (BCVA) of ≥15 ETDRS letters was achieved in 30% of the Ozurdex 0.7 mg group (n = 291), 26% of the 0.35 mg group (n = 260) and 13% of the sham group (n = 279), 60 days after injection (peak response) in patients with BRVO. A statistically significant difference between each Ozurdex group and sham was seen up to 90 days after injection. In the CRVO group, an increase of ≥15 letters was seen in 29% of the 0.7 mg group (n = 136), 33% of the 0.35 mg group (n = 154) and 9% of the sham group (n = 147), 60 days after injection (peak response). A statistically significant difference was observed up to 60 days for the 0.7 mg group and up to 90 days for the 0.35 mg group in this CRVO cohort. At 90 days after injection, there was a significant improvement ($p < 0.001$) in central retinal thickness in both Ozurdex groups, compared with the sham group. The only complications that were significantly greater in the Ozurdex groups compared with sham were elevated intraocular pressure and anterior chamber cell. Most eyes with elevated intraocular pressures were successfully managed with topical therapy, but five eyes required a procedure to adequately lower the pressure. In the 6 months of this study, there was no difference in the rate of cataract formation, and there were no endophthalmitis cases reported. A long term study of repeated treatments is currently underway and will help determine the safety and optimal interval for retreatment.

Of these treatments, only the use of IVTA has gained widespread acceptance. Sheathotomy, radial optic neurotomy, and L-CRA have limited use in clinical practice due to the lack of data from large multicenter, randomized controlled studies. Although Ozurdex has gained US FDA approval for the treatment of macular edema in RVOs, experience with its use is limited and it remains to be seen whether Ozurdex will gain popularity in clinical practice.

Anti-VEGF for macular edema

More recently, intravitreal anti-VEGF agents such as pegaptanib (Macugen®), bevacizumab (Avastin®) and ranibizumab (Lucentis®) have been used to treat macular edema from diabetic retinopathy and RVOs. Since macular edema in RVOs is likely in response to elevated VEGF levels, inhibition of the VEGF pathway is an obvious target for therapy. Numerous early case series and small prospective studies have been reported with good success. A retrospective study of 16 eyes with CRVO, treated with intravitreal bevicizumab 1.25 mg showed a significant improvement in vision from an average of 20/600 to 20/138 with a corresponding reduction in mean central macular thickness of 515 µm [32]. A small prospective study in seven eyes with ischemic CRVO treated with intravitreal bevicizumab 2 mg also showed significant improvement in vision from 20/320 to 20/100 and a reduction in mean central macular thickness of 470 µm, however, recurrence of macular edema was noted between 6 and 12 weeks after injection [33]. Another small prospective series in nine patients with CRVO and 12 with BRVO showed similar results in both CRVO and BRVO groups with significant improvements in vision and central macular thickness [34]. Other early studies using ranibizumab showed equally impressive gains in vision and reduction in central macular thickness [35,36]. Phase 2 studies of pegaptanib for the treatment of CRVO and BRVO also showed significant improvements in vision and central macular thickness [37,38]. However, due to limited enrollment with the increasing use of bevacizumab and ranibizumab, larger trials with pegaptanib have not been conducted. These early studies suggested that larger prospective, randomized, placebo-controlled studies were necessary to further evaluate the use of

anti-VEGF agents in patients with RVO.

■ BRAVO

As a result of the early successes with anti-VEGF agents, a Phase III prospective, multicenter, randomized, controlled study to evaluate the efficacy and safety of ranibizumab in the treatment of macular edema from BRVO was conducted (BRAVO study). The 6-month data from this study were recently reported [39]. We will review the 6 months data and a preview the 12 month data will be discussed.

Patients aged 18 years and over with macular edema involving the fovea, vision between 20/40 and 20/400, BRVO diagnosed within the past 12 months, and OCT (Zeiss Stratus) measured central subfield thickness ≥250 µm were eligible for the BRAVO study. Exclusion criteria are listed in **Box 1** and were designed to exclude patients recently treated for RVO, patients with spontaneous improvement, and other causes of vision loss that could not be attributed to macular edema from RVO. Patients were randomized into three groups, sham injection (n = 132), ranibizumab 0.3 mg (n = 134), and ranibizumab 0.5 mg (n = 131). A 28 day screening period excluded patients with spontaneous and rapid improvement in vision of >10 ETDRS letters. Patients received monthly intravitreal injections of sham, 0.3 or 0.5 mg of ranibizumab for the first 6 months followed by as needed (prn) dosing from months 6 to 12. Sham injections were performed by indenting the eye with the hub of a needleless syringe with the plunger depressed to mimic an intraocular injection. Rescue macular grid laser was available starting at month 3. The timing of initial treatment for rescue laser, if necessary, was no different than the BVOS study parameters. At month 3, a patient was eligible for rescue laser if a gain of <5 ETDRS letters, or improvement of <50 µm in central subfield thickness was observed compared with the visit 3 months prior. If rescue laser was not applied at month 3, the same criteria were used to determine eligibility for rescue laser at each subsequent monthly visit.

Baseline study eye characteristics were similar between all three groups **(Table 1)**. At the end of the first 6 months, both ranibizumab groups gained an impressive 16.6 (0.3 mg group) and 18.3 (0.5 mg group) ETDRS letters compared with a gain of 7.3 letters in the control group ($p < 0.0001$ for each group vs sham). Subgroup analysis showed patients with BRVO less than 3 months duration, worse baseline vision, and central subfield thickness ≥450 µm showed the greatest improvement in BCVA over baseline. The percentage of patients who improved greater than 15 ETDRS letters was also significantly greater in the 0.3 mg (55.2%) and 0.5 mg (61.1%) ranibizumab groups compared with control (28.8%). Both treatment groups also seemed to have a significantly lower percentage of patients with poor visual outcomes and vision worse than 20/200: 0.3 mg ranibizumab (1.5%), 0.5 mg ranibizumab (0.8%) and control (9.1%). Concurrent with the improvement in visual acuity, there was also a significantly greater decrease in central foveal thickness (CFT) in the ranibizumab 0.3 mg (-337.3 µm) and 0.5 mg (-345.2 µm) groups compared with control (-157.7 µm, $p < 0.0001$ for each group vs sham). During the first 6 months, 54.5% of the control group required rescue laser therapy compared with 18.7% in the ranibizumab 0.3 mg and 19.8% in the 0.5 mg groups.

After the first 6 months, all three groups were allowed to receive prn intravitreal ranibizumab at monthly intervals if they had vision ≤ 20/40 or mean CFT ≥ 250 µm. Despite receiving only prn treatments, patients in both ranibizumab groups maintained their vision gain at 12 months **(Figure 1A)** [40]. Although the control group showed a benefit from the prn treatment regimen, the final vision gained at 12 months was not equivalent in all three groups **(Figure 1A)**. However, the data at

Box 1. Exclusion criteria.

- Prior episode of RVO†
- Laser photocoagulation for macular edema ≤4 months prior to day 0†
- Intraocular corticosteroid use ≤3 months prior to day 0†
- History of anti-VEGF treatment
  - Intravitreal ≤3 months prior to day 0
  - Systemic ≤
  - 6 months prior to day 0
- Brisk afferent pupillary defect†
- BCVA gain >10 letters between screening and day 0†
- Stroke or myocardial infarction ≤3 months prior to day 0

†in the study eye

BCVA: Best corrected visual acuity; RVO: Retinal vein occlusion

Table 1. Baseline characteristics of study eye (BRAVO).

	Sham/ 0.5 mg (n = 132)	Ranibizumab 0.3 mg (n = 134)	Ranibizumab 0.5 mg (n = 131)
Age in years, mean (SD)	65.2 (12.7)	66.6 (11.2)	67.5 (11.8)
Months from diagnosis to treatment, mean (SD)	4.4 (3.7)	4.3 (4.1)	4.0 (3.1)
<3	69 (52.3)	69 (51.5)	74 (56.5)
≥3	63 (47.7)	65 (48.5)	57 (43.5)
BCVA (ETDRS letter score), mean (SD)	54.7 (12.2)	56.0 (12.1)	53.0 (12.5)
CFT (µm), mean (SD)	488.0 (192.2)	522.1 (201.9)	551.7 (223.5)

BCVA: Best corrected visual acuity. CFT: Central foveal thickness; ETDRS: Early treatment diabetic retinopathy study; SD: Standard deviation.

groups was similar. One patient in the 0.5 mg ranibizumab group suffered from endophthalmitis, which is a known complication of intravitreal injections.

The BRAVO study showed that ranibizumab is superior to traditional laser treatment for macular edema from BRVO with little risk of adverse events. The current recommendation is, therefore, to treat patients diagnosed with macular edema from BRVO with monthly 0.5 mg ranibizumab. If treatment fails after 3 months (<5 ETDRS letter gain, or improvement of <50 µm in central subfield thickness), then traditional grid macular laser should be performed. The BRAVO study showed that prn treatment did not adversely affect the visual outcome after five scheduled monthly injections. However, the timing of when to switch to prn treatment was not evaluated in the BRAVO study and, thus, the decision to switch to prn dosing should be based on factors such as improvement in visual acuity, residual macular edema on OCT imaging, success of prior injections, and expectations of the patient.

Figure 1. Results from the BRAVO study. (A) Mean change from baseline BCVA. *p < 0.0001 vs sham. Earliest statistically significant difference was at day 7. Vertical bars are ±1 standard error of the mean. At the 6 months visit, the sham group received ranibizumab 0.5 mg if they met the pro re nata retreatment criteria. **(B)** Proportion of patients who gained >15 ETDRS letters from baseline. *p < 0.0001 vs sham. **(C)** Mean change from baseline central foveal thickness. *p < 0.0001 vs sham. Earliest statistically significant difference was at day 7. Vertical bars are ±1 standard error of the mean.

12 months for the control group includes both patients who received prn ranibizumab and patients who did not. Similarly, the percentage of patients who experienced a gain of ≥15 ETDRS letters did not change significantly at 12 months after prn treatment was initiated in the ranibizumab groups (Figure 1B). More control patients attained ≥15 ETDRS letters at 12 months after prn treatments were initiated (Figure 1B). Not surprisingly, the mean change in CFT was maintained in both ranibizumab groups at 12 months while there was a significant improvement observed in the control group after prn treatment was initiated (Figure 1C). At the end of 12 months, the incidence of adverse events in all

Table 2. Baseline characteristics of study eye (CRUISE)

	Sham/ 0.5 mg (n = 130)	Ranibizumab 0.3 mg (n = 132)	Ranibizumab 0.5 mg (n = 130)
Age in years, mean (SD)	65.4 (13.1)	69.7 (11.6)	67.6 (12.4)
Months from diagnosis to treatment, mean (SD)	3.5 (2.9)	4.2 (3.2)	3.9 (3.7)
<3	78 (60.0)	66 (50.0)	72 (55.4)
≥3	52 (40.0)	66 (50.0)	58 (44.6)
BCVA (ETDRS letter score), mean (SD)	49.2 (14.7)	47.4 (14.8)	48.1 (14.6)
CFT (µm), mean (SD)	687.0 (237.6)	679.9 (242.4)	688.7 (253.1)

BCVA: Best corrected visual acuity; CFT: Central foveal thickness; ETDRS: Early treatment diabetic retinopathy study; SD: Standard deviation.

■ CRUISE

The CRUISE study was the parallel study to BRAVO for patients with macular edema from CRVO. The 6 months data has previously been reported [41] and will be reviewed here with the 12 month data [42].

Inclusion criteria for the CRUISE study were identical to the BRAVO study except a more narrow range of vision (between 20/40 and 20/320) was accepted in an attempt to exclude patients with severe macular ischemia. Exclusion criteria are listed in Box 1, and are identical to the BRAVO study. Patients were randomized into three groups, sham injection (n = 130) ranibizumab 0.3 mg (n = 132) and ranibizumab 0.5 mg (n = 130). A 28 day screening period was used and the protocol was identical to the BRAVO study except no rescue laser was given. After a series of five monthly injections, all three groups received prn injections if they had vision ≤20/40 or mean CFT ≥250 µm measured on the Zeiss Stratus.

Baseline study eye characteristics were similar between all three groups (Table 2). At the end of the first 6 months, both ranibizumab groups gained 12.7 (0.3 mg group) and 14.9 (0.5 mg group) ETDRS letters compared with a gain of only 0.8 letters in the control group (p < 0.0001

for each group vs sham). Subgroup analysis showed patients with worse baseline vision, and central subfield thickness ≥450 µm showed the greatest improvement in BCVA over baseline, however, there was no significant difference seen with the duration of CRVO prior to enrollment. The percentage of patients who improved greater than 15 ETDRS letters was also significantly greater in the ranibizumab 0.3 mg (46.2%) and 0.5 mg (47.7%) groups compared with control (16.9%). Both treatment groups also seemed to have a significantly lower percentage of patients with poor visual outcomes and vision worse than 20/200 ($p < 0.005$ each treatment group vs sham): ranibizumab 0.3 mg (15.2%), ranibizumab 0.5 mg (11.5%), and control (27.7%). Concurrent with the improvement in visual acuity, there was also a significantly greater decrease in CFT in the ranibizumab 0.3 mg (-433.7 µm) and 0.5 mg (-452.3 µm) groups compared with control (-167.7 µm, $p < 0.0001$ for each group vs sham).

After the first 6 months, all three groups received prn intravitreal ranibizumab at monthly intervals if the retreatment criteria described above were met. Patients in both ranibizumab groups maintained their vision gain at 12 months (Figure 2A). Although the control group showed a benefit from the prn treatment regimen, the final vision gained at 12 months was not equivalent in all three groups (Figure 2A). The percentage of patients who experienced a gain of ≥15 ETDRS letters was maintained after prn treatment was initiated in the ranibizumab groups (Figure 2B), while more patients attained ≥ 15 ETDRS letters at 12 months after prn treatments were initiated in the control group (Figure 2B). The mean change in CFT was maintained in both ranibizumab groups at 12 months while there was a significant improvement observed in the control group after prn treatment was initiated (Figure 2C). At the end of 12 months, the incidence of adverse events in all groups was similar. No significant differences in rates of cataracts or glaucoma were observed between groups and there were no significant differences in nonocular adverse events.

The CRUISE study showed that ranibizumab is an effective treatment for macular edema from CRVO with little risk of adverse events. The current recommendation is therefore to treat patients diagnosed with macular edema from CRVO with monthly ranibizumab 0.5 mg for 6 months followed by prn treatment. Gains in vision were maintained after switching to prn treatment, however, the timing of when to switch to prn treatment was not evaluated. The decision to switch to prn dosing should therefore be determined on an individual basis.

Future perspective

Figure 2. Results from the CRUISE study. (A) Mean change from baseline BCVA. *p<0.0001 vs sham. Earliest statistically significant difference was at day 7. Vertical bars are ±1 standard error of the mean. At the 6 months visit, the sham group received ranibizumab 0.5 mg if they met the pro re nata retreatment criteria. **(B)** Proportion of patients who gained >15 ETDRS letters from baseline. *p<0.0001 vs sham. **(C)** Mean change from baseline central foveal thickness. *p<0.0001 vs sham. Earliest statistically significant difference was at day 7. Vertical bars are ±1 standard error of the mean.

With the success of both the BRAVO and CRUISE studies and the favorable safety profile of intravitreal anti-VEGF therapy, its use for macular edema associated with RVOs will rapidly increase. Most practices already use anti-VEGF therapy for the treatment of exudative macular degeneration and thus transitioning to its use in RVOs should be seamless. In the future, longer lasting anti-VEGF delivery devices or drugs will likely be favored over monthly injections. Alternate delivery methods including topical, local depot injections, or perhaps even systemic delivery will likely emerge. Combination therapy with anti-VEGF agents acting to rapidly reduce macular edema, and therapy aimed at restoring blood flow such as L-CRA for CRVO or vitrectomy with or without sheathotomy for BRVO may merit future investigation to limit the need for prn treatments of anti-VEGF agents.

Intravitreal corticosteroids have also been shown to be effective in the treatment of macular edema from RVOs, however the high incidence of glaucoma and cataract may limit its use.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Executive summary

Retinal vein occlusions

- Branch retinal vein occlusion (BRVOs) are caused by compression of a branch retinal vein at arteriovenous crossings.
- Central retinal vein occlusions (CRVOs) are caused by compression of the central retinal vein near the lamina cribosa.
- Macular edema is a major cause of vision loss from retinal vein occlusion.
- Intraocular VEGF levels are high after retinal vain occlusion, causing macular edema.

Historic treatments for vein occlusions

- The BVOS established macular grid photocoagulation as the standard of care in patients with BRVO and vision loss from macular edema.
- Laser therapy is ineffective in treating macular edema in patients with CRVO.

Other treatments

- Other treatments have been attempted, such as laser-induced chorioretinal venous anastamosis (L-CRA), optic neurotomy, sheathotomy and vitrecomy with limited success and limited strength of evidence in large-scale, randomized, controlled trials.
- The SCORE-BRVO trial showed that intravitreal corticosteroid therapy is inferior to macular grid photocoagulation.
- The SCORE-CRVO trial showed that although intravitreal corticosteroids are effective at improving vision and macular edema after CRVO, its use may be limited by the increased risk of glaucoma and cataract.
- The GENEVA trial showed that sustainedrelease intravitreal dexamethasone is effective at improving vision and macular edema after BRVO and CRVO. Long-term retreatment studies are underway.

Anti-VEGF for macular edema

- The BRAVO and CRUISE studies demonstrated that monthly intravitreal ranibizumab is an effective treatment for macular edema from RVOs.
- The safety profile of intravitreal ranibizumab is superior to that of intravitreal corticosteroid.
- Impressive gains in vision and anatomic restoration of the fovea are achieved with intravitreal ranibizumab.
- As-needed dosing after 5-monthly intravitreal injections of ranibizumab is effective at maintaining gains in vision.

No writing assistance was utilized in the production of this manuscript.

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- ■ of interest
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