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TAILORING THERAPY TO THE NEOVASCULAR AMD PATIENT:

Implementing Novel Treatment Strategies to Improve Outcomes

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a roundtable discussion.

ACTIVITY DESCRIPTION

By 2040, an estimated 228 million people worldwide will be diagnosed with age-related macular degeneration (AMD). Treatment with anti-VEGF intravitreal injections has been shown to improve vision by 6 to 10 letters from baseline, but real-world results differ from clinical trial results. Therefore, it is clear that retina specialists need to be fully educated on the various treatment options to deliver the best patient care.

TARGET AUDIENCE

This certified CME activity is designed for retina specialists and eye care professionals involved in the medical management of patients with retina disorders.

LEARNING OBJECTIVES

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

- **Explain** the differences in short-term and long-term outcomes with current neovascular AMD treatment options in clinical practice as compared to clinical trial outcomes
- **Describe** the relationship between drugs, treatment frequency, visual, and anatomic outcomes
- **Develop** best practices and recommendations to ensure optimal treatment outcomes for patients
- **Describe** the existing barriers to treatment and ways to overcome them
- **Identify** the newer compounds in development that may reduce treatment burden while maintaining efficacy

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PRETEST QUESTIONS

Please complete prior to accessing the material and submit with
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1. Please rate your confidence in your ability to apply updates in age-related macular degeneration (AMD) treatment in the clinic based on this activity (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. Please rate how often you intend to apply advances to AMD treatment to "real-world" patient management (based on a scale of 1 to 5, with 1 being never and 5 being always).

a. 1
b. 2
c. 3
d. 4
e. 5

3. A Latino male patient in his 80s has exudative macular degeneration in his left eye, which has left him with monocular vision only. His right eye has developed wet AMD, but visual acuity (VA) is still fairly good at 20/40. What treatment interval do you recommend for maximum VA gains in his right eye?

a. Three loading doses, then 2-week treat-and-extend
b. Eight-week treat-and-extend
c. Three loading doses, then observation
d. Monthly

4. In the CATT study, _____ was associated with better VA.

a. Subretinal fluid
b. Intraretinal fluid
c. Both subretinal and intraretinal fluid
d. Macular hemorrhage

5. What is the minimal average number of injections needed in the first year to optimize treatment outcomes in patients with wet AMD?

a. Four
b. Five
c. Six
d. Seven

6. In both the CEDAR and SEQUOIA trials, inflammation was seen with which of the following new agents?

a. Faricimab
b. Abicipar
c. OPT-302
d. RGX-314

7. What is the primary reason long-term outcomes seen in clinical trials are often different from outcomes seen in clinical practice?

a. Insurance companies won't approve payment of branded drugs.
b. Patients in the real-world experience significant injection fatigue or receive fewer injections in the clinic than in clinical trials.
c. Real-world patients have fewer comorbidities than clinical trial patients.
d. Only patients with high-deductible insurance coverage are enrolled in clinical trials.

8. An elderly patient with exudative AMD and fluctuating vision has remaining subretinal fluid after more than 20 injections of aflibercept and ranibizumab. What is an acceptable treatment option?

a. Keep treating with aflibercept
b. Watch and wait
c. Switch back to ranibizumab
d. Switch to brolucizumab

9. What are the potential advantages of a port delivery system (PDS) and what are the potential disadvantages?

a. The implant procedure is short (5 to 10 minutes), but the risk of endophthalmitis is very high (>50%).
b. The PDS is placed into the suprachoroidal space, but the surgery takes more than 1 hour.
c. The PDS may provide up to 6 months of durability but there is a higher risk of adverse events compared to intravitreal injections.
d. All patients have gone out to 15 months without needing rescue injections, but vitreous hemorrhage rates hover around 75%.

10. Faricimab is one molecule that blocks which target(s)?

a. VEGF-B and VEGF-C
b. VEGF-A and Angiopoeitin-2
c. VEGF-B and Angiopoeitin-2
d. VEGF-A and tyrosine kinase receptor

Tailoring Therapy to the Neovascular AMD Patient:

Implementing Novel Treatment Strategies to Improve Outcomes

The approval of anti-VEGF therapies for age-related macular degeneration (AMD) transformed the management of patients with neovascular AMD (nAMD) and have, without a doubt, saved the sight of millions of Americans. The effectiveness of these agents is well documented; 95% of patients with nAMD will stay within 3 lines of their baseline vision 2 years after beginning anti-VEGF therapy, and 40% will have an improvement of 3 lines from baseline in the same timeframe.[1]

There is still work to be done, however. AMD has no cure. Patients must have constant, frequent injections in order to maintain or salvage vision, leading to significant injection burden, financial hardship, and poor compliance/loss to follow up. Further, approximately 10 to 25% of patients will not respond well to initial anti-VEGF treatment.[2,3] *Alternative therapies and drug delivery methods are urgently needed to resolve these issues.*

The following roundtable reviews best practices and recommendations to ensure optimal treatment outcomes in patients using current therapies, treatment barriers and potential solutions, and novel compounds, delivery systems and agents in development.

— Arshad M. Khanani, MD, MA, Moderator

CURRENT TREATMENT OPTIONS FOR AMD

Q | ARSHAD KHANANI, MD, MA: What are the current treatment options for the management of AMD and how do you approach these patients?

JONATHAN PRENNER, MD: I am old enough to remember a time before the anti-VEGF era and the days of thermal laser as the main treatment option for nAMD. Thankfully, we progressed into the modern era with the advent of anti-VEGF therapy. I utilize anti-VEGF monotherapy for all patients with exudative macular degeneration. My general treatment paradigm when I meet a new patient with exudative AMD is to examine the patient and then image with fluorescein angiography, optical coherence tomography (OCT), OCT angiography (OCTA), and sometimes indocyanine green angiography.

I think it's important to continue to use extensive imaging when making the initial diagnosis of AMD. It is critical to respect the fact that there is a true differential diagnosis with neovascular AMD, and we should be sure that we have the correct diagnosis prior to committing a patient to a long treatment course. I typically treat people with branded anti-VEGF therapy, but I first make sure they don't have financial exposures before committing them to a costly treatment regimen. I also generally do not treat patients on the same day as their initial workup. If someone has a macular hemorrhage or is monocular, I will treat on the same day.

I use a treat-and-extend paradigm for patients who are seeing reasonably well in their fellow eye. I am more conservative and generally do not extend patients who are monocular.

DR. KHANANI: I agree. Anti-VEGF agents have revolutionized how we treat patients. We can now stabilize and improve visual acuity (VA) in most of our patients but this comes with a significant treatment burden. When you see a new patient, what do you tell them about their disease? What do you tell them about your treatment strategy and short- and long-term goals?

NANCY HOLEKAMP, MD: We don't only manage disease, we manage patients through this journey. For them to hear that they have wet AMD is shocking and unexpected. To then follow up that diagnosis with details on how they'll be getting injections in their eye is almost equally as shocking.

During the first visit, I spend time setting expectations for this journey. The most important thing to do is set the expectation that they will need multiple injections, given at least monthly at first. I also stress that it's uncertain what their future injection burden will be. I like to set the expectation that they're going to see me frequently, be monitored closely, and get injections that are appropriate for their individual disease. I also mention that although their friends may have macular degeneration and get shots on a certain schedule, their disease may be different. If both eyes are involved, the disease may vary between them and require different treatments.

From the very first visit, I set the expectation that we're in this together, this is teamwork, they're going to see me frequently, and then I give them a shot on the first day.

DR. KHANANI: Do you manage these patients with a treat-and-extend regimen?

DR. HOLEKAMP: I give three monthly loading doses and then watch them for a while. It usually morphs into treat-and-extend. I practice all three treatment paradigms because we know that many patients can't be extended beyond monthly dosing. We have a small, but not insignificant, portion of our patients who are on monthly dosing. I start patients with the expectation they'll see me monthly, and if we're really smart, we'll figure out how many shots they need

and at what interval. There's actually another small, but not insignificant, portion of the patients who do well with their first three injections and just need to be monitored. These patients don't have a very high treatment burden.

This is supported in the literature. There were some patients in the HARBOR study who received three injections, and they never needed treatment during the next 2 years.[4-8] In HARBOR, 1,098 treatment-naive patients with subfoveal wet AMD were randomly assigned to receive intravitreal ranibizumab 0.5 mg or 2.0 mg monthly or *pro re nata* (PRN) after three monthly loading doses. At year 2, the mean increase in baseline best-corrected visual acuity (BCVA) was 9.1 letters (0.5 mg monthly arm), 7.9 letters (0.5 mg PRN arm), 8 letters (2.0 mg monthly arm), and 7.6 letters (2.0 mg PRN arm). Although the visual gains were similar across all four groups, the number of injections that patients needed was way across the board, without any peak incidents of how many injections, in total, a patient may require over 2 years.[8]

DR. KHANANI: You're trying to figure out their sweet spot. In 2018, the US FDA gave a breakthrough device designation to the Notal Vision Home OCT System, a cloud-based OCT platform that provides remote monitoring of retinal fluid changes in patients with wet AMD.[9] Do you think home OCT will help you monitor select patients, and then bring them in if there is fluid occurrence?

DR. HOLEKAMP: Absolutely. I think that's an exciting prospect that they can be monitored more closely than every month and maybe have more timely and appropriate therapy. But it remains to be seen how we can incorporate the technology into our practice.[10]

MICHAEL SINGER, MD: When I first see a patient, I also have a long discussion about what treatment involves. I explain that this is chemotherapy, and that I'm going to be giving treatment for a while. Our goal is to control the disease, not to cure the disease. Hopefully the treatments will either keep their vision stable or improve it.

I also like to use branded drugs and will do my best to get them approved through their insurance. I'll also give the first shot on their first day, if they can do it. My practice is in Texas, and some of our patients travel long distances to come to the office. If travel is an issue, I will use a sample of a branded drug that day. I also do three loading doses, and then treat-and-extend for 1 or 2 weeks. If after three shots they're dry, I'll give another couple of shots to ensure that they will stay dry. I'll then adjust my treat-and-extend 1 to 2 weeks based on that.

DR. KHANANI: Is everyone using a treat-and-extend regimen?

DR. SINGER: I'll treat monocular patients monthly. Patients will inevitably get injection fatigue, so I discuss the data from ANCHOR/MARINA and VIEW 1/2 that shows that patients who receive more frequent treatment have better vision.[11-13] The HORIZON study showed what happens when people are not treated as often, they actually lose the visual improvements they initial gained with anti-VEGF therapy.

The SEVEN-UP study assessed long-term outcomes in 65 patients from the ANCHOR, MARINA, and HORIZON trials.[14,15] The primary endpoint was the percentage of patients with 20/70 or better BCVA. After a little over 7 years after enrollment into the ANCHOR or MARINA trials, 37% of eyes had 20/70 or better vision and 23% had 20/40 or better vision. However, another 37% of eyes had BCVA of 20/200 or worse. Some patients lost 15 letters or more. When you pool the populations together, there was a mean loss of about 8 letters, primarily due to undertreatment. Patients in SEVEN-UP had average of 6.8 ranibizumab injections. Patients who received 11 or more injections gained more letters than the other patients.

It's important to remember that although clinical trials are informative, but we don't just see clinical trial patients in a real-world setting. We often treat patients who are excluded from clinical trials. We can explain to patients that these drugs performed well in clinical trials, but it requires frequent dosing. Since we are treating all types of patients there will be variability in response to treatment. Injection fatigue occurs in almost all patients, even in those patients who have good response.

DR. KHANANI: For me, I think the injection fatigue comes from the fact that they stop noticing improvement after three or six injections.

DR. HOLEKAMP: I set the table with the expectation that they will see me monthly. I teach them how to look at and read their OCT. Then, when I do extend them out, they feel like they're doing better if their OCT is looking better. I'm not facing fatigue, I'm facing relief because I've relaxed their expectations.

DR. KHANANI: What is your goal for the treatment of neovascular AMD? Are you using OCT as your only objective measure and control of disease? Are there a certain patient characteristics on the exam or on OCT that help you decide how frequent the patient will need treatment?

DR. PRENNER: I generally utilize a treat-and-extend paradigm. I extend in 2-week intervals, and I'll extend out to 12 weeks. My metric for choroidal neovascularization (CNV) quiescence and subsequent extension is the combination an spectral domain-OCT that demonstrates absent intraretinal and subretinal fluid and an OCTA that shows absent CNV growth. When I see growth of the CNV on OCTA without having active exudation, I am worried about biologic control and I don't think that is an eye that is appropriate for reducing drug exposure.

DR. KHANANI: Do you get an OCTA on every visit?

DR. PRENNER: Yes, I do an SD-OCT and OCTA on every visit.

DR. KHANANI: I find OCTA to be time consuming and don't perform it at every visit, but I agree that it has great value for monitoring disease. Does anyone treat certain fluid subtypes more aggressively than others?

DR. HOLEKAMP: We're all treating to dry, but unfortunately dry isn't possible for a small but significant number of patients. The ceiling on treatment is every 4 weeks, so it's difficult to treat more

frequently for people with persistent fluid. I think there are definitely fluid subtypes that affect prognosis. We know that intraretinal fluid is bad. It damages vision, and it's probably disrupting the architecture of the very fabric of the retina itself.[16-19] The vision can't recover.

Subretinal fluid tends to be a little more forgiving regarding vision. Subretinal fluid has been shown to exist in eyes that are being treated to dry, but when subretinal fluid persists, people can still do very well visually.[18,20-23]

DR. KHANANI: And that's based on CATT, HARBOR, and VIEW 1 and VIEW 2?

DR. SINGER: Yes. We were involved with a similar analysis that Dr. Holekamp and others did on HARBOR. We looked at the VIEW analysis and found similar results that intraretinal fluid is bad for vision but subretinal fluid may be associated with better vision. I believe the subretinal fluid which is present 6 to 12 months later is different.[13] It may have different factors and modulators.

DR. KHANANI: So, you're saying it's not active exudation?

DR. SINGER: I think it's something different. When we look at fluorescein angiograms (FAs), we know that our treatments change the underlying disease process over time. This is represented by different staining and leakage patterns, It could be that the subretinal fluid is different in those patients who did better, than the subretinal fluid that you typically see when you start treatment.

DR. KHANANI: If you have a patient who has persistent subretinal fluid on monthly therapy, do you continue monthly? Or do you try to extend them?

DR. PRENNER: Some patients surely see better when subretinal fluid is present, a phenomenon first illustrated in the CATT trial.[22,23] Ironically, one may change drugs or increase dosing frequency to treat residual fluid, but when the fluid dries out vision may decline.

DR. SINGER: How many shots do you have to give where the subretinal fluid hasn't changed to be okay with not treating the patient to dry?

DR. HOLEKAMP: The ALTAIR study allowed for fluid as long as it was stable and not worsening.[24] With that treatment paradigm, they were able to get a higher percentage of patients, almost 50%, to 12-week dosing. In ALTAIR, patients being adjusted on their treat-and-extend regimen every 2 weeks had 42.3% of patients achieve 12-week dosing by the end of year 1. For patients in the ALTAIR study being adjusted every 4 weeks that number reached 49.6%. The VA results were very, very good, with a mean change in BCVA of +9.0 letters in the 2-week group and +8.4 letters in the 4-week group. I think there's a difference between stable, small subretinal fluid and worsening subretinal fluid. We clearly shouldn't tolerate a worsening situation, but given the treatment burden, tolerating some fluid may be a good compromise as long as patients still received consistent treatment and consistent monitoring.

DR. KHANANI: To summarize the fluid discussion, we are all attempting to treat to dry with the maximum treatment frequency with current agents. If we can't get there, and the patient has a small amount of subretinal fluid, we try to extend the treatment interval if possible. However, if the patient has intraretinal fluid, we continue to treat them aggressively to get them dry.

TREATMENT BURDEN AND BARRIERS

Q | DR. KHANANI: What are the current treatment burdens for patients with nAMD?

DR. SINGER: There are obviously barriers to get patients in for monthly shots. The frequency of anti-VEGF therapy has increased by threefold in recent years, from an average of three to nine visits yearly.[25] This injection burden has placed service pressures on clinicians, time constraints on caregivers, and increased anxiety and financial stressors for patients.[26] Patients with nAMD are typically older with comorbidities, so they already have a lot of other doctor's appointments.

Injection fatigue is another issue. Humans are interesting in that we typically remember the bad, not the good. These patients struggle with returning to the clinic month after month when they aren't seeing sustained improvement.

We recently ran a study looking at the cancelation and no-show rates of 100,000 charts of patients with diabetes and DME or wet AMD in the United States and Europe.[27] A large percentage of patients in the United States no-showed and cancelled, especially if they had wet AMD. Thirteen percent of appointments were cancellations and 3% were no-shows in the wet AMD group. In the DME group, 14% were cancellations and 10% were no-shows. The magic injection number seems to be six; you have to come in at least every other month for shots, because if you don't, you're going to lose what you gained.

DR. PRENNER: Our group published a study that tracked patients and their caregivers throughout the cycle of an anti-VEGF injection.[28] We discovered that it's a huge burden on many people involved throughout the process. As physicians, we see a patient for a limited amount of time, but for the patient, it's a 12-hour process. They have to get up, perhaps use a walker, take a shower, get ready, may be picked up by a caregiver, and get to the appointment. After seeing us that process is repeated in reverse. There is a significant societal cost to this process. Twenty-two percent of caregivers took time off work to take the patient to the clinic, while 28% took time away from personal activities.

DR. KHANANI: What does the literature tell us about undertreatment? What happens in the real world to patients who aren't coming in for injections?

DR. HOLEKAMP: I spent many years doing real-world analyses. It didn't matter if we looked at a Medicare database, a commercial database, or a closed health care system database.[29] What we found is in the beginning of the anti-VEGF era, people were undertreated.[30] In fact, the average number of injections that people received the

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—Jonathan Prenner, MD

first year, across multiple studies, was between four and five. The VA results were subsequently poor. When we look at all the registration clinical trials, where patients received eight to 12 injections in the first year, the VA results are very good. From that, we can conclude that the implications of undertreatment is less than comparable VA gains in the real-world than we saw in the randomized clinical trials.

When we look across all the data, the number six comes out as almost a fulcrum. It you got six or more injections in the first year of treatment, you had better VA than people who had less than six. Now of course, it's important to remember that we're looking at means; we're not looking at individual patients.

Now that we've been in the anti-VEGF era a longer period of time, we're looking beyond year 1 and 2 and out to year 7. The only examples where we have good VA outcomes is with patients getting at least six or more injections in those subsequent years. The take-home message is that consistent injections are necessary to have good VA.

DR. PRENNER: If that's true, then why are you attempting to give people no injections after loading them?

DR. HOLEKAMP: Because there's a difference between talking about means in a large population of patients and talking about the individualized presentation of this disease in certain people. I think the take-home message is good VA comes from consistent treatment and close monitoring. The people who aren't getting injections and are doing poorly aren't getting monitored either.

DR. KHANANI: We also recently published the SIERRA-AMD study looking at the real world outcomes for patients with nAMD.[31] Our study also showed that patients with nAMD are losing vision in the real world. In terms of controlling the disease, what are the unmet needs currently for patients to do well? What will future treatments bring that will help them get better vision?

DR. SINGER: Although a lot of the disease is VEGF-mediated, there are other factors involved. We need medicines with different modes of action. Faricimab, for example, is the first bispecific antibody for intravitreal administration that targets VEGF and Ang-2. The phase 2 BOULEVARD study compared the safety and efficacy of 20 weeks of monthly faricimab injections (1.5 mg and 6 mg) versus ranibizumab (0.3 mg) in 224 patients with DME.[32] Patients on 6 mg faricimab had better BCVA at week 24 than patients on ranibizumab, with an average increase of 3.6 letters.

Faricimab was studied further in the phase 2 STAIRWAY trial. Patients were randomized into three arms: faricimab 6 mg every 16 weeks, faricimab 6 mg every 12 weeks, or ranibizumab 0.5 mg every 4 weeks. A total of 65% of patients in the combined faricimab arms had no disease activity 12 weeks after the loading injections, and visual outcomes were similar between all three arms. The safety profile of faricimab was also in line with other anti-VEGF agents.[33] The phase 3 YOSEMITE/RHINE studies are currently evaluating the efficacy and durability of faricimab versus aflibercept in patients with DME. While TENAYA and LUCERNE are evaluating patients with AMD. I think this agent will be of great value.

I also believe that a more consistent dosing schedule may actually have better control of the geographic atrophy that happens over time. Port delivery systems may address this. If you look at most diabetics over time, the goal is to get them on an insulin pump so that their blood sugar is stable. It's the same concept with AMD.

DR. PRENNER: I think the major unmet needs are therapeutic durability and the limitations of anti-VEGF monotherapy. Clinical trial results are difficult to replicate in the real world and we find it challenging to achieve monthly dosing in most patients. Anti-VEGF monotherapy has a ceiling that we currently reach, in terms of vision gain and vision loss. Even in clinical trials, when monthly injections are given, the majority of patients have suboptimal outcomes.

Our patients would benefit from either a long-acting anti-VEGF agent, or a drug that affects complementary targets to go along with anti-VEGF inhibition.

DR. KHANANI: We've established that there is a significant treatment burden for patients and caregivers in terms of coming into the clinic. We also know that patients seem to hit a ceiling of efficacy with anti-VEGF agents. We are lucky to have so many new drugs and delivery systems that are currently under evaluation. We have agents that dry the retina better, like the recently approved brolucizumab, and we have sustained delivery platforms to control the disease better like the port delivery system and gene therapy. We also have longer lasting injectables like KSI-301 and GB-102. We have new

molecules that target new pathways, such as faricimab, which blocks Ang-2 and VEGF-A,[33,34] and OPT-302, which blocks VEGF-C and VEGF-D. OPT-302 showed positive phase 2 data in terms of superiority to anti-VEGF alone.[35] Which of these new approaches are you excited about? What will make a difference for our patients in terms of efficacy and durability in the real world?

DR. HOLEKAMP: Brolucizumab was approved by the Food and Drug Administration in October 2019. In the clinical trials, it seemed to have better drying after three loading doses than aflibercept.[36,37] Drying is a key step toward increasing durability. It remains to be seen if we see better drying in a real-world setting and if it leads to increased durability. But it's an exciting prospect.

DR. PRENNER: The HAWK and HARRIER trial design makes it challenging to draw conclusions because of the way that the dosing was mapped out between the two arms. Eyes were randomized 1:1:1 to brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg in HAWK or 1:1 to brolucizumab 6 mg or aflibercept 2 mg in HARRIER.[36] There's a lot of uncertainty.

DR. KHANANI: There was a matched phase where patients received three injections, and then they came back 8 weeks later. Patients who were treated with brolucizumab had 30 to 40% less fluid than patients treated with aflibercept.[36] Is that something that resonates with you?

DR. PRENNER: It does. But the flip side of that data point is that 25% of patients who received brolucizumab were actively leaking.[36]

How am I going to use this drug? It will be a challenge for treatment-naive patients, given the label as one can't give the drug monthly. I'm going to load people, give them three doses, and I'm going to bring them in presumably for another visit to look at week 12. Then at week 16, I can redose them. At that point, 25% of clinical trial patients will be actively leaking, and who knows what percentage of nonclinical trial patients may be more difficult and less VEGF-sensitive and could be leaking.

Given these uncertainties and limitations, I'll likely use brolucizumab in patients who are extended to 8 weeks, but who I can't extend beyond that. I'm going to try loading them and then extending them to see if I can get to 12 or 16 weeks.

DR. KHANANI: Say you have a patient on monthly aflibercept, and they still have fluid. You give them one brolucizumab injection, and then that fluid is gone. Are you going to give that patient two more injections or are you going to extend them?

DR. HOLEKAMP: What's interesting is that after the three loading doses, the percentage of patients treated with brolucizumab who had persistent fluid was 24%. They were only treated at the 8-week interval, and we cannot say that was harmful to vision because they were still gaining vision.[36]

DR. KHANANI: The MERLIN study is ongoing, and will be looking at monthly dosing (NCT03710564). These are real-world things issues we all have to consider when we use new agents. Let's move on to some other new agents. The clinical trials for abicipar have finished.[38,39] Does this agent address an unmet need in our patients?

DR. SINGER: Abicipar showed that a large percentage of people could have success with 3-month dosing. The problem is inflammation, which occurred occurred in 15% of patients in the CEDAR and SEQUOIA trials.[33] Then the MAPLE trial showed by improved manufacturing a decrease in ocular inflammation.[34] Inflammation in MAPLE decreased to 9% of patients with no retinitis or vasculitis.[34]

It is important to remember that when ranibizumab came out, the incidence of inflammation were really high, but it improved over time. We'll need to see this with abicipar as well; they'll need to keep lowering the inflammation rates for it to be usable.

DR. PRENNER: I'll likely use abicipar as a fourth- or fifth-line treatment option.

DR. HOLEKAMP: No one will use abicipar if there's a significant inflammatory adverse event profile. That has to be resolved. What I give the trial design credit for is having an entire arm on 12-week dosing with no rescue, no drop down, and a very low drop-out rate. When we talk about brolucizumab being an every 12-week drug, it really means 50% of patients are on that dosing schedule. But in the trial design for abicipar, 100% of people in the 12-week arms stayed on that schedule. It's a different drug design platform. It may be our first look at a true fixed 12-week drug, but the inflammation is a challenge. If the inflammation rate is not brought down to levels similar to ranibizumab, aflibercept, and brolucizumab, there's no drug on the market.

DR. KHANANI: If you look at the 1-year data, the 12-week arm is slightly inferior in VA and has more OCT fluctuations. The *P* value may not be significant, but in a clinical trial, we're allowing more fluid. Can you comment on the fact that in the real world, will we have to use this drug more frequently because you are going for a dry retina and stable OCT?

DR. HOLEKAMP: At year 1, the difference in VA between monthly ranibizumab, which is the gold standard, and 12-week abicipar was 2.4 letters, on average. In a 2-year period, patients on abicipar received 10 injections and patients on ranibizumab received 25 injections for a 2-letter difference.[38,39] Now, everyone has to make their own decisions for patients, but there may be situations where someone can't come back monthly, but could come back six times in a year.

DR. KHANANI: So we have a drug that has more OCT fluctuation, a little bit less vision, but less frequent dosing. When you look at the data, do you think you'll use abicipar in the subset of patients who can't come in regularly?

DR. PRENNER: Yes, I would. You have to tailor the care to the individual. But I think most patients would choose 15 fewer injections in 2 years to give up 2 letters of vision.

"I'm excited about the prospect of combination therapy, and I believe it's more likely to be durable. Ten years from now, I think we'll be using combination therapy for everything."

—Michael Singer, MD

DR. KHANANI: Faricimab is one molecule blocking two targets, VEGF-A and Ang-2, in one injection. All arms gained vision in the phase 2 trials.[33,34] STAIRWAY showed that patients treated with faricimab every 16 weeks and every 12 weeks did as well as monthly ranibizumab in terms of VA and CST.[33] There were some fluctuations here in OCT, too, but all patients did well. Based on these data, can faricimab address the unmet need of having better efficacy or durability compared to just blocking anti-VEGF-A?

DR. SINGER: I look at this like I look at oncology care today—no cancer in 2019 is treated with monotherapy, it's combination therapy. In ophthalmology, we haven't found the right combination therapy with a sustainable side-effect profile. I'm excited about the prospect of combination therapy, and I believe it's more likely to be durable. Ten years from now, I think we'll be using combination therapy for everything.

DR. PRENNER: I think faricimab is very promising. The science looks good from the bench through the patients whom we've seen. That said, you have to be very careful with these types of predictions because most of the time, things don't work. But hopefully, we'll have another target, another drug soon, and that is exciting.

SUSTAINED DELIVERY

Q | **DR. KHANANI:** Dr. Holekamp, I know you're very involved with the port delivery system (PDS) with ranibizumab[40] and have performed several of these surgeries. Tell me about the procedure. How are the patients doing? How do they like it?

DR. HOLEKAMP: The PDS with ranibizumab changes the paradigm for treating our patients with nAMD because it's a surgical procedure. You implant a small, reusable, permanent drug-delivery system into the eye through a 3.5 mm scleral incision in the pars plana. It currently is capable of holding 20 µL of ranibizumab. The surgery takes about 30 minutes. The tradeoff to undergoing surgery is the patient has more durable drug exposure. This is continuous drug delivery.

That's exciting to me because when we looked at the LADDER trial, we had thoughts of disease modification, because people were going 15 months without needing rescue injections.[40] We don't know if continuous drug delivery has advantages because we've never had it before. It's exciting. The evidence points to at least 6 months of durability, which is also new. But only through phase 3 clinical trials can you have true efficacy and also a good, well-defined safety profile established. A phase 3 trial is currently ongoing (NCT03677934).

DR. PRENNER: The data look exciting, and I think it's going to be part of the armamentarium. My concern is the safety profile? Obviously, there was a problem with vitreous hemorrhage in earlier periods of the study prior to modification. Will that complication continue to be abated in a larger study cohort?

A second concern is endophthalmitis. Will we see a baseline rate that is acceptable or not? I don't think we can say until we have the registration trial data and expose more patients to the technology.

DR. KHANANI: We have been actively involved in the port delivery trials including LADDER, ARCHWAY, PORTAL, AND PAGODA. In my experience, there is a learning curve to surgery and the in-clinic refill procedures but overall the surgery and refill procedures are not difficult to learn. Initially, the vitreous hemorrhage rate was 50% but after the laser was added to the surgical procedure, those rates are less than 5% now.[40,41] In a clinical trial, vitreous hemorrhage is a big deal. But we all do surgeries, we have some vitreous hemorrhages postoperatively, and the patients recover with observation. In terms of endophthalmitis, three cases were reported in the LADDER study. I think these numbers will improve as we learn more about the procedure and optimize it. Surgery is never going to match the safety profile of intravitreal injection but if the outcomes are as good as monthly injections then it can be an excellent option for our patients.

DR. PRENNER: It seems like the procedure has improved. We need to determine what the threshold is for choosing a surgical option. Some patients may not want to take on the risks, while others think the procedure is reasonable because they cannot manage the burden of intravitreal injections.

DR. SINGER: This is really an elective procedure, the first we've had to offer these patients. Standardization is going to have to become even better. The physicians in the clinical trials are closely monitored. Even if the clinical trial data looks good for safety, it may be different in the real world.

DR. HOLEKAMP: Can you translate what's happening in the clinical trials to the real-world and get the same results?

DR. PRENNER: I don't think it will happen quickly; there will be a learning curve. The physicians who participated in the clinical trials are experts at the surgery now. In the real world, it will take practice for physicians to become facile with the procedure.

DR. HOLEKAMP: A clinical trial is also not long enough to provide long-term safety data. There could be extrusion and delayed-onset endophthalmitis.

DR. KHANANI: The PORTAL study may shed some light on those issues (NCT03683251). Regardless, sustained-delivery is new, but a step in the right direction. What about refilling the port in the clinic? How is that different compared to an intravitreal injection?

DR. HOLEKAMP: Refilling the PDS in the office is an injection, but it requires a special needle that flushes out the device while simultaneously injecting new ranibizumab. It's a four-fold volume exchange. Although it is an office procedure, it's not like your other injections.

DR. SINGER: I agree. Refilling the system requires a lot of time, and it's much more difficult than giving an intravitreal injection. There's a learning curve with the refill as well. But we will adapt. It's going to take a little while to understand it, and it may not be as smooth as you'd like it to be the first couple of times, but eventually it will become more routine.

GENE THERAPY FOR AMD

Q | **DR. KHANANI:** Let's move on to gene therapy. We currently have two options: ADVM-022, which is intravitreal, and RGX-314, which is delivered to the subretinal space with vitrectomy.[42-44] We have early data on both. We have data from six patients from ADVM-022, and 42 patients from phase IB/2A from RGX-314. Do you think gene therapy efficacy is real this time?

DR. PRENNER: Yes. I think we're seeing a biologic effect. It's a small, select patient cohort, but it's still very exciting. There's a lot to learn, however. What should be the route of administration: intravitreal injection, suprachoroidal, or transvitreal delivery? What kind of durability will we see? What kind of inflammatory response are we going to get as more and more patients are exposed to these agents? There are many unanswered questions.

It is our responsibility as investigators to figure out what's best for our patients over time. It will take time, energy, and expertise, but I'm excited about it. I think we will have other options besides monthly anti-VEGF injections in the future. This is an incredibly exciting time for our field.

DR. SINGER: Gene therapy is a platform that shows early promise, but it has a long way to go. We'll see how it plays out. Obviously, the routes of delivery are going to change. We started with subretinal, and now we're talking about suprachoroidal and intravitreal therapies.

DR. KHANANI: The data is encouraging so far. Recently presented gene therapy data has shown that both RGX-314 and ADVM-022 have been well tolerated. If you look at cohort 5 of the RGX-314 trial, 75% of patients have received no rescue injection at 5 to 6 months. For ADVM-022, there were zero rescue injections at the median follow-up of 34 weeks for the six patients in cohort 1. Both studies have enrolled previously treated patients who have been heavily pretreated, so we don't expect much vision improvements, rather stabilization of vision and OCT.[43,44]

DR. HOLEKAMP: To see this type of signal in a phase 1 trial is very impressive. I do think it's far out on the horizon, however.

DR. KHANANI: I agree. We have to evaluate long-term safety. Given all the new treatments on the horizon, how will you treat a patient 10 years from now?

DR. HOLEKAMP: Ten years from now, nAMD management could be an intravitreal injection of a gene therapy agent and monitoring. Hopefully, there will be no need to control inflammation with drops.

DR. SINGER: Ten years from now, I think there will be lots of options. We'll know more about the disease process, and I think there will be different therapies for different parts of the disease. I also think we'll have a better understanding of macular degeneration with new technologies. We've learned a lot with OCTA. We're going to have a lot more tools, and it will be interesting to see what pans out. I'm excited about many of the preliminary findings.

DR. KHANANI: These are exciting times in retina, and we are lucky to be involved with the clinical trials for all the upcoming treatments. We have many agents and delivery systems in clinical trials and most of them seem to be working. Hopefully all of this will lead to better disease control, better efficacy, better durability and will improve real-world outcomes in our patients with nAMD.

CASE 1: Persistent Active Disease

DR. SINGER: Our first case is a 75-year-old woman with exudative AMD who has been treated for a long time. She originally presented in 2016 with pigment epithelial detachment and subretinal fluid. Her vision was 20/30 and 20/60. Her OCT revealed active disease (Figure 1). The FA revealed some early leakage, although it definitely is more staining than leakage (Figure 2). It definitely did cause fluid. This is more of a type 1 lesion rather than a type 2 lesion. This patient received more than 25 monthly shots of ranibizumab or aflibercept, and she still had persistent fluid.

This is a great example of a patient we can't seem to get dry and someone with a significant injection burden. Figure 3 shows the imaging from the last shot she received. There's a little bit of change of subretinal fluid, which makes me want to keep treating her, because the fluid isn't the same fluid over time.

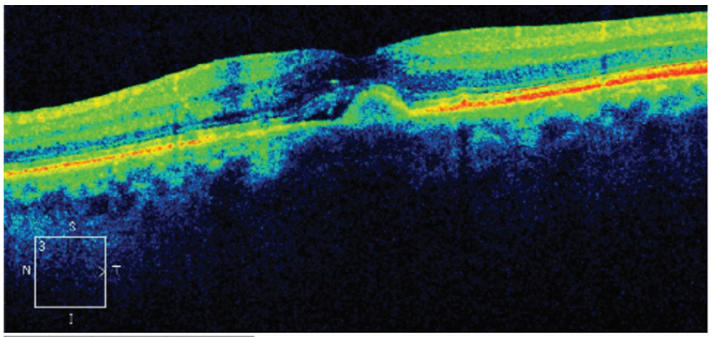
What are the next steps? Do I watch and wait or do I extend treatment? I'm already giving monthly shots, and it's not making a big difference in terms of changing her overall vision or OCT structure.

DR. HOLEKAMP: It's fluctuating. It's not stable.

DR. SINGER: Correct. This is not the same type of fluid described in HARBOR or VIEW. This patient, who is on aflibercept, almost every month, is probably one of the first people I'll use brolucizumab on.

DR. HOLEKAMP: I agree with trying a new agent. Despite the fact that all of our current drugs are anti-VEGF agents, there is always the fact of chemistry reacting with a patient's own biology. This is clearly a case to test that hypothesis.

DR. PRENNER: I would change her drug and utilize brolucizumab.



Central Subfield Thickness (µm)	Cube Volume (mm³)	Cube Average Thickness (µm)
274	9.7	272

Figure 1. Presenting OCT of a woman with exudative AMD.

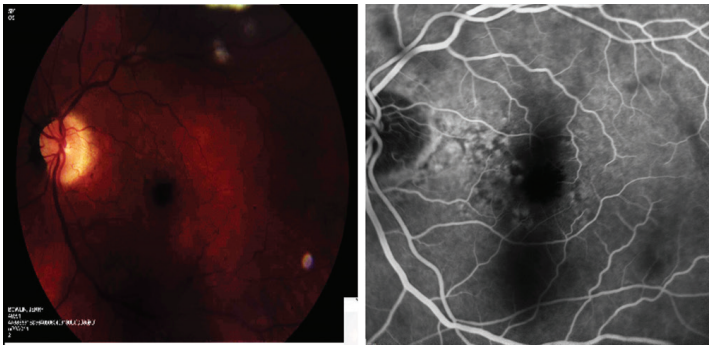
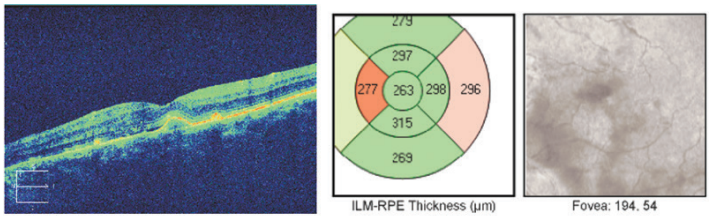


Figure 2. Presenting FA of a woman with exudative AMD.



Central Subfield Thickness (µm)	Cube Volume (mm³)	Cube Average Thickness (µm)
263	9.8	275

Figure 3. OCT after 25+ monthly shots of ranibizumab.

DR. KHANANI: Excellent case. This clearly highlights the unmet need for an agent that can dry the retina better than current available agents. I would also consider brolucizumab for this patient. This patient may benefit also from faricimab or OPT-302 once they are available.

CASE 2: Incomplete Fluid Resolution

DR. PRENNER: Our next case is a 68-year-old man with nAMD in his right eye. He's had a number of monthly injections with ranibizumab and aflibercept. He has mature CNV with multiple foci and tangles of neovascularization. He has a bit of fluid at a 5- to 6-week interval, so we treat him. The fluid somewhat resolves, but comes back again at the same 5- to 6-week interval.

Over time, this becomes a repetitive pattern. You see a relatively incomplete fluid resolution. Sometimes he gets complete fluid resolution, but he just can't sustain it. This is not someone I would extend. I'm interested to see what happens with brolucizumab and CNV size on OCTA. Are we going to see a biomarker there that we haven't seen yet with some of the other anti-VEGF agents? I don't know. But it would certainly be encouraging in terms of giving us some more space between injections.

DR. HOLEKAMP: Again, I think it is reasonable to try a new anti-VEGF agent in this patient and see what happens. However, we know that regardless of agent, some patients have a high VEGF need and cannot be extended. We all have some of these patients in our practice.

DR. KHANANI: I agree with Dr. Holekamp. This case highlights the unmet need of durability. We need agents that dry the retina better and last longer than current agents. I would consider brolucizumab here. If the PDS is approved, this patient will be a good candidate for it as the LADDER data has shown outcomes with the high-dose ranibizumab in the port being similar to monthly injections.

CASE 3: New Wet AMD Onset in Contralateral Eye

DR. HOLEKAMP: Our final case is an 84-year-old white female with AMD. Her right eye hasn't done well. It has chronic exudative AMD, and she's 20/200 with injections every 12 weeks. Her left eye is fine, with 20/20 vision and dry AMD with pigment alterations of the retinal pigment epithelium. During one of her routine visits, I see that her left eye has developed a new onset of wet AMD (Figure 4).

She's completely asymptomatic, but I give her three monthly loading doses because it's her good eye. Most people with wet AMD do well if you catch it early on when they are asymptomatic. She did well for the first year and is quickly extended to 12 weeks for both eyes. She then started to have symptoms and real fluid in her left eye, even though she's 20/20. I shortened the interval to 8 weeks. The lesion responded to the shortened interval, but there was still persistent fluid (Figure 5). Three months later, we continued with the 8-week anti-VEGF injections, but the subretinal fluid worsened (Figure 6). Her left eye maintained good VA, at 20/30. The decision is made to go to 4-week anti-VEGF injections. This gets down to the fact that many people prefer monthly dosing for monocular patients. This patient isn't technically monocular, but this is her better seeing eye.

DR. KHANANI: The bottom line is that we need better drugs and delivery systems. All three cases have highlighted patients with persistent fluid in spite of frequent treatments. These cases clearly point to the unmet need for agents that dry the retina better or last longer. We'll have to see if these unmet needs can be addressed with more potent anti-VEGF agents like brolucizumab or if these patients benefit from blocking additional pathways like Ang-2 inhibition with Faricimab or VEGF-C/D inhibition with OPT-302. Also, KSI-301, GB-102, PDS and gene therapy, if approved, can be beneficial in increasing durability in these patients.

DR. HOLEKAMP: This is exactly someone who needs some other treatment.

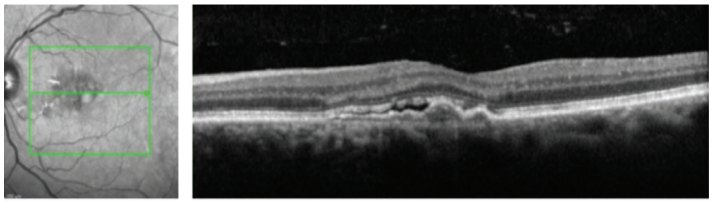


Figure 4. OCT of newly onset wet AMD in an 84-year-old asymptomatic patient.

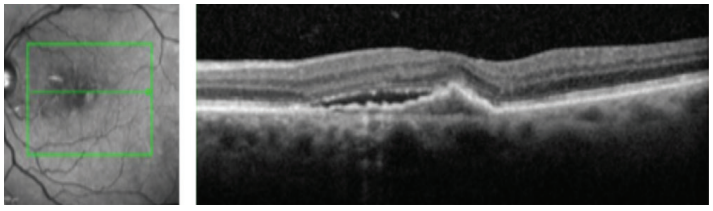


Figure 5. OCT on shortened interval of 8 weeks.

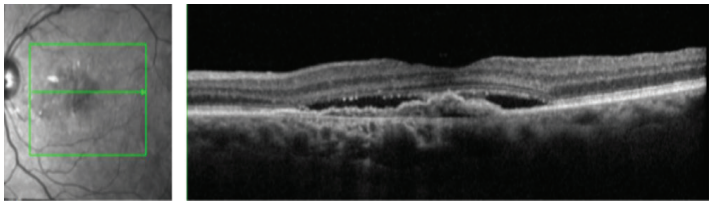


Figure 6. OCT after 3 months of 8-week anti-VEGF intervals.

DR. PRENNER: I would treat with monthly anti-VEGF therapy but would change agents. Some patients will have a preferential response to one of the four available drugs, and I would cycle through those options to see if the patient benefits from one drug in particular.

DR. KHANANI: Thank you for your thoughtful comments and cases for treating patients with AMD. ■

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TAILORING THERAPY TO THE NEOVASCULAR AMD PATIENT:
Implementing Novel Treatment Strategies to Improve Outcomes

Release Date: January 2020
Expiration Date: January 2021

INSTRUCTIONS FOR CREDIT

To receive credit, you must complete the attached Posttest/Activity Evaluation/Satisfaction Measures Form and mail or fax to Evolve Medical Education LLC; 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950. To answer these questions online and receive real-time results, please visit https://evolvemeded.com/online-courses/1925-supplement. If you are experiencing problems with the online test, please email us at info@evolvemeded.com. Certificates are issued electronically; please be certain to provide your email address below.

Please type or print clearly, or we will be unable to issue your certificate.

Name _____ ❑ MD/DO participant ❑ OD ❑ non-MD participant

Phone (required) _____ ❑ Email (required) _____

Address _____

City _____ State _____ Zip _____

License Number _____

OE Tracker Number _____

DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ OD
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ > 20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this educational activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
___ 50+

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

Setting
___ Solo Practice
___ Community Hospital
___ Government or VA
___ Group Practice
___ Other
___ I do not actively practice

Models of Care
___ Fee for Service
___ ACO
___ Patient-Centered Medical Home
___ Capitation
___ Bundled Payments
___ Other

LEARNING OBJECTIVES

DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?	AGREE	NEUTRAL	DISAGREE
Explain the differences in short-term and long-term outcomes with current neovascular AMD treatment options in clinical practice as compared to clinical trial outcomes	_____	_____	_____
Describe the relationship between drugs, treatment frequency, visual, and anatomic outcomes	_____	_____	_____
Develop best practices and recommendations to ensure optimal treatment outcomes for patients	_____	_____	_____
Describe the existing barriers to treatment and ways to overcome them	_____	_____	_____
Identify the newer compounds in development that may reduce treatment burden while maintaining efficacy	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to apply updates in age-related macular degeneration (AMD) treatment in the clinic based on this activity (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident.).

a. 1
b. 2
c. 3
d. 4
e. 5

2. Based on this activity, please rate how often you intend to apply advances AMD treatment to "real-world" patient management (based on a scale of 1 to 5, with 1 being never and 5 being always).

a. 1
b. 2
c. 3
d. 4
e. 5

3. A Latino male patient in his 80s has exudative macular degeneration in his left eye, which has left him with monocular vision only. His right eye, has developed wet AMD, but visual acuity (VA) is still fairly good at 20/40. What treatment interval do you recommend for maximum VA gains in his right eye?

a. Three loading doses, then 2-week treat-and-extend
b. Eight-week treat-and-extend
c. Three loading doses, then observation
d. Monthly

4. In the CATT study, _____ was associated with better VA.

a. Subretinal fluid
b. Intraretinal fluid
c. Both subretinal and intraretinal fluid
d. Macular hemorrhage

5. What is the minimal average number of injections needed in the first year to optimize treatment outcomes in patients with wet AMD?

a. Four
b. Five
c. Six
d. Seven

6. In both the CEDAR and SEQUOIA trials, inflammation was seen with which of the following new agents?

a. Faricimab
b. Abicipar
c. OPT-302
d. RGX-314

7. What is the primary reason long-term outcomes seen in clinical trial are often different from outcomes seen in clinical practice?

a. Insurance companies won't approve payment of branded drugs.
b. Patients in the real-world experience significant injection fatigue or receive fewer injections in the clinic than in clinical trials.
c. Real-world patients have fewer comorbidities than clinical trial patients.
d. Only patients with high-deductible insurance coverage are enrolled in clinical trials.

8. An elderly patient with exudative AMD and fluctuating vision has remaining subretinal fluid after more than 20 injections of aflibercept and ranibizumab. What is an acceptable treatment option?

a. Keep treating with aflibercept
b. Watch and wait
c. Switch back to ranibizumab
d. Switch to brolucizumab

9. What are the potential advantages of a port delivery system (PDS) and what are the potential disadvantages?

a. The implant procedure is short (5 to10 minutes), but the risk of endophthalmitis is very high (>50%).
b. The PDS is placed into the suprachoroidal space, but the surgery takes more than 1 hour.
c. The PDS may provide up to 6 months of durability but there is a higher risk of adverse events compared to intravitreal injections.
d. All patients have gone out to 15 months without needing rescue injections, but vitreous hemorrhage rates hover around 75%.

10. Faricimab is one molecule that blocks which target(s)?

a. VEGF-B and VEGF-C
b. VEGF-A and Angiopoeitin-2
c. VEGF-B and Angiopoeitin-2
d. VEGF-A and tyrosine kinase receptor

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.

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 _____

This activity improved my competence in managing patients with this disease/condition/symptom. _____ Yes _____ No

I plan to make changes to my practice based on this activity. _____ Yes _____ No

Please identify any barriers to change (check all that apply):

_____ Cost
_____ Lack of consensus or professional guidelines
_____ Lack of administrative support
_____ Lack of experience
_____ Lack of time to assess/counsel patients
_____ Lack of opportunity (patients)
_____ Reimbursement/insurance issues
_____ Lack of resources (equipment)
_____ Patient compliance issues
_____ No barriers
Other. Please specify: _____
_____
_____
_____

The design of the program was effective for the content conveyed. ___ Yes ___ No

The content supported the identified learning objectives. ___ Yes ___ No

The content was free of commercial bias. ___ Yes ___ No

The content was relative to your practice. ___ Yes ___ No

The faculty was effective. ___ Yes ___ No

You were satisfied overall with the activity. ___ Yes ___ No

Would you recommend this program to your colleagues? ___ Yes ___ No

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

_____ Patient Care

_____ Practice-Based Learning and Improvement

_____ Professionalism

_____ Medical Knowledge

_____ Interpersonal and Communication Skills

_____ System-Based Practice

Additional comments:

_____

_____ I certify that I have participated in this entire activity.

This information will help evaluate this CME activity; may we contact you by email in 3 months to see if you have made this change? If so, please provide your email address below.

_____