CONTINUING MEDICAL EDUCATION

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Evolving Treatment Strategies in Age-related Macular Degeneration Therapy

Experts discuss the use of anti-VEGF monotherapy, same-day triple therapy and other combinations to prevent vision loss and improve visual acuity.

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COMPLETION TIME:
The estimated time to complete this activity is 1 hour.

TARGET AUDIENCE:
This CME is intended for all ophthalmologists.

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

1. Discuss the various combination therapies available for exudative age-related macular degeneration (AMD).

2. Describe how to make the best treatment decisions using optical coherence tomography and fluorescein angiography.

3. Discuss the efficacy of same-day triple therapy for neovascular AMD and how it compares to monotherapy.

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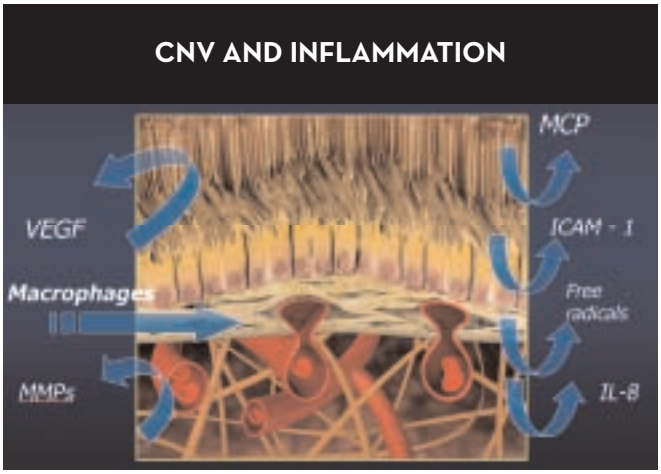
Deciphering the Details of Combination Therapy for Exudative Age–related Macular Degeneration

Mark S. Hughes, MD, FACS, (moderator): Now that we can improve visual acuity in more than half of our patients with exudative age-related macular degeneration (AMD), many of us are trying to preserve the improvements and use treatments that are less burdensome to our patients and our practices. Today, we will discuss strategies to help us achieve our goals, using photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Ophthalmics), pegaptanib sodium (Macugen, (OSI) Eyetech), off-label bevacizumab (Avastin, Genentech), ranibizumab (Lucentis, Genentech) and corticosteroids. Our discussion will include the benefits of administering fewer intravitreal injections and the possible systemic risks associated with our interventions.

Let us begin discussing the concept of combination therapy. About 2 1/2 years ago in our practice, we started looking at maintenance therapy facilitated by off-label bevacizumab and pegaptanib. We also considered Subhransu K. Ray, MD's, data on combining PDT, ranibizumab and dexamethasone, as well as Richard F. Spaide, MD's, approach to combining triamcinolone acetonide (Kenalog, Bristol-Myers Squibb) with PDT in 2003. Please share your insights on this issue?



VEGF, macrophages, interleukin-8, ICAM-1 expression and other molecules may play a role in neovascular development.

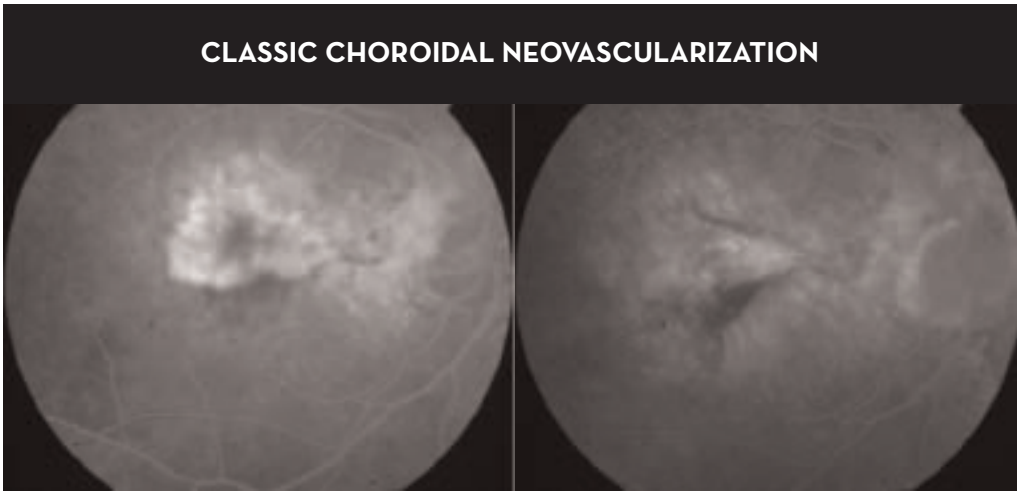
LOOKING BEYOND THE DATA

Subhransu K. Ray, MD, PhD: The data associated with ranibizumab show that we can decrease vision loss and improve visual acuity with anti-vascular endothelial growth factor (VEGF) treatment.[1,2] However, we must consider additional factors, including interleukin-8, migration of macrophages and other leukocytes, MHC class II expression, intercellular adhesion molecule-1 (ICAM-1) expression and a host of other molecules.[3] The question is: Which of these factors plays a significant role at any given time? Or, is VEGF the only pharmacologic consequence?

VEGF may be important at one stage of neovascular development. However, further along or perhaps at an earlier point in the disease process, these other factors also may play a role. The goal of combining therapies is to create a broad-spectrum suppression of inflammatory mediators as well as to add a specific anti-VEGF blockade. The reasons we first introduced dexamethasone as one of the adjunct treatments are well documented in animal models.[4,5] Dexamethasone has a shorter duration of action, which may be all that is needed after PDT. It is a more potent anti-inflammatory agent and potentially poses fewer risks of adverse effects than other corticosteroids.

Edwin H. Ryan Jr., MD: Dr. Spaide taught us that the combination of PDT and triamcinolone could improve our patients' visual outcomes,[6] which we found to be true after treating 1500 patients in our practice. However, complications, such as pseudo-endophthalmitis, endophthalmitis and cataract formation, were a concern. Most concerning was a higher rate of macular infarction in patients who had full fluence PDT and intravitreal triamcinolone. The rate was as high as 1.5%.

Consequently, I began using reduced fluence PDT in 2005. At the time, off-label bevacizumab was introduced with much excitement. Now, 2 years later, that initial excitement has led to sound improvement in the quality of patients' lives.[7] It has occurred to me that bevacizumab might be a safer alternative to triamcinolone when administering PDT. I have treated several patients accordingly and have been very impressed by how effective this combination appears to be.



Treatment for classic CNV with bevacizumab (left) resulted in 20/60 visual acuity in this patient. Two months following reduced fluence PDT-bevacizumab, leakage cleared and vision improved to 20/50.

AVOIDING SEVERE VISION LOSS

Dr. Hughes: Dr. Shah, at the Barnes Retina Institute, you have begun a study of the therapeutic effects of the combination of ranibizumab plus reduced fluence verteporfin PDT in patients with exudative AMD. What are your thoughts?

Gaurav K. Shah, MD: I agree with Dr. Ryan. PDT with full fluence is overly destructive. It increases VEGF and inflammation. However, inhibiting VEGF alone attacks the end result more than the disease process itself. Dual or triple therapy appears to be more effective.

One of the deepest concerns is severe vision loss after PDT. However, if you combine all of the data from the Visudyne in Minimally Classic Choroidal Neovascularization (VIM) trial[8] and other PDT studies, you learn that the incidence of severe vision loss after full fluence PDT is about 0.8%. We need to see what the incidence might be after reduced fluence.

Dr. Ray: Our hope is that we will not see severe vision loss when using combination therapy and some form of reduced fluence. On occasion, we still can see, through optical coherence tomography (OCT), increased fluid or pockets of subfoveal fluid that have increased after PDT treatment. The increased fluid in these cases may be an intrinsic by-product of effective therapy. Consequently, when the fluid decreases, vision improves, and the lesion regresses.

Dr. Ryan: I have had patients whose vision decreased to 20/200 or worse after treatment due to edema. Three weeks later, their vision was better than it was before treatment.

Dr. Hughes: That is a good point. Everyone wants to avoid seeing a patient with visual acuity of 20/200 after a treatment, but we need to view it in a long-term context, such as after 6 monthly injections.

CONSIDERING DEXAMETHASONE

Dr. Hughes: Sustained delivery of dexamethasone raises the risk of glaucoma and cataract. However, after a rapid pulse of dexamethasone with PDT, the drug leaves the eye quickly before it can produce these adverse effects.[9,10] Therefore, dexamethasone can be very helpful.

Dr. Ray: I believe the reason dexamethasone works so well is that the eye does not get a chance to respond defensively to its short-acting properties. Furthermore, the shorter duration makes it less prone to developing adverse reactions as seen with triamcinolone acetonide or other longer-acting sterioids.

Dr. Hughes: Recently, we looked at combination therapy, using dexamethasone and PDT in reduced duration. We are not sure what the appropriate duration should be — 42, 60 or 70 seconds. However, I think the biological effect we see from reduced fluence or reduced duration indicates that human AMD may not follow the animal model of monkey subretinal neovascularization, the basis of the original PDT data. We have changed the paradigm by combining PDT with new therapies. When performing triple therapy, we reduced the duration of PDT and administered a larger dose of dexamethasone: 800 mcg instead of 500 mcg within 1 day for most patients. Three to 5 days later, we added ranibizumab. Our 9-month data showed very good results.

We have another case series, using the same approach but with the 500-mcg dose of dexamethasone and 1.25-mg dose of bevacizumab. The intravitreal injections are performed on the same day as PDT. We do not have as much data on this group, but after 3 to 4 months, the approach seems to be working. You create a different environment by reducing the edema and using an anti-VEGF agent. RP

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Using the Right Tools for An Accurate Diagnosis and Treatment Plan

Dr. Hughes: We have discussed several of the combination therapies available for treating patients with exudative age-related macular degeneration (AMD). Now I want to focus on how to reach treatment decisions. Please describe your preferred work-up.

ANGIOGRAPHY AND OCT

Dr. Ray: I like using fluorescein angiography and optical coherence tomography (OCT) to confirm a lesion, determine the amount of leakage and gauge how much fibrosis is present. These factors help me determine treatment and prognosis.

If angiography shows that most of the lesion consists of fibrosis with very little leakage, I treat but also make sure the patient has realistic expectations. I know that I may be able to stabilize the lesion, but I may not be able to restore visual acuity that's required for driving or reading small print. Plus, I advise that we may need 6 months before I can offer a more definitive prognosis.

In advanced AMD, I do not over-promise for the affected eye, but I begin a discussion of how we must carefully watch the fellow eye.

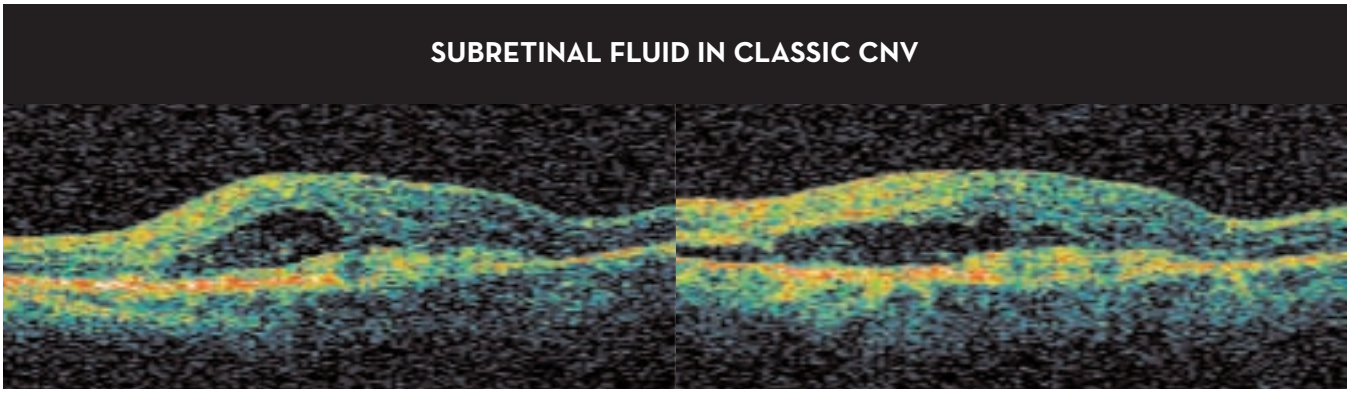
Beyond that, I advocate bringing indocyanine green (ICG) back into our practice. It is commercially available again and may help better define certain lesion types, such as occult membranes, pigment epithelium detachments, retinal angiomatous proliferation (RAP) and polypoidal choroidal vasculopathy.[1]

"Studies have shown that retinal thickness and OCT findings vary by time of day. OCT is quite variable, depending on who performs the scan, the patient's responses and other factors."

— Gaurav K. Shah, MD

Dr. Hughes: Your points are well taken. OCT findings are anatomical and qualitative. Quantitative OCT measurements need correlation with clinical findings. OCT enables us to look at the cystic space, subretinal fluid and other factors, but it is not a substitute for clinical examination.

Dr. Ryan: In addition, reproducible OCT scans are difficult to establish, making the macular thickness numbers less meaningful. I rely on history and the length of time the lesion has been present. I prefer fluorescein angiography and, in some



Optical coherence tomography (OCT) shows subretinal fluid in classic choroidal neovascularization. OCT is a useful tool to assess the cystic space and determine if subretinal fluid is present, but it is not considered a substitute for clinical examination.

cases, such as an atypical evolving central serous retinopathy, ICG.

Dr. Shah: I tend to use OCT and angiography like most physicians initially. Then, I obtain a fluorescein angiogram to determine if I am going to start or stop therapy. What we will find as time and technology progresses is how inaccurate time domain OCT is compared to spectral domain OCT. I believe the new technology will give us reproducible results.

LIMITATIONS OF OCT

Dr. Ray: I believe that physicians who rely solely on OCT scans to guide their treatment decisions fail to recognize that OCT tells us only if fluid is present — not if the membrane is leaking. The presence of fluid and a leaking membrane are not synonymous, but have to do with the established equilibrium of fluid leakage from the choroidal neovascular membrane and evacuation by the RPE.

"I like using fluorescein angiography and optical coherence tomography (OCT) to confirm a lesion, determine the amount of leakage and gauge how much fibrosis is present."

— Subhransu K. Ray, MD, PhD

I have seen patients with subfoveal classic choroidal neovascular membranes who do well with primary monotherapy based on OCT and vision perspective but who show lesion enlargement from an angiographic perspective.

Dr. Shah: Studies have shown that retinal thickness and OCT findings vary by time of day.[2] OCT is quite variable, depending on who performs the scan, the patient's responses and other factors. I rely on fluorescein angiography to determine when I begin or end therapy.

VISUAL ACUITY AS A DISEASE INDICATOR?

Dr. Shah: Visual acuity also is an uncertain indicator of disease. Even when we measure poor vision with a Snellen chart, some patients report they are seeing better.

Dr. Hughes: It is hard to quantify contrast sensitivity in the office. After treatment, the patient reports the ability to recognize faces, yet visual acuity shows no improvement. Improvement in visual function without improvement in measured visual acuity may be a reflection of reduced scotoma size or reduced distortion.

Dr. Ryan: I think the absence of fluid makes a difference in addition to visual acuity.

Dr. Hughes: Does visual acuity matter at all?

Dr. Shah: Yes and no. If a patient's vision is better than 20/40, I give the patient bevacizumab (Avastin, Genentech) or ranibizumab (Lucentis, Genentech). Recently, I have started using combination therapy on patients whose visual acuity is 20/40 or better since I have not had any patients with severe vision loss.

If it is 20/50 or worse, I give the patient the option of anti-VEGF and combination therapy. Small lesions may not need combination therapy, so I let the patient decide. AMD is such a variable disease that two eyes belonging to the same patient can behave differently.

Dr. Hughes: Does the status of the fellow eye — the other eye being 20/50 or worse — alter your treatment decisions?

Dr. Shah: Not for me personally. But again, I discuss all of those options with the patient. RP

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Same-day Triple Therapy, Other Combinations: An Assessment Of Efficacy

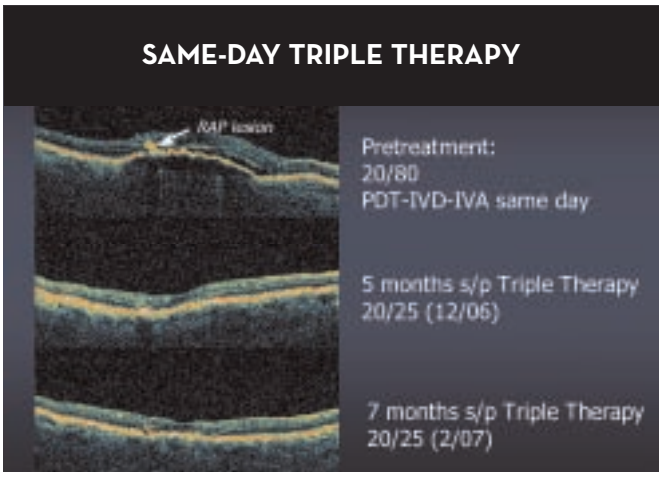
Dr. Hughes: Now that we have discussed what diagnostic tools are preferable to diagnose patients with neovascular age-related macular degeneration (AMD), I want to focus on choosing the optimal treatment combinations. Let us start with off-label bevacizumab (Avastin, Genentech). We continue to see good results with bevacizumab.[1] The unanswered question is how to determine dosing frequency, which is so variable.

Dr. Ryan: AMD is such a diverse disease that group data provide only general guidelines, not specific directions on how to treat an individual patient.

RESPONDING TO PED

Dr. Hughes: Of course, few of our cases involve straightforward decisions. I wonder how the presence of a pigment epithelium detachment (PED) changes your approach to treating subretinal neovascularization.

Dr. Shah: I do not treat PEDs unless the patient is symptomatic. We either do nothing or treat the patient with bevacizumab or ranibizumab (Lucentis, Genentech). A new report looked at using selective photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Ophthalmics) for treating hot spots and then administering bevacizumab for PEDs.[2]



A retinal angiomatous proliferation resolved 7 months after same-day triple therapy with PDT-dexamethasone-ranibizumab.

Overall, though, PEDs are difficult to treat because of the patient's risk for developing a retinal pigment epithelium (RPE) rip.[3] Many of us have treated them and ended up with a patient who went from visual acuity of 20/50 to 20/200. I am reluctant to use PDT in these cases. The size of the PED helps me decide which treatment option to use.

Dr. Ryan: A symptomatic patient with a small, vascularized, PED with leakage is actually a better candidate for combination therapy than for monotherapy. I do not think I have had an RPE rip in that setting. However, many patients end up seeing well even after an RPE rip, but they need chronic, ongoing treatment that is not very appealing. Whether you administer monotherapy with either bevacizumab or ranibizumab, or combination therapy, the lesion persists. These patients need 12, 14 or 16 anti-vascular endothelial growth factor (VEGF) injections.

Dr. Ray: When my partners started the PDEX trial at Bay Area Retina Associates more than a year ago, which compared the combination of PDT plus intravitreal dexamethasone and ranibizumab to monthly intravitreal ranibizumab monotherapy to treat AMD, we excluded two patients with PEDs larger than 50% of the lesion to avoid the potential risk of an RPE rip associated with PDT treatment. These patients received ranibizumab monotherapy instead, and both developed RPE rips.

I see more RPE rips after monotherapy with anti-VEGF agents than with combination treatments. I do not know if this is because the patients who have larger PEDs often are not treated with PDT, resulting in an internal selection bias, or if this is because most of the current PDT treatments involve triple therapy, which includes dexamethasone. Does the collapse of the RPE result from a sudden change in the fluid or disruption of the fibrovascular tissue that may cause these rips? Is it possible that the corticosteroid attenuates that change, helping many patients avoid RPE rips? This is all conjecture until we have more data from the current trials.

EMBRACING TRIPLE THERAPY

Dr. Ray: When I see a patient with a PED and a lesion that I believe will respond to PDT, I do not shy away from using triple therapy.[4] I have seen good responses with this approach.

Dr. Ryan: I always warn patients about the risk of vision loss. I

have created rips in different ways — with a laser, pegaptanib sodium (Macugen, (OSI) Eyetech), ranibizumab and bevacizumab.

Dr. Hughes: If a patient has a PED but is seeing 20/40, I would not use triple therapy. On the other hand, I had one patient at 20/400 with subretinal leakage, persistent RPE detachment, significant subretinal fluid and a neovascular component. She had received 3 bevacizumab and 4 ranibizumab injections from another physician. I offered triple therapy and explained the risks, which she accepted. Three months later, her acuity was 20/50.

Dr. Shah: So much depends on the patient. The reason this disease is so variable is that we see the patient at a specific point in time, when we may not know if the membrane, PED, or occult or classic lesion is on the up-slope or down-slope. Even before these new therapies were available, you would have the occasional patient who was 20/50 and did not want laser therapy. You would see him again in 5 to 6 years, and he would be at 20/30.

BETTER BUT WORSE

Dr. Ryan: I reviewed data from 100 patients in my practice who received monotherapy with bevacizumab and 156 patients from two practices who received combination treatment. Vision decreased for some patients in each group, despite better anatomic outcomes. Quite a few patients whose vision decreased were those with PEDs that disappeared. There seems to be an atrophic effect, whether they have had monotherapy or PDT.

Dr. Shah: What I really worry about is vision loss 12, 15 or 16 months after therapy. I see these patients who have had monotherapy and who develop RPE rips and atrophic changes. I think that is what leads to gradual vision loss more than sudden, severe vision loss.

PERSPECTIVE ON TRIPLE THERAPY

Dr. Hughes: Dr. Ray, you are the principal investigator of the prospective PDEX trial. Can you discuss how and when you administer triple therapy and what risks are involved?

Dr. Ray: We have been conducting the trial for a year now. The protocol calls for the patient to receive triple therapy on the same day. PDT is immediately followed by separate injections of ranibizumab and dexamethasone. In the cases I have reviewed, no patient has developed an RPE rip. We do have RPE rips in our monotherapy arm, but the percentages are certainly not out of the expected norm, and the numbers are far too small to determine if it is a by-product of treatment or natural history.

OTHER TRIPLE THERAPY APPROACHES

Dr. Ryan: In my practice, I looked at the difference between administering PDT after prior treatment with bevacizumab and same-day treatment with PDT and bevacizumab. Reviewing a year's worth of results, I found that the same-day group fared better by about 1 line of vision. You could argue that waiting a week to provide PDT is safer, but we have decided to continue exclusively with same-day treatment. When we have done triple therapy, we have done it on the same day as well.

Dr. Ray: If I were using PDT alone, I also would use the anti-VEGF agent on the same day to minimize the effects of PDT. Because we are adding dexamethasone on the day of PDT, I feel comfortable waiting a week to add the anti-VEGF treatment.

Dr. Shah: We have used combination therapy on the same day as well as the anti-VEGF injection a week before PDT. To date, our data show no difference in either approach. We have about 7 patients enrolled in a randomized trial looking at ranibizumab and PDT either on the same day or 1 week apart. We have a PDT laser in only 1 of our offices, therefore I try to make this approach most convenient for our patients.

USING DEXAMETHASONE SAFELY

Dr. Ray: As we move forward with these combination approaches using dexamethasone, I think it is important to remember the difference between treatment-naïve patients and patients who have been undergoing chronic therapy. In some patients who receive triple therapy following previous monotherapy with 3, 4 or 5 injections, there is an acute increase in fluid.

There is a theoretical basis for this outcome: Every time we give patients an injection, we suppress 95% of the endogenous VEGF activity. Because these patients received the treatment 4 to 6 times, there may have been structural modifications to the underlying choriocapillaris, hindering its ability to respond to any type of ischemic injury. When you administer PDT, which induces an ischemic event, and you follow that treatment with dexamethasone and an anti-VEGF agent at the same time, I think you blunt the patient's ability to respond to another stress. Therefore, in patients who have had previous monotherapy, I wait at least a week after same-day PDT plus dexamethasone before administering the anti-VEGF agent. Others in my group, however, have used triple therapy in these same types of patients and have seen no significant difference between staging the treatment or providing it simultaneously. But there may be a fundamental difference in the response seen in treatment-naïve and previously-treated patients.

ADMINISTERING ANTI-VEGF WITH CARE

Dr. Ray: VEGF is an important molecule within the eye that is not expressed only in the pathological neovascular state. I do not know if ranibizumab and bevacizumab are equal, but I try to minimize their use. With either drug, you are still suppressing a normal biological agent.

Dr. Hughes: These are great words of caution we should all keep in mind. RP

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Comparison Between the Efficacy Of Monotherapy and Combination Therapy

Dr. Hughes: The introduction of several new approaches to treat neovascular age-related macular degeneration (AMD) has presented us with new insights based on case series data, unproven theories, anecdotal reports and clinical experience.

Please share with us the triumphs and challenges you are experiencing in your practices as you strive to optimally manage your patients with the new therapeutic tools.

DETERMINING THE BEST THERAPY

Dr. Ryan: In my experience, monotherapy with either bevacizumab (Avastin, Genentech) or ranibizumab (Lucentis, Genentech) and combination therapy both improve visual acuity during the first 3 to 4 months of treatment. I have not seen any patients lose vision after photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Ophthalmics). I have treated at least 20 patients whose vision was 20/40 or better with combination therapy. I have had 1 patient with recurring angioid streaks, and she was 20/20 after 4 treatments using combination therapy with reduced fluence PDT and bevacizumab.

Dr. Hughes: I had a patient just like that. She was 20/200 OD with angioid streaks and a subretinal membrane. We administered combination therapy with reduced duration PDT (42 seconds at full fluence) and 1.25 mg of intravitreal bevacizumab, and the result was phenomenal. Her vision improved to 20/20, and she has not had a repeat treatment in more than a year. These types of anecdotal reports are encouraging.

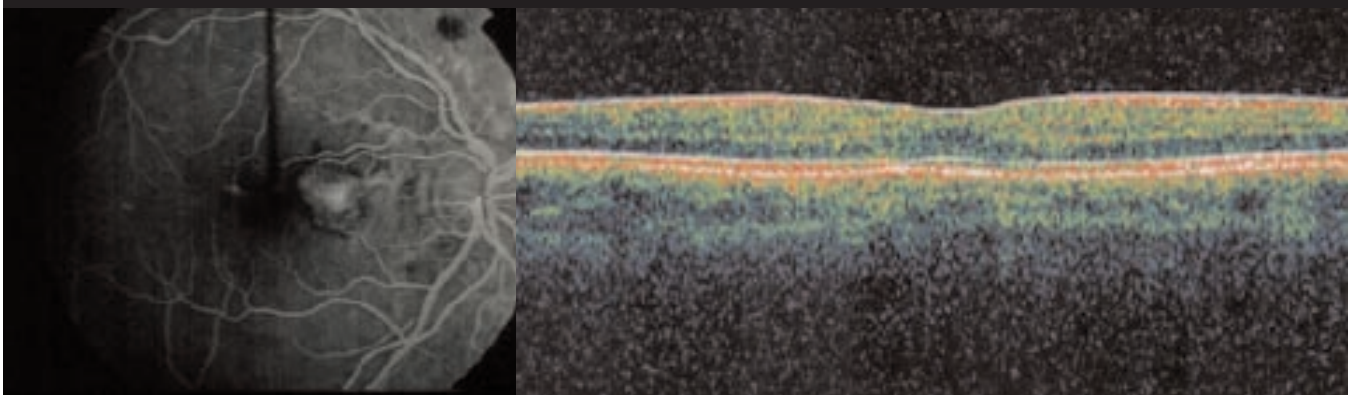
Dr. Ryan: I do not know if this means combination therapy is more effective than monotherapy. I think the duration between the treatments is probably a good gauge of efficacy. During monotherapy, we have seen classic membranes gradually enlarge, a form of "creep," which ablative therapy with PDT halts. I have noticed that young patients with angioid streaks will detect problems that are very difficult to discern through fluorescein angiography. As a result, I do not use good vision as a reason to rule out treatment.

Dr. Ray: I agree. Baseline vision is less important than other factors, such as lesion appearance, or if a large pigment epithelium detachment (PED) is present. The patient's ability to travel is also a factor. The status of the fellow eye plays a critical role as well.

REDUCED FLUENCE AND DURATION

Dr. Hughes: What are your thoughts on reduced fluence and reduced duration PDT?

SUBRETINAL NEOVASCULAR MEMBRANE DUE TO ANGIOID STREAKS



Fluorescein angiography (left) shows a juxtafoveal subretinal neovascular membrane due to angioid streaks. After administering combination therapy with reduced duration PDT followed by bevacizumab, the subretinal fluid resolved as shown on OCT (right).

"In my experience, monotherapy ... and combination therapy both improve visual acuity during the first 3 to 4 months of treatment. I have not seen any patients lose vision after photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Ophthalmics)."

— Edwin H. Ryan Jr., MD

Dr. Ryan: I choose reduced fluence based on the data from the Visudyne in Minimally Classic Choroidal Neovascularization (VIM) Study.[1]

Dr. Shah: If you look at reduced fluence and reduced duration, you are trying to reduce the collateral damage associated with PDT. The part that I am unsure about is the effect of full fluence when you cut the time in half.

The question is: When do you eliminate the oxygen? At 20 seconds? Ten seconds? I follow the findings of the VIM trial[1] and the paper presented by Ursula M. Schmidt-Erfurth, MD.[2] Even at 3 months, indocyanine green (ICG) angiography shows changes in the choriocapillaris. However, no one has shown if full fluence or reduced fluence is better. I hope we get answers from the DENALI study, which will randomize to PDT at full or half light doses, combined with ranibizumab and ranibizumab alone.

There is so much left to discover. We do not know if reducing duration means 42, 62 or 58 seconds. Most of our colleagues who are offering combination therapy prefer to reduce fluence rather than duration. However, it may be advisable to do the opposite. Albert J. Augustin, MD, who conducted a recent study[3] on reduced duration, tried 60 seconds. He found it was not enough and went up to 70 seconds. How much difference did that last 10 seconds make?

Dr. Ryan: I have been happy with 83 seconds. I prefer not to change too many variables at once. Reducing fluence has some theoretical support.

Dr. Hughes: The other issues are how much biological activity you need and when you need it. I think these and other factors need to be evaluated, not simply in the context of the Treatment of AMD with Photodynamic Therapy (TAP) Study,[4] which evaluated PDT as a monotherapy. In the age of anti-VEGF, we need to look at these issues differently. If we were delivering too much power with PDT in years past, then less power plus a corticosteroid and an anti-VEGF treatment may provide a better combination. Unfortunately, dose-response curves are not available.

Dr. Shah: Another example is data from the FOCUS trial[5] relating to ranibizumab and PEDs. As treatment paradigms have changed, the subgroup analysis from studies does not always apply.

REVISITING THE LASER

Dr. Hughes: I want to turn our attention to colleagues who have drifted away from using PDT but are now open to triple therapy. What advice can you offer for incorporating the laser back into their treatment regimens?

Dr. Ray: We have 6 offices, 3 of which have PDT lasers. My advice would be to get as much done as you can during a single visit, provided the services are reimbursable. But obviously, what guides the treatment decision the most is safety and efficacy.

Dr. Ryan: We take a similar approach. I perform PDT, and then I'll give the patient the injection. It really doesn't take any additional time.

Dr. Shah: It may take more time during that visit; however, in the end, you come out ahead.

Dr. Hughes: You create availability in the office schedule to see more patients because you have reduced the need for monthly injections.

Dr. Ray: The preliminary 12-month data from the PDEX trial, which compared the combination of PDT plus intravitreal dexamethasone and ranibizumab to monthly intravitreal ranibizumab monotherapy to treat AMD, show that the monotherapy patients had to receive 12 injections. The average number of treatments for the triple therapy group was between 3 and 4. We have a long way to go before learning if triple therapy is a noninferior treatment compared to anti-VEGF monotherapy with respect to visual outcomes, and whether these outcomes can be maintained with fewer treatments. However, based on the emerging PDEX data, we may be able to reduce the number of visits with similar efficacy. RP

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Counting the Exorbitant Cost Of AMD Treatment

Dr. Hughes: How much does economics influence your treatment decisions when you are managing neovascular age-related macular degeneration (AMD) patients in today's ever-changing environment?

MATTERS OF DOLLARS AND CENTS

Dr. Shah: We need to discuss the cost of treatment with patients when reviewing the ramifications of using anti-vascular endothelial growth factor (VEGF) agents. Insurance is complicated. None of us can keep track of what company covers which procedure.

Most patients typically have Medicare and a secondary plan. The biggest problems seem to stem from health maintenance organizations (HMOs). Capitated patients are often in a bind. Initially, when I speak with a patient about treatment, cost issues usually do not come up. Later on, these issues arise.

Dr. Hughes: Medicare-only patients may have to pay 20% for approved treatments. And they will be most concerned with the $400-plus monthly payment for ranibizumab (Lucentis, Genentech).

Dr. Shah: For Medicare patients on a fixed income, even with the Single Point of Contact (SPOC) program provided by Genentech, which helps with payment, the $400 is still an issue. If you have to get a specific dose for a patient from a specialty pharmacy, that can be a logistical challenge as well. The patient may have to come to a particular office and, if you decide not to give the treatment, you may have to send the drug back. Having a J-code helps with some of these issues, but only when patients are covered by Medicare and secondary plans.

REDUCED FEES

Dr. Ryan: In Minnesota, we deal with reduced fee-for-service more than capitation. I think about the cost of this treatment to society — $2,000 x 12 months a year. What is the cost to the Medicare patient who has a copayment of $400 for 12 months of the year? It would not take too many failed payments to become unprofitable and decide it's too expensive to provide care.

When we started offering photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Ophthalmics) and bevacizumab (Avastin, Genentech), cost was definitely a factor in deciding when to administer treatment. We had no idea if we would get paid for using bevacizumab. We knew that we would get paid for PDT. So cost played a role in deciding to use PDT plus bevacizumab.

If everyone were treated with the most expensive protocol, we would have a much bigger crisis. So cost-effectiveness is going to become increasingly important in making treatment decisions.

Dr. Ray: There are 3 types of costs: the cost to the patient, the cost to the practice and, as Dr. Ryan mentioned, the cost to society. If a patient will be burdened by the copayment, I will not use ranibizumab. I will use bevacizumab instead. From the patient's financial standpoint, the most important issue is if he or she will be charged for the drug, treatment and/or copay. Secondly, the cost to the practice and society as it impacts on the sustainability of future treatments, also will weigh heavily on every retinal surgeon's mind. One of the ways to address these issues is to conduct randomized clinical trials. With such trials, we can more accurately determine if reduced-treatment frequency, use of combination therapies, off-label use of bevacizumab and other forms of treatment can compare to the gold-standard visual outcomes seen in the MARINA[1] and ANCHOR[2] trials. Combining resources, experience and knowledge over multiple practices may better serve our patients, practices and society.

COST ANALYSIS

Dr. Ryan: Part of the cost analysis will involve comparing 12 visits a year for monotherapy using ranibizumab with fewer

"The economics have awakened us. We need to keep track of every vial and every injection. On the one hand, we are trying to cut overhead. However, if a vial or 2 of a drug that costs $2,000 is inadvertently given without an approval, a practice can lose a lot of profit margin."

— Gaurav K. Shah, MD

visits needed for combination therapy. All the imaging and other costs that are not included in drug costs are substantial.

Dr. Hughes: Even if you add imaging and office visits, the cost is diminished by a single $2,000 payment for one ranibizumab injection. The implications of the pharmaceutical costs are huge.

Dr. Shah: The cost of research was never an issue in the past because drug costs never amounted to much. If you look at your monthly statements now, the figures are astounding. The time it used to take for us to get reimbursed was 55 days and now it's back to 85 or 90 days.

The economics have awakened us. We need to keep track of every vial and every injection. On the one hand, we are trying to cut overhead. However, if a vial or 2 of a drug that costs $2,000 is inadvertently given without an approval, a practice can lose a lot of profit margin. We have people who spend all of their time triple-checking when a drug is being used, which adds to our expense.

MANAGING RISK

Dr. Ray: That is a large percentage. Drugs account for approximately 50% of our accounts receivable. The retinal surgeons are really absorbing all of the risks (buying, storing, injecting, collecting and tracking the drug) for a marginal profit. When you talk to the pharmaceutical companies, their hands are tied to a certain extent. For instance, federal laws guide how much profit physicians can make on a given drug.

Dr. Hughes: We have to deal with the challenge of payment delays from secondary insurance companies. For one insurer in Massachusetts, we were still sending letters for an injection that had been administered 8 months earlier. Essentially, we have become bill collectors.

Dr. Ray: Plus, how many extra people do we have to hire to do that bill collection? There are many hidden administrative costs to the practice that may not be adequately reimbursed beyond the risks already mentioned.

Dr. Shah: Waiting several weeks to receive payment can be too expensive for a private practice. In large academic settings, such an expense is absorbed by the hospital pharmacy. Not so in private practice.

Dr. Hughes: What amazes me is hearing a story of a large multispecialty group that has more than 25 physicians, including 7 retina specialists. And the number 2 cost, after personnel, is ranibizumab at more than $6 million. In one practice, one physician's revenue for ranibizumab equaled that of the rest of his professional receipts.

REDUCING THE NUMBER OF INJECTIONS

Dr. Hughes: One of the most impressive results 9 months into our combination series (Reduced Duration PDT Plus Intravitreal Dexamethasone Plus Ranibizumab) is the fact we can reduce the injection burden, starting at baseline and after more than 9 months of follow-up. We have administered 60 ranibizumab injections to 40 treatment-naïve patients, instead of a maximum of 400 injections. That represents a 76% savings in pharmaceutical costs. More importantly, the case series revealed 40% of patients improved visual acuity by 3 lines or more, and only 1 patient lost 1 line of vision during the 9 months of follow-up.

Dr. Ryan: I looked at our data and found that, over a year, the average patient's pharmaceutical costs were $2,400. In the PrONTO study,[3,4] the costs were at least $12,000.

Dr. Hughes: When do you require combination-therapy patients to return to the office for follow-up treatments?

Dr. Ryan: At 6 to 8 weeks. At that point, I treat with bevacizumab if I see leakage on fluorescein angiography.

Dr. Shah: I do the same. If optical coherence tomography (OCT) shows fluid, I administer either bevacizumab or ranibizumab, not PDT. Then I bring them back in another 6 to 8 weeks. If angiography shows leakage and I am treating a lesion that has grown, I add the PDT or the anti-VEGF agent.

I see them again in 6 weeks. We know from our data that recurrences typically surface at about 4 months. After this point, if they are stable, I am likely to push the visits out even further. In a year, a typical patient will have 4 to 5 visits, compared with the 8 to 10 under our old approach. RP

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Evaluate the Systemic Risks Of Intravitreal Anti-VEGF Agents

Dr. Hughes: We have no randomized clinical trials establishing possible increased risks of systemic complications of one treatment versus another when managing neovascular age-related macular degeneration (AMD). What are your thoughts on the possible long-term risks of pan-vascular endothelial growth factor (VEGF) agents?

EXAMINING THE RISKS

Dr. Shah: All possible systemic adverse events, such as stroke, heart attack and myocardial infarction (MI), are a concern.[1,2] However, most patients choose vision over a theoretical risk of stroke, especially if they have bilateral disease. We track patients who have not returned for visits to determine why. Typically, it is because they could not get transportation to the office, not because of the probable risk of stroke or heart attack or other arterial thromboembolic event (ATE).

The doses of bevacizumab (Avastin, Genentech) in the cancer studies are 400 to 600 times higher than the doses we administer intravitreally, and those cancer patients are already at high risk for ATEs.[3] Nonetheless, we always document patient history. If a patient has had a recent stroke, we need to consider that factor. Ultimately, does it change what I do? I would have to say no.

Dr. Ryan: I think about systemic risks quite often. Because we had far more patients on bevacizumab than ranibizumab (Lucentis, Genentech), we began to track the incidence of stroke among our bevacizumab patients. We found a low percentage in this category, consistent with what one would expect in this patient population. However, it was tough to determine if the strokes were directly linked to bevacizumab.

Without a doubt, increased exposure to the drug is a potential risk. Every time you inject one of these drugs into the vitreous cavity, some systemic absorption occurs. Using a treatment that enables you to administer fewer anti-VEGF injections makes sense for the additional reason that VEGF is, in fact, neuroprotective.[4,5]

OCULAR SIDE EFFECTS

Dr. Ray: Patients are usually more concerned about the ocular side effects than I am about systemic adverse events. Chronic usage inside the eye can lead to retinal nerve fiber layer damage, choroidal damage or other adverse effects that are related to VEGF's normal role in retinal vascular homeostasis.

The only time systemic adverse effects become an issue is if a patient recently has had a stroke or an MI. In those cases, I still do not withhold therapy, but I will be much more cautious about chronic, prolonged treatment. If a new patient has just developed a leaking neovascular membrane and the other eye already has damage, the patient generally will choose treatment over the potential for a systemic adverse event. I contact either the cardiologist or, as needed, the neurologist. I explain the risks and what we are planning to do.

If a patient has been undergoing treatment for 6 months or already has received 3 ranibizumab injections when he or she has a stroke or MI, I typically skip the next 1 or 2 injections until I can thoroughly examine the medical situation.

STROKE VS. MYOCARDIAL INFARCTION

Dr. Hughes: Do you differentiate between stroke and MI when considering whether to resume bevacizumab or another treatment?

Dr. Ray: In both situations, especially after an MI, you probably want to see some level of activity from the choroidal neovascular membrane before resuming treatment. If a patient has had either an MI or a stroke within the past 6 weeks, I generally withhold treatment, even if he or she wants to accept the risk of therapy.

However, I will stress that in our practice the most important aspect of evaluating the extent of systemic risk is getting his or her other doctors involved.

Dr. Ryan: Patients with these issues often are too sick to come in for treatment. I would be very hesitant to treat them with an anti-VEGF agent unless I felt that the threat to their

"I don't feel as comfortable treating stroke patients, particularly in view of the low but statistically significant increased risk of stroke in patients with a previous history of stroke."

— Mark S. Hughes, MD, FACS

vision was fairly significant. However, I have treated people who have a stroke risk with photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Ophthalmics) and corticosteroids.

Dr. Shah: I just saw a patient with AMD 2 weeks after he suffered a transient ischemic attack (TIA). We started talking about PDT combined with triamcinolone acetonide (Kenalog, Bristol-Myers Squibb). Patients treated with these regimens have done fairly well.[6] Most of them already have had their cataracts removed, so clouding of the crystalline lens is not an issue. Increased IOP can be managed.

Dr. Hughes: I have a patient who presented with a new subretinal neovascular membrane 2 weeks after experiencing a minor MI. After speaking with the patient's cardiologist a few times, we decided to wait 2 months after the MI before I administered a pan-VEGF blockade agent. After a lengthy discussion with the patient, I treated her with reduced duration PDT (42 seconds) plus intravitreal dexamethasone (800 mcg) and intravitreal pegaptanib sodium (Macugen, (OSI) Eyetech) rather than wait 2 months. Three months following treatment, her vision improved from 20/200 to 20/50, at which point we were free to treat her with any agent if there was a recurrence.

An 83-year-old patient came in for her third ranibizumab injection and told me she had suffered a TIA the previous weekend. I established that it really had been a stroke. She had amblyopia in her right eye. She was 20/50 in her left eye with persistent leakage. Stroke needs to be fully discussed with neurology, which is very different from cardiology. I don't feel as comfortable treating stroke patients, particularly in view of the low but statistically significant increased risk of stroke in patients with a previous history of stroke.[7] I have heard too many variable waiting periods from neurology.

Dr. Ray: Because no one knows.

Dr. Hughes: Should we wait 6 months for remodeling? Twelve months? Is the role of VEGF important for the neurons as they try to recover from an ischemic event?

Dr. Ray: In my opinion, if you want to treat AMD in these cases, you probably want to stay away from anti-VEGF agents and use either PDT and dexamethasone or PDT and triamcinolone acetonide.

THE ISSUE OF HYPERTENSION

Dr. Ray: Hypertension is also an important consideration. I have had a few doctors ask me to stop treating their patients with ranibizumab or bevacizumab because of the effect it seemed to have on their patients' blood pressure. Again, no one really knows if anti-VEGF agents increase blood pressure. However, we are obligated to stop treatment from the standpoint of having collaborated with the medical doctors and the possible legal implications in the event of a related complication.

Dr. Shah: I have had several blood pressure issues when using bevacizumab for diabetes patients.

Dr. Ray: When I consider ranibizumab and bevacizumab, I lean toward ranibizumab because of its shorter duration of action. These two drugs are obviously different and their reactions in the eye and body may be different. For example, we have had patients who have developed uveitis after receiving ranibizumab but not bevacizumab. Their body's systemic reaction to each drug also may be slightly different. The shorter half-life of ranibizumab may be favorable in these cases where systemic risk factors coexist with active ocular disease.

Dr. Ryan: At the same time, we have seen inflammation in bevacizumab patients that has subsided when we switched them to ranibizumab.

Dr. Shah: We are all struggling to determine the similarities and dissimilarities of these drugs.

RELATIVE EFFICACY

Dr. Ray: We may see small or large differences in the group data, which will help us make treatment decisions for Medicare and other insurers. But what matters most is how each individual patient responds to treatment, particularly those who may develop uveitis, who have had previous strokes, MIs, hypertension and other ATEs or have a suboptimal response to the reciprocal therapy. RP

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Evolving Treatment Strategies in Age-related Macular Degeneration Therapy

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

1. **Edwin H. Ryan Jr., MD, was concerned about pseudo-endophthalmitis, endophthalmitis and which other complication when he combined photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis Ophthalmics) and triamcinolone acetonide (Kenalog, Bristol-Myers Squibb) to treat patients with exudative age-related macular degeneration?**
   a. Cataract formation
   b. Glaucoma
   c. Macular edema
   d. Retinal detachment

2. **Mark S. Hughes, MD, FACS, says that after a rapid pulse of dexamethasone with PDT, the drug leaves the eye quickly before it can produce cataract and which other adverse effect?**
   a. Retinal pigment epithelium rip
   b. Macular hole
   c. Uveitis
   d. Glaucoma

3. **According to Subhransu K. Ray, MD, PhD, physicians who rely solely on optical coherence tomography (OCT) scans to guide their treatment decisions fail to realize that OCT only tells them which of the following?**
   a. That a membrane is leaking
   b. The actual size of the lesion
   c. If fluid is present
   d. How much fibrosis is present

4. **Gaurav K. Shah, MD, relies on which of the following to determine when he begins and ends therapy?**
   a. Optical coherence tomography
   b. Fluorescein angiography
   c. Indocyanine green
   d. Visual acuity

5. **Dr. Shah says a pigment epithelium detachment (PED) in an AMD patient is difficult to treat because of the patient's risk for developing which complication?**
   a. Retinal pigment epithelium rip
   b. Retinal detachment
   c. Cystoid macular edema
   d. Retinal hemorrhage

6. **In the prospective PDEX trial, PDT is immediately followed by separate injections of ranibizumab (Lucentis, Genentech) and which other drug?**
   a. Triamcinolone acetonide (Kenalog, Bristol-Myers Squibb)
   b. Fluocinolone acetonide
   c. Dexamethasone
   d. Pegaptanib sodium (Macugen, (OSI) Eyetech)

7. **Patients receiving same-day triple therapy, who have already received at least 3 anti-VEGF treatments for active lesions, have a higher risk for developing significant fluid than treatment-naïve patients. This is because every time you administer an injection, you suppress what percentage of endogenous VEGF activity?**
   a. 25%
   b. 45%
   c. 75%
   d. 95%

8. **In Dr. Ryan's experience, monotherapy and combination therapy both improve visual acuity within how many months of starting treatment?**
   a. 1 to 2 months
   b. 3 to 4 months
   c. 5 to 6 months
   d. 7 to 8 months

9. **The 12-month data from the PDEX trial shows that patients receiving triple therapy needed 3 to 4 injections on average versus how many in the monotherapy group?**
   a. 12
   b. 10
   c. 8
   d. 6

10. **According to Mark S. Hughes, MD, FACS, one of the most impressive results 9 months into his combination series (Reduced Duration PDT Plus Intravitreal Dexamethasone Plus Ranibizumab) is the fact researchers administered only 60 ranibizumab injections to 40 treatment-naïve patients instead of a maximum of how many injections?**
    a. 100
    b. 200
    c. 300
    d. 400

11. **Dr. Ryan requires patients who receive combination therapy to return to the office for follow-up treatments in how many weeks?**
    a. 2 to 4 weeks
    b. 4 to 6 weeks
    c. 6 to 8 weeks
    d. 8 to 10 weeks

12. **According to Dr. Ray, which of the following ocular side effects can result from intravitreal anti-VEGF injections?**
    a. Mitochondrial damage in the inner segments of photoreceptors
    b. Damage to the retinal nerve fiber layer and choroid
    c. Retinal pigment epithelium atrophy
    d. Retinal neuronal damage with progressive retinal thinning

13. **After speaking with a cardiologist about a patient who presented with a new subretinal neovascular membrane 2 weeks after experiencing a minor myocardial infarction (MI), how many months did Dr. Hughes wait after the MI before administering an anti-VEGF injection?**
    a. 2 months
    b. 4 months
    c. 6 months
    d. 8 months

14. **In Dr. Ray's experience, patients have developed uveitis after receiving which of the following treatments?**
    a. Bevacizumab (Avastin, Genentech)
    b. Ranibizumab
    c. Pegaptanib sodium
    d. Triamcinolone acetonide

RETINAL PHYSICIAN
JANUARY/FEBRUARY 2008

Evolving Treatment Strategies in Age-related Macular Degeneration Therapy

To successfully complete this activity, you must read the entire publication, then complete and submit the Evaluation Form by Feb. 28, 2009. You must score at least 70% on the post-test to receive credit. Mail the completed Evaluation Form to: NACCME, 83 General Warren Blvd., Suite 100, Malvern, PA 19355 or fax it to (610) 560-0501. You also may complete this activity online at visioncarecme.com. Certificates will be mailed within 8 weeks of receipt to those who successfully complete the post-test. There is no fee to participate in this program.

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	**13.**	A	B	C	D
4.	A	B	C	D	**9.**	A	B	C	D	**14.**	A	B	C	D
5.	A	B	C	D	**10.**	A	B	C	D					

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Evaluation (circle one)	**Excellent**	**Good**	**Satisfactory**	**Poor**
Accuracy and timeliness of content	4	3	2	1
Relevance to your daily practice	4	3	2	1
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Relevance of the content to the learning objectives	4	3	2	1
Effectiveness of the teaching/learning methods	4	3	2	1

Did this activity avoid commercial bias or influence? YES NO

Now that you have read this article, can you

1. Discuss the various combination therapies available for exudative age-related macular degeneration (AMD)? YES NO
2. Describe how to make the best treatment decisions using optical coherence tomography and fluorescein angiography? YES NO
3. Discuss the efficacy of same-day triple therapy for neovascular AMD and how it compares to monotherapy? YES NO

What questions do you still have?

_____

_____

How will you use what you have learned from this activity? _____

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