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REVIEW

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VOLUME 3 — ISSUE 3: TRANSCRIPT

Featured Cases: Therapies for Choroidal Neovascularization from Age-Related Macular Degeneration

After participating in this activity, the participant will demonstrate the ability to:

- Evaluate therapies for choroidal neovascularization from age-related macular degeneration, including the choice of anti-VEGF agents for initial therapy and follow-up;
- Describe infection and cardiovascular safety concerns with the use of anti-VEGF agents; and
- Determine the most appropriate therapeutic option for the management of retinal vein occlusion, including observation, intraocular steroids, and intraocular anti-VEGF therapies

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to Age-related Macular Degeneration and Retinal Vein Occlusion, as reported from the Retina Society 47th Annual Scientific Meeting in Philadelphia, Pennsylvania. The format for this round-table discussion is case-study scenarios for the clinical practice.

Unlabeled/Unapproved Uses

The authors have disclosed that their discussion will include the unlabeled or unapproved uses of avastin, bevacizumab, and triamcinolone.

Faculty Disclosures

Dr. Neil Bressler has disclosed that, in the past year, he has served as a principal investigator of research projects at the Johns Hopkins University sponsored by Bayer, Genentech, Novartis, and Regeneron.

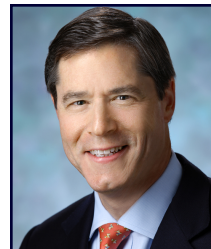
Dr. David Brown has disclosed that he has served as a consultant, and has received honorarium and grant funding from: Genentech, Regeneron, Allergan, Novartis, Bayer, Clearside Biomedical, and Xcovery. In addition he serves as a committee member for Genentech and Regeneron.

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The activity has been developed for ophthalmologists and retina specialists.

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STATEMENT OF NEED

- Clinicians lack confidence that their knowledge of new AMD developments will allow them to provide optimal patient care.
- Clinicians are unprepared to integrate new diabetic retinopathy and diabetic macular edema research findings into their current treatment paradigms.
- On-going research into retinal vein occlusion treatments has created clinician uncertainty about choosing the most appropriate therapeutic options.
- Clinicians require additional knowledge about new therapies to develop best practices in treating vitreomacular abnormalities.

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There are drusen in the right eye, which is 20/20. The patient tells you that the left eye which is 20/80, recently dropped to difficulty seeing or reading and interferes with the right eye. Looking in the back of the eye you see hemorrhage in the retina and fluid in the macula, and you conclude that this person has choroidal neovascularization from macular degeneration in the left eye.

My first question is, would you even get a fluorescein angiogram in trying to diagnose this? It's clearly choroidal neovascularization, you think what else could it be?

DR. BROWN: We still get fluorescein angiography. You're right, 95 percent of the time you can pinpoint this. Sometimes there's a comorbidity such as an old vein occlusion, or other things that can fool you, especially if the patient's of Asian descent we're looking for polyps, which you can easily see on the fluorescein. Sometimes you go for an ICG for that but we always start with fluorescein angiography to make sure that my clinical assumption is correct.

DR. BRESSLER: So Dr. Regillo, let's say you did get a fluorescein and it was typical for what you might consider as choroidal neovascularization. We have excellent data from many well-designed trials around the world looking at aflibercept, bevacizumab, and ranibizumab to treat these cases. I'd like to know if you decide that you are going to treat this patient with one of these anti-VEGF agents, which one do you decide to use?

DR. REGILLO: I typically start with an FDA-approved anti-VEGF agent, be either ranibizumab or aflibercept. The VIEW phase 3 clinical study showed essential equivalence of the drugs, and whether one lasts longer than the other we just don't know for sure at this time. I feel very comfortable with their safety and efficacy profile but it's essentially a flip of the coin.

DR. BRESSLER: Do you flip a coin in front of the patient or you choose one?

DR. REGILLO: I let them know a little bit more about the background, the history, when they came out, and so forth. Some patients like the new kid on the block, some patients say give me the one that's well established and has been around a while. So half the time it's one or the other.

DR. BRESSLER: Dr. Brown, how about you, do you just flip a coin or are you usually going to look at specifics of the patient and what they desire and decide to use ranibizumab or aflibercept, or do you even decide to use bevacizumab off-label?

DR. BROWN: In our market, approximately one-third of the patients get off-label bevacizumab because they are in the managed care program or really don't have access to one of the other drugs. In the patient you're describing who apparently has great insurance and the option is ours, we often choose ranibizumab to begin with just because the access programs and the sampling programs are more developed. And ranibizumab is easier to get your hands on and you know you're going to be paid for it.

DR. BRESSLER: I'd like to get into how we actually treat these patients, Dr. Regillo, and maybe we could go through a couple of specific questions. One of them is, we hear that it's essential to use povidone iodine or some antiseptic directly over the area where you're going to treat, let it dry for at least 30 seconds, and then do the injection. What do you do about the patient who had such an injection maybe in their other eye and they tell you they've had terrible irritation with that, burning for the next day or two, and they think it's from this antiseptic. Do you avoid using the antiseptic? How do you manage that person?

DR. REGILLO: I don't avoid it; I always use it to some degree, and they're probably right, they probably have irritation. It's probably not an allergic reaction, but it's probably significant irritation to the cornea from the Betadine that can dry on the cornea and cause irritation right after the injection, and it can be pretty severe and uncomfortable for some patients, especially if a patient has some underlying predisposing condition like a dry eye.

So my usual prep is a drop of proparacaine followed by a drop of Betadine to bathe the entire ocular surface and lids. And then wait a minute and repeat. That's the usual prep. But if a patient is having problems consistently with the Betadine after the injection, I'll then modify it to minimize the exposure of the cornea to Betadine by simply doing the anesthetic and then putting the Betadine at just the injection site on a Q-Tip to minimize the access of the Betadine to the cornea.

DR. BRESSLER: Very good. So always using the antiseptic. Dr. Brown, another question that comes up is, is there value to give this person any topical antibiotics before injection or after injection to perhaps prevent endophthalmitis? How do you approach that question?

DR. BROWN: For years we did it as part of our clinical trials. During that period we gave it routinely to everybody in the practice because it was hard to tell a patient you need to do the eye drops for a trial but not for clinical practice. Now we typically don't use antibiotics either way, except in patients who really have to minimize the Betadine, because it makes me feel a little better to have some prophylactic antibiotics on board in those I'm not giving the amount of antiseptic that's been proven.

DR. BRESSLER: So it might be a psychological comfort because the level of that antibiotic inside the vitreous couldn't possibly stop endophthalmitis.

DR. BROWN: Absolutely dogma or psychological.

DR. BRESSLER: Very good. Another thing that comes up during these injections, Dr. Regillo, is whether you should consider withholding, for example, Coumadin in patients who are taking it because they have a greater chance of bleeding in the eye. Or how about their aspirin? These questions come up all the time because the patients tell us, oh, you're doing a procedure, I bleed easily. how do you manage that?

DR. REGILLO: I tell them not to worry, I never would consider altering a systemic antiplatelet or anticoagulation regimen. With pars plana small needle injection, it's extraordinarily rare to have any bleeding complication. We'll do pars plana vitrectomy in patients and not alter their coagulation status. So for an injection, it's never a problem.

DR. BRESSLER: Dr. Brown, before we get to follow-up of this patient, do you care about the patient's pressure, does that influence injecting this .05 cc of medication, do you check it before, do you check it after, do you change your regimen if the person has damage to the optic nerve from glaucoma?

DR. BROWN: That's an excellent question. One of the main things a retinal surgeon needs to make sure of before starting therapy is the status of the optic nerve. Often with multiple injections we see increases in

pressure each time. If a patient has glaucomatous damage or even a scary optic nerve, I'll often do an AC tap before I do the injection. Typically that's not the first injection; that's somebody who we know gets amaurosis after the injection or gets a pressure spike afterwards that doesn't come immediately down.

DR. BRESSLER: Now I'd like to take our patient who has been started on an anti-VEGF agent. Dr. Regillo, I want to talk about follow-up. Let me start with one of two common scenarios, and that is, you start injecting the left eye, which we told you was about 20/80. It starts to improve and when you inject again a month later it's still improving, and again a month later, it's still improving. Now the patient comes back, and the eye is 20/25. You see no evidence of VEGF activity on your clinical examination, you can't see any fluid, and all the hemorrhage has resolved. You get an OCT that's completely flat. Do you still inject the eye at that point and do you get a fluorescein angiogram at that point?

DR. REGILLO: The second part of the question's easy: I don't get a fluorescein angiogram because I favor a more continuous style of therapy and what you're describing is now the maintenance phase. Starting off, that's the easy part. We do frequent and regular injections, regardless of the medicine, until the macula, as you describe it, is probably at its best. Vision is perhaps as good as it's going to get. So thereafter I'll inject because I typically use a treat-and-extend approach, which is a treatment at every encounter, but I'm going to start to spread the encounters out by a week or two — typically two — as long as the patient's macula and vision status is as good as it has been or as good as I can get it. And then I'll usually extend out to 12 weeks, if that's possible, but most patients can't be extended that far.

DR. BRESSLER: What stops them from being extended that far?

DR. BROWN: They'll get a recurrence in the signs of exudation, and we certainly want to minimize the number and degrees of recurrences to get the best long-term outcomes. The goal is to keep the macula dry and use the least amount of therapy to accomplish that. So you try to find that sweet spot of an interval that seems to work best for the patient.

DR. BRESSLER: Dr. Brown, how about you? You have a patient whose VEGF activity seems to have resolved

and you can't identify any. How do you manage that person at that visit?

DR. BROWN: Here I have a conversation with the patient and tell them that there's probably a 20 percent chance that with three injections the eye is quiet for now. They have a choice of either having an injection and extending out further than the four weeks, something like six or seven, or they can come to me closely. In other words, if they want to come back in two or three weeks, four weeks, and ensure that the drug is still actively working in the eye. Most patients refer treat and extend, because it's fewer visits to my office and less burden to their family, although some patients say, No problem, I love your waiting room.

DR. BRESSLER: And I think we heard at the Retina Society Meeting that numerous case series suggest that those approaches may work, and we just don't have any definitive information yet to know if there's a true benefit or a slight harm from them. Clearly I think a large harm from such an approach has been ruled out and I look forward to having more information in the future to help guide us in this.

There's another situation — and Dave, I'll start with you — where you inject and the eye gets better from 20/80 to let's say 20/50, and you inject again, but it doesn't change. And you inject a third and fourth time and it still doesn't change. You see thickening on the OCT, you see persistent fluid in the macula, and the vision, as I said, is still decreased to 20/50. What do you do with the patient who, despite three, four, or five injections, initially improved and now has reached a point of stability but is still abnormal and shows evidence of VEGF activity a month after that injection.

DR. BROWN: In those patients, the first thing I want to do is make sure I didn't miss a masquerade syndrome. If they have a thick choroid and predominantly subretinal fluid — even old patients can have chronic central serous retinopathy, polyps, polypoidal — you want to rule out, then you add PDT if they have polypoidal. Otherwise your options are to change anti-VEGF agents. If the patient is on ranibizumab, I'd switch to aflibercept; if on aflibercept I will consider tightening the interval to even more than four weeks. I think fluid in the retina is bad and I do everything I can to get rid of it.

DR. BRESSLER: Dr. Regillo, how about you. What do you do for the patient who had some improvement, so you know they responded, and then they hit a plateau where there's still VEGF activity yet it's not changing to any obvious degree when you see the patient monthly.

DR. REGILLO: I echo Dave's comments. I'll attempt to intensify the treatment regimen. As you said, sometimes patients need treatments even more frequently than every four weeks. I'll consider switching because plenty of anecdotal studies, small series, have reported that suggest switching sometimes does get better control of exudation. And it could be switching among any of these agents, so I attempt all that. Low-fluence photodynamic therapy, as Dave mentioned, is an option, particularly for the polypoidal-like variant of wet AMD. But otherwise right now we're hoping the future will have another type of agent we can add to the mix.

DR. BRESSLER: And again, in Philadelphia we see several phase I studies that have suggested other treatments that might be added to our anti-VEGF regimens and may indeed lead to drugs that will have additive outcomes. So we'll see; time will tell. I'd like to end, Dave, with a couple of safety questions about these anti-VEGF agents. Certainly when they're given systemically, intravenously — for example, bevacizumab for metastatic colon cancer — there is a slight increased risk systemically that that injection will increase the chance of stroke. That's not necessarily true injecting it into the eye, but what do you do with the patient who has had a stroke a year ago and now presents to you for the first time with choroidal neovascularization and you want to start an anti-VEGF agent?

DR. BROWN: The data that systemic effects of our agents is not strong, but you also know that it takes a large population-based study to prove that and we don't have anything like that. In these situations I definitely try to steer away from bevacizumab, which has a very long systemic half-life. I'd prefer ranibizumab in these situations. A stroke a year ago doesn't bother me so much. A more difficult thing is a patient who has a stroke the day after an injection: is it related or is it bad luck? That's what takes a lot more discussion with a patient. I tell patients though I think the risk is low that it's hurting you and you have to make the decision, is maintaining your vision important to you? Certainly most monocular patients

will take any amount of risk to maintain their vision and independence.

DR. BRESSLER: Carl, how about you. Same situation, but as Dave said the person had a stroke a week after the injection and comes in a month later, would you consider giving it if they are comfortable with these yet unknown risks?

DR. REGILLO: I am concerned about a patient with a stroke history. There is the potential that the intravitreal injection could put them at increased risk. Signals in some studies suggest that might be the case. There are many ways to minimize the exposure. As Dave pointed out, this is where there may be some differences in the drugs. Theoretically, ranibizumab would be the safest in this setting with the least systemic exposure, so ranibizumab and maybe aflibercept would be preferable over bevacizumab. Sometimes I'll switch to a PRN style to minimize exposure. I'll give the patient the option of holding and watching on the treatment, or even lowering the dose might be an option. We know that 0.3 milligrams of ranibizumab is probably more or less equivalent to 0.5, and so I might cut the dose back a little. So these are different ways we can minimize the exposure and potentially decrease the risk.

DR. BRESSLER: Certainly these are all theoretical concerns. We don't have any definitive evidence that injecting in the eye increases the risk, but we haven't ruled out a small risk in these patients. So these discussions seem very worthwhile, and I appreciate your sharing them with us.

BOB BUSKER: We'll return with Dr. Bressler and his guests in just a moment.

I'm Bob Busker, managing editor of eOphthalmology Review. If you found this program on iTunes or on the web, please be sure to subscribe. This podcast is part of the Johns Hopkins eOphthalmology Review, an educational program providing case-based discussions with leading retina specialists. Presented as both podcasts and downloadable transcripts, eOphthalmology Review activities are certified for CME credit by the Johns Hopkins School of Medicine and are presented without charge. For more information or to subscribe to receive our podcasts directly to your email, please visit www.eophthalmologyreview.org.

DR. NEIL BRESSLER: Welcome back to this eOphthalmology Review Podcast. I'm Dr. Neil Bressler from the Johns Hopkins University School of Medicine. My guests today are Dr. David Brown, a clinical professor of ophthalmology at the Baylor College of Medicine in Houston, Texas, and Dr. Carl Regillo from the Wills Eye Institute in Philadelphia, Pennsylvania.

In the first part of today's program we talked about age-related macular degeneration. Now I'd like to turn the discussion to retinal vein occlusion.

I'd like to switch now to a patient who has a retinal vein occlusion. Dr. Regillo, let's start with you. You have a patient in their mid 70s suddenly lost vision in their right eye, and it's about 20/100. You see signs of a central vein occlusion, there are intraretinal hemorrhages in all four quadrants, the veins look dilated and tortuous, and the macula looks very thickened. On OCT indeed central subfield is 550 microns thickened. I know you'll typically start this patient with an anti-VEGF agent and my question is, is there any evidence that we should choose one agent over another? We have three that are commonly used in these situations — aflibercept, bevacizumab, and ranibizumab — would you choose one over the other or is your approach similar to your approach in macular degeneration?

DR. REGILLO: There's really nothing from a comparative standpoint among these drugs. We know they all work well, we know their safety profile in this setting and in other settings like patients with diabetic retinopathy and so forth. So, no, there's no specific preference, I think we're going to get a good result regardless of the drug chosen.

DR. BRESSLER: How about your treatment regimen, Dr. Brown. Do you decide to treat this patient with an anti-VEGF agent — I'll just say aflibercept for whatever reason. Do you give them six monthly injections and then try to decide if they need treatment, or do you decide at each visit starting from the beginning what they should do? We don't have as many trials in retinal vein occlusion as we do in macular degeneration or diabetic macular edema to look at these other regimens.

DR. BROWN: Vein occlusions are incredibly variable. Even though it looks terrible, if you look at the natural history studies by Dr. Sohan Hayreh, a certain

percentage of these are going to do pretty well with no treatment. Almost all my patients get an anti-VEGF regimen. I tell them we're going to start with three, but if they're absolutely dry at one month, I might start treating and extending very early as opposed to mandating a three- or six-shot regimen.

DR. BRESSLER: Carl, let me switch to the patient with a pseudophakic eye: we know that there's no risk of cataract forming and interfering with clearance of the vision; we know they won't need cataract surgery in the presence of edema from that vein occlusion. Do you consider corticosteroids in some way in the patient I just described, or would you still start with an anti-VEGF agent first?

DR. REGILLO: As Dave mentioned, I will almost always still start with an anti-VEGF agent. I'll consider introducing steroids into the mix during the maintenance phase if the patient can't come off treatment, which sometimes they can for vein occlusion after a few months of treatment. Unlike wet AMD where it's almost always a continuous and definite time course for treatment, vein occlusions can sometimes improve naturally and may not need continuing therapy. But for those that do, and there's a lot out there, and often they're needing frequent anti-VEGF injections, I do like the extended durability of effect of a steroid, whether it be off-label triamcinolone or, or Ozurdex, the dexamethasone sustained-release implant.

DR. BRESSLER: And Dave, you have a patient with a pseudophakic eye who is no longer responding, who may have gone from 550 to 400 microns, but now you're seeing the patient monthly, injecting the eye monthly with one of the anti-VEGF agents, and it's no longer improving. Do you switch to a steroid regimen, or would you switch anti-VEGF agents first?

DR. BROWN: It's often the younger patients with vein occlusion for whom all the anti-VEGF in the closet isn't enough. These patients are excellent candidates to switch over to the Ozurdex implant. I prefer the Ozurdex implant over off-label triamcinolone, because it's essentially a high dose pulse therapy. You get about 40 to 60 days of high dose steroid and then it essentially turns off. That gives you a better safety profile on the intraocular pressure rises, although you often see a creep in the pressures with multiple Ozurdex injections.

DR. BRESSLER: Carl, how about the patient who has vein occlusion and open angle glaucoma. We see this not uncommonly. They may have optic nerve damage and then developed the retinal vein occlusion. Do you consider corticosteroids in that person who has not completely resolved the edema with anti-VEGF agents?

DR. REGILLO: I sometimes will. I proceed cautiously, of course, and I'll get some input perhaps from the doctor managing their glaucoma as to its severity and how well it's under control. I might test the waters with a very low-dose intravitreal injection. At least with off-label triamcinolone you have the latitude of decreasing the dose.

Through the years I've gone away from 4 mg and down to 2 mg if I'm going to use it because it does have a lesser degree of IOP rise with lower doses. You could even reduce it to 1 mg potentially, as was used in the SCORE studies. But I do proceed cautiously, though, and if there is a pressure problem, I tend to avoid it going forward.

DR. BRESSLER: Dave, let me end our discussion with sort of a full medical approach, and that is the person who walks in with a retinal vein occlusion. Commonly we hear people say, you need to work them up for diabetes or for high blood pressure or for some sort of systemic coagulopathy. Do you do this in the 65 year old who walks in with a central vein occlusion and otherwise tells you they've been getting their regular physical examinations and they have no substantial medical problems?

DR. BROWN: Typically, I'm going to get a widefield angiogram in all these patients, which will usually tell you if there's some concomitant diabetic retinopathy, especially if you see it in the fellow eye, which should be unaffected.

Hypertension is just incredibly prevalent in these CRVO/BRVO patients. And so in a patient who says they have absolutely no hypertension, I will tell them maybe you should check it sometimes outside your doctor's office to make sure they're not having a BP spike. Typically, I don't do systemic workup for anticoagulants unless they've had multiple thrombotic events.

DR. BRESSLER: Certainly we don't have evidence that such a workup will save somebody at this time,

and I think these vein occlusions, as you have pointed out on numerous presentations here and elsewhere, are really caused by this abnormality or kinking of the artery over the vein, and it's a real local phenomena.

I'd like to thank Dr. Brown and Dr. Regillo for participating in this eOphthalmology Review today. I'd like to quickly summarize our discussion and just return to our learning objectives.

Our first objective was to discuss how we applied new therapies for choroidal neovascularization from age related macular edema. And Dr. Regillo and Dr. Brown clarified for us how they choose anti-VEGF agents initially, and more important, how they decide what follow-up regimen they might use to treat that patient.

We also discussed the safety of these anti-VEGF agents, both safety for injecting to try to avoid endophthalmitis, as well as trying to discuss the risks of having stroke or heart attack in the mix and how you might approach these.

We learned that we should always use topical antiseptic when treating these conditions and that we don't know if there's a small risk of stroke or heart attack from intravitreal injections, and perhaps we should have a discussion with the patient and tell them the small risks that might exist but that we can't be certain.

We also discussed retinal vein occlusions today and what our options are for treating it. We had consensus that these should be treated initially when they have macular edema with an anti-VEGF agent if it's not rapidly just improving and going away on its own and that we might still consider intraocular corticosteroids for pseudophakic eyes that are not responding, but we have the option of switching to multiple different anti-VEGF agents.

We ended with a brief discussion about the systemic workup for patients, and we really don't have evidence that a complete systemic workup may be necessary in these patients. Certainly anyone who's over the age of 65 may have high blood pressure or diabetes, and it's good to have a regular exam for that.

I want to thank Dr. Brown and Dr. Regillo for participating in this eOphthalmology Review Podcast during this busy time at the Retina Society in Philadelphia. Dr. Brown, thank you.

DR. BROWN: Thank you.

DR. BRESSLER: Dr. Regillo, thank you very much.

DR. REGILLO: Thank you.

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