Current Management of Retinal Vascular Diseases: Optimizing Treatment Protocol

Rishi P. Singh, MD, moderator
Jeffrey S. Heier, MD
Dante Pieramici, MD
Jonathan Prenner, MD
This continuing medical education (CME) activity captures content from roundtable discussion held in August 2016 in San Francisco, Ca.

**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:

- Understand the most recent monotherapy and combination therapy clinical study evidence using available anti-VEGF, steroid, and photodynamic therapies for common retinal diseases, including AMD, RVO, and DME
- Discuss the outcomes of pivotal studies in AMD, RVO, and DME as well as how study results may differ from real-world dosing methods
- Develop plans to initiate treatment for conditions such as AMD, RVO, and DME using anti-VEGF agents as well as better understand when to change therapeutic strategies and/or therapeutic classes
- Evaluate practice flow to determine the most efficient patient experience
- Develop plans to reduce reimbursement denials

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- **Rishi P. Singh, MD**, moderator
  Cole Eye Institute, Cleveland Clinic
  Cleveland, Ohio

- **Jeffrey S. Heier, MD**
  Tufts University/Ophthalmic Consultants of Boston
  Boston, Massachusetts

- **Dante Pieramici, MD**
  California Retina Consultants and Research Foundation
  Santa Barbara, California

- **Jonathan Prenner, MD**
  Rutgers Robert Wood Johnson Medical School
  New Brunswick, New Jersey

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Current Management of Retinal Vascular Diseases: Optimizing Treatment Protocol

It is a little surprising to realize that the anti-VEGF era is more than a decade old. The first phase 2 and 3 studies of an anti-VEGF drug in ophthalmology, pegatanib sodium, demonstrating a slowing of progression of neovascularization associated with age-related macular degeneration, were published in 2004, and that the drug became commercially available later that year. Two years later, ranibizumab gained market approval for use in patients with neovascular age-related macular degeneration based on the seminal ANCHOR and MARINA studies; and by 2011, a third agent, afibercept, gained FDA approval, although unlike its predecessors, it was tested in a dosing scheme that would reduce the injection burden.

Since then, anti-VEGF treatments have been approved for a multitude of indications, including macular edema from retinal vein occlusions, diabetic macular edema, and diabetic retinopathy. What this all adds up to is an increasing volume of pharmacologic offerings, often provided in complicated treatment paradigms, and overall complexity and logistical questions for a profession that was, by and large, trained as a surgical specialty.

Today, the practice of retina is faced with an interesting question of how to become better at delivering the medicines that we know will help patients save vision, given the burden on the process. Simply put, how can practitioners maintain a high volume of patient throughput, ensuring that every patient is afforded the quality care he or she deserves while balancing all the other demands of a busy practice and navigating the changing tides of medicine?

For this roundtable event, the sponsors of this activity invited high-volume practitioners to offer their insights on the practical measures they utilize to improve patient care with respect to anti-VEGF injection practices. We hope this information proves valuable to readers and helps foster the sense of collaborative learning that epitomizes our profession.

—Rishi P. Singh, MD, moderator

**Rishi P. Singh, MD:** Let us begin with what goes in to setting up a practice for success in terms of process. How does each of you manage the first patient encounter and does it differ for follow-up appointments?

**Jonathan Prenner, MD:** Our patient intake process differs for a new patient who receives a comprehensive workup and a patient returning for a follow-up visit. During the initial encounter, we ask our technicians to obtain as much information as possible before the patient interacts with the doctor. We have a routine and well-defined list of examination components that every patient receives on that first encounter, regardless of diagnosis. We have found that mapping out what we hope to accomplish during subsequent visits helps keep us organized and efficient during follow-up examinations.

**Jeffrey S. Heier, MD:** We also rely on technicians for gathering the correct imaging, although the appropriate tests have to be ordered in advance by the clinician. For initial encounters, either the fellows are responsible for ordering appropriate imaging, or if the patient is not seen first by a fellow, then the technician will ask the clinician if he or she wants certain tests in advance of the examination (such as an optical coherence tomography [OCT] for a patient referred with a macular hole). During the follow-up visit for a patient with age-related macular degeneration (AMD), for example, we detail the order for our technicians to capture an OCT at the next visit. In either case, establishing ahead of time what tests will be conducted during the examination helps make sure the patient experience is managed efficiently. For us, it comes down to resource management: Delegate time-consuming tasks to technicians and use the personnel at the practice’s disposal to optimize the efficient flow of patients from the time they step through the clinic door. This, in turn, minimizes redundancy and maximizes the ability of the most resource-dependent person—the treating physician—to use his or her time efficiently and effectively.

**Dante Pieramici, MD:** Dealing with new patients is inherently more complicated logistically than dealing with returning patients. Returning patients can have orders written specifying testing upon arrival, while new patients generally require examination followed by testing. This can add to the inefficiency of the examination.
**Dr. Singh:** Do you ever have patients come in for OCT and injections on different days?

**Dr. Pieramici:** We do on occasion have patients come in for OCT imaging on a different day from their planned injection just to maximize efficiency. At some of our locations we have multiple OCT machines so that same-day testing does not slow down the flow of patients. In some cases, the patient can come in on another day and get an undilated OCT, which can reduce the workload on days when obtaining the OCT can be the rate-limiting step of the examination process.

**Dr. Singh:** Does anyone use planned procedure days to perform injections only, or do most of you perform injections as part of regular clinic workflow?

**Dr. Heier:** I perform injections as part of regular clinic and do not hold injection-only clinics.

**Dr. Singh:** Does anyone perform same-day bilateral injections to maximize efficiency?

**Dr. Prenner:** I almost never perform bilateral injections, but this has more to do with theoretical safety and patient comfort than anything else. I think it is surprisingly challenging for patients to recover from injections, in general, and even more of an issue when both eyes are treated on the same day. There are a number of retrospective case series that have looked at the safety of bilateral injections that found no difference in complications; however, there is no good data on what effect, if any, bilateral injections of anti-VEGF drugs might have on systemic bioavailability. The 12- and 24-month HARBOR study results showed no difference in safety outcomes between the 0.5-mg group and the 2.0-mg group, suggesting that there is no evident dose response or dose exposure relationship. But these are somewhat limited data, and there are other safety factors to consider. For instance, if the lot being used on a particular clinic day is compromised, bilateral injection exposes each eye to this risk.

**Dr. Heier:** A lot of my patients want bilateral injections because they are convenient, especially for those who depend on a family member to get to the clinic. I am cognizant of the potential risk Dr. Prenner mentioned regarding exposing patients to potentially contaminated batches, so we use different lots for each eye. I would also disagree slightly with the recovery question, as some patients would rather just deal with the after-effects of injections in both eyes on the same day rather than spreading the discomfort out to 2 days.

**Dr. Singh:** In terms of efficiency, one of the complicated issues we face is patients’ insurance status with respect to formulary. How does everyone manage that aspect of patient care in new patients to the practice? Do you use drugs that are preapproved or do you have patients return after you have sought approvals?

**Dr. Prenner:** This can be a tricky scenario in terms of balancing what drug the patient prefers with what the practice needs to do to maintain viability. The profit margins for practices using branded anti-VEGF drugs are surprisingly small; if nonpreapproved drugs are used, the practice can find itself upside down financially very quickly. The manufacturers of each of the branded anti-VEGF drugs, ranibizumab and aflibercept, offer well-run programs to help practices obtain third-party preauthorizations for drug use. We utilize those programs to make sure that our patients are going to be covered financially for these biologics prior to receiving them.

**Dr. Singh:** Do you obtain the preauthorization before a new patient comes to the practice?

**Dr. Prenner:** We do on occasion have patients come in for OCT and injections on different days when obtaining the OCT can be the rate-limiting step of the examination process.

**Dr. Singh:** Do you ever have patients come in for OCT and injections on different days?

**Dr. Prenner:** We do. Our staff is instructed to get a consent form from the patient during the first visit that will allow us to approach their insurance company about the preauthorization. It helps to have a protocol in place to manage the process.

**Dr. Singh:** Do you ever have patients come in for OCT and injections on different days?
managed by people in the office who have experience with it. Not that any of this is overly complicated, but it has to be done efficiently, and well-trained staff members can anticipate patients’ questions and answer them appropriately. Each of the manufacturers of the anti-VEGF drugs offer website portals to help manage these processes, and they can be tremendously helpful for maintaining efficiency. From my perspective, those kinds of tools are most beneficial when they are managed by one dedicated individual in the practice.

**Dr. Pieramici:** Preparation and planning is key. Each day, we have the staff review the next day’s charts to determine who is approved and who needs to start the approval process. We want to know what to expect when the patient walks in the door. It facilitates their process and eliminates confusion that can be unsettling for the patient.

**EMRs: HELP OR HINDRANCE?**

**Dr. Singh:** The advent of electronic medical records (EMRs) has been heralded as way to make our offices more efficient. In our center, we have had a positive experience with electronic records, as they facilitate our recordkeeping with respect to authorizations and reminders to check on status before the authorization expires. Are EMRs a help or hindrance in managing the logistics of anti-VEGF drugs?

**Dr. Pieramici:** Our practice has nearly transitioned completely to EMR, and it has been an adventure. We transitioned slowly during the past year so as to maintain productivity while implementing it. The key for us has been the use of scribes, which is also reflected in a sharp increase in overhead spending. At the current time, we are comfortable with our EMR, but I am not sure we are doing a better or more efficient job of caring for the patients than when we used paper charts.

**Dr. Prenner:** Some of our retina colleagues are bound to certain EMR systems by virtue of their institutional affiliations. However, for those of us with a little more latitude to select and customize our own electronic records systems, technology may offer some solutions to the logistical problems of anti-VEGF drug delivery. In our system, we have macros to denote various practical elements, such as whether the patient has a preapproval for branded drug use, if they participate in our patient portal, etc. We can also tell at a glance when the preauthorization will expire and when our staff has to reapply for the patient.

**Dr. Heier:** I appreciate Dr. Prenner’s point about being able to customize one’s EMR program, because the medical system that our clinic is affiliated with is about to change its electronic records system. To stay affiliated, we will also have to change. My staff and I are concerned what this may mean for our operations. I have a very long conversation with my patients prior to their first anti-VEGF injection where I review the relevant study data (Table). This is tailored to each patient and his or her diagnosis. I present an overview of their particular disease state and anatomy, including what their imaging tests are showing me. Then I discuss the drug choices more specifically to make sure patients are making an informed decision. This part of the conversation will cover what we know about side effects, including that while we do not have definitive data on the systemic safety risks of anti-VEGF drugs, we are reasonably sure of their systemic safety. When it comes to potential ocular complications, I spend time discussing that endophthalmitis occurs in about 1 in 2,000 injections, and that it may lead to blindness. I also mention that other complications, including bleeding, retinal tears, iatrogenic cataract, and retinal detachments, are rare and usually manageable.

I also spend time discussing the financial aspects of treating these diseases during the informed-consent process, including what systemic costs and potential out-of-pocket costs could look like. The various programs offered by the drug companies are a major help in ensuring patients access to the medications they need, and we carefully explore the various options before asking patients to pay out of pocket for an expensive treatment.

**Dr. Pieramici:** I have a similar conversation with my patients. We could honestly have a very exhaustive conversation about all

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**One thing that may make our use of EMRs a bit easier is the use of scribes. Several years ago I began to use a second scribe and it has made a world of difference in terms of staying organized, compliant, and efficient.**

—Jeffrey S. Heier, MD
### TABLE. SUMMARY OF EFFICACY OUTCOMES FROM MAJOR CLINICAL TRIALS INVOLVING INTRAVITREAL ANTI-VEGF DRUGS

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Agent</th>
<th>Treatment Overview</th>
<th>Efficacy Outcome</th>
<th>Important Notes</th>
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| **AMD**    | Pegatanib sodium | Injection q6 weeks for 54 weeks; re-randomization for injection q6 weeks through 96 weeks | Treated eyes: 45% -15 letters; 10% +15 letters
Untreated eyes: 59% -15 letters; 4% +15 letters | Treatment decreased the progressive loss of vision associated with NVAMD; led to subsequent approval of pegatanib for treatment of AMD |
| VISION     | Ranibizumab | Monthly ranibizumab for 2 years vs verteporfin PDT | 10% (ranibizumab) vs 66% (PDT) ≥ -15 letters; 41% (ranibizumab) vs 6% (PDT) ≥ +15 letters | First phase 3 trials to show improvement in VA for all forms of choroidal neovascularization in NVAMD; led to subsequent approval of ranibizumab for treating AMD |
| MARINA     | Ranibizumab | Monthly ranibizumab for 2 years | 10% -15 letters; 33% +15 letters | First phase 3 trials to show improvement in VA for all forms of choroidal neovascularization in NVAMD; led to subsequent approval of ranibizumab for treating AMD |
| VIEW 1/ VIEW2 | Aflibercept | 0.5 mg 2q4; 2.0 mg 2q4; 0.5 mg x3 monthly then 2q8; vs ranibizumab 0.5 mg monthly | 4% (0.5 2q4), 5% (2.0 2q4); 4% (2q8); 6% (ranibizumab) -15 letters; 30% (0.5 2q4), 34% (2.0 2q4); 31% (2q8); 33% (ranibizumab) +15 letters | Registration trial led to approval of aflibercept for AMD |
| CATT       | Ranibizumab, bevacizumab | Ranibizumab 0.5 mg q4 weeks or PRN; bevacizumab 1.25 mg q4 weeks or PRN | Ranibizumab: 6% (q4), 5% (PRN); Bevacizumab: 6% (q4); 9% (PRN) -15 letters
Ranibizumab: 34% (q4), 25% (PRN); Bevacizumab: 31% (q4); 28% (PRN) +15 letters | No statistically significant differences in efficacy, safety |
| **DME**    | Ranibizumab | 0.3 mg dosed monthly; 0.5 mg dosed monthly, followed for 24 months | RISE: ≤ 15 letters: 44.8% (0.3 mg) vs 39.2% (0.5 mg) vs 18.1% (sham); overall +12.5 letters (0.3 mg)
RISE/RIDE ≤ 15 letters: 33.6% (0.3 mg) vs 45.7% (0.5 mg) vs 12.3% (sham); overall +10.9 letters (0.3 mg) | Anatomic outcomes correlated with VA findings
FDA registration trial; led to subsequent label indication for ranibizumab in treatment of DME |
| Protocol I | Ranibizumab | 0.5 mg dosed for four monthly loading doses, followed by PRN; evaluations every 4 weeks thereafter; prompt or deferred laser as adjunct
Triamcinolone + prompt laser as comparator
Sham controlled | 12 months: +9 letter (ranibizumab + prompt or deferred laser); +4 (triamicinolone/prompt laser); +3 (sham + prompt laser)
CST reductions comparable with triamicinolone, ranibizumab; greater in both groups than sham | Demonstrated superiority of ranibizumab with prompt/deferred laser vs laser alone
Showed PRN is viable for visual and anatomic outcomes
VA gains in year 1 maintained in subsequent years with fewer treatments: average four in year 2, two in year 3, one in year 4 |
| RESTORE    | Ranibizumab | Three loading doses monthly 0.5 mg followed by PRN dosing with monthly visits vs laser monotherapy | 12 months +6.1 letters (monotherapy) vs +0.8 (laser monotherapy) | Demonstrated superiority of ranibizumab with prompt/deferred laser vs laser alone
Showed PRN is viable for visual and anatomic outcomes
VA gains in year 1 maintained in subsequent years with fewer treatments: average four in year 2, two in year 3, one in year 4 |
| VIVID/VISTA | Aflibercept | 2.0 mg every 4 weeks for five loading doses followed by 2q4 or 2q8 treatment
Parallel phase 3 studies | 100 week outcomes:
VIVID: +11.5 (2q4), +11.1 (2q8), and +0.9 letters (laser)
≥15 letters from baseline: 38.3% (2q4), 33.1% (2q8), and 13.0% (laser)
VISTA: +11.4 (2q4), +9.4 (2q8), and 0.7 letters (laser)
≥15 letters from baseline: 38.2% (2q4), 31.1% (2q8), and 12.1% (laser) | Most robust VA gains in first 12 months, more modest improvement thereafter
FDA registration trial; led to subsequent label indication for aflibercept in treatment of DME |
the nuances of treatment but, at a certain point, you reach the law of diminishing returns in terms of information overload. I stick to the more common vision-threatening safety items, including endophthalmitis and retinal detachment. I will also mention potential systemic risks if the patient has had a recent stroke history. I will add two things to what Dr. Prenner mentioned. The first is that we have patients sign an additional form stating that if they have decreased vision or pain after the injection, they are to call the office ASAP. Also, in the interest of managing expectations, I want patients to understand up front that we are not providing a cure, but instead we are providing a treatment strategy that has been proven in several clinical trials to be extremely beneficial for managing their chronic disease. I also convey that we will be providing multiple injections, and that there is not a clear end date.

**Dr. Singh:** Does anyone repeat the informed-consent process, either in part or in whole, with subsequent injections?

**Dr. Prenner:** I have the long conversation before the first treatment, and patients sign a consent form before each subsequent injection.

**Dr. Heier:** The consent form we use is good for 1 year, and it is specific to each drug. If we change within the class to a different agent, we repeat the informed-consent discussion.
Safety of Intravitreal Anti-VEGF Injections

Multiple clinical trials have demonstrated that the three anti-VEGF agents approved for use in the United States, pegaptanib sodium, ranibizumab, and aflibercept, are effective and appropriately safe for use for treatment of major retinal pathologies.

Perhaps the most notable concern with anti-VEGF agents pertains to the injection process and not to the drug itself. Endophthalmitis occurs rarely at a rate of about 1 in 4,000 cases.1 However, not all post-injection infections are due to a microbial insult, and even if endophthalmitis is infectious, the potential to cause blindness is extremely rare. Furthermore, certain precautions may lower the risk even further. Due to concerns that the care provider may be a nidus of contamination, some physicians have advocated for a no-talking policy during injection delivery; use of a face mask has been suggested, although its role is not entirely clear.2 Prophylactic antibiotics have not been demonstrated to provide a definitive benefit, and, as a result, they are not widely used or recommended.3,4

An issue related to the use of off-label bevacizumab is that it is only available from compounding pharmacies, there is a potential risk for dose or lot contamination.5,6 While rare, reports of binding endophthalmitis after use of compounded bevacizumab have been recorded in the literature.6 Retina physicians would be wise to understand the source of compounded lots, as well as the procedures and safeguards the compounding pharmacy uses to prevent potential contamination.

Safety issues with anti-VEGF drugs have been consistently low in clinical trials, with the most commonly reported instances being retinal tears, retinal detachment, vitreous hemorrhage, and traumatic iatrogenic cataract.7 Among the less common complications of anti-VEGF use are the potential to induce a retinal pigment epithelium tear and elevated pressure following chronic use, occurring in 3.5% to 11% of patients,8 10 which may or may not require treatment.

One of the most widely talked about aspects of anti-VEGF safety is whether chronic inhibition might have systemic implications, especially as it may pertain to stroke risk. The bottom line is that while there have been reports of pharmacokinetic differences between market-available anti-VEGF agents,11 there is insufficient evidence at the current time to determine whether their use confers any risk for thromboembolic events.

Dr. Pieramici: I agree, and I will add that if we are using bevacizumab, it is important to mention that, while there is clinical trial data to support its use in AMD,13 diabetic macular edema,14,15 and retinal vein occlusion,16,17 this is an off-label use of the drug.

Dr. Heier: I have a population of patients that is both generally very well educated and sensitive to costs, and so the discussion about off-label drugs can sometimes get challenging. I tell patients that bevacizumab is a very reasonable treatment option and that many, if not most, patients experience a benefit. I explain that the reason bevacizumab is cheaper is not because it is not as effective, but because it was developed as a cancer drug that is now being compounded into individual doses. Ranibizumab and aflibercept were specifically developed for use in the eye, and so the higher development cost is reflected in their price. However, I am also clear that I have a very low threshold for changing drugs if we are not getting the response we anticipate.

Dr. Singh: And you repeat the consent process when you switch?

Dr. Heier: That is correct.

Dr. Singh: Does anyone change the safety discussion with respect to potential comorbid conditions? For example, individu-
Angiogenesis has been noted to play an important role in several different pathologic pathways in diseases of the retina. Even if distinct neovascularization does not occur, angiogenic factors, and VEGF, in particular, may be present and active in disease processes that often couple with inflammatory mediators to drive disease activity. Macular edema secondary to retinal vein occlusion (RVO) is one example of a disease entity believed to be simultaneously mediated by VEGF inflammatory cytokines.\(^8\)

Following is a brief synopsis of the important role VEGF plays in selected retinal pathologies: age-related macular degeneration (AMD), diabetic macular edema (DME) in the presence of diabetic retinopathy (DR), and RVO. This is not intended to be an exhaustive review, but rather is intended to provide insight on the role and rationale for VEGF inhibition in these pathologies.

**AMD**

While DR was the first ocular condition in which the role of VEGF was elucidated,\(^9\) AMD was the first major eye disease in which therapeutic inhibition of VEGF was successfully achieved. Localization of VEGF in choroidal neovascular membranes in eyes with AMD\(^8,10\) spurred intensive research to develop an inhibitory agent that would stop and/or reverse the angiogenesis. The assumption underlying this work was that several disease features of AMD, namely drusen formation, choroidal ischemia, and vitreoretinal adhesion, could contribute to hypoxia and ischemia that stimulates production of VEGF, in turn driving neovascular mechanisms to resupply the retina with nutritional pathways.\(^9\)

After murine models of retinopathy of prematurity demonstrated the potential to inhibit neovascularization,\(^10\) interest turned to developing a relevant animal model, which would propel further development of anti-VEGF agents for use in AMD.\(^11\) The development of pegaptanib sodium would soon follow,\(^12\) and later phase 3 clinical studies would lead to the release of ranibizumab and aflibercept for this indication.

**DME**

VEGF activity is consequential to both manifestations of diabetic eye disease, DR and DME.\(^13\) Its role in DR is significant insofar as DR can lead to formation of DME; in addition, evidence points to the fact that VEGF is independently active in DME pathogenesis. VEGF plays a prominent and multifactorial role in the neovascular process in proliferative diabetic retinopathy (PDR), both controlling pathological angiogenesis and increasing vascular permeability.\(^14\) Aiello et al demonstrated that intraocular VEGF levels correlate with the severity of DR.\(^11\) Moreover, increases in intraocular VEGF levels initiate a positive feedback loop in which ischemia is produced that promotes additional expression of VEGF.

At a cell biology level, VEGF appears active in pericyte activity that is fundamental to the early stages of angiogenesis.\(^14\) Furthermore, tyrosine kinase receptors VEGFR-1 and VEGFR-2 are each active in regulation of angiogenesis; VEGFR-2, expressed primarily on vascular endothelial cells, stimulates endothelial cell proliferation, migration, survival, and angiogenesis in PDR.\(^15\)

As it pertains to DME, VEGF plays a critical role in the breakdown of the blood-retina barrier, the consequence of which is increased vascular leakage. In turn, VEGF inhibition has proven a highly successful strategy for treating DME,\(^16,17\) a finding that is reinforced in major registration trials for the FDA-approved anti-VEGF agents ranibizumab and aflibercept.\(^18-20\) Whether suggested differences between these agents may lead to differences in therapeutic effect and/or pharmacokinetics remains unclear. Higher binding affinity associated with aflibercept may potentiate longer inhibition of VEGF-A,\(^20\) although how this may translate to efficacy is uncertain given the role of other factors in inducing vascular permeability.\(^21-25\) Meanwhile, some studies have suggested a role for the Fc-binding receptor present on bevacizumab—which is often used off-label for VEGF inhibition—and aflibercept in affecting transport across the retina and into the circulation.\(^26\)

Others have suggested the potential for the Fc domain to interact with similar domains in immune cells in the system.\(^27\) However, studies have also demonstrated that all three of these agents have a similar half-life, and, therefore, the Fc portion may not be significant in transport out of the retina.\(^20\)

**RVO**

As noted earlier, macular edema, a prominent feature in some cases of branch, retinal, and hemispheric RVO, is mediated by local cytokine and VEGF activity.\(^1,4\) Although it is not clear which plays a more prominent role. Other factors are likely involved in formation of macular edema, most notably the hemodynamic changes due to the obstruction of the affected blood vessel. More than likely, the mechanical obstruction establishes conditions for natural homostatic and responsive mechanisms to increase local activity of chemical mediators. For instance, marked increase in the flow of blood into the retina coupled with increased vessel pressure likely compromises perfusion and leads to an ischemic state; this, in turn, triggers VEGF stimulation, which is intended to produce new vessels to bypass the obstruction so as to supply the retinal tissue with nutrition. One of the negative consequences of this activity is an increase in vascular permeability,\(^28,29\) establishing conditions that can yield leakage and continued edema.

Higher levels of VEGF have been noted in eyes evaluated for CRVO relative to branch RVO, suggesting a higher propensity for chemical mediator activity in the former.\(^30\) Treatment with anti-VEGF agents that bind to VEGF-A isoforms has been shown to significantly improve macula edema.\(^31,32\) However, incomplete response in studies involving such agents\(^33,34\) has led researchers to propose that additional VEGF isoforms may be present and active in the disease pathway. Specifically, Noma and colleagues have demonstrated the activity of soluble(s) VEGFR-2 in the pathogenesis of macular edema associated with branch RVO.\(^35-37\) Although it is unclear what if any interactions occur between VEGF-1 and VEGF-2 receptors, simultaneous inhibition would seem to silence the activity of chemical mediators that have been shown to be highly active in RVO pathology.
THOUGHTS ON MAXIMIZING EFFICIENCY

Dr. Singh: How are people managing the injection process to maximize efficiency? How involved are your technicians in the process and who is responsible for what in terms of the actual injection procedure?

Dr. Prenner: I also rely on our technical staff. Their support is critical to the process. In my practice, I may circulate between two or three different rooms, but technicians are stationed in one room, which we have found really maximizes efficiency. That may sound like a lot of staff costs, but our technicians perform several different jobs. For example, they act as EMR scribes and also as photographers. Once the decision has been made to deliver an injection, the technician is responsible for pulling, identifying, and entering that information into our electronic inventory management system. They also deliver the anesthesia and prep the eye with betadine. That same technician cleans and rinses the eye after injection, the technician is responsible for pulling, identifying, and entering that information into our electronic inventory management system. They also deliver the anesthesia and prep the eye with betadine. That same technician cleans and rinses the eye after injection, the technician is responsible for pulling, identifying, and entering that information into our electronic inventory management system. They also deliver the anesthesia and prep the eye with betadine.
Dr. Heier: I would say that about 25% of my patients do not get a lid speculum placed, and I hold the lids open with one hand, and, because I am holding the syringe in the other, the technician places a drop of betadine on the ocular surface just prior to the injection. There are all kinds of eventualities like that that we need to prepare for, but the important thing to reinforce is to not rush just to try and save time and to be thoughtful about each patient interaction.

Dr. Prenner: My version of that is to soak a cotton swab in betadine and press the cotton swab right on the injection site, wait 30 seconds, do it a second time, then proceed with the injection. There are patients who prefer not to have a speculum placed, and while I respect their wishes, it does make me a little nervous about the informed-consent process. There are retrospective studies in large patient populations showing that a lid speculum may not be necessary. That said, the risk of endophthalmitis without using a lid speculum has not been definitively tested.

Dr. Heier: The purpose of the lid speculum is to keep the sebaceous excretions from the lid out of the field. When I hold the lid open with my fingers, in essence, I am the lid speculum.

Dr. Prenner: I would agree with that.

Dr. Pieramici: In most cases, I use a lid speculum, but sometimes patients do not tolerate it well. In these cases, I have my technicians hold the eyelids open with cotton swabs, which is an effective alternative way of stabilizing the lids and well tolerated by those who are speculum phobic.

Dr. Heier: The only problem with these practices is that if the patient manages to blink while you manually hold the eye open, the lid hits the needle. There is a company called OcuJect that has come up with a device they are calling the VitreJect needle, which is basically a needle designed with a circular hub fitted with a measuring device. The device is placed over the eye and the injection is administered by depressing a plunger. The clever design protects the lid from ever encountering the needle.

Dr. Singh: What needle gauge does everyone use for injection?

Dr. Prenner: I use the 30-gauge needle.

Dr. Pieramici: I use the 30-gauge needle, as well.

Dr. Heier: I use the 32-gauge needle mostly but some 30-gauge. The VitreJect device is a 33-gauge needle, and I have been using it for many patients who do not like the use of the lid speculum as it protects against the lid closing and hitting the needle directly.

Dr. Pieramici: I can see the advantage of that kind of device, but I do wonder whether it will be feasible economically, especially as our margins are getting smaller.

Dr. Singh: Does anyone have patients who are allergic to betadine?

Dr. Prenner: This is an interesting question because, theoretically, one cannot be allergic to the active ingredient in betadine—iodine—as it is an element. In addition, if you have a thyroid, you have systemic exposure to iodine making allergy theoretically unlikely. Patients can be allergic to other components of the betadine formulation, but typically they are describing the irritating result of betadine on the ocular surface. I think Dr. Heier described this correctly earlier when he said that some patients are more sensitive to betadine than others.

Dr. Heier: I have three patients who, after they get the betadine drop, the cornea sloughs. I have those patients use an antibiotic for 3 days before the injection and for 1 day after.

Dr. Pieramici: A recent study suggested that the risk of endophthalmitis when betadine is not used could be as high as 10%. The interesting thing about this study, though, is that when the investigators performed subsequent injections in patients who developed endophthalmitis, they used betadine without difficulty, even though there was a supposed betadine allergy. It is notable that there were absolutely no issues surrounding betadine sensitivities in those follow-up injections, which I think really shows that, in most cases, this is not a real allergy.

Dr. Prenner: I do not perform intravitreal injections without betadine. In a case with extreme corneal sensitivity, I will place a contact lens prior to betadine exposure, and then remove the contact lens after performing the injection.

patient call back

Dr. Singh: Despite out best efforts, treatment may not always go according to plan. What are some concerns you might hear a patient report that would have you suspect a follow-up examination is prudent?

Dr. Pieramici: Reports of decreased vision and floaters are the two things that I am most concerned about. I have found that most of the time reports of pain are nonspecific and not helpful. Another thing that concerns me is the patient who calls the day after the injection to report worsening of symptoms. When I hear something to the effect of, ‘my eye was a little red yesterday, but its worse today,’ or, ‘the pain got worse overnight,’ then I immediately want that patient back in the office.

Dr. Heier: My threshold to call a patient back is extremely low. I will forewarn patients that floaters are a possibility and there may be air bubbles in the injection that could cause some visual symptoms. However, if floaters increase after the first day, or if pain increases or vision decreases after the first day, I want the patient to call my office and schedule an immediate follow-up. A lot of times when those patients come in, we find a corneal abrasion or something innocuous, and it is usually a very quick examination, but it is better to be sure than to leave any question.
Dr. Pieramici: Has anyone seen endophthalmitis in a patient the same day as the injection?

Dr. Heier: I have not, no.

Dr. Prenner: I have seen several cases of noninfectious endophthalmitis on the same day, but have not seen infectious endophthalmitis that quickly.

Dr. Pieramici: I have not either, and that is why I am usually comfortable in saying that any same-day discomfort is likely related to surface irritation. A significant change in vision is more alarming, but that may be also due to a corneal issue or the very rare vitreous hemorrhage. It is the cases that are initially doing well following the injection, that then get worse during the first few days following the injection that concern me the most.

Dr. Singh: Who handles that phone call in your office? Do you do it personally or is that staff?

Dr. Pieramici: The technicians but they document and show to the doctor. They are also on alert that any recent injection patients need special attention.

Dr. Heier: It is the same in our office. The technicians handle those phone calls, but we have trained them to know what to listen for.

Dr. Pieramici: We have a triage system where the technician brings a form that has been filled out with the patient’s complaints. That allows the doctors to at least get a glimpse of what is going on to make a determination whether further action is necessary.

FINAL THOUGHTS

Dr. Singh: Let us conclude with this: If one of your colleagues asked you for one tip or one pearl to help him or her be more efficient with their injection protocol, what would you offer?

Dr. Prenner: I would try to convey the importance of having an abundance of well-trained staff and how important that is to developing an efficiently run practice. One really needs to think about the revenue-generating potential and return on investment for each person in the practice. The retina physician is obviously at the top of that list, and so any work that can be delegated to staff preserves the time that physicians can be taking care of patients and generating revenue. When considering your staff in that kind of value-based analysis, raising the practice’s overhead by hiring more staff members may be more palatable. Another way to look at this question is to consider whether additional staff will add quality in addition to quantity of patient care. By that I mean that if having more hands on deck to help manage patients will lessen the stress on each individual, it may be worth sacrificing some overhead to make sure everyone is having a better experience—patients, staff, and physicians alike.

Dr. Pieramici: I agree completely. What I really value in staff members is a certain level of intelligence but also a willingness to learn and be trained. If you can train new staff not just on the nuts and bolts of checking vision and pressure but also educate them on the eye, the retina, and the disease process so they really have an understanding of what is going on, then the relationship becomes more meaningful. It can make your job as a physician a lot easier, especially in the era of EMR.

Dr. Prenner: To continue Dr. Pieramici’s point, when you have an educated staff who understand what is happening, they feel engaged in the process and get to really recognize that they are helping people. That is what motivates all of us.

Dr. Pieramici: When I am reviewing the OCT, I explain the findings to the technicians—where I am seeing fluid, what the anatomy is telling me. I find that the technicians in our office are truly interested in learning and expanding their knowledge, which is tremendously helpful, because they can take that knowledge and help us triage patients, input EMR data, and educate patients.

Dr. Prenner: I agree. Staff members often have more face time with patients than physicians.

Dr. Heier: That is a critical point. When I talk to colleagues who are maybe struggling a little or not doing as well as they would like, I usually find that they do not have either the numbers of or kinds of patients they want—and that is where the staff can be important. The staff greet the patient at the front door, the technicians are the ones working the patient up, the scribes are walking them from room to room, and so these people have much more contact with patients that the physicians in the typical practice do. And guess what? Each of those encounters is an opportunity to make that patient feel special and important, or at least, to convey the sense that you, the physician, are going to do your best to help them with whatever medical problem they are having. And so, I think there are several important characteristics of good staff, including a pleasant attitude and willingness to learn, but also some compassion and understanding that attending the clinic is a disruption to the patients’ daily life. The more you can alleviate that and personalize the treatment, the better. A more subtle aspect of what Dr. Prenner was referring to earlier with how staff help the primary revenue generator focus, is that when the doctor enters the room, he or she can provide undivided attention to ensure outstanding care.

Dr. Singh: The patient’s experience is becoming increasingly important, and it is something we will all be judged on.

Dr. Prenner: At the end of every patient encounter I try to remember to ask, “Have I answered all your questions?” It is such a small thing, but you do not want people leaving the office feeling like they did not have a chance to ask questions.

Dr. Pieramici: I ask medical students and fellows all the time, “As retina specialists, what do we really provide for our patients? What is our job?” The answer is usually that we cure disease or improve vision. What we really do is improve patients’ quality of life. We may...
do this by improving vision or curing disease, but sometimes we accomplish that goal by treating patients compassionately when they come in the office, or by telling them that they are not going to go blind. Thus, our patients’ experiences are about so much more than simply making a diagnosis and recommending treatment. Each person who comes in contact with the patient can enhance or reduce their experience in our practice. The front desk has to make the patient feel comfortable and welcome, the technicians should be capable and compassionate, and so on and so forth all the way up to the retina physician who is also mindful of the customer service aspect of running a medical practice not just the medical aspects.

Dr. Singh: Do you measure patients’ experiences?

Dr. Prenner: We use a consulting group (Press Ganey) that surveys our patients. It is a costly process, but it is something we feel is well worth the investment. On a practical level, being able to demonstrate quality by these measures facilitates negotiations with third party payers. Measuring the patient experience helps us ensure we are delivering a positive one for every patient who walks through the door.

Dr. Pieramici: We mostly measure patients’ experiences indirectly through the referral sources. We want to make sure the referral sources are hearing good things from patients who return to them.

Dr. Heier: We use online surveys and patient surveys that have been formalized to our group.

CONCLUSION

Dr. Singh: We will be challenged in the future by the demands of delivering increasing numbers of intravitreal injections—and anti-VEGF, in particular—to a growing number of patients. We face the prospect of more complicated logistics in an era of uncertain reimbursement. However, we can be bolstered by the fact that much research has been dedicated over the past decade to understand how we can be more efficient in our operations so that we can better deliver high-quality care to our patients. Yet, in all this planning for higher volume practices, one fundamental fact must not be obscured: While the onus has been placed on care providers to figure out how to deliver care, the only reason that is our reality is because pharmacologic options offers such awesome potential for our patients. We may face difficult questions, but they are only questions because intravitreal injections—and anti-VEGFs, in particular—are a substantial answer to a lot of different retinal pathologies.

1. What is the suspected role of VEGF in the pathophysiology of retinal vein occlusion (RVO)?
   a. VEGF is a mediator of the RVO disease process
   b. The RVO disease process is mediated by inflammatory mediators
   c. Neither A nor B
   d. Both A and B

2. Which of the following anti-VEGF agents are approved for use in the treatment of diabetic macular edema?
   I. Pegatanib sodium, II. Ranibizumab, III. Aflibercept, IV. Bevacizumab
   a. I, II, and IV
   b. II and III
   c. I, II, and III
   d. All of the above

3. Although the exact pathophysiology of diabetic retinopathy (DR) and diabetic macular edema (DME) are not completely defined, the current understanding of the role of VEGF in these entities can best be described by the following statement:
   a. VEGF plays a prominent role in neovascularization that is prominent in proliferative DR and, in addition, is active in the breakdown of the blood-retinal barrier, in turn, leading to vascular leakage and consequential macular edema.
   b. VEGF increases vascular permeability and is a driver of angiogenesis, but there is no suspected role for VEGF in the DME disease process.
   c. Ischemia that develops as a consequence of macular edema leads to upregulation of VEGF activity, in turn, spurring release of chemical factors that underlie DR.
   d. VEGF is fundamental to pericyte activity that causes angiogenesis, and, in turn, formation of macular edema.

4. Which of the following is MOST TRUE about the role of facemask use during the delivery of anti-VEGF injections?
   a. Published studies have not definitively demonstrated that using a facemask prevents spread of microbes and thus their use is not considered standard of care.
   b. While talking during the delivery of an anti-VEGF injection increases the risk of microbial spread, other factors are more likely related to risk of endophthalmitis, thus rendering the use of a facemask moot.
   c. Published studies have definitively demonstrated that using a facemask prevents spread of microbes and thus their use is considered standard of care.
   d. Guidelines for anti-VEGF delivery suggest the use of a facemask and splatter shield to minimize the risk of microbial spread from the care provider team to the patient.

5. What is the published rate of IOP increase associated with chronic use of anti-VEGF agents?
   a. 1% to 3%
   b. 3.5% to 11%
   c. 12% to 20%
   d. ≥20%

6. Which of the following is FALSE about the risk of arterial thrombotic events (ATE) following anti-VEGF injections?
   a. Studies have shown that the Fc domain present on some anti-VEGF formulations may interact with similar binding sites on systemic immune cells, while other studies show that because the half-life of commonly used agents are about the same, the former finding may be of little consequence.
   b. The Fc domain present on some anti-VEGF formulations has been definitively proven to affect transport of the molecule across the blood-retinal barrier and into the system.
   c. There is inconclusive evidence in published studies to determine if the use of anti-VEGF agents may lead to an increased risk of ATE.
   d. Studies have suggested that risk of stroke may be higher among individuals with a very recent stroke history (ie, in the previous 6 months).

7. Higher levels of VEGF have been isolated in eyes with central versus branch retinal vein occlusion, therefore suggesting it is more active in that disease process.
   a. True
   b. False

8. Which of the following is FALSE about the DRCR.net Protocol T study?
   a. There were noticeable differences in safety outcomes between the agents under investigation.
   b. There were modest differences in the overall population, largely driven by differences in subgroup analysis among individuals with worse vision at baseline.
   c. There were no new safety signals detected in the study.
   d. Visual and anatomic outcomes were consistently better with either ranibizumab or aflibercept compared with bevacizumab.

9. What did the panel suggest was the most likely explanation for suspected allergic reaction to the betadine used prior to an anti-VEGF injection?
   a. An allergic reaction to the main ingredient, iodine
   b. Allergy to the main ingredient, iodine, is exceptionally rare but has been known to occur in some individuals.
   c. These individuals have likely been exposed to high levels of iodine in their past history, which, in turn, drives a hypersensitivity reaction.
   d. Allergic reaction to iodine is unlikely, but individuals may be hypersensitive to other ingredients in the formulation.

10. Delivery of bilateral injections of anti-VEGFs is an unsafe practice and should not be used in clinical practice.
    a. True
    b. False
**Did the program meet the following educational objectives?**

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<th>Objective</th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
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<td>Understand the most recent monotherapy and combination therapy clinical study evidence using available anti-VEGF, steroid, and photodynamic therapies for common retinal diseases, including AMD, RVO, and DME</td>
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<td>Discuss the outcomes of pivotal studies in AMD, RVO, and DME as well as how study results may differ from real-world dosing methods</td>
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<td>Develop plans to initiate treatment for conditions such as AMD, RVO, and DME using anti-VEGF agents as well as better understand when to change therapeutic strategies and/or therapeutic classes</td>
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<td>Evaluate practice flow to determine the most efficient patient experience</td>
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<td>Develop plans to reduce reimbursement denials</td>
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