CONTINUING MEDICAL EDUCATION

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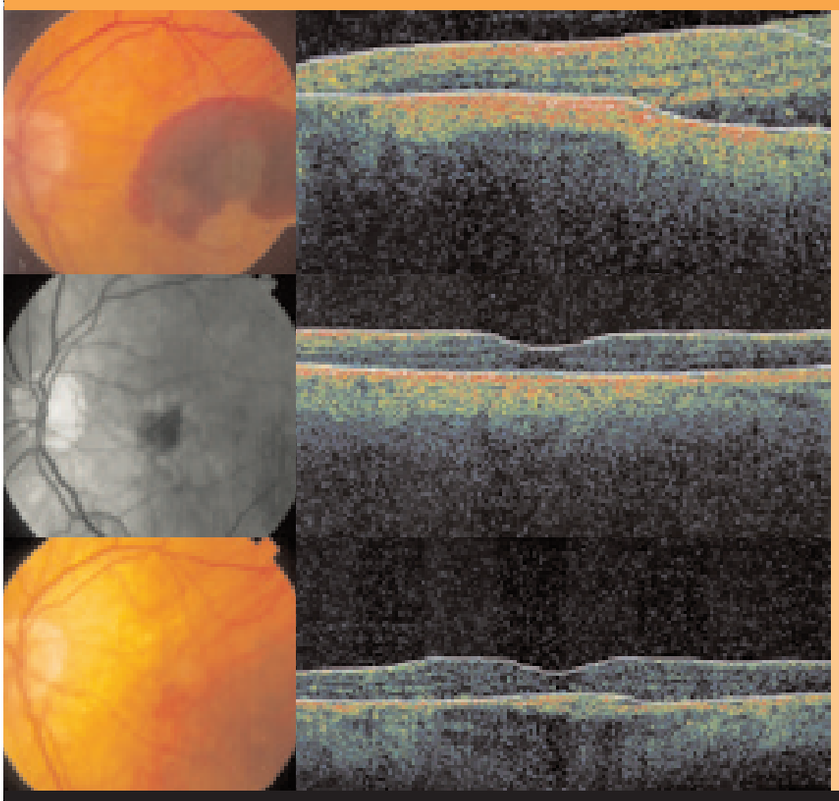
Exploring the Latest Approaches to Induction-maintenance Therapy With Anti-VEGF Agents



Learn about the various methods of induction-maintenance therapy for age-related macular degeneration, and how to choose the right candidates and manage systemic risks.

Highlights from a roundtable discussion in February 2008

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COMPLETION TIME
The estimated time to complete this activity is 1.5 hours.

TARGET AUDIENCE
This CME is intended for all ophthalmologists.

EDUCATIONAL OBJECTIVES
Upon completion of this educational activity, participants should be able to:

1. Discuss various approaches to induction-maintenance therapy with VEGF inhibitors in age-related macular degeneration (AMD).

2. Explain how to choose the right candidates for an induction-maintenance regimen.

3. Describe how to manage the risks of systemic adverse events associated with VEGF blockade.

4. Identify patients who may require booster injections with nonselective VEGF inhibitors.

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Charles H. Barnes, MD, has received grant/research support from Ophthotech Corp. and (OSI) Eyetech. He is a consultant to (OSI) Eyetech.

Michael D. Bennett, MD, has received grant/research support from Alcon Inc., Genentech Inc., (OSI) Eyetech, Pfizer Inc. and OPKO Health Inc. He is a consultant and a member of the speakers bureaus for Alcon, Genentech, (OSI) Eyetech and Pfizer.

David S. Dyer, MD, has received grant/research support from Alcon, Allergan Inc., Genentech and (OSI) Eyetech. He is a consultant to Alcon, (OSI) Eyetech and Synergetics. He is a member of the speakers bureaus for Alcon, Novartis Ophthalmics and (OSI) Eyetech.

Mark H. Nelson, MD, is a member of the speakers bureau for Novartis Ophthalmics and (OSI) Eyetech.

Reviewer Ingrid U. Scott, MD, MPH, is a consultant for Genentech and (OSI) Eyetech.

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Discussing Various Approaches to Induction-maintenance Therapy in Age-related Macular Degeneration

Mark S. Hughes, MD, (moderator): In the rapidly evolving treatment of exudative age-related macular degeneration (AMD), we have reason to be optimistic. Not long ago, we were evaluating the early success of ranibizumab (Lucentis, Genentech), as documented in the initial data of the landmark ANCHOR[1] and MARINA[2] trials. Heightened concern over the potential adverse effects of pan-vascular endothelial growth factor (VEGF) suppression has not tempered our early enthusiasm for this treatment modality. However, as always, we continue to explore effective ways to use new and existing treatments to reduce risk and increase efficacy. Rather than treat our patients every 4 weeks with anti-VEGF monotherapy, for example, we can use induction-maintenance or combination therapy in an attempt to replicate the initial successes investigators experienced with ranibizumab monotherapy.

If we can develop alternative regimens that are less treatment-intensive than continuous pan-VEGF blockade and that mirror the outcomes of the early ANCHOR[1] and MARINA[2] data, we can make significant strides for our patients and the healthcare system.

Today, we have gathered a panel of leading specialists to discuss these evolving approaches. First, we will concentrate on induction-maintenance therapy.

DESCRIBING DIFFERENT APPROACHES

Dr. Hughes: How do you use induction-maintenance therapy to treat AMD in your practice?

Charles H. Barnes, MD: In my practice, we initiate therapy with a nonselective VEGF blockade, such as ranibizumab or off-label bevacizumab (Avastin, Genentech), and then convert the patient to a selective agent, such as pegaptanib sodium (Macugen, [OSI] Eyetech).

Mark H. Nelson, MD: I use the same method of induction maintenance as Dr. Barnes. I am careful to evaluate the macula at the end of induction to confirm there is no residual leakage (ie, the lesion is 'bone dry'). In addition, I use intravitreal fluorescein angiography and indocyanine green (IVFA/ICG) angiography to confirm suppression of neovascularization. My maintenance plan involves treat and extend. I treat with pegaptanib twice at 6-week intervals, then another two times at 8-week intervals. Afterward, I extend to every 10 weeks as long as there is no evidence of deterioration.

David S. Dyer, MD: My experience is somewhat different because I have not been able to successfully extend the injection interval on pegaptanib beyond 6 weeks. I think it would be difficult to get a patient past 12 weeks on maintenance therapy using any anti-VEGF agent based on what we have learned from the PIER data. My goal is to determine how long I can extend the dosing interval for each patient.

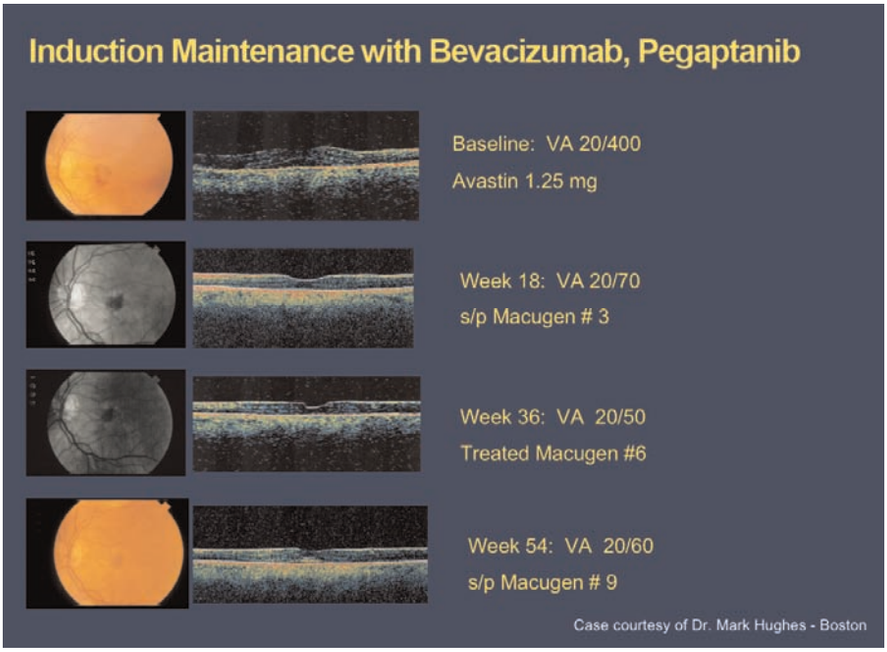
"In my practice, we initiate therapy with a nonselective VEGF blockade, such as ranibizumab or off-label bevacizumab, and then convert the patient to a selective agent, such as pegaptanib sodium."

— Charles H. Barnes, MD

TOUGH TO RESTORE LOST VISION

Dr. Hughes: As we saw in the VISION[3] trials, restoring a patient's vision is difficult once it is lost, even when you use pan-VEGF blockade, which was not available during VISION. We need to be careful as we extend the interval between injections.

Michael D. Bennett, MD: I agree. The ANCHOR[1] and MARINA[2] studies have become the gold standard and clearly demonstrate our visual goals. After acknowledging the results and limitations of the 40-patient PRONTO data, the randomized, controlled PIER participants seemed to lose all of their initial visual gains when the ranibizumab treatment intervals were



Induction therapy with bevacizumab was given to an AMD patient with 20/400 visual acuity. Maintenance treatments with pegaptanib sodium at weeks 18, 36 and 54 resulted in 20/60 visual acuity.

extended. Once the visual gain slope turned negative, repeated administration did not appear to sustain visual improvement. This indicates that diligence is needed as well as some form of sustained anti-VEGF agent to treat this chronic process.

"I use PDT, but only in rare cases when vision worsens or a lesion enlarges, despite anti-VEGF therapy with pan-VEGF suppression, using ranibizumab or bevacizumab."

— David S. Dyer, MD

EXAMINING THE LEVEL DATA

Dr. Hughes: Most of the panel members here are involved in the ongoing LEVEL[4] study, which is looking at the effects of a variety of induction treatments, followed by pegaptanib maintenance. Has anyone tried photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Ophthalmics) as an option for induction therapy?

Dr. Dyer: I use PDT, but only in rare cases when vision worsens or a lesion enlarges, despite anti-VEGF therapy with pan-VEGF suppression, using ranibizumab or bevacizumab. Besides PDT, I sometimes administer an intravitreal injection of triamcinolone acetonide (Kenalog, Bristol-Myers Squibb) as a second treatment modality.

Dr. Hughes: That is helpful information. At the annual meeting of the American Society of Retina Specialists in 2007, data were presented on 211 patients participating in the LEVEL[4] trial. Slightly more than 10% of patients had undergone PDT. The point is that pan-VEGF blockade does not have to be limited to nonselective anti-VEGF therapy.

IMPORTANCE OF DRY LESIONS

Dr. Hughes: Regardless of the type of induction therapy used, the goal is to switch to maintenance therapy when the patient has improved or is stable. Is a bone-dry lesion critical before you make the transition? And what test criteria are used?

Dr. Dyer: I am fairly aggressive when I treat patients. I use ranibizumab for induction once a month until I see no leakage on the angiogram and no intraretinal or subretinal fluid on OCT.

I was surprised by the interim LEVEL[4] data, which showed that 41% of patients needed anti-VEGF booster treatments. In a study based on my practice, only 14% of patients needed booster treatments at the 6-month follow-up visit following induction therapy (17% after 11 months), using a pan-VEGF blocker and maintenance therapy with pegaptanib. These patients may need fewer boosters because we give more induction injections (3–4) than the number provided in the LEVEL[4] trial (2.7–2.8). Once a lesion is dry, though, pegaptanib effectively maintains a patient's vision.

Dr. Nelson: Data based on a study of my patients are about the same as Dr. Dyer's. I have experienced an 11% failure rate with 70 patients and 72 eyes. I have identified certain types of lesions that do not respond to pegaptanib treatment or any anti-VEGF agents, which, in hindsight, suggests my success rate could have been higher if I had excluded patients with these types of lesions from the study.

HELPING RAPID RESPONDERS

Dr. Barnes: If a patient needed 5 or 6 injections to dry his lesion, I am less willing to try pegaptanib. But I believe in the use of an induction-maintenance regimen for patients who rapidly respond to therapy.

In appropriate cases, I will extend pegaptanib treatments to 8- to 12-week intervals. If I cannot convert a patient to pegaptanib, I will extend with ranibizumab up to 12 weeks.

Dr. Bennett: We have been using pegaptanib for 2–3 years in some patients since it was approved. We switched to bevacizumab in patients who were experiencing new breakthrough leakage. Now, we typically use 3 or 4 induction treatments to achieve a peak in initial visual gains then switch to pegaptanib every 6 weeks if any new leakage occurs. If vision declines, we

Anticipating New Insights From the SAILOR Data

Mark S. Hughes, MD: While we are continuing to discover new approaches to effectively treat exudative age-related macular degeneration (AMD), we still need to learn more about the disease and how best to manage it. Because of past limitations in the availability of the most advanced imaging technology, there was a possibility that we were underdiagnosing recurrences of subretinal fluid, and that more retreatments might have been indicated. This factor needs to be balanced against potential risks of increased VEGF suppression.

We will gain more insight on this issue now that we have the data from cohort 1 of the phase 3b SAILOR[1] trial, a multicenter study of the efficacy and safety of 2 different doses (0.5 milligrams vs 0.3 milligrams) of ranibizumab (Lucentis, Genentech) in subjects with subfoveal choroidal neovascularization.

David S. Boyer, MD, presented the latest findings of cohort 1 at the 2008 Bascom Palmer Institute's Angiogenesis, Exudative and Degeneration meeting, demonstrating that there is a safety signal in stroke incidence, although it is not statistically significant. At one year, the incidence of stroke in the 0.5-milligram dose group was 1.2% vs 0.7% in the 0.3-milligram dose arm; and patients with a prior history of stroke in the 0.5-milligram dose group had a 9.6% rate of stroke, compared with a 2.7% rate in the 0.3-milligram dose arm. Both sets of findings were not statistically significant. In addition, efficacy data suggested that treatment with ranibizumab for recurrences on a prn basis may lead to less favorable outcomes than monthly treatments.

In light of these results, several questions arise: Is the safety signal important although the difference in stroke incidence between the two dosage groups was not statistically significant? Did the study include an adequate number of patients to address the safety issues? How should we, as clinicians, alter our treatment patterns in view of clinical trial outcomes such as these?

Investigators in the PIER and SAILOR studies used existing optical coherence tomography (OCT) technology that was limited in the early detection of subretinal fluid recurrences. This has significantly changed with increasing availability of spectral domain OCT. Is it possible that older OCT technology was associated with delayed diagnosis and undertreatment? Would we have been able to achieve better outcomes with better diagnostic ability to detect recurrences and, therefore, earlier retreatments?

These questions can only be answered through randomized clinical trials. As responsible physicians, we have to take all the information available under consideration: Results from clinical trials, findings from prospective case studies, as well as information from basic scientific research and animal models. We also recognize that there are many subcategories of wet AMD, and that not every case may benefit from the same treatment. We have to individualize our approaches to treatment for each patient.

It is now clear that the combination of therapies is an acceptable approach. Issues of safety and efficacy are being addressed in ongoing, prospective studies and clinical trials. I foresee our treatment of AMD involving a range of monotherapy and combination therapies and decision-making that is founded on evidence-based medicine in the future.

Reference

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"Regardless of the type of induction therapy used, the goal is to switch to maintenance therapy when the patient has improved or is stable."

— Mark S. Hughes, MD

will boost with bevacizumab or ranibizumab. We have had 125 eyes achieve the 2-year mark, and another 100 are approaching that milestone.

We have used induction-maintenance to achieve, on average, 9 letters of visual gain. After 2 years, we have found that many patients appear to be able to extend from 6–10 weeks on pegaptanib, as Drs. Nelson and Barnes have experienced.

DIFFERENT LESION TYPES?

Dr. Hughes: All of these insights are very helpful. Perhaps some of the differences among your case studies and the heterogeneous findings of the multicenter data sets are related to different lesion types, which have been suggested by some of your comments. Much of this perspective will become clearer with time and experience. Next, we will discuss how to determine which patients are the best candidates for induction-maintenance therapy with anti-VEGF agents. **RP**

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Choosing the Right Candidates for Induction-maintenance Therapy

Dr. Hughes: We have discussed the different approaches to administering induction-maintenance therapy, but how do you determine if an exudative age-related macular degeneration (AMD) patient is likely to do well with induction maintenance? In addition, what diagnostic techniques do you use to make your decision?

RECOGNIZING POOR CANDIDATES

Dr. Nelson: I use a high-speed indocyanine green (ICG) study to determine the anatomy of the vessels that comprise the exudative lesion. Lesions associated with arterialized neovascular vessels and polypoidal vasculopathy do not respond well to pegaptanib sodium (Macugen, [OSI] Eyetech). In addition, they do not respond well to nonselective anti-VEGF agents. You can control polypoidal lesions with nonselective anti-VEGF agents, but leakage returns as soon as you switch the patient to maintenance therapy.

Dr. Dyer: I agree. Patients with retinal angiomatous proliferation, multiple-feeder-vessels and polypoidal lesions have not responded to induction-maintenance therapy — or most treatments.

Dr. Barnes: I sense that, for certain pigment epithelium detachments (PEDs), leakage slowly returns after converting to pegaptanib therapy from induction with ranibizumab.[1]

Dr. Hughes: PEDs challenge us because of their many unfavorable characteristics. They may be treated in several different ways, ranging from observation for an indolent case associated with stable vision to induction with an anti-VEGF approach for active subretinal leakage.

Dr. Bennett: Some patients who are expected to respond do not, and we have not identified the parameters to weed them out. Patients who may not be ideal for maintenance therapy are found in the two landmark anti-VEGF studies: ANCHOR[2] and MARINA.[3] Approximately 21% of patients did not gain letters over 3–4 months of treatment in the ANCHOR trial.[2] The percentage of patients in this category climbed to 25% in the MARINA study.[3] If patients do not do well when induced, I continue to treat them monthly and explore other options for improving their vision.

DIAGNOSING FOR INDUCTION MAINTENANCE

Dr. Hughes: When do you choose maintenance therapy? Describe your diagnostic process.

Dr. Dyer: I start with OCT and monitor the progress of induction with a traditional fluorescein camera. I do not repeat OCT unless I see a lack of progress or I am ready to switch to maintenance therapy, usually after the third or fourth induction treatment. I look at the OCT to see if all of the subretinal and/or intraretinal fluid is gone and if there is no leakage on the angiogram.

Dr. Barnes: I begin my workup with fluorescein angiography, using digital imaging or, for unusual cases, high-speed ICG. I depend on OCT to determine which lesion is dry and which type of lesion I am treating. I like to see recovery of the foveal contour, under 250 micrometers, preferably closer to 200 micrometers, and a nice green and blue retinal thickness map on OCT.

Dr. Nelson: I agree with Dr. Barnes. It is critical to observe the exudative lesion over the course of maintenance therapy. Very often, new vessels might develop or old vessels might mature, which would make them less responsive to anti-VEGF therapy.

Dr. Bennett: If OCT has a central zone below 250 micrometers with no evidence of retinal or subretinal fluid, we consider the patient dry. Spectral domain OCT combined with registration and the ability to view patients' fluorescein angiography and ICG results simultaneously has become the mainstay in our practice. Now we can detect degrees of fluid and peculiar manifestations on ICG that I previously have not seen. When we evaluate the accumulated data produced by this advanced diagnostic equipment, we may discover that we are significantly undertreating patients. The 1-year data from the open-label phase 3b SAILOR study of ranibizumab (Lucentis, Genentech) in AMD, will be helpful in this regard.

BENEFITS OF ADVANCED SYSTEMS

Dr. Hughes: These are important points to consider. Spectral OCT will enable us to acquire more informative and detailed scans than time domain OCT. We will benefit from pinpointing what we are imaging in relation to fluorescein angiography, and we will be able to visualize findings we previously may have missed. This will help us determine if we are undertreating patients and how we should proceed with induction-maintenance therapy. In our next discussion, we will review preliminary data from ongoing studies that shed light on how to approach AMD treatment with induction-maintenance therapy. **RP**

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Comparing Clinical Trial Data

Dr. Hughes: Some of you are using induction-maintenance therapy as part of your research in the LEVEL[1] trial. Please give us a progress report of your ongoing case studies involving this approach to treating exudative age-related macular degeneration (AMD). I would like to begin with Dr. Bennett, who has teamed up with Michael Tolentino, MD, to study a group of patients with exudative AMD who have been treated with induction-maintenance therapy. Please discuss the results of your study, especially as they compare to the ANCHOR[2] and MARINA[3] trials.

"In the ANCHOR and MARINA trials, patients lost 1–1.5 letters between the first and second years. With maintenance, including booster injections ... , patients improved 6–7 letters at the end of 1 year."

— Michael D. Bennett, MD

NINE LETTERS GAINED

Dr. Bennett: We have 2 years of data involving 200 patients from a nonrandomized, uncontrolled study we conducted. With all of the study's caveats, patients gained an average of 8.5–9 letters of visual acuity. Thirty-three percent gained more than 3 lines of vision; 87% had no vision loss. This increase is a little less than the 11-letter gain found in the LEVEL[1] study. Our results show that you can gain some vision with induction-maintenance therapy.

Dr. Dyer: Are the visual gains happening during induction or during the maintenance phase?

Dr. Bennett: The visual gains are happening during both phases. We have seen the early improvement during the induction phase that is demonstrated in ANCHOR[2] and MARINA.[3] We were able to maintain that gain with pegaptanib sodium (Macugen, [OSI] Eyetech) injections.[4] This is where it gets interesting. Some patients slowly improve step by step while others will plateau only to improve late in the second year of treatment. In the ANCHOR[2] and MARINA[3] trials, patients lost 1–1.5 letters between the first and second years. With maintenance, including booster injections when needed, patients improved 6–7 letters at the end of 1 year and, serendipitously, this increased to 8–9 letters near the end of 2 years.

Dr. Dyer: I think these results validate the benefits of an aggressive approach to treatment.

Dr. Bennett: Our goal was to treat as aggressively as possible for visual gain, using boosters of bevacizumab (Avastin, Genentech) and/or ranibizumab (Lucentis, Genentech) when needed. We were not trying to get by with administering as few injections as possible. Simply, we were attempting to achieve maximum visual acuity gains.

HOW MANY BOOSTERS?

Dr. Barnes: Dr. Bennett, how many patients in your 2-year study received boosters after induction?

Dr. Bennett: Earlier in our discussion (see "A Discussion of Various Approaches to Induction-maintenance Therapy in Age-related Macular Degeneration"), Dr. Dyer said he was surprised that 41% of patients in the LEVEL[1] study required booster treatments. I am probably one of the reasons why this is the case. At least half of the patients in our 2-year study received a booster during the first 12–18 months following induction; 32% were treated with ranibizumab only, and an additional 18% received both bevacizumab and ranibizumab. When receiving selective VEGF-A_{165} blockade alone, these patients will invariably break through, demonstrating either a visual decline or new leakage.

When new leakage occurs, something causes VEGF up-regulation. Is an inflammatory component involved? Are we dealing with hypoxia-inducible factor? Decreased perfusion? We are still treating a chronic disease. I think these patients always shift on a physiologic level, and some of them will always need a booster.

Dr. Barnes: After administering the booster, do you return these patients to pegaptanib or continue to give them nonselective agents?

Dr. Bennett: I will continue to give them pegaptanib and boosters as needed, usually every 6 weeks to ensure they return to a bone-dry state. Normally, I give them an injection on top of the pegaptanib during one of their 6-week visits.

"Generally, I induce with 3 injections of ranibizumab that are given at 4-week intervals. Then I convert to pegaptanib given every 6 weeks."

— Charles H. Barnes, MD

losing ground.

I could maintain about 66%–70% of these patients on an induction-maintenance regimen. Now that ranibizumab is available, I am more willing to keep patients exclusively on a nonselective anti-VEGF treatment, although I monitor them closely because I am concerned about the risks involved.[3]

Generally, I induce with 3 injections of ranibizumab that are given at 4-week intervals. Then I convert to pegaptanib given every 6 weeks. If the lesion remains dry after several injections, I will start extending the interval between injections an extra week after each injection, going out to 8 or more weeks between pegaptanib injections. If there is recurrent leakage with pegaptanib, I will go back to ranabizumab, but still follow a treat-and-extend protocol.

Dr. Dyer: We have submitted an abstract to The Association for Research in Vision and Ophthalmology on 112 consecutive cases out of the 130 in which we have administered induction-maintenance therapy to date. I have been aggressively treating patients with an average of 3.5 injections of ranibizumab at monthly intervals, sometimes using as many as 6 injections on a 4-week interval between injections. I have used fluorescein angiog-

EVOLVING APPROACHES TO BOOSTER THERAPY

Dr. Barnes: My approach has changed over time. Before ranibizumab was available, I induced patients with a single dose of off-label bevacizumab. I did not check to see if the patients were dry. I would simply boost with bevacizumab if they seemed to be

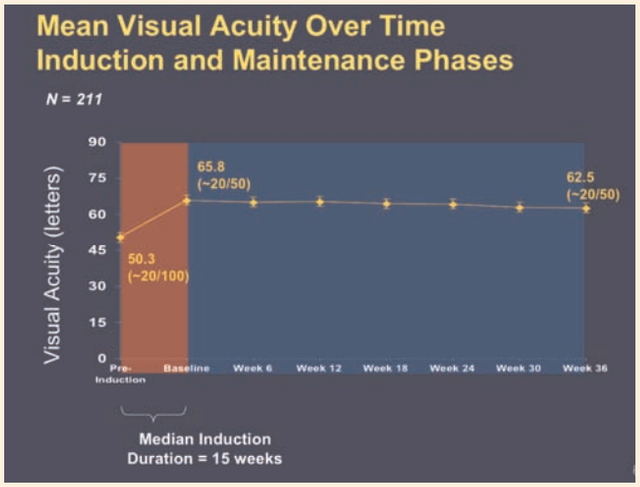
LEVEL Data May Influence Induction-maintenance Therapy

Mark S. Hughes, MD, (moderator): In response to findings from the LEVEL trial,[1] there is a high likelihood that we may elect to modify our approach to induction-maintenance therapy.

Some of you are participating in the LEVEL[1] trial. Currently, we are 36 weeks into the main portion of the study and 48 weeks into the segment involving a smaller group of 107 patients. Can you explain how the preliminary findings have influenced the way you treat exudative AMD?

Charles H. Barnes, MD: I was following the treatment protocol in the LEVEL trial before the study was under way. I am not sure we need to provide booster injections to 40% of patients.

Michael D. Bennett, MD: I am impressed with the preliminary data from the LEVEL trial. If you compare the data to that of the ANCHOR[2] and MARINA[3] studies, you find that the LEVEL findings show an improvement in visual acuity of more than 11 letters. This may not be statistically significant at this point, but it is still well beyond what we expected — even from PIER.



Patients in the LEVEL trial gained more than 11 letters of vision during the 15-week induction phase.

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raphy and optical coherence tomography (OCT) to determine if the macula is dry, and then I have switched them to pegaptanib.

My patients either have experienced breakthrough leakage early on, within 6–8 weeks after switching to pegaptanib, or they have experienced leakage more than 6 months later.

I have not established any reason for these tendencies. However, in patients who have 6 months of follow-up, 14% have needed booster therapy, which I usually provide with ranibizumab. For patients who have had 11 or more months of follow-up, 17% have needed booster injections of ranibizumab.

I believe you need chronic suppression. Therefore, I keep patients on strict maintenance therapy with injections of pegaptanib every 6 weeks. I have not noticed any trend toward improvement in vision. However, my patients have had extremely stable vision after the initial visual gains achieved with induction. I am comfortable with this approach.

I am very interested in Dr. Bennett's data. Using spectral OCT, we may discover more eyes that are starting to leak that were not identified as such with time domain OCT. With this enhanced technology, I may need to provide booster treatments more often.

"I have been aggressively treating patients with an average of 3.5 injections of ranibizumab at monthly intervals, sometimes using as many as 6 injections on a 4-week interval between injections."

— David S. Dyer, MD

COMPARING VISUAL ACUITIES

Dr. Hughes: Dr. Dyer, when you achieve stable vision with a selective VEGF blockade agent, how do the visual acuity results compare to those reported in ANCHOR[2] and MARINA[3] during 6 or more months of maintenance therapy?

Dr. Dyer: The visual acuity results are very similar to what we have found in ANCHOR[2] and MARINA,[3] perhaps even somewhat better. Remember, however, that these acuities were measured with a Snellen chart and analyzed retrospectively. My data is not as clean as a prospective, randomized trial.

Dr. Hughes: That is true. However, the exclusion criteria for prospective, randomized trials are probably more rigorous. For example, a patient who has retinal pigment epithelium atrophy or subretinal fibrosis may not be included in trials such as ANCHOR[2] and MARINA,[3] but you would customarily treat such a patient in an office setting.

It is notable that you have been able to maintain significant visual improvements. Even though Snellen visual acuity measurements are not the same as Early Treatment Diabetic Retinopathy Study (ETDRS) acuity testing, it is what people use in the daily practice of ophthalmology. These are the measurements we abide by when monitoring clinical improvement.

Dr. Dyer: I agree. I would like to add that lesion size and the age of the lesions in my group of patients encompass the entire spectrum. I am encouraged that we are able to achieve long-term stability even with large lesions of indeterminate age.

Dr. Hughes: That is encouraging news for us and our patients. Frequent dosing of intravitreal anti-VEGF agents raises safety concerns for patients, but induction-maintenance therapy can offer us the opportunity to reduce risk and maintain, or increase, efficacy. Research shows that systemic exposure to anti-VEGF agents may be associated with an increased risk of arterial thromboembolic events, which we will discuss next. RP

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Managing the Risks of Systemic Adverse Events When Using Nonselective VEGF Inhibitors

Dr. Hughes: As we have discussed, some patients may require 6 or more doses of ranibizumab (Lucentis, Genentech) or off-label bevacizumab (Avastin, Genentech) before we can switch them to maintenance therapy. Systemic exposure to pan-anti-vascular endothelial growth factor (pan-VEGF) agents, such as bevacizumab, has been associated with an increased risk of arterial thromboembolic events (ATEs), such as stroke, heart attack and myocardial infarction (MI).

When we received the interim analysis of the cohort group from the SAILOR[1] trial, the data showed a 4-fold increase in stroke risk for the extended-therapy group. We have not been sure how to respond. The 0.3% stroke risk associated with a dosage of 0.3 milligrams increased to a 1.2% risk in the 0.5-milligram group. Although this has been considered statistically significant, this increase is also significantly below what has been found in other studies regarding the risk of stroke in this patient population.

"If a patient has a recent history of heart attack or stroke, I become concerned about using nonselective anti-VEGF therapy. I might try PDT and triamcinolone first, or even use pegaptanib sodium as monotherapy."

— Mark H. Nelson, MD

The good news is that the 1-year data from the phase 3b SAILOR[2] trial are in. Results demonstrate that ranibizumab is safe and is not associated with a higher risk of stroke in patients with exudative AMD. The data also show that although the FDA-approved dose of ranibizumab (0.5 milligrams) trended toward a higher incidence of stroke (1.2% vs 0.7% in the 0.3-milligram group), the results were not statistically significant. Is anyone concerned about the long-term use of nonselective, pan-VEGF blockades? If so, how do you manage these risks in your practice?

CASES OF CONCERN

Dr. Nelson: If a patient has a recent history of heart attack or stroke, I become concerned about using nonselective anti-VEGF therapy. I might try photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Ophthalmics) and triamcinolone acetonide (Kenalog, Bristol-Myers Squibb) first, or even use pegaptanib sodium (Macugen, [OSI] Eyetech) as monotherapy. Hopefully, this will buy some time during the period of highest risk after which I can reinduce with ranibizumab. In addition, I am mindful about patients who have bilateral lesions, as ranibizumab injections within the same week could increase their systemic risk.

Dr. Hughes: When you treat with PDT, do you use monotherapy, reduced fluence or reduced duration? And do you alter any of the treatment parameters?

Dr. Nelson: I reduce the duration by one half. Using a high-speed indocyanine green (ICG) study allows me to precisely locate the originating vessels responsible for the neovascularization. The smaller size reduces the possibility of toxic effects. Using this technique, especially with the addition of intravitreal triamcinolone acetonide, I have not seen acute vision loss following PDT.

Dr. Hughes: Dr. Bennett, are you concerned about giving 6 or more nonselective anti-VEGF injections in patients who have experienced recent strokes or MIs?

Dr. Bennett: Some of my patients have developed profound geographic atrophy. I do not know if nonselective VEGF inhibition or natural history induced the atrophy. For a patient who has suffered a stroke or MI within the previous 6 months, I am very hesitant to use nonselective agents. If I use rani-

bizumab or bevacizumab, I usually reduce the dose to 0.3 mg or less than half of a milligram, respectively.

INCREASED USE CAN LEAD TO INCREASED RISK

Dr. Dyer: The longer I use a nonselective VEGF blocker, the more I believe patients are exposed to systemic risk, especially if they are receiving monthly injections for an extended period.[3,4] With this in mind, I specifically ask my patients about history of hypertension, transient ischemic attacks (TIAs), strokes and coronary artery disease.

I often will learn about high blood pressure or some other cardiovascular issue while a patient is on induction therapy. I do not know if adverse systemic events are a result of nonselective therapy or if they are associated with a patient population at high risk for cardiovascular and cerebrovascular events. No matter what the cause, if patients are at high risk due to a recent vascular event or uncontrolled hypertension, I will switch them to pegaptanib sodium as the induction agent, or I will administer PDT.

We have to pay closer attention to this issue. I have had many patients who were taking antihypertensive medication during induction and then after switching them to pegaptanib, their physicians either reduced or terminated their medication.

I continue to treat patients with hypertension with pan-VEGF suppression as long as they are medically stable and are not experiencing stroke or coronary artery disease symptoms. However, as with my other patients, I ask them about heart disease and stroke symptoms during each visit.

Dr. Barnes: I have patients who have experienced strokes or MIs while I was treating them with nonselective anti-VEGF therapy. As a result, I have switched them to pegaptanib, regardless of whether their lesions were totally dry. We do not know which patients are likely to experience ATEs regardless of the type of therapy. However, it is sobering when a patient experiences these issues while under your care.

GETTING THE 'OK' TO TREAT

Dr. Hughes: As ambiguous as this situation may be, we have an obligation to monitor all patients closely and take careful histories. How do you proceed when you become aware of a patient who has had an ATE?

Dr Dyer: It depends on how recently the event has occurred. If it is within 90 days, I will contact the neurologist, cardiologist or primary physician and seek his guidance on treatment options. However, I have found that many physicians do not fully understand what we are doing and how anti-VEGF therapy may affect their patients systemically. I try to educate these physicians and then follow their recommendations. If necessary, I will try an alternative treatment. If more than 90 days have passed since the ATE, most physicians will say that nonselective therapy is not contraindicated.

Dr. Barnes: I also find that many physicians are not familiar with the drugs we use, so even though they are likely to approve of their continued use, I do not depend on their input alone when it comes to making treatment decisions.

Dr. Hughes: After a patient has suffered an MI, cardiologists tell me that we should give the myocardium 2–3 months to heal before resuming nonselective VEGF blockade. During this period, I consider using combination therapies, such as PDT with pegaptanib or PDT with dexamethasone.

"When treating patients with active lesions after a stroke, I prefer to use selective VEGF blockade in conjunction with a corticosteroid, and possibly PDT. Then I put them on maintenance therapy with pegaptanib."

— Mark S. Hughes, MD

Neurologic issues have been more difficult for me to manage. As we know, the brain's ability to heal after a stroke or a TIA is not as well understood as cardiac recovery. Neurologists have offered me varied advice, sometimes suggesting that I avoid treating with nonselective VEGF inhibitors anywhere from 6–12 months.

When treating patients with active lesions after a stroke, I prefer to use selective VEGF blockade in conjunction with a corticosteroid, and possibly PDT. Then I put them on maintenance therapy with pegaptanib.

Dr. Bennett: I am not concerned about treating patients who have had MIs or strokes with pegaptanib. The VISION trials did not show an increased incidence in ATEs compared to the sham group.[5]

Dr. Nelson: My biggest problem has been with clopidogrel

"I have had many patients who were taking antihypertensive medication during induction, and then after switching them to pegaptanib, their physicians either reduced or terminated their medication."

— David S. Dyer, MD

bisulfate. Patients taking this drug have drug-eluting stents that require extended medical treatment. In addition, clopidogrel has been used to prevent cerebrovascular events. Communication between medical and ophthalmic specialists is critical to balance the risks and benefits of anti-VEGF therapy.

MONITORING OCULAR HEALTH

Dr. Hughes: I believe we need to be aware of the systemic health of our retina patients. If we do not monitor the overall health of our patients, no one else will.

As we move forward, we also must consider ocular safety, such as the risk of endophthalmitis, retinal detachment, hemorrhage and other complications that can arise from intravitreal injections. In addition, ocular safety involves long-term issues, such as prolonged pan-VEGF blockade within the eye and the possibility of increasing geographic atrophy or retinal thinning.

Some of the most impressive OCTs I have seen belong to patients who have been on prolonged pan-VEGF blockade for more than 3 years and who have increasing RPE atrophy with reduced central retinal thickness. Animal research data raises important questions about these long-term issues, but we do not have enough human data at this point.

Given these considerations, are you doing anything differently to monitor the globe and retina long-term, such as performing more OCT evaluations or doing electroretinograms?

Dr. Nelson: My concern is geographic atrophy and how this might be a correlate for permanent vision loss. I am watching the autofluorescence patterns carefully to assess the health of the retinal pigment epithelium and photoreceptors. I hope to avoid these issues by using selective anti-VEGF agents as my maintenance therapy.

Dr. Dyer: I agree. My goal is to get the maximum benefit out of a nonselective blocker by achieving visual gain and drying the lesion, then switching the patient to a selective blocker, which is much safer and less likely to cause long-term changes.

Many animal models show that you start to lose capillaries with a nonselective blocker. Often, when you stop treatment in these models, capillaries reperfuse. However, if geographic atrophy already exists, it does not matter if you have reperfused capillaries. The damage may be done.

Dr. Hughes: In addition to using nonselective and selective VEGF inhibitors as induction-maintenance therapy, we have another approach that we can take: induction with triple therapy, which we will discuss next. RP

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Inducing AMD Patients With Triple Therapy

Dr. Hughes: The use of triple therapy is another viable approach to induction-maintenance for exudative age-related macular degeneration (AMD). Triple therapy involves the use of photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Ophthalmics), an intravitreal corticosteroid injection and an anti-vascular endothelial growth factor (anti-VEGF) agent. Do you believe there is a place for triple therapy in the induction phase of induction-maintenance treatment?

HIGH-FLOW AND POLYPOIDAL LESIONS

Dr. Nelson: Triple therapy is my treatment of choice if I see high-flow lesions during initial fluorescein indocyanine green (ICG) angiography. I combine PDT, triamcinolone acetonide (Kenalog, Bristol-Myers Squibb), and either pegaptanib sodium (Macugen, [OSI] Eyetech) or ranibizumab (Lucentis, Genentech). Patients with treatment-naïve lesions have done extremely well when I have taken this approach. Lesions resolve promptly and vision improves. I am considering using triple therapy as primary treatment in patients with polypoidal lesions because I do not think their pathology is VEGF driven. I believe polypoidal lesions require a destructive component.

Dr. Hughes: Do you place patients with either high-flow or polypoidal lesions on maintenance therapy? Do you consider pegaptanib or off-label bevacizumab (Avastin, Genentech) or post-PDT triple therapy 1 or 2 months later?

Or, do you simply reassess the patient at 3 or 4 weeks and — if you see no leakage and find that optical coherence tomography (OCT) reveals no intra- or subretinal fluid — then continue to monitor them?

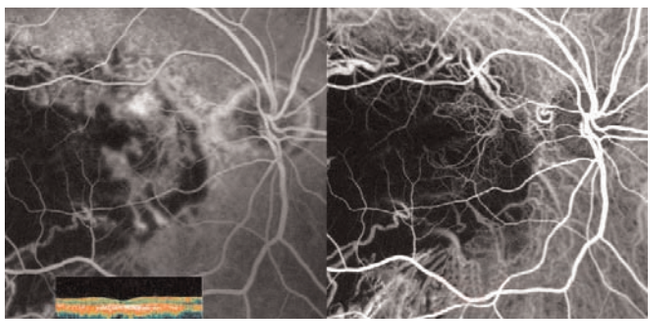
Dr. Nelson: I do not use maintenance therapy in patients with high-flow or polypoidal lesions. I induce and reinduce them, because I believe they will need all 3 components of triple therapy when their vessels reopen. So far, I have treated only one polypoidal lesion. For high-flow lesions, the treatments last about 6 months. At about 4 months, I start seeing vessels reopen. I sometimes see a small amount of leakage on OCT, but their vision remains stable. However, I have had some patients go a full year without the need for reinduction.

CONSERVATIVE APPROACH

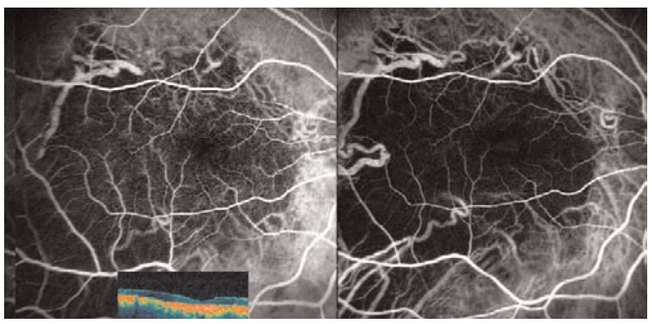
Dr. Hughes: Dr. Dyer, do you offer triple therapy in this context?

Dr. Dyer: I do not use triple therapy often. I agree that high-risk, polypoidal, high-flow and large lesions are less likely to respond to nonselective or selective VEGF suppression. However, I want to avoid causing choriocapillaris damage with destructive therapy.[1]

A low percentage of patients experience significant vision loss from PDT.[2] This may be a reasonable risk in a high-risk patient. However, I like to avoid even this small risk during



Fluorescein angiography and ICG show a polypoidal lesion in a patient before the use of triple therapy with PDT, triamcinolone acetonide and ranibizumab.



Fluorescein angiography and ICG show the resolved polypoidal lesion after a patient receives triple therapy with PDT, triamcinolone acetonide and ranizibumab.

treatment. I would like to see a pharmaceutical combination for high-risk cases. I do not believe we have found the right combination yet.

Dr. Hughes: Soon, we may have new anti-VEGF aptamers that will help in combination therapy.[3] Meanwhile, I believe PDT as monotherapy is more destructive to the cells surrounding the choroidal neovascularization (CNV) than PDT as part of combination therapy. Under the TAP study,[2] the treatment parameters for PDT resulted in angio-occlusion. In addition, PDT monotherapy increases VEGF production and inflammation. Today, we can use reduced fluence or reduced duration PDT in combination with steroids and anti-VEGF therapy to minimize destruction and reduce inflammation and VEGF production, as demonstrated in research by Augustin and colleagues.[4]

In addition, the pharmaceutical components of triple therapy can minimize the side effects associated with PDT. Corticosteroids are anti-inflammatory. The VEGF blockade agent, administered within a short time, provides additional protection, as shown in the FOCUS trial. So this combination may be a viable part of an induction program, unlike PDT monotherapy of the past.

PDT FOR SMALL LESIONS

Dr. Nelson: When you use PDT for small lesions, you are not introducing a destructive component. I like to use ICG-directed PDT for small lesions. They are usually no more than 1.5 millimeters, including the feeder vessels, which are outside of the fovea. None of my patients have experienced additional vision loss as a result of this treatment.

Dr. Hughes: That is an excellent point. ICG-directed PDT is not the same as traditional PDT monotherapy, which treats the greatest linear dimension of the lesion in addition to a 1-mm sphere.

Dr. Bennett: We need to discuss some factors that often get overlooked. For example, Dr. Augustin's data[4] on reduced duration is outstanding, but some of the triple therapy results are based on patients in whom he has performed a small vitrectomy. The Pa_{O2} of a vitreous-filled eye is ≤10 mm Hg. Once the eye is vitrectomized, the Pa_{O2} rapidly increases almost 80%. By reducing the relative hypoxia, are we altering hypoxia-inducible factors (HIF-1) that have an influence on VEGF induction? When we add anti-inflammatory agents, are we addressing macrophage VEGF production? We are talking about multiple factors — occluding the vasculature, using corticosteroids and using anti-VEGF agents. Individually, all of these treatments are valid, but when used in tandem the results appear encouraging.

Dr. Hughes: The 104 patients in Dr. Augustin's study[4] experienced about a 5% recurrence rate over 9 or more months. That percentage is lower than what many other physicians have reported in their research. Dr. Augustin also used 800 micrograms of dexamethasone and a slightly higher dose of bevacizumab (1.5 milligrams). He performed the small vitrectomy to make a single incision, prevent reflux and simultaneously inject both drugs. The exact role and effect of vitrectomy is not known.

CONSIDERING THE VARIABLES

Dr. Barnes: I agree there is a role for triple therapy. However, we need to consider many variables, including reduced fluence, reduced duration of treatment, dexamethasone vs triamcinolone administration, and the order in which we offer these treatments. We also need to consider that monotherapy with ranibizumab works effectively on most lesions. Only a few patients may need these alternative approaches.

Dr. Hughes: That is true if you are using triple therapy as rescue therapy for patients with recurrence, instead of induction, for treatment-naïve patients with classic choroidal neovascularization.

For triple therapy patients, there is no conclusive data concerning the optimal order in which to use agents. For example, we do not know if we should give the corticosteroid the same day as PDT, or if the anti-VEGF agent should be given 1 day after PDT or 7 days later. We will be looking at the FOCUS data for these answers.

We might be able to spread out the initial administration of triple therapy instead of performing all 3 steps during the first 24 hours. Several questions need to be answered: Is there any value in using an intravitreal steroid? When should the steroid be injected? Is triamcinolone acetonide or dexamethasone phosphate a better agent? When should the anti-VEGF agent be injected in relation to PDT, and is bevacizumab, ranibizumab or pegaptanib the correct agent? Finally, the type of lesion may determine which therapy to choose.

Dr. Barnes: This is important research. However, transferring these ideas to clinical practice is difficult to justify when we have a dependable therapy in ranibizumab. We may discover down the road that triple therapy is superior when we sort out these variables.

Dr. Hughes: The SUMMIT Trial Program, which will include the DENALI Trial and the companion MONT BLANC Trial, also will provide helpful information on combination therapy once we see initial results sometime next year.

NOT A ONE-SIZE-FITS-ALL TREATMENT

Dr. Hughes: One obvious conclusion from today's discussion is that we are not going to treat all patients the same way. Induction-maintenance therapy clearly will play a role, as will other options. I know we will be excited to see the results of studies that are under way and to watch the induction-maintenance approach gain credibility as the positive data accumulates. RP

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Exploring the Latest Approaches to Induction-maintenance Therapy With Anti-VEGF Agents

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Please select the single best answer and indicate your choice on the Evaluation Form on the next page.

1. When David S. Dyer, MD, uses photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Ophthalmics) for induction, he sometimes administers an intravitreal injection of which of the following agents?
   a. Off-label bevacizumab (Avastin, Genentech)
   b. Ranibizumab (Lucentis, Genentech)
   c. Triamcinolone acetonide (Kenalog, Bristol-Myers Squibb)
   d. Pegaptanib sodium (Macugen, [OSI] Eyetech)
2. In a study based on Dr. Dyer's practice, what percentage of patients needed booster treatments at the 6-month follow-up visit following induction therapy that included a pan-VEGF blocker and maintenance treatment with pegaptanib sodium (Macugen, [OSI] Eyetech)?
   a. 14%
   b. 20%
   c. 25%
   d. 30%
3. Phase 3b of the SAILOR trial was a multicenter study of the efficacy and safety of which 2 doses of ranibizumab in subjects with choroidal neovascularization?
   a. 0.6 milligrams vs 0.3 milligrams
   b. 0.5 milligrams vs 0.3 milligrams
   c. 0.4 milligrams vs 0.2 milligrams
   d. 0.3 milligrams vs 0.1 milligrams
4. According to Mark H. Nelson, MD, lesions associated with arterialized neovascular vessels and polypoidal vasculopathy do not respond well to which anti-VEGF drug?
   a. Off-label bevacizumab
   b. Ranibizumab
   c. Triamcinolone acetonide
   d. Pegaptanib sodium
5. In the 2-year study of 200 patients with exudative AMD conducted by Michael D. Bennett, MD, how many patients received boosters during the first 12–18 months following induction?
   a. At least half
   b. 40%
   c. 30%
   d. 20%
6. If you compare the preliminary data of the LEVEL trial to that of the ANCHOR and MARINA studies, the LEVEL findings show an improvement in visual acuity of how many letters within the induction phase?
   a. 5 letters
   b. 9 letters
   c. 11 letters
   d. 13 letters
7. According to Mark S. Hughes, MD, how many doses of ranibizumab or off-label bevacizumab may patients require before you can switch them to maintenance therapy?
   a. 3 or more
   b. 6 or more
   c. 8 or more
   d. 10 or more
8. Systemic exposure to pan-vascular endothelial growth factor agents, such as bevacizumab, has been associated with an increased risk of which of the following arterial thromoembolic events (ATEs)?
   a. Stroke
   b. Heart attack
   c. Myocardial infarction (MI)
   d. All of the above
9. Within how many days of an ATE will Dr. Dyer contact a patient's neurologist, cardiologist or primary physician to seek guidance on anti-VEGF treatment options for AMD?
   a. 90
   b. 60
   c. 45
   d. 30
10. After a patient has suffered an MI, cardiologists tell Dr. Hughes that he should give the myocardium how many months to heal before resuming nonselective VEGF blockade?
    a. 1–2 months
    b. 2–3 months
    c. 3–5 months
    d. 5–7 months
11. During the time it takes for the myocardium to heal in patients who have suffered an MI, Dr. Hughes considers using combination therapies, such as PDT with pegaptanib or PDT with which corticosteroid?
    a. Triamcinolone acetonide
    b. Fluocinolone acetonide
    c. Prednisolone acetate ophthalmic suspension USP 1% (Pred Forte)
    d. Dexamethasone
12. According to Charles H. Barnes, MD, monotherapy with which of the following VEGF blockades works effectively on most lesions?
    a. Ranibizumab
    b. Bevacizumab
    c. Pegaptanib sodium
    d. Triamcinolone acetonide

RETINAL PHYSICIAN
APRIL 2008

Exploring the Latest Approaches to Induction-maintenance Therapy With Anti-VEGF Agents

Answers (Refer to questions on previous page.) Circle one letter for each answer.

1.	A	B	C	D	**6.**	A	B	C	D	**11.**	A	B	C	D
2.	A	B	C	D	**7.**	A	B	C	D	**12.**	A	B	C	D
3.	A	B	C	D	**8.**	A	B	C	D					
4.	A	B	C	D	**9.**	A	B	C	D					
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Did this program meet the following educational objectives? 5 = Strongly Agree, 1 = Strongly Disagree

A. Can you discuss various approaches to induction-maintenance therapy with VEGF inhibitors in AMD?	☐
B. Can you explain how to choose the right candidates for an induction-maintenance regimen?	☐
C. Can you describe how to manage the risks of systemic adverse events associated with VEGF blockade?	☐
D. Can you identify patients who may require booster injections with nonselective VEGF inhibitors?	☐
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