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REVIEW

Treatment of macular edema due to retinal vein occlusions

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Abstract: Retinal vein occlusion (RVO) is a prevalent retinal vascular disease, second only to diabetic retinopathy. Previously there was no treatment for central retinal vein occlusion (CRVO) and patients were simply observed for the development of severe complications, generally resulting in poor visual outcomes. The only treatment for branch vein occlusion (BRVO) was grid laser photocoagulation, which reduces edema very slowly and provides benefit in some, but not all patients. Within the past year, clinical trials have demonstrated the effects of three new pharmacologic treatments, ranibizumab, triamcinolone acetonide, and dexamethasone implants. The benefit/risk ratio is best for intraocular injections of ranibizumab, making this first-line therapy for most patients with CRVO or BRVO, while intraocular steroids are likely to play adjunctive roles. Standard care for patients with RVO has changed and will continue to evolve as results with other new agents are revealed.

Keywords: vascular endothelial growth factor, triamcinolone acetonide, dexamethosone implant, sustained release, vascular leakage, ischemia

Introduction

There are two types of retinal vein occlusions (RVO), central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO). In CRVO, there is obstruction of the major outflow channel of the eye, resulting in effects throughout the entire retina, including hemorrhages; cotton wool patches, which represent nerve layer infarcts; edema; and capillary occlusion. Hemorrhages can vary from dense and almost confluent to sparse and scattered. Likewise, cotton wool patches and capillary occlusion can each range from little or none to extensive. In BRVO, a tributary of the central retinal vein is obstructed and only the portion of the retina that is drained by the tributary is affected. The more proximal the occlusion, the greater the area of retina affected; obstruction of the superior or inferior branch of the central retinal vein affects roughly half the retina and is called a hemiretinal vein occlusion. The consequences of BRVO are similar to those seen in CRVO (hemorrhages, cotton wool patches, edema, capillary occlusion), but tend to be less severe because a portion of the retina has normal venous drainage.

Prevalence and incidence

The prevalence of RVO based upon several studies in the United States, Europe, Asia, and Australia is estimated to be 5.2 per 1,000.[1] In the Beaver Dam Eye study, RVO accounted for 12% of eyes with visual acuity (VA) worse than 20/200.[2] RVOs are the second most common type of retinal vascular disease, second only to diabetic retinopathy.

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The incidence of RVOs is estimated to be 180,000 per year in the US and BRVOs account for nearly 80% of those.[3]

Risk factors and pathogenesis

Risk factors for CRVO include hypertension, diabetes mellitus, atherosclerosis, smoking, age > 65, open angle glaucoma, and conditions that promote a hypercoagulable state.[4] Most of these risk factors lead to diffuse disease of the vascular endothelium and it is likely that there are anatomical or physiologic differences in the central retinal vein that predispose to thrombosis when its endothelium is compromised. Glaucoma appears to be one such factor; it is postulated that glaucoma-induced bowing of the lamina cribosa distorts the central retinal vein, altering blood flow in a way that promotes damage to the endothelium which promotes thrombosis. Histopathology has confirmed the presence of a thrombus in the central retinal vein in several cases.[5] Local differences that predispose to thrombosis in nonglaucomatous eyes are unknown. Congenital or acquired kinking of the central retinal vein could be a predisposing factor, but there is no understanding of how or why it occurs.

Hypertension and atherosclerosis are risk factors for BRVO, and both cause thickening of arteriole walls. BRVO occurs at sites where retinal arterioles cross over veins and it appears that thickening of the arteriole wall compresses the vein, causes turbulent flow, damages endothelium, and promotes thrombosis.

The obstruction in venous outflow after CRVO or BRVO increases intraluminal venous pressure and causes transudation of plasma and blood, resulting in edema and hemorrhages throughout all or most of the retina for CRVO and throughout the drainage area of a BRVO. Severe edema appears to increase interstitial pressure and compromise arterial perfusion resulting in variable amounts of capillary occlusion and cotton wool patches. It is likely that differences in the amount of pre-existent arterial insufficiency from atherosclerosis determines differences in the amount of capillary nonperfusion. In general, there is a wide spectrum with some patients showing very little nonperfusion and others showing larger areas of nonperfusion. Extensive nonperfusion is associated with a poor prognosis and patients who have it are said to have ischemic BRVO or CRVO. In some patients, ischemia increases over time and they are viewed as undergoing a transition from nonischemic to ischemic. Severe retinal ischemia can be complicated by retinal neovascularization (NV), neovascular glaucoma, and a very poor visual outcome. Thus the amount of retinal ischemia is one of the major determinants of outcome.

Treatment

Laser photocoagulation

The use of laser photocoagulation to treat diabetic macular edema prompted its use in branch vein occlusion. The Branch Vein Occlusion Study was a prospective, randomized, multicenter trial that investigated the effects of grid laser treatment in 139 eyes of patients with macular edema following BRVO occurring within 3–18 months of study entry, with best-corrected visual acuity (BCVA) of 20/40 or worse and sufficient clearing of retinal hemorrhage to allow safe laser photocoagulation.[6] At the 3-year primary endpoint, patients treated with laser photocoagulation showed a statistically significant mean improvement of 1.33 lines of vision compared with 0.23 lines in the control group. After publication of the Branch Vein Occlusion Study, grid laser therapy became the standard of care for BRVO. However, since many patients with BRVO present with BCVA of 20/80 or worse, an average improvement of 1.33 lines may leave affected patients with substantial visual disability in the affected eye. Since visual improvement occurs very slowly after laser treatment, there is a need for more effective treatments that provide rapid and complete restoration of vision.

The benefits seen in patients with BRVO with grid laser photocoagulation resulted in many clinicians trying grid laser therapy in CRVO and in some cases there appeared to be reduction in macular edema. However, the Central Retinal Vein Occlusion Study demonstrated that despite some reduction in macular edema from grid laser therapy, there was no visual benefit compared to observation.[7] Thus for many years, patients with CRVO were observed watching for retinal or iris neovascularization and if that occurred, scatter photocoagulation was done.

Ranibizumab

Signs of retinal ischemia in patients with CRVO or BRVO such as cotton wool patches and capillary nonperfusion led to the hypothesis that VEGF released by ischemic retina contributed to macular edema. The development of ranibizumab, (Lucentis, Genentech, Inc, San Francisco, CA), a humanized, affinity-matured anti-VEGF antibody fragment that binds to and neutralizes all isoforms of VEGF-A and their biologically active degradation products[8] made it possible to test that hypothesis.

A small interventional pilot study in patients with CRVO or BRVO demonstrated that monthly injections of 0.3 mg or 0.5 mg ranibizumab for 3 months caused a marked reduction in macular edema and a mean improvement in BCVA of approximately 15 letters in all ranibizumab treatment groups.[9]

Other pilot trials had similar results.[10,11] This provided the rationale for two large multicenter trials, the Ranibizumab for the Treatment of Macular Edema after *C*entral *R*etinal Vein Occl*U*s*I*on (CRUISE) *S*tudy[12] and the Ranibizuma*B* for the Treatment of Macular Edema following B*RA*nch Retinal *V*ein *O*cclusion (BRAVO) Study.[13] In the CRUISE Study, 392 patients with macular edema following central retinal vein occlusion (CRVO) were randomized to receive monthly intraocular injections of 0.3 mg (n = 132) or 0.5 mg (n = 130) of ranibizumab or sham injections (n = 130).

Patients were eligible if they had foveal-involved macular edema from a CRVO occurring within 12 months of study entry, BCVA of 20/40 to 20/320, and center subfield thickness (CST) ≥250 µm (Stratus OCT3). Patients were excluded if they had a brisk afferent pupil defect, had scatter laser photocoagulation within 3 months, an intraocular injection of steroid or a VEGF antagonist within 3 months, or had an improvement of ≥10 ETDRS letters in BCVA between screening and baseline.

Baseline characteristics were well balanced among the three groups; the mean age was 68 years, mean BCVA was 20/100, the mean time from diagnosis of CRVO was 3.3 months, and the mean center point thickness (CPT) was 685 µm. At 6 months, the primary endpoint, mean change from baseline BCVA letter score was 12.7 and 14.9 in the 0.3 mg and 0.5 mg ranibizumab groups and 0.8 in the sham group ($P < 0.0001$). The percentage of patients who gained ≥ 15 letters in BCVA was 46.2% (0.3 mg) and 47.7% (0.5 mg) in the ranibizumab groups and 16.9% in the sham group ($P < 0.0001$). The percentage of patients with a Snellen equivalent BCVA of 20/40 or better was 43.9% (0.3 mg) and 46.9% (0.5 mg) compared with 20.8% in the sham group ($P < 0.0001$). The percentage of patients with a Snellen equivalent BCVA of 20/200 or worse was 15.2% (0.3 mg) and 11.5% (0.5 mg) compared with 27.7% in the sham group ($P < 0.005$). Based upon the NEI VFQ-25 survey, patients who received ranibizumab felt they had greater improvement (improvement from baseline in NEI VFQ score: 7.1, 0.3 mg; 6.2, 0.5 mg: 2.8, sham). There was greater reduction of macular edema in the ranibizumab groups because CPT was reduced by 433.7 µm (0.3 mg) and 452.3 µm (0.5 mg) compared to 167.7 µm in the sham group. The percentage of patients with CPT ≤ 250 µm at 6 months was 75.0% (0.3 mg), 76.9% (0.5 mg), and 23.1% (sham, $P < 0.0001$). This study demonstrated that six sessions of monthly injections of 0.3 mg or 0.5 mg reduced macular edema and provided substantial visual benefit in patients with CRVO.

In the BRAVO study, 397 patients with macular edema following branch retinal vein occlusion (BRVO) were randomized to receive monthly intraocular injections of 0.3 mg (n = 134) or 0.5 mg (n = 131) of ranibizumab or sham injections (n = 132). Patients were eligible if they had foveal-involved macular edema from a BRVO occurring within 12 months of study entry, BCVA of 20/40 to 20/400, and CST ≥250 µm (Stratus OCT3). Exclusion criteria were the same as those in the CRUISE trial. Baseline characteristics were well balanced among the three groups; mean BCVA was 20/80, the mean time from diagnosis of BRVO was 3.5 months, and the mean CPT was 520 µm. Starting at month 3, patients were eligible for grid laser treatment if hemorrhages had cleared sufficiently to allow safe application of laser and the following criteria were met: Snellen equivalent BCVA ≤ 20/40 or mean CST ≥ 250 µm, and compared with the visit 3 months before the current visit, the patient had a gain of <5 letters in BCVA or a decrease of <50 µm in mean CST. If rescue laser was not given at month 3, the same criteria were applied at month 4, and if rescue laser was not given at month 4, the criteria were applied at month 5.

At month 6, the primary endpoint, mean change from baseline BCVA letter score was 16.6 and 18.3 in the 0.3 mg and 0.5 mg ranibizumab groups and 7.3 in the sham group ($P < 0.0001$). The percentage of patients who gained ≥ 15 letters in BCVA was 55.2% (0.3 mg) and 61.1% (0.5 mg) in the ranibizumab groups and 28.8% in the sham group ($P < 0.0001$). The percentage of patients with a Snellen equivalent BCVA of 20/40 or better was 67.9% (0.3 mg) and 64.9% (0.5 mg) compared with 41.7% in the sham group ($P < 0.0001$). The percentage of patients with a Snellen equivalent BCVA of 20/200 or worse was 1.5% (0.3 mg) and 0.8% (0.5 mg) compared with 9.1% in the sham group ($P < 0.01$). Based upon the NEI VFQ-25 survey, patients who received ranibizumab felt they had greater improvement (improvement from baseline in NEI VFQ score: 9.3, 0.3 mg; 10.4, 0.5 mg: 5.4, sham). There was greater reduction of macular edema in the ranibizumab groups because CPT was reduced by 337.3 µm (0.3 mg) and 345.2 µm (0.5 mg) compared to 157.7 µm in the sham group. The percentage of patients with CPT ≤ 250 µm at month 6 was 91% (0.3 mg), 84.7% (0.5 mg), and 45.5% (sham, $P < 0.0001$). More patients in the sham group (54.5%) received rescue grid laser therapy than in the 0.3 mg (18.7%) or 0.5 mg (19.8%) ranibizumab groups. There were no safety signals identified in either trial.

After the primary endpoint in the CRUISE and BRAVO trials, patients were evaluated every month and if study

eye Snellen equivalent BCVA was ≤20/40 or mean CST was ≥250 μm, they received an injection of ranibizumab; patients in the ranibizumab groups received their assigned dose and patients in the sham group received 0.5 mg. In patients with CRVO, the mean number of ranibizumab injections during the observation period was 3.9, 3.6, and 4.2 in the 0.3 mg, 0.5 mg, and sham/0.5 mg groups; and the percentage of patients that did not receive any injections during the observation period was 7.0, 6.7, and 4.3, respectively.[14] At month 12 in the ranibizumab groups, the improvement from baseline in ETDRS letter score was 13.9, very similar to the month 6 results, indicating that vision is well maintained when injections are given only if there is recurrent or residual macular edema. Patients in the sham group showed substantial improvement during the observation period when they were able to receive ranibizumab; improvement from baseline in letter score was 0.8 at month 6 and 7.3 at month 12. The percentage of patients who had an improvement from baseline BCVA letter score ≥ 15 at month 12 was 47.0% (0.3 mg) and 50.8% (0.5 mg) in the ranibizumab groups, almost identical to the month 6 results. In the sham group, 33.1% of patients improved from baseline ≥ 15 in letter score at month 12 compared to 16.9% at month 6. At month 12, 43% of patients in the two ranibizumab groups had a Snellen equivalent BCVA of 20/40 compared to 35% in the sham/0.5 mg group.

In patients with BRVO, the mean number of ranibizumab injections during the observation period was 2.9, 2.8, and 3.8 in the 0.3 mg, 0.5 mg, and sham/0.5 mg groups; and the percentage of patients that did not receive any injections during the observation period was 17.2, 20.0, and 6.5, respectively.[15] At month 12 in the ranibizumab groups, the improvement from baseline in ETDRS letter score was 16.4 (0.3 mg) and 18.3 (0.5 mg), very similar to the month 6 results, indicating that vision is well maintained when injections are given only if there is recurrent or residual macular edema. Patients in the sham group showed substantial improvement during the observation period when they were able to receive ranibizumab; improvement from baseline in letter score was 7.3 at month 6 and 12.1 at month 12. The percentage of patients who had an improvement from baseline BCVA letter score ≥ 15 at month 12 was 55.2% (0.3 mg) and 61.1% (0.5 mg) in the ranibizumab groups, almost identical to the month 6 results. In the sham group, 43.9% of patients improved from baseline ≥ 15 in letter score at month 12 compared to 28.8% at month 6. At month 12, 67.9% (0.3 mg) and 64.4% (0.5 mg) of patients in the ranibizumab groups had a Snellen equivalent BCVA of 20/40 compared to 56.8% in the sham/0.5 mg group. Thus, in both CRUISE and BRAVO, patients in the sham groups showed a substantial improvement in vision during the second 6 months when they were able to receive ranibizumab as needed, but their vision at month 12 was not as good as that in patients in the ranibizumab groups. This raises a question as to whether delay in treatment carries a visual penalty; hopefully this question will be answered by additional follow-up.

An important question is whether suppression of VEGF has deleterious effects on the retina, particularly in eyes that have retinal ischemia. In fact, some retina specialists have questioned whether suppression of VEGF might worsen macular ischemia. A detailed evaluation of fluorescein angiograms from BRAVO and CRUISE is needed to answer that question, but it is reassuring that loss of vision was rare in patients with RVO treated with ranibizumab and worsening of macular ischemia was not reported as an adverse event in any patients that received ranibizumab.

The only data available for time points longer than 1 year are from relatively small pilot trials.[16] Patients with BRVO given 3-monthly injections of ranibizumab had a mean improvement of 16.1 letters. After that, they were seen every 2 months and were given an injection of ranibizumab if foveal thickness was ≥250 μm. At month 24, the mean improvement in BCVA was 17.8 letters, 60% had a Snellen equivalent of 20/40 or better, and 65% had foveal thickness ≤ 250 μm. This indicates that visits every 2 months with injections of ranibizumab as needed is sufficient to control edema and maintain vision in patients with BRVO. Patients with CRVO given 3-monthly injections of ranibizumab had a mean improvement of 12.0 letters. After that, they were seen every 2 months and were given an injection of ranibizumab if foveal thickness was ≥250 μm. At month 24, the mean improvement in BCVA was 8.5 letters, 30% had a Snellen equivalent of 20/40 or better, and 30% had foveal thickness ≤ 250 μm. This indicates that visits every 2 months with injections of ranibizumab as needed is not sufficient to control edema and maintain vision in patients with CRVO. At month 24, only 5 of 17 patients with BRVO and 3 of 14 patients with CRVO had complete resolution of edema and had not needed injections for at least 1 year. Two baseline characteristics that predicted a poor visual outcome in patients with BRVO or CRVO were the presence of macular edema for greater than 1 year and extensive closure of perifoveal capillaries. Thus, the long-term outcomes for treatment of CRVO or BRVO with ranibizumab are excellent, but it may be difficult to completely wean patients off injections even after 2 years. Furthermore, compared to patients with BRVO, those with

CRVO on average require more frequent follow-up and a greater number of injections to control edema and maintain visual benefits.

Intraocular steroids

The Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) Studies compared intraocular injections of preservative-free triamcinolone acetonide (TA) to standard care in patients with macular edema due to CRVO[17] or BRVO.[18] In the CRVO study, 271 patients were randomized to receive 1 mg (n = 92) or 4 mg (n = 91) of TA or observation (n = 88). In the BRVO study, 411 patients were randomized to receive 1 mg (n = 136) or 4 mg (n = 138) of TA or grid laser (n = 137). In both studies, patients were eligible if they had foveal-involved macular edema from a CRVO occurring within 12 months of study entry, BCVA of 20/40 to 20/400, and CST ≥ 250 μm (Stratus OCT3). Patients were excluded if they had a prior intraocular steroid injection or vitrectomy, had laser photocoagulation within 3.5 months, or had a history of glaucoma or intraocular pressure (IOP) ≥ 25.

In the CRVO study, baseline characteristics were well balanced among the three groups; the mean age was 68 years, mean BCVA was 20/100, the mean time from diagnosis of CRVO was 4 months, and the mean CPT was 659 μm. At month 12, the primary endpoint, mean change from baseline BCVA letter score was −1.2 in the two TA groups and −12.1 in the observation group. The percentage of patients who gained ≥ 15 letters in BCVA was 26.5% (1 mg) and 25.6% (4 mg) in the TA groups and 6.8% in the observation group. Reduction in CPT at month 12 was 196 μm (1 mg) and 261 μm (0.5 mg) compared to 277 μm in the observation group. The percentage of patients with CPT ≤ 250 μm at month 12 was 32% (0.3 mg), 45% (4 mg), and 28%. More patients in the TA groups (4 mg-35%;1 mg-26%) required initiation of IOP-lowering drops compared to the observation group (8%). Significantly more patients in the 4 mg group (21) than in the observation group (3) required cataract surgery in the study eye between 1 and 2 years. The study recommended injection of 1 mg TA for patients with macular edema due to CRVO with repeat injections every 4 months for persistent/recurrent edema. In the BRVO study, baseline characteristics were well balanced among the three groups; the mean age was 67 years, mean BCVA was 20/80, the mean time from diagnosis of BRVO was 4 months, and the mean CPT was 525 μm. At month 12, the primary endpoint, mean change from baseline BCVA letter score was 5.7 (1 mg) and 4.0 (4 mg) in the TA groups and 4.2 in the grid laser group. The percentage of patients who gained ≥ 15 letters in BCVA was 26% (1 mg) and 27% (4 mg) in the TA groups and 29% in the laser group. Thus, TA injections were not superior to grid laser.

The GENEVA Trials were two Phase III trials comparing the effects of intraocular injection of 0.7 mg or 0.35 mg dexamethosone (DEX) implants to sham injections in patients with macular edema due to CRVO or BRVO.[19] The trials were identical and therefore the pooled results were reported; 0.7 mg (n = 427), 0.35 mg (n = 414), sham (n = 426). Patients were eligible if they had foveal-involved macular edema from a CRVO (1.5–9 months) or BRVO (1.5–12 months), BCVA of 20/50 to 20/200, and CST ≥ 300 μm (Stratus OCT2 or OCT3). Patients were excluded if they had glaucoma or ocular hypertension requiring more than one medication. Twice as many BRVO (n = 830, 66%) as CRVO (n = 437, 34%) were enrolled. The design of this study is unusual. In particular, data from the entire population which combines outcomes for CRVO and BRVO are difficult to interpret because of differences in their natural history; BRVO has a higher rate of spontaneous improvement of macular edema, lower rates of vitreous hemorrhage and neovascular glaucoma which can adversely affect visual outcomes, and there are potential confounding effects from rescue grid laser. Therefore, the subgroup analyses provide the information most relevant to patient care.

In the BRVO subgroup at the 6-month primary endpoint, the mean change from baseline BCVA letter score was 7.5 in the two DEX implant groups compared to 5.0 in the sham group (P = 0.008). The percentage of patients who gained ≥ 15 letters in BCVA was 23% (0.7 mg) and 21% (0.35 mg) in the implant groups and 20% in the sham group. In the CRVO subgroup, the mean change from baseline BCVA letter score was 0 (0.7 mg) and 2 (0.35 mg) in the two DEX implant groups, not significantly better than sham (–2). The percentage of patients who gained ≥ 15 letters in BCVA was 18% (0.7 mg) and 17% (0.35 mg) in the implant groups and 12% in the sham group (NS). Thus, 6 months after injection there was little evidence of benefit in patients with BRVO and no benefit in CRVO. However, both patient populations showed some evidence of benefit at earlier time points. Peak effects were at 60 days. In the CRVO subgroup, the mean change from baseline BCVA letter score was 9 (0.7 mg) and 10 (0.35 mg) in the two DEX implant groups, significantly better than sham (0), and 29% and 33% of patients gained ≥ 15 letters in BCVA compared to 9% for sham. At 3 months, the mean change from baseline BCVA letter score was 4 (0.7 mg) and 6 (0.35 mg) in the two DEX implant groups, significantly better than sham (0), and 18%

and 24% of patients gained ≥ 15 letters in BCVA compared to 10% for sham. In the BRVO subgroup, the mean change from baseline BCVA letter score was 10 (0.7 mg) and 9 (0.35 mg) in the two DEX implant groups, significantly better than sham (5), and 30% and 26% of patients gained ≥ 15 letters in BCVA compared to 13% for sham. At 3 months, the mean change from baseline BCVA letter score was 9 (0.7 mg) and 8 (0.35 mg) in the two DEX implant groups, significantly better than sham (5), and 24% and 23% of patients gained ≥ 15 letters in BCVA compared to 15% for sham. Based upon the shorter than anticipated duration of action of the DEX implants, it would be useful to know the effect of repeated injections at 3 month intervals and hopefully such a trial will be considered in the future. Tables 1 and 2 show a comparison of outcomes from the BRAVO, CRUISE, SCORE, and Geneva trials.

Summary and recommendations

Recent studies have provided new options for the management of CRVO and BRVO. For CRVO, we have gone from no treatments to three possible options. The options are not mutually exclusive but choices must be made based upon relative benefit/risk ratios as to which option becomes first-line treatment and which take on adjunctive roles. Using separate trials to assess relative benefit/risk ratios can be hazardous because differences in patient populations and procedures can cloud the issue. In comparing the CRUISE and SCORE CRVO trials, it is clear that there were population differences, because the changes in mean BCVA letter score in control groups were different (CRUISE: 6 months, +0.8 vs SCORE: 8 months, −11.7, 12 months, −12.1) and 17% of the CRUISE control group gained ≥ 15 letters compared to 7% in SCORE. Differences in eligibility criteria may explain the differences. For CRUISE, patients were excluded for BCVA < 20/320 (compared to BCVA < 20/400 in SCORE), an afferent pupil defect, or CRVO > 1 year. The first two criteria may have limited the number of patients with poor visual prognosis (regardless of therapy) due to severe retinal ischemia. Duration of CRVO prior to initiation of treatment can negatively impact outcome[16] and the mean duration of CRVO was 3.3 months in CRUISE compared to 4 months in SCORE.

The percentage of patients who gained ≥ 15 letters in BCVA was 46.2% (0.3 mg) and 47.7% (0.5 mg) in the ranibizumab groups and 16.9% in the corresponding control group, a difference of 28%–30%. The percentage of patients who gained ≥ 15 letters in BCVA was 26.5% (1 mg) and 25.6% (4 mg) in the TA groups and 6.8% in the corresponding control group, a difference of 19%–20%. Thus, although the differences in study populations and design make comparison difficult, the relative benefit seems to be greater with ranibizumab and considering the risk of cataract and increased IOP with TA, ranibizumab has a clear edge.

Differences in study design are the main confounding factor in comparing ranibizumab with DEX implants. Comparison of monthly injections of ranibizumab to a single injection of a DEX implant at 6 months is easy, because the mean change from baseline BCVA letter score was 0 (0.7 mg) and 2 (0.35 mg) in the two DEX implant groups, not significantly better than their control group (−2). It is anticipated that two DEX implant injections 3 months apart would provide greater efficacy, but could also result in greater toxicity. Therefore, with our current state of knowledge, ranibizumab is favored for primary therapy.

Our recommendation for CRVO is to give six injections of 0.5 mg ranibizumab at monthly intervals. After 6 months, it is best to continue monthly follow-up visits and ranibizumab injections for recurrent edema have been shown to maintain visual benefit to at least 1 year.[14] Some patients continue to have recurrent edema after 1 year or longer of treatment[16] and we do not yet have a guide as to how to manage such patients. An ongoing clinical trial is investigating whether laser photocoagulation to areas of capillary nonperfusion can reduce the frequency of ranibizumab injections required. Although most patients respond quite well to ranibizumab injections, in the rare cases where patients who have substantial residual edema and reduced vision after six sessions of monthly injections, it would be reasonable to consider a DEX implant. Ranibizumab levels may decline more rapidly in vitrectomized eyes, so the threshold may be lower for considering a DEX implant in a vitrectomized eye that appears to be responding poorly to ranibizumab injections. Hopefully future studies will provide guidance regarding combination therapy in patients who respond suboptimally to ranibizumab injections.

The comparative analysis is very similar for patients with BRVO and favors ranibizumab; however, integration of drug treatment with grid laser therapy is an additional consideration. Visual acuity improves rapidly after injection of ranibizumab whereas benefit occurs slowly after grid laser therapy and the presence of intraretinal hemorrhages in the macula often precludes laser for several months. Our recommendation for BRVO with macular edema is to give six sessions of monthly injections of ranibizumab. This has the advantage of causing more rapid clearing of hemorrhages in addition to improving vision and macular

Table 1 Comparison of outcomes of recent clinical trials on treatment of CRVO

	CRUISE			SCORE			GENEVA		
				CRVO			CRVO		
N	**392**			**271**			**437**		
Primary endpoint	**Month 6**			**Month 12**			**Month 6**		
Arms	0.3 mg RBZ	0.5 mg RBZ	Sham	1 mg TA	4 mg TA	Observe	0.7 mg DEX	0.35 mg DEX	Sham
Mean ΔBCVA	12.7	14.9	0.8	−1.2	−1.2	−12.1	0	2	−2
% ≥15 letters gained	46.2	47.7	16.9	26.5	25.6	6.8	18	17	12
% ≥15 letters lost				25.6	25.3	43.8			
% snellen 20/40 or better	43.9	46.9	20.8						
% snellen VA 20/200 or worse	15.2	11.5	27.7						
Improvement in NEI-VFQ-25	7.1	6.2	2.8						
Mean change in CPT/μm	434	452	168						
Median change in CPT/μm				196	261	277			
% CPT ≤ 250	75	77	23	32	45	28			

Abbreviations: ΔBCVA, change in best corrected visual acuity; CPT, central point thickness; DEX, dexamethasone implant; RBZ, ranibizumab; TA, triamcinolone.

Table 2 Comparison of outcomes of recent clinical trials on treatment of BRVO

	BRAVO			SCORE			GENEVA		
				BRVO			BRVO		
N	**397**			**411**			**830**		
Primary endpoint	**Month 6**			**Month 12**			**Month 6**		
Arms	0.3 mg RBZ	0.5 mg RBZ	Sham	1 mg TA	4 mg TA	Grid laser	0.7 mg DEX	0.35 mg DEX	Sham
Mean ΔBCVA	16.6	18.3	7.3	5.7	4	4.2	7.5	7.5	5
% ≥15 letters gained	55.2	61.1	28.8	26	27	29	23	21	20
% ≥15 letters lost				5.7	4.0	14.9			
% snellen 20/40 or better	67.9	64.9	41.7						
% snellen VA 20/200 or worse	1.5	0.8	9.1						
Improvement in NEI-VFQ-25	9.3	10.4	5.4						
Mean change in CPT/μm	337	345	158						
Median change in CPT/μm				149	170	224			
% CPT ≤ 250	91	85	46	37	45	53			

Abbreviations: ΔBCVA, change in best corrected visual acuity; CPT, central point thickness; DEX, dexamethasone implant; RBZ, ranibizumab; TA, triamcinolone.

edema.[15] Even the small percentage of patients that would have experienced spontaneous improvement obtain benefit from more rapid return of vision. If there is recurrent edema after six ranibizumab injections, it is reasonable to consider grid laser therapy in combination with ranibizumab as needed. If despite grid laser treatment, frequent injections of ranibizumab continue to be needed to control edema after 1 year, it would be reasonable to discuss the pros and cons of a DEX implant with the patient.

Questions and future directions

Our understanding of RVOs has greatly increased over the past few years, but there are still many remaining questions. 1) Can bevacizumab be substituted for ranibizumab? 2) Can higher doses of ranizibumab provide greater benefit than that seen with 0.5 mg? 3) What role will VEGF-Trap Eye play in management in the future? 4) What is the role of peripheral capillary nonperfusion in the development, persistence, and recurrence of edema, and can scatter photocoagulation to areas of nonperfusion provide benefit? 5) Do other pro-permeability factors in addition to VEGF play a role in RVO and do they account for residual edema seen in some patients treated with anti-VEGF agents? One way to address this issue is to measure aqueous levels of pro-permeability factors in RVO patients that have residual edema despite intensive treatment with an anti-VEGF agent. The feasibility of this approach has been demonstrated in a small study,[20] but a larger study is needed. 6) Are there strategies that can promote permanent resolution of edema and reduce the duration of anti-VEGF injections required? The Ranibizumab DosE Comparison (0.5 mg and 2.0 mg) and the Role of LAser in the ManagemenT of REtinal Vein Occlusion – (RELATE) study is currently recruiting patients with BRVO and CRVO. It seeks to determine if six sessions of monthly injections of 2.0 mg of ranibizumab provides superior outcomes compared to six injections of 0.5 mg. At 6 months, there is a second randomization to determine if laser photocoagulation to areas of capillary nonperfusion can help to achieve complete resolution of edema with fewer ranizibumab injections and whether visual benefits are maintained despite laser treatment. Hopefully this study and others will provide additional guidance as to how our treatment regimens can be modified to further enhance the outstanding outcomes that are being achieved while at the same time reducing burden of frequent follow-up and injections in our patients with RVO.

Disclosure

PAC has standard consulting agreements with LPath, Ora, Amira, Allergan, Pfizer, and Bristol Myers Squibb and has institutional consulting agreements with Genentech and GlaxoSmithKline through which his employer, Johns Hopkins University, receives compensation. He receives research support from Genentech, Alimera, Alcon, GlaxoSmithKline, Oxford BioMedica, and Genezyme. The other authors have no potential conflicts.

References

1. Rogers S, McIntosh RL, Cheung N, et al. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. *Ophthalmology*. 2010;117:313–319.
2. Klein R, Klein BEK, Lee KE, Cruickshanks KJ, Gangnon RE. Changes in visual acuity in a population over a 15-year period: the Beaver Dam Eye Study. *Am J Ophthalmol*. 2006;142:531–539.
3. Klein R, Moss SE, Meuer SM, Klein BE. The 15-year cumulative incidence of retinal vein occlusion: the Beaver Dam Eye Study. *Arch Ophthalmol*. 2008;126:513–518.
4. Turello M, Pasca S, Daminato R, et al. Retinal vein occlusion: evaluation of "classic" and "emerging" risk factors and treatment. *J Thromb Thrombolysis*. 2010;29:459–464.
5. Green WR, Chan CC, Hutchins GM, Terry JM. Central vein occlusion: a prospective histological study of 29 eyes in 28 cases. *Trans Am Ophthalmol Soc*. 1981;79:371–421.
6. The Branch Vein Occlusion Study Group. Argon laser photocoagulation for macular edema in branch vein occlusion. *Am J Ophthalmol*. 1984;98:271–282.
7. The Central Vein Occlusion Study Group. Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. The central vein occlusion study group M report. *Ophthalmology*. 1995;102:1425–1433.
8. Ferrara N, Damico L, Shams N, Lowman H, Kim R. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. *Retina*. 2006;26:859–870.
9. Campochiaro PA, Hafiz G, Shah SM, et al. Ranibizumab for macular edema due to retinal vein occlusions; implication of VEGF as a critical stimulator. *Molec Ther*. 2008;16:791–799.
10. Pieramici DJ, Rabena M, Castellarin AA, et al. Ranibizumab for the treatment of macular edema associated with perfused central retinal vein occlusions. *Ophthalmology*. 2008;115:47–54.
11. Spaide RF, Chang LK, Klancnik JM, et al. Prospective study of intravitreal ranibizumab as a treatment for decreased visual acuity secondary to central retinal vein occlusion. *Am J Ophthalmol*. 2009;147:298–306.
12. Brown DM, Campochiaro PA, Singh RP, et al. Efficacy and safety of ranibizumab in the treatment of macular edema secondary to central retinal vein occlusion: 6-month results of the phase III CRUISE study. *Ophthalmology*. 2010;117:1124–1133.
13. Campochiaro PA, Heier JS, Feiner L, et al. Ranibizumab for macular edema following branch retinal vein occlusion: 6-month primary endpoint results of a phase III study. *Ophthalmology*. 2010;117:1102–1112.
14. Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: 12-month outcomes of a phase III study. *Ophthalmology*. 2011; In press.
15. Brown DM, Campochiaro PA, Bhisitkul RB, et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. *Ophthalmology*. 2011. In press.

16. Campochiaro PA, Hafiz G, Channa R, et al. Antagonism of vascular endothelial growth factor for macular edema caused by retinal vein occlusion: two-year outcomes. *Ophthalmology*. 2010;117:2387–2394.
17. The SCORE Study Research Group. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion. The standard care vs corticosteroid for retinal vein occlusion (SCORE) study report 5. *Arch Ophthalmol*. 2009;127:1101–1114.
18. The SCORE Study Research Group. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular edema secondary to branch vein occlusion. The standard care vs corticosteroid for retinal vein occlusion (SCORE) study report 6. *Arch Ophthalmol*. 2009;127:1115–1128.
19. Haller JA, Kuppermann BD, Blumenkranz MS, et al. Randomized controlled trial of an intravitreous dexamthasone drug delivery system in patients with diabetic macular edema. *Arch Ophthalmol*. 2010;128:289–296.
20. Campochiaro PA, Choy DF, Do DV, et al. Monitoring ocular drug therapy by analysis of aqueous samples. *Ophthalmology*. 2009;116:2158–2164.