Current and Emerging Considerations in the Management of AMD, DME, and RVO

Highlights from a CME symposium held April 30, 2011, in Fort Lauderdale, Florida

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Content Source
This continuing medical education (CME) activity captures content from an interactive, case-based CME symposium held April 30, 2011, in Fort Lauderdale, Florida.

Activity Description
This monograph discusses highlights from a CME Symposium held April 30, 2011. It will describe new research and incorporate expert guidance for individualizing anti-vascular endothelial growth factor (VEGF) therapy for patients with age-related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusions (RVOs).

Learning Objectives
After successfully completing this activity, you will have improved your ability to:

- Discuss alternate treatment protocols for patients with AMD in whom long-term anti-VEGF therapy poses a safety concern
- Review the current and emerging treatment options for DME and RVO
- Choose optimal dosing strategies from the available therapies for patients with AMD, DME, or RVO

Target Audience
This educational activity is intended for retina specialists.

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Off-Label Discussion
This activity includes off-label discussion of bevacizumab for AMD, DME, and RVO; pegaptanib for DME and RVO; ranibizumab for DME.

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Current and Emerging Considerations in the Management of AMD, DME, and RVO

Are We Undertreating Neovascular AMD?

Scott W. Cousins, MD

Consider a patient with age-related macular degeneration (AMD) and classic choroidal neovascularization (CNV) with 20/100 vision. He receives 3 doses of an anti-vascular endothelial growth factor (VEGF) agent and has a very favorable response with good visual acuity, no leakage of fluid on fluorescein angiography (FA), and no fluid on optical coherence tomography (OCT). Now what do you do? After the initial induction, how many anti-VEGF treatments per year, on average, are required to maintain good vision?

The ranibizumab registry trials (MARINA® and ANCHOR®) evaluated monthly injections through 2 years of therapy; the drug is labeled for indefinite monthly injections. Is it possible to achieve similar outcomes with less frequent dosing? There are at least 4 popular regimens.

Option 1: Ranibizumab induction with quarterly retreatment

Two published studies, PIER® and EXCITE®, have evaluated the regimen of 3 monthly induction doses of ranibizumab followed by scheduled quarterly retreatments. In comparison to the outcomes of the ANCHOR trial, the PIER protocol was associated with significant loss of visual acuity during the maintenance phase. Similarly in the EXCITE study, quarterly injections were associated with substantially smaller gains of visual acuity than the monthly therapy provided in ANCHOR and MARINA. These studies demonstrate that induction with 3 monthly injections followed by quarterly maintenance is inadequate for gaining and maintaining visual acuity.

Option 2: Ranibizumab induction with variable retreatment

At least 6 studies have evaluated the regimen of initial monthly induction dosing followed by variable dosing based on clinical criteria: PRONTO®, SAILOR®, SUSTAIN®, CATT®, HORIZON®, and a study from the Cleveland Clinic.†† PRONTO included 40 patients who received 3 doses of ranibizumab and then were followed on a monthly basis with examination, visual acuity, and OCT, with retreatment based on specific indications. By following this rigorous protocol, patients maintained their initial good visual acuity gains for up to 2 years.

The recent CATT study was a head-to-head comparative efficacy study that evaluated monthly ranibizumab versus monthly bevacizumab versus PRN ranibizumab and PRN bevacizumab (Figure 1). Monthly ranibizumab and monthly bevacizumab were each associated with similar excellent results. In the PRN groups, the 2 drugs were comparable, but, while not statistically significant, there was a trend toward a slight decrease in visual acuity compared with that achieved with monthly dosing for both drugs. Importantly, the PRN groups received an average of 7 injections for ranibizumab and 8 injections for bevacizumab in the first 12 months, compared with the 12 injections in the monthly groups, to maintain good vision. A substantial proportion of patients in all treatment groups showed evidence of persistent leakage on fluorescein and OCT testing at 12 months.

![Figure 1. Visual acuity outcomes in CATT.](image-url)
Option 3: Ranibizumab induction followed by pegaptanib maintenance

Ranibizumab inhibits all VEGF isoforms while pegaptanib selectively inhibits VEGF165. While the 2 drugs have never been compared in a head-to-head trial, cross-trial comparison suggests that chronic pan-VEGF inhibition is superior to selective VEGF165 inhibition. In an effort to minimize adverse events associated with pan-VEGF inhibition, might a regimen of ranibizumab or bevacizumab induction followed by pegaptanib maintenance be effective? The recent LEVEL study addressed this question. In the study, 36% of the patients were induced with bevacizumab, 42% were induced with ranibizumab, and 19% received multiple agents. After the initial improvement in vision, maintenance with pegaptanib, a VEGF165-selective agent, over the next year showed stable maintenance of visual acuity. There was no difference if patients were induced with bevacizumab or with ranibizumab, and the OCT thickening did not change during the course of the year. The patients did not develop recurrent leakage (Figure 2).

Figure 2. Mean visual acuity changes in the LEVEL study. Reprinted with permission.

Option 4: Treat and extend

The “treat-and-extend” regimen consists of induction therapy followed by gradually increasing the interval between treatments based on clinical status. There are only a few observational studies suggesting that this approach may have some benefit. These studies showed that the treat-and-extend approach can produce long-term stable vision. In both studies, patients required, on average, 7 to 8 injections during the course of the year to maintain visual gains.

Current Practice Patterns

Since frequent, scheduled injections are the only proven approach to maintaining initial vision gains, and patients generally need 7 to 8 injections during the course of a year, how closely do current practice patterns in the United States adhere to this regimen?

Our group conducted a Medicare claims analysis to identify the average number of injections received during each of the first 2 years following a new diagnosis of neovascular AMD. In the first 12 months, patients received an average of 4 injections; during the second 12 months, the number dropped to an average of only 2 injections. Only 21% of patients who were treated with ranibizumab and 10% of patients treated with bevacizumab received more than 6 injections. In contrast, recall that patients in the PRN arms of CATT received 7 to 8 injections, on average. The duration of therapy was also surprising. Fifty percent of patients received only induction and no maintenance injections, and 80% of patients received no further injections at all after the first 18 months. The bottom line is this: Patients with neovascular AMD are being undertreated in the real world.

Question 2. True or False? Most important drug toxicities are identified during phase 3 pivotal trials.

False. Phase 3 trials are typically powered to detect a 1% incidence of catastrophic adverse events. This is very different from being powered to detect a 1% increase in incidence compared with a control group or a baseline rate, a value that would be more useful. The population from which we draw study patients for AMD trials is the elderly population, and those patients often have background health issues such as atherothrombotic events, stroke or heart attacks, systemic hypertension, and any kind of systemic hemorrhage, such as gastrointestinal or urinary. Phase 3 trials are generally not powered to detect small but clinically significant differences in adverse event rates from baseline or between groups.

What do we know about safety from the key phase 3 trials? In the VEGF165-selective pegaptanib trial, there was no increase in adverse events seen in the pegaptanib groups over those seen in the sham group, even at the highest dose, which was 10-fold greater than the approved dose. In the MARINA ranibizumab trial, there was a 50% increase in the incidence of stroke in the patients who received the pan-VEGF inhibitor rather than sham. In the SAILOR trial, which was the extension trial following MARINA and ANCHOR, patients were randomized to either 0.5 mg or 0.3 mg of ranibizumab. The larger-dose group showed a slight increase in stroke rate compared with the lower-dose group, though not statistically significant. Notably, however, the patients who had a prior stroke suffered an almost 10% rate of second stroke if they received the higher dose that is currently commercially available. A meta-analysis of the MARINA, ANCHOR, and FOCUS studies demonstrated that treated patients experienced almost a 3-fold increase in rate of strokes compared with control patients. In the RISE study of ranibizumab for diabetic macular edema (DME), there was a trend toward increased rate of stroke and death in patients receiving the higher doses of ranibizumab. Finally, in the CATT study, there was a doubling of the rate of death from any cause in the PRN bevacizumab group compared with the other groups, and an increased rate of serious systemic events that required hospitalization, also in the bevacizumab group.

In summary, the clinical trial data suggest safety signals regarding the risk of stroke in patients receiving ranibizumab and, perhaps, bevacizumab, but the phase 3 trials are not designed to give us absolute confirmation of safety. Postmarketing surveillance is necessary to fully characterize the safety profiles of drugs.

Question 3. True or False? Drugs administered intravitreally do not enter the systemic circulation and pose no systemic safety risks.

False. Virtually every drug that we inject into the eye can and does reach the systemic circulation. From a safety perspective, the issue is not whether the drug reaches the systemic circulation, but rather how long that drug persists within the systemic circulation. Pegaptanib and ranibizumab are smaller molecules and have very short half-lives, but bevacizumab is a full-length antibody and has a longer half-life. Our data demonstrate that bevacizumab can last in the blood for as long as 6 weeks post-injection (unpublished).

Question 4. True or False? The small amount of systemically absorbed anti-VEGF medication is inadequate to significantly inhibit systemic VEGF levels.

False. VEGF is present in blood, where it serves an important role in regulating blood pressure, promoting vascular repair, stimulating collateral vessel formation and other physiological functions. Most blood VEGF resides in platelets, which are essentially little bags of growth factors and clotting factors that are released from the bone marrow. This VEGF, when released from platelets in the setting of vascular injury, induces vascular repair and dilation around the thrombus and also induces collateral formation. So, systemic VEGF is critical to maintaining healthy blood vessels. The average patient’s serum VEGF level, after clot-induced release of platelet VEGF, is approximately 380 pg/mL, but there is a surprisingly large range of values from almost undetectable to more than 1000 pg/mL (Figure 3). It has been demonstrated recently that intravitreal anti-VEGF therapy lowers systemic VEGF levels for as long as a month after an injection. Perhaps those patients with low systemic VEGF levels are most susceptible to systemic VEGF blockade because they don’t have adequate reserves of systemic VEGF to maintain cerebral vascular integrity, and are therefore more at risk for stroke when receiving anti-VEGF therapy.

Figure 3. The range of serum VEGF levels in patients with neovascular AMD. Scott W. Cousine, MD, unpublished.

Scott W. Cousine, MD

Should Safety Issues Guide VEGF Inhibition Treatment Choices?

Consider a patient with neovascular AMD, an occult CNV lesion, visual acuity of 20/60, with OCT evidence of retinal fluid and outer retinal disruption. Chronic pan-VEGF inhibition seems like a reasonable therapy. But suppose the patient suffered a stroke 1 month ago. Should this health issue change our management? To address this important issue, we will consider 4 true/false questions.

Question 1. True or False? The United States and the European Union have a robust process for monitoring postmarketing safety.

False. The postmarketing safety surveillance system is the medical community reporting adverse events to the US Food and Drug Administration (FDA) MedWatch system. This process requires that we clinicians fill out a form, then submit it, either by e-mail or fax, to the FDA every time we suspect that a patient suffered an adverse event that may or may not be caused by a drug. How many readers of this monograph have ever reported a safety issue to MedWatch? I suspect very few. That is why our postmarketing safety surveillance system is not effective. It is not part of our culture to report adverse events in organ systems for which we are not primarily responsible.

10%–50% is VEGF 121

Scott W. Cousine, MD, unpublished.
**Diabetic Macular Edema: Examining the Clinical Evidence and Applying It to Practice**

**Victor H. Gonzalez, MD**

Laser photocoagulation has remained the standard therapy for DME for years. Recently, a number of major clinical trials have evaluated novel therapies for DME.

The DRCR.net study compared ranibizumab with immediate or delayed laser to triamcinolone plus laser or laser alone. Four monthly injections were followed by a PRN monthly retreatment schedule; following initial laser (prompt or deferred), PRN retreatment up to every 4 months was permitted. The group of individuals who received ranibizumab with either prompt or delayed laser had a significantly better visual acuity outcome compared with those who received laser treatment alone, and triamcinolone was of no additional benefit when combined with laser. Although ETDRS and other trials have demonstrated that laser photocoagulation is clearly superior to observation, the DRCR.net study suggests that pharmacologic treatment with ranibizumab is superior to laser alone. The role for combination approaches with laser and pharmacologic therapy remains to be determined.

The DRCR.net study raised an important question: How effective is ranibizumab alone without laser? This important question was answered by the RESTORE study. In RESTORE, which was a multicenter, randomized, double-masked trial conducted in Europe, patients with DME were assigned to therapy with ranibizumab alone, laser alone, or the combination of ranibizumab plus laser. Injections were given monthly, for 3 injections, then PRN. The 2 groups receiving ranibizumab fared significantly better than the laser-only group, and there was no difference in the ranibizumab group versus the ranibizumab-plus-laser group. The RISE and RIDE studies, of similar design, confirmed these findings. No increase in cardiovascular or cerebrovascular adverse events was noted in the ranibizumab groups in the RESTORE study.

Pegaptanib has also been evaluated in a multicenter, randomized, double-masked phase 3 DME trial in Europe. Patients with DME received either pegaptanib or sham injections every 6 weeks, and could also receive laser after week 18 and up to every 17 weeks thereafter. Unlike the DRCR.net study, in which retreatment was determined by a reading center based on FA and OCT results, the pegaptanib study permitted the investigators to determine the need for retreatment. This is more real-world in its approach. At the 52-week primary end point, outcomes were significantly better in the pegaptanib group compared with the sham group. Further, significantly fewer patients treated with pegaptanib required laser therapy. Importantly, there were no safety signals in the pegaptanib group compared with the sham group.

The DME treatment paradigm is evolving, driven by the aforementioned and ongoing studies exploring the role of novel therapies in this common disease process. Important questions remain unanswered. How should we select the right drug for each patient? How long must we continue anti-VEGF therapy to maintain control of DME? Further study and more head-to-head trials are needed to clarify the optimal drugs and dosing regimens for DME.
In the past few years, our therapeutic options for macular edema associated with retinal vein occlusion (RVO) have expanded substantially. The recent SCORE study demonstrated that intravitreal triamcinolone was superior to observation in eyes with macular edema due to central retinal vein occlusion (CRVO), but no better than grid laser photocoagulation in eyes with macular edema due to branch retinal vein occlusion (BRVO).\textsuperscript{21,22} The dexamethasone intravitreal injectable implant demonstrated efficacy against macular edema due to RVO for as long as 30 to 60 days at a time, and was approved by the FDA for this indication in 2009.\textsuperscript{23}

Pegaptanib for CRVO was the first published study to demonstrate a benefit to vision with anti-VEGF therapy in CRVO.\textsuperscript{24} More recently, the BRAVO and CRUISE studies demonstrated that intravitreal ranibizumab, given as 6 monthly injections followed by PRN retreatment for an additional 6 months, was highly effective at improving visual acuity.\textsuperscript{25,26} In 2010, the FDA expanded the ranibizumab label to include macular edema associated with BRVO and CRVO.

Despite the lessons learned from these important trials, there remain several unanswered questions. When should we initiate treatment? What is the optimal drug? What is the optimal dosing interval? How long should we continue treatment? Is there a role for combination therapy with laser and anti-VEGF drugs? Steroids have some advantages over VEGF inhibitors. They are less expensive and can be administered less frequently. But they also have disadvantages, which are generally related to safety, including cataract, glaucoma, and higher rates of neovascularization. For these reasons, I prefer anti-VEGF therapy to steroid therapy in eyes with macular edema due to RVO.

Clinical therapeutic approaches to patients with RVO are discussed in the cases. (see Sidebar)

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**Case 1**

An 83-year-old man presents for routine examination and is found to have a mild, nonischemic CRVO in the right eye, with 20/30 vision and mild macular edema. Past history includes chronic systemic hypertension and a CRVO in his left eye 20 years ago that resolved spontaneously.

I elected to observe his right eye because the natural history of macular edema in nonischemic CRVO suggests that approximately 30% of cases resolve without treatment.\textsuperscript{2,3} Two weeks later, however, he returned and his vision had dropped to counting fingers and he had significant macular edema. It is unknown whether treating him 2 weeks earlier would have prevented this from happening.

We discussed therapeutic options and he was reluctant to undergo monthly anti-VEGF injections. We gave an intravitreal triamcinolone 2 mg/0.05 cc injection and after 27 days, his edema was better, though not resolved, and his vision was marginally better, at 20/40.

Three months after the initial injection (during which time he had begun taking warfarin), macular edema persisted, but there was new ruberosis. At this point, I administered bevacizumab 1.25 mg and performed perifoveal photocoagulation (PRP). He missed his next appointment and returned in 7 weeks’ time with massive edema but no ruberosis. Despite a second bevacizumab injection, severe macular edema persisted and ruberosis recurred; another bevacizumab injection and more PRP was given. Regrettably, at this visit he also had an asymptomatic CRVO in the left eye with no macular edema. He and I discussed treatment in the left eye and elected to observe initially.

Four weeks later he had minimal edema in the left eye and his vision was 20/40. No treatment was given. The right eye was stable with poor vision and mild macular edema but no ruberosis or glaucoma.

A few weeks later, he presented with significant macular edema in both eyes and vision of counting fingers with the right eye and 20/300 with the left eye. Because the vision potential in the right eye was poor, we elected for treatment in the left eye only. He subsequently received a series of 8 bevacizumab injections in that eye over 9 months. At last follow-up, left eye vision was 20/60, with no macular edema clinically or on OCT, and no ruberosis in that eye.

Considerations relating to this case include whether or not initiating treatment earlier, before the severe macular edema and the vision loss, would have resulted in a better visual outcome and, as suggested by the CRUISE, SCORE, and dexamethasone intravitreal implant trial results, that anti-VEGF therapy gives better vision outcomes and reduces the risk of ruberosis compared with steroids. Also, chronic therapy may be required to maintain vision gains and resolution of macular edema.\textsuperscript{28}

**Case 2**

A 70-year-old man in excellent health, except that he is a former smoker, presents with a BRVO (Figure 5). His presenting acuity is 20/60 and he has significant macular edema and hemorrhage. In deciding whether or not to treat him, it is worth noting that the natural history of BRVO suggests that approximately 18% to 41% of eyes with BRVO and macular edema resolve without treatment, but it is uncommon for untreated eyes to achieve better than 20/40 vision.\textsuperscript{29} Conversely, the potential advantages of early treatment include prevention of macular tissue damage from chronic edema, more rapid resolution of hemorrhage, faster visual improvement, and prevention of neovascularization. In BRAVO, eyes with shorter durations of edema had better vision after treatment and eyes receiving ranibizumab after 6 months of sham injections had less vision improvement than eyes treated from baseline.

I recommended treatment, but the patient elected observation and returned in 6 weeks with worse vision and so elected treatment at that time. After 2 bevacizumab injections, his vision improved to 20/30 and there was less hemorrhage and reduced edema. After 5 injections, he had persistent edema, though much less than before. At this point, I performed grid laser. Six weeks later, his visual acuity was 20/40, but he had worsening edema. After a few more injections, I arranged to see him 2 weeks after the last injection. At 2 weeks post-injection, he was nearly fluid-free. The lesson here is that RVO may be associated with a high VEGF load; injections more frequently than every 4 weeks may be necessary. Also, in this case of BRVO, the addition of grid laser treatment did not seem to reduce the need for continued anti-VEGF therapy to control macular edema and maintain vision. Similarly, in the DRCRnet trial comparing ranibizumab and deferred laser to ranibizumab plus prompt laser for diabetic macular edema, the addition of laser to anti-VEGF therapy did not appear to significantly alter the number of anti-VEGF treatments given over the first year.\textsuperscript{30} This case, and many others in my personal clinical experience, suggests a similar phenomenon may be found in treating macular edema due to BRVO.

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**Photo Courtesy John A. Wells III, MD**

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**Sidebar**

**ANCHOR**—Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration

**BRVO**—Study of the Efficacy and Safety of Ranibizumab Injection in Subjects With Clinically Significant Branch Retinal Vein Occlusion

**CATT**—Comparison of AMO Treatment Trials

**CRUISE**—Study of the Efficacy and Safety of Ranibizumab in Patients With Macular Edema Secondary to Branch Retinal Vein Occlusion

**DRCRnet**—Diabetic Retinopathy Clinical Research Network

**ETERS**—Early Treatment Diabetic Retinopathy Study

**EXCITE**—Efficacy and Safety of Ranibizumab in Patients With Subretinal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration

**HORIZON**—Extension Study to Evaluate the Safety and Tolerability of Ranibizumab in Subjects With Choroidal Neovascularization Secondary to AMD or Macular Edema Secondary to RVO

**LEVEL**—Evaluation of Efficacy and Safety in Maintaining Visual Acuity with Sequential Treatment of Neovascular AMD

**MARINA**—Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD

**PIER**—Randomised, Double-Masked, Sham-Controlled, 2-Year Study Designed to Assess the Safety and Efficacy of Ranibizumab in Patients With Neovascular (Well-Aged-Related Macular Degeneration (With or Without Choroidal Neovascularization)

**PRONTO**—Prospective Optical Coherence Tomography Imaging of Patients With Neovascular AMD Treated With Intra-Ocular Ranibizumab

**RESTORE**—Ranibizumab Monotherapy or Combined With Laser Versus Laser Monotherapy for Diabetic Macular Edema

**RISE**—Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema With Center Involvement Secondary to Diabetes Mellitus

**RISE-2**—Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema With Center Involvement Secondary to Diabetes Mellitus

**SAILOR**—Safety Assessment of Intravitreal Lucentis® for Age-Related Macular Degeneration

**SCORE**—Standard Care vs Corticosteroid for Retinal Vein Occlusion

**SUSTAIN**—Study of Ranibizumab in Patients With Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration

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**Figure 5.** Classic BRVO. Left, red-free fundus photograph; Right, FA.
References


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• Discuss alternate treatment protocols for patients with AMD in whom long-term anti-VEGF therapy poses a safety concern  5  4  3  2  1
• Review the current and emerging treatment options for DME and RVO  5  4  3  2  1
• Choose optimal dosing strategies from the available therapies for patients with AMD, DME, or RVO  5  4  3  2  1

1. Please list one or more things, if any, you learned from participating in this educational activity that you did not already know.
____________________________________________________________________________________________________________________________________________

2. As a result of the knowledge gained in this educational activity, what changes, if any, do you plan to make in your practice?
____________________________________________________________________________________________________________________________________________

3. Related to what you learned in this activity, what barriers to implementing these changes or achieving better patient outcomes do you face?
____________________________________________________________________________________________________________________________________________

4. Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced for you through participation in this activity.

□ Patient Care □ Practice-Based Learning and Improvement □ Professionalism
□ Medical Knowledge □ Interpersonal and Communication Skills □ Systems-Based Practice

5. What other topics would you like to see covered in future CME programs?
____________________________________________________________________________________________________________________________________________

Additional Comments ______________________________________________________________________________________________________________________________________________

Post Test Answer Box

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Current and Emerging Considerations in the Management of AMD, DME, and RVO