
CME ACTIVITY

Applying New Data to Improve the Standard of Care in Retinal Diseases

Managing Macular Edema Associated With Retinal Venous Occlusions

By Michael Singer, MD; and Krishna Surapaneni

STATEMENT OF NEED

Retinal vein occlusion (RVO) is a common ocular disease that remains poorly understood due to the multifactorial nature of its presentation and contributing systemic factors. Several associated systemic factors have been identified and continue to be studied for their impact on RVO, including hypertension, diabetes, hypercholesterolemia, thyroid disorder, and ischemic heart disease. Increased intraocular pressure and axial length are other factors that play roles in this disease.^{1,2}

For many years, clinicians have followed the recommendations set forth by the Branch Vein Occlusion Study³ and the Central Vein Occlusion Study.⁴ The former demonstrated that grid laser photocoagulation leads to a greater improvement in visual acuity than natural history, but the latter showed that grid laser photocoagulation did not improve visual acuity even though the macular edema decreased.

The SCORE central RVO (CRVO) study included 271 people; 73% had high blood pressure, and 23% had diabetes. After 1 year, 27% of patients receiving 1-mg corticosteroid injection and 26% of patients receiving 4-mg injection experienced a substantial gain of 3 or more lines of visual acuity.⁵ These results appeared to last up to 2 years, although the 2-year results included a smaller number of patients. The SCORE branch RVO (BRVO) trial included 411 people; 70% had high blood pressure. After 1 year, 29% of patients in the laser treatment group, 26% of patients in the 1-mg corticosteroid injection group, and 27% of patients in the 4-mg injection group experienced a substantial gain of 3 or more lines of visual acuity.⁶ These results appeared to last up to 3 years, although the 3-year results included a smaller number of patients.

The dexamethasone intravitreal implant 0.7-mg (Ozurdex, Allergan) is the most recent agent approved by the US Food and Drug Administration (FDA) for the treatment of macular edema secondary to RVO. In the pivotal phase 3 GENEVA trial, which enrolled 1267 patients, there was a visual acuity gain and reduction in macular edema at 2 months in the treatment arm that was not observed in the placebo arm.⁷ The dexamethasone intravitreal implant is a biodegradable implant that delivers extended release of the corticosteroid after intravitreal insertion.

Ranibizumab was recently FDA-approved for the treatment of macular edema following both BRVO and CRVO, based on the results of the BRAVO⁸ and CRUISE⁹ studies.

BRAVO randomized 397 patients to 6 monthly injections of ranibizumab, either 0.3 mg or 0.5 mg, or to sham injections. The primary efficacy outcome was mean change from baseline best corrected visual acuity (BCVA) at 6 months. Secondary outcomes included the percentage of patients who gained 3 lines (15 letters) of BCVA at 6 months. The mean gain from baseline at month 6 was 16.6 letters in patients receiving 0.3 mg ranibizumab, 18.3 letters in those receiving 0.5 mg, and 7.3 in those receiving sham injection. By month 6, most patients in the 2 ranibizumab groups gained at least 3 lines of BCVA (55.2% in the 0.3 mg group and 61.1% in the 0.5 mg group), while most of those in the sham group did not (28.8%). Safety profiles were consistent with those found in studies of ranibizumab for age-related macular degeneration.

CRUISE randomized 392 patients with visual acuity between 20/40 and 20/320 with CRVO to 0.3 mg ranibizumab, 0.5 mg ranibizumab, or sham injections. The patients all had macular edema secondary to central RVO. BCVA improvements occurred rapidly for those in the ranibizumab groups, averaging 9 letters improvement in 7 days, with around a 440 μ m decrease in central foveal thickness as well. Safety profiles were consistent with those found in studies of ranibizumab for AMD.

The COPERNICUS study evaluated aflibercept for the treatment of macular edema secondary to CRVO. At 6 months, 56.1% of patients receiving monthly 2-mg aflibercept gained at least 15 letters of visual acuity from baseline, compared with 12.3% of patients receiving sham injections ($P < .0001$).¹⁰ Treated patients gained a mean 17.3 letters of visual acuity, compared with a mean loss of 4.0 letters in those receiving sham injections ($P < .001$). These results were confirmed by the GALILEO trial.¹¹

There has also been a small study evaluating the fluocinolone acetonide implant (Iluvien, Alimera Sciences) for CRVO, showing that the implant has a benefit but with the side effects of cataract and IOP.¹²

In light of these data, there is a need for ophthalmologists to understand how the treatments available for RVO can be best utilized for improved patient outcomes.

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TARGET AUDIENCE

This certified CME activity is designed for retina specialists and general ophthalmologists involved in the management of patients with retinal disease.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- Recognize various forms of macular edema and inflammation using the latest developments in medical literature and new insights from case-based learning.
- Understand the new data available on treatments for RVO and how to apply this information in monotherapy and combination therapy treatment schemes.
- Treat various forms of macular edema and inflammation, based on assessment of patient need, latest developments in medical literature, and insights from case-based learning.

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FACULTY CREDENTIALS

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FACULTY/STAFF DISCLOSURE DECLARATIONS

Dr. Singer states that he is a consultant to Allergan Inc. and that he has received lecture fees and research grants from the company.

Mr. Surapaneni states that he has no financial relationships to disclose.

All of those involved in the planning, editing, and peer review of this educational activity report no relevant financial relationships. ■

Managing Macular Edema Associated With Retinal Venous Occlusions

BY MICHAEL SINGER, MD; AND KRISHNA SURAPANENI

Retinal vein occlusions (RVOs) are the second most common type of retinal vascular disorders, affecting an estimated 180 000 eyes per year in the United States.^{1,2} Macular edema is a frequent cause of vision loss following an RVO.^{3,4} Five years ago the decision to treat a patient was straightforward. If the patient had a branch retinal vein occlusion (BRVO) the treatment was grid laser photocoagulation, as demonstrated by the results of the Branch Vein Occlusion Study (BVOS).⁵ If the patient presented with macular edema associated with central retinal vein occlusion (CRVO) the Central Vein Occlusion Study (CVOS) recommended observation initially and panretinal photocoagulation only when the patient presented with neovascularization. Today a physician's arsenal is much more diverse, and subsequently the decision tree has become much more complicated.

Treatment options for macular edema after BRVO now include laser photocoagulation,⁵ intravitreal corticosteroids,^{6,7} and intravitreal anti-VEGF agents.⁸ For CRVO, both intravitreal corticosteroids^{5,7,9} and anti-VEGF agents^{10,11} are effective in the treatment of macular edema.

LASERS

Many treatments for RVOs were attempted over the years before the BVOS and CVOS, but laser photocoagulation seemed to be the only treatment confirmed by level 1 data.

The BVOS trial demonstrated the effectiveness of peripheral scattered argon laser photocoagulation in improving best corrected visual acuity (BCVA) in patients with BRVO. This study compared argon laser treatment to no treatment. The number of patients who gained 2 lines of vision or greater was significantly larger in the treatment group compared with the nontreatment group.¹² Hence, laser became the standard of care for treating BRVO until the introduction of newer treatments.

The CVOS trial demonstrated that macular grid photocoagulation was not effective in improving BCVA in patients with CRVO. This study compared macular grid photocoagulation with no treatment. There was no statistically significant difference in BCVA between the treatment and nontreatment groups, although the treatment clearly reduced angiographic evidence of macular

edema. Hence, the CVOS trial did not support macular grid photocoagulation for macular edema in CRVO.¹³

STEROIDS

The SCORE study was a phase 3 prospective clinical trial that demonstrated the effectiveness of triamcinolone injections in improving BCVA in patients with BRVO and CRVO. Patients were given 2 doses of triamcinolone (1 and 4 mg) or standard-of-care laser treatment. The percentage of patients with BRVO who gained at least 3 lines of vision was 26% in the 1-mg triamcinolone group, 27% in the 4-mg triamcinolone group, and 29% in the laser treatment group. These gains were maintained at 3 years in the treatment groups. Hence, the SCORE BRVO trial showed that triamcinolone and laser treatment have a similar impact on vision; however, laser may be the preferred treatment given that was associated with fewer complications.¹⁴ The percentage of patients with CRVO who gained at least 3 lines of vision was 27% in the 1-mg triamcinolone group, 26% in the 4 mg triamcinolone group, and 7% in the laser treatment group. These gains were maintained at 2 years in the treatment group. Hence, the SCORE CRVO trial identified the first long-term, effective treatment for vision loss due to macular edema in patients with CRVOs.^{15,16}

The GENEVA study was a phase 3 prospective clinical trial that demonstrated the effectiveness of dexamethasone intravitreal implant (Ozurdex, Allergan) in improving BCVA in patients with BRVOs and CRVOs. Patients were given 1 of 2 intravitreal dexamethasone (0.35 and 0.7 mg) or sham treatment. The percentage of patients with CRVO and BRVO who gained at least 15 letters of BCVA was 41% in the 0.7 mg dexamethasone group, 40% in the 0.35 mg dexamethasone group, and 23% in the sham group. Furthermore, patients who received the dexamethasone implant achieved a 15-letter improvement significantly faster than those who received sham treatment.^{17,18}

In the study, longer duration of macular edema at the time of treatment with the dexamethasone intravitreal implant was associated with a significantly lower likelihood of achieving improvements in vision or anatomy at 6 or 12 months after treatment.

CASE NO. 1

A 49-year-old man had a history of CRVO for over 2 years (Figure 1). He was enrolled in the SHORE study in 2011 and never was able to be randomized because his CFT and vision never stabilized. He received 14 monthly ranibizumab injections, and his CFT was still swollen at the conclusion of the study. His vision and CFT at the time of presentation were 20/63 EDTRS and 684 μm , and his fluorescein angiogram showed macular edema (Figures 1 and 2). At

the end of the study, (5 weeks after his last mandated injection), his vision and CFT were 20/100 ETDRS and 504 μm (Figure 3). He was given aflibercept and seen 2 weeks later when his vision remained stable at 20/100 Snellen and CFT was 342 μm (Figure 4). He then received the dexamethasone intravitreal implant, and 4 weeks later his OCT was dry at 252 μm (Figure 5) and his vision improved to 20/40 Snellen. His vision remained stable for 4 months.

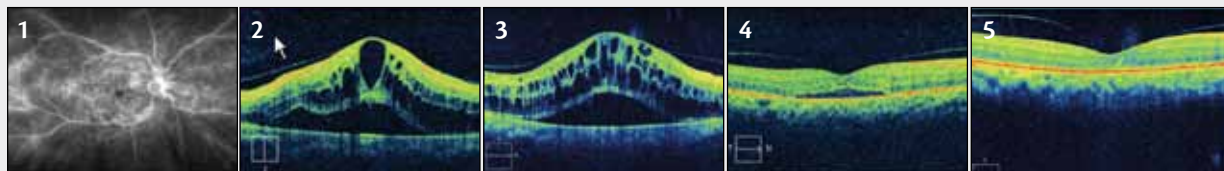


Figure 1. Optos fluorescein angiography of CRVO with macular edema.

Figure 2. CRVO on enrollment into the trial with CFT of 684 μm .

Figure 3. After 14 monthly injections of ranibizumab (last injection 4 weeks prior), CFT is 503 μm .

Figure 4. Two weeks after aflibercept injection, still swollen with CFT is 342 μm .

Figure 5. Four weeks after dexamethasone intravitreal implant, CFT is 252 μm . His OCT remained dry for 4 months.

INTRAVITREAL ANTI-VEGF AGENTS

Intravitreal bevacizumab has been a widely used off-label anti-VEGF treatment due to its relative effectiveness and low cost. A 2009 prospective clinical trial by Prager et al¹⁹ demonstrated its effectiveness in improving BCVA and central foveal thickness (CFT) on optical coherence tomography (OCT) in patients with BRVO and CRVO. Patients were treated with 3 initial intravitreal bevacizumab injections of 1 mg at monthly intervals, and retreatment was based on CFT. Patients gained a mean of 16 letters BCVA, and CFT decreased by a mean of 249 μm . The main drawback, however, has been the short durability of therapeutic effect and frequent need for retreatments. The use of different intravitreal anti-VEGF agents are based on the respective pivotal studies used in their US Food and Drug Administration (FDA) approval.

The BRAVO and CRUISE trials demonstrated the effectiveness of intravitreal injections of ranibizumab (Lucentis, Genentech) in improving BCVA and CFT in patients with BRVO and CRVO, respectively. These findings led to FDA approval for use of ranibizumab in treatment of macular edema following RVO.^{5,10} The BRAVO trial was a phase 3 prospective double-masked clinical trial for BRVO patients that compared 2 doses of ranibizumab (0.3 mg and 0.5 mg) to sham. Patients gained a mean of 18.3 letters of BCVA from baseline at 6 months and these gains were maintained in the treated group at 1 year. Additionally, 61.1% of ranibizumab patients gained 3 lines of vision as opposed to 28.8%

of patients in the sham group, and these gains were maintained at 1 year in the treated group. The CRUISE trial was a phase 3 prospective double-masked clinical trial for CRVO patients that compared 2 doses of ranibizumab (0.3 and 0.5 mg) to sham. Treated patients gained a mean of 14.9 letters of BCVA from baseline at 6 months, and these gains were maintained in the treated group at 1 year. Additionally, 47.7% of ranibizumab patients gained 3 lines of vision as opposed to 16.9% of patients in the sham group, and these gains were maintained at 1 year in the treated group as well.⁸

The GALILEO and COPERNICUS studies were phase 3 prospective pivotal trials that demonstrated the effectiveness of intravitreal injections of aflibercept (Eylea, Regeneron) in improving BCVA in patients with CRVO. These studies compared monthly aflibercept 2-mg injections to sham. Treated patients in the COPERNICUS study gained 17.3 letters of mean BCVA while those in the GALILEO study gained 18.0 letters over the first 6 months and these results were maintained over the first year. The percentage of patients who gained at least 15 letters of EDTRS BCVA in the COPERNICUS study was 56%, comparable to the GALILEO study, in which 60% of patients met this benchmark over the first 6 months. These results were maintained over the first year with monthly injections.^{11,20}

The VIBRANT study was a phase 3 prospective double-masked clinical trial that demonstrated the effectiveness of intravitreal injections of aflibercept in improving BCVA in patients with BRVO. This study compared monthly aflibercept 2-mg injections to standard-of-care

CASE 2

A 66-year-old woman presented with BRVO and macular edema and lipid. Her vision was 20/100 and her CFT on OCT was 556 μm (Figures 1 and 2). She was initially started on combination therapy, with bevacizumab (Avastin, Genentech) and the dexamethasone intravitreal implant. There was some vision improvement to 20/70 but a persistence of edema and lipid (Figure 3). She underwent 2 more cycles of bevacizumab and the dexamethasone intravitreal implant, but she still had residual edema. She was switched to ranibizumab alone because of concern that her vision has worsened to 20/150 due to increasing cataract. She had 4 injections of ranibizumab, but she still had persistent edema with CFT on OCT of 436 μm (Figure 4). She underwent cataract surgery, and her vision increased to 20/60 on day 1, but she still had persistent edema. Four weeks later, her vision decreased to 20/150 and her OCT showed more swelling. She was given another cycle of combination therapy with ranibizumab and the dexamethasone intravitreal implant, and her vision increased to 20/60. Six weeks after combination therapy, she was given targeted panretinal photocoagulation to ischemic areas identified by Optos widefield angiography. Her edema, however, recurred and lipid remained. She underwent another cycle of combination therapy with ranibizumab and the dexamethasone intravitreal implant, but still the edema returned. She then underwent another ranibizumab injection to pretreat the macular edema and received focal laser. Two months later, there was persistent edema, so she received another dexamethasone intravitreal implant, and she was finally dry with 20/40 vision with the lipid almost totally absorbed (Figure 5).

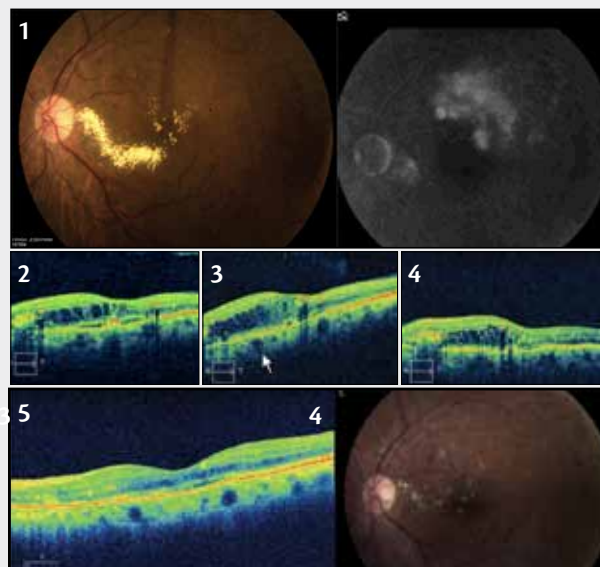


Figure 1. Fundus photo and FA of BRVO with macular edema.

Figure 2. OCT shows macular edema and CFT of 406 μm .

Figure 3. OCT after combination therapy. Central macular edema is improving, but there is still lipid present and OCT is swollen with CFT of 328 μm .

Figure 4. OCT after 4 rounds of ranibizumab. CFT is 436 μm , lipid is still present and vision is 20/150, due to cataract.

Figure 5. OCT and fundus images after multiple cycles of combination therapy with anti-VEGF, dexamethasone intravitreal implant, and laser (focal and targeted PRP). OCT has no fluid and lipid is almost totally absorbed. Vision is 20/40.

laser treatment. At 6 months, patients receiving aflibercept gained a mean 17.0 letters of BCVA compared with a mean 6.9 letters of BCVA in those receiving laser. The percentage of aflibercept patients who gained at least 15 letters of EDTRS BCVA was 53%, compared with 27% of patients who received laser treatment.²¹⁻²³

DISCUSSION

The anti-VEGF pivotal trials are based on the administration of monthly injections. The difficulty that clinicians face in interpreting the trials is that in practice they typically do not give as many monthly injections, and monthly injections are very difficult to maintain over an extended period of time. The SHORE study was conducted to assess the need for monthly injections of ranibizumab as opposed to monthly observations with as-needed (prn) injections once patients had reached a stable state. Patients in the SHORE study received 7 monthly injections of ranibizumab and were then analyzed to see if vision was stable. This was defined as stability in both visual acu-

ity and OCT. If patients were not stable at this monthly assessment, they received a ranibizumab injection and were reassessed 1 month later. This process was repeated for the duration of the study. If patients were considered stable, they were randomized into 2 arms: monthly ranibizumab and monthly evaluation with prn ranibizumab.²⁴

The development of these different therapies has increased the options for treating RVO disease, but have not provided any insight regarding when to use different therapies in a given patient. In addition, these studies have shown that RVO patients have a chronic disease that relapses when the therapeutic effects wear off. These represent challenges to both physicians and patients. These patients are younger than those with macular degeneration, are more likely to be employed, and may not be able to come to the office for monthly injections. One way to manage these hard-to-treat patients is to use combination or contiguous therapy, particularly for patients who do not resolve quickly or require a large number of injections. By using medicines

with different mechanisms of action, there can be a synergy similar to chemotherapy use in oncology. The case studies herein (see Case 1 and Case 2, pages 5 and 6) illustrate examples of different therapeutic challenges that clinicians face in treating patients with RVO.

SUMMARY

RVO is a disease that is chronic in nature. The visual loss due to macular edema, although generally controlled by modern therapies, usually recurs when these therapies wear off. This places a burden on the physician and the patient due to the need for frequent follow-up and frequent administration of these therapies.

The goal of treatment is to control difficult cases and to try to predictably treat all of our patients to help lessen the burden. Although it is known that early intervention and initiation of treatment for macular edema related to RVO is associated with better visual outcomes,²⁵⁻²⁷ it still unknown what combination of medicines and for how long each individual patient needs to obtain permanent resolution of macular edema, while still maintaining the visual acuity gains that we have now come to expect from these medicines. In order to address these problems, one may consider using a mixed-mechanism approach (anti-VEGF, steroids, and laser) to try leverage the synergy of combining these different types of therapies. ■

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To answer these questions online and receive real-time results, please visit www.dulaneyfoundation.org and click "Online Courses." If you are experiencing problems with the online test, please email us at support@dulaneyfoundation.org. Certificates are issued electronically, so supply your email address below. Please type or print clearly, or we will be unable to issue your certificate.

Name _____ ☐ MD participant ☐ non-MD participant

Phone (required) _____ ☐ Email (required) _____

City _____ State _____

1 AMA PRA Category 1 Credit™

CME QUESTIONS

1. The percentage of patients in SCORE-CRVO who gained at least 3 lines of vision in the 1-mg triamcinolone group was ____ compared with ____ in the 4-mg triamcinolone group, compared with ____ in the laser treatment group.

- a. 47%; 27%; 9%
- b. 27%; 26%; 5%
- c. 27%; 26%; 7%
- d. 37%; 25%; 7%

2. The VIBRANT study, which evaluated intravitreal injections of aflibercept compared with laser, showed that ____% of patients gained at least 15 letters of BCVA with aflibercept compared to 27% of patients with laser.

- a. 65
- b. 25
- c. 53
- d. 35

3. The clinical trials for RVO treatments have shown that, in chronic disease, macular edema recurs when therapeutic levels of drug have worn off.

- a. true
- b. false

4. The SHORE study found that:

- a. there is a benefit to earlier treatment with the dexamethasone implant
- b. longer duration of macular edema at time of treatment with dexamethasone implant was associated with poorer visual and anatomic outcomes
- c. laser is effective in treating macular edema
- d. A and B
- e. none of the above

Did the program meet the following educational objectives?

I recognize various forms of macular edema and inflammation using the latest developments in medical literature and new insights from case-based learning.

I understand the new data available on treatments for RVO and how to apply this information in monotherapy and combination therapy treatment schemes.

I will treat various forms of macular edema and inflammation based on assessment of patient need, latest developments in medical literature, and insights from case-based learning.

Agree Neutral Disagree

ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity as required by the Accreditation Council for Continuing Medical Education (ACCME). Please complete the following course evaluation and return it via fax to FAX # 610-771-4443.

Name and email _____

Do you feel the program was educationally sound and commercially balanced? ☐ Yes ☐ No

Comments regarding commercial bias:

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low _____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low _____

Would you recommend this program to a colleague? ☐ Yes ☐ No

Do you feel the information presented will change your patient care? ☐ Yes ☐ No

If yes, please specify. We will contact you by email in 1 to 2 months to see if you have made this change.

If no, please identify the barriers to change.

Please list any additional topics you would like to have covered in future Dulaney Foundation CME activities or other suggestions or comments.