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VOLUME 2 — ISSUE 3: TRANSCRIPT

Featured Cases: Neovascular AMD

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

- Develop an appropriate diagnostic assessment and initial treatment of a patient presenting with symptoms of neovascular macular degeneration;
- Apply the results of the pivotal phase 3 studies of ranibizumab, bevacizumab, and aflibercept to eyes with choroidal neovascular lesions;
- Integrate the safety results of the MARINA, ANCHOR, VIEW 1, VIEW 2, IVAN, and CATT studies into clinical practice.

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to neovascular AMD, as reported from the 2012 annual meeting of the American Academy of Ophthalmology Meeting in Chicago, Illinois. The format for this round-table discussion is case-study scenarios for the clinical practice.

Unlabeled/Unapproved Uses
The authors have indicated that this presentation will include off-label or unapproved use of the drug bevacizumab for treating neovascular macular degeneration.

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Dr. Judy Kim discloses she has received grants and/or research support from Genentech and Regeneron.

Dr. Susan Bressler discloses that she has received grants and/or research support from Allergan, Bausch + Lomb, Genentech, Lumenis, Notal Vision, Novartis, Regeneron, and Thrombogenics. She also is a consultant advisor for GlaxoSmithKline.

Dr. Neil Bressler has disclosed he has received grants and/or research support from Abbott Medical Optics, Inc., Allergan, Bausch & Lomb, Bristol Myers Squibb, Carl Zeiss Meditec, ForSight Labs, LLC, Genentech, Genzyme Corporation, Lumenis, Notal Vision, Novartis Pharma AG, Optovue, Inc., Pfizer, Inc., Quark Biotech, Inc., Regeneron and Thrombogenics.

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⇩ PROGRAM BEGINS BELOW

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- **Susan Bressler, MD** has disclosed that she has served as a consultant for GlaxoSmithKline, and also has received grant/research support form Allergan, Bausch & Lomb, Genentech, Lumenis, Notal Vision, Novartis, Regeneron and Thrombogenics.

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STATEMENT OF NEED
The treatment of retinal diseases is an area of medicine where research and innovation are very strong. Newly presented information-and information due to come out very soon-will very likely change the ways clinicians provide optimal patient care. Many of these new trial results have not yet been published; the initial findings of much of the most important new data were first made public at key ophthalmology and retina specialist meetings in 2011. Trial updates, initial findings from ongoing trials, and guidance translating this critical information into practice protocols are expected to be presented at similar meetings throughout 2012.

Clinicians are either not aware of this new information and/or are not sure how they can best integrate it into their practices. Four key (interrelated) retinal treatment areas where increased clinician awareness will provide the most immediate patient benefit have been identified by the program directors.

- **Retinal Vein Occlusion:** New retinal vein occlusion treatment approaches have created uncertainty about choosing the most appropriate therapeutic option.
- **Macular Degeneration:** Newly released data may herald significant changes in the treatment of AMD that clinicians are unprepared to implement.
- **Diabetic Retinopathy/Diabetic Macular Edema:** Integrating ongoing research likely to change current diabetic retinopathy/diabetic macular edema treatment protocols has led to clinician confusion about best practices.
- **Vitreomacular Adhesion:** Clinician unfamiliarity with therapies currently in development may delay delivery of optimum benefit for patients with vitreomacular adhesion.

BOB BUSKER: Welcome to this Volume 2, Issue 3 *eOphthalmology Review* podcast. *eOphthalmology Review* is presented by the Johns Hopkins University School of Medicine, and is supported by educational grants from Alcon Laboratories, Genentech, Inc., and Regeneron Pharmaceuticals, Inc. This activity has been developed for ophthalmologists and retina specialists, and there are no fees or prerequisites to participate.

I'm Bob Busker, managing editor of eOphthalmology Review. Today's program comes from the 2012 American Academy of Ophthalmology Meeting in Chicago and is hosted by eOphthalmology Review course director Dr. Neil Bressler of the Johns Hopkins University School of Medicine. Dr. Bressler is the James P. Gills Professor of Ophthalmology and chief of the Retina Division at the Wilmer Eye Institute at Johns Hopkins in Baltimore.

Dr. Bressler has disclosed that he has received grants and/or research support from Abbott Medical Optics, Inc., Allergan, Bausch & Lomb, Bristol Myers Squibb, Carl Zeiss Meditec, ForSight Labs, LLC, Genentech, Genzyme Corporation, Lumenis, Notal Vision, Novartis Pharma AG, Optovue, Inc., Pfizer, Inc., Quark Biotech, Inc., and Regeneron.

Today's topic is the *Treatment of Neovascular AMD*. Dr. Bressler's guests are Dr. Judy Kim from the Froedtert & Medical College of Wisconsin in Milwaukee and Dr. Susan Bressler from the Wilmer Eye Institute at the Johns Hopkins University School of Medicine.

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Learning objectives for this audio program are, that after participating in this activity, the participant will demonstrate the ability to:

- Develop an appropriate diagnostic assessment and initial treatment of a patient presenting with symptoms of neovascular macular degeneration;
- Apply the results of the pivotal phase 3 studies of ranibizumab, bevacizumab, and aflibercept to eyes with choroidal neovascular lesions; and,
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And now our host, Dr. Neil Bressler.

DR. NEIL BRESSLER: Thank you, Bob. Let me start out by introducing my colleagues. Joining me today from the 2012 American Academy of Ophthalmology Meeting in Chicago are Dr. Judy Kim. Dr. Kim is a professor of ophthalmology at Froedtert & The Medical College of Wisconsin in Milwaukee. Dr. Kim has disclosed that she has received grants and/or research support from Genentech and Regeneron. Dr. Kim, thank you for joining us today.

DR. JUDY KIM: Thank you, Neil, it's a pleasure to be here.

DR. BRESSLER: Also joining me at this AAO meeting in Chicago is Dr. Susan Bressler. Dr. Bressler, who is also my spouse, is the Julia G. Levy PhD Professor of Ophthalmology at the Wilmer Eye Institute within the Retina Division of The Johns Hopkins University School of Medicine. Dr. Susan Bressler discloses that she has received grants and/or research support from Allergan, Bausch + Lomb, Genentech, Luminous, Notal Vision, Novartis, Regeneron, and Thrombogenics. She also is a consultant advisor for GlaxoSmithKline. Susan, thank you for also being a part of today's program.

DR. SUSAN BRESSLER: Thank you, Neil, for including me, and it's a pleasure to be here with both you and Judy.

DR. BRESSLER: Our discussion today will include the off-label use of bevacizumab, or Avastin, for treating neovascular macular degeneration. We've had a lot of new presentations at the American Academy of Ophthalmology about treating neovascular AMD, and this is a very common problem in our practice, in the country, and around the world. I'd like to start with one of our patients to get feedback on how you might initiate either the management or the treatment of this patient.

This 74-year-old patient is on Medicare and has an additional insurance that covers any copayments that are not paid for by Medicare; I just want you to be aware of that. The patient presents with large drusen in the right eye, and when you look in, the right eye has no visible subretinal fluid, there is no hemorrhage in the macula and you don't see any lipid. You don't see any obvious elevation of the retinal pigment epithelium except for these large drusen.

The patient's vision is 20/20 in the right eye, but she reports being bothered by decreased vision in her left eye for at least the past month, and her best corrected visual acuity in that left eye is 20/80. You see what appears to be some thickening of the retina and hemorrhage, and you think you can even detect some elevation of the retinal pigment epithelium in the center of the macula.

Dr. Kim, I would like to start with you. This patient obviously has macular degeneration; in fact, it seems obvious that she probably has choroidal neovascularization with some hemorrhage. Would you get a fluorescein angiogram, and if so, why, in that left eye?

DR. KIM: In this era of anti-VEGF therapy, the type of CNV and even the size don't seem to matter as much; however, I am still somewhat old fashioned and I do get a baseline fluorescein angiogram. I like to know what I'm starting out with so that in the future if I need to compare, I have something to compare it with. And sometimes we may see some masquerading diseases, and I do find the fluorescein angiogram helpful in explaining what the patient has.

DR. BRESSLER: That's a good point. Probably we could be 95% or 97% correct that there is, indeed, choroidal neovascularization. Maybe there's no masquerade syndrome, but I'm not sure 100%, and maybe if we're going to embark on some treatment, we should be fairly certain and have that additional information.

Susan, would you get an angiogram, as well, or do you have different reasons to consider that for this left eye?

DR. SUSAN BRESSLER: I would also definitely get the fluorescein angiogram. One of the additional reasons I think it's important to consider the angiogram beyond just confirming that we're really dealing with neovascular AMD rather than some other entity is that I would like to know the location of the process. Because depending on the location, I may not consider anti-VEGF therapy for the intervention.

For example, if clearly doesn't involve the fovea, I might consider photocoagulation, though I am more apt to consider photodynamic therapy if it's a reasonable distance away from the foveal center. I think identifying location is more clearly delineated with an angiogram than with an OCT.

DR. BRESSLER: Judy, what's a reasonable distance to you to be far enough away from the fovea if subretinal fluid is causing some distortion in vision and yet the choroidal neovascularization on the angiogram is clearly, clearly not in the center of the macula? Does it have to be 500 microns away, a disc diameter away, or it doesn't matter because you will never laser-photocoagulate the lesion?

DR. KIM: We published that. Just the foveal choroidal neovascular membranes do very well with anti-VEGF. For just the foveal lesions, I would probably still do anti-VEGF therapy. If it were much farther away I could consider it, but in usual cases I would start with anti-VEGF therapy.

DR. SUSAN BRESSLER: Neil, I agree with Judy, and if you were asking for a potential distance, I'd probably say a disc diameter away, and I'm willing to consider some other therapy. I recognize that I'm talking about a pretty rare presentation, but nonetheless, it's such a prevalent disease that even though it's a minority presentation, it does happen.

DR. BRESSLER: Susan, if you did obtain a fluorescein angiogram of the left eye — because as Judy mentioned, the more common reason would be to rule out any masquerade and perhaps to be able to see what you're dealing with, how large it is, what it might change in follow-up — would you instruct the person taking the angiogram to get any images of the right eye? The right eye, I'll remind you, in this patient, had a visual acuity of 20/20, and you saw no abnormalities other than the large drusen.

DR. SUSAN BRESSLER: I would definitely instruct my photographers to take mid and late images of the contralateral eye, both in the macula and in the disc region, as long as the patient had no contraindications to being dilated in the other eye at that particular

visit. Certainly, the person who has neovascular AMD in at least one eye is at higher risk of having neovascular AMD in the second eye, compared to someone who does not have neovascular AMD in either eye.

Sometimes neovascular AMD is completely asymptomatic. In fact, cases that are asymptomatic tend to be smaller and of an occult composition, exactly the kind of lesions that have the best prognosis if we encounter them early and initiate therapy early. I'm screening that contralateral eye for unrecognized neovascular AMD, and if it's not present, having those images available as a baseline reference for an eye that's at high risk of developing advanced disease, be it neovascular or geographic atrophy in the future, becomes helpful for that reason as well.

DR. BRESSLER: Dr. Kim, let's say you get a fluorescein angiogram in the left eye, it confirmed a moderately sized area of choroidal neovascularization accounting for these changes, and you got late-phase frames of the right eye, which showed only staining of the drusen. Do you tell the person who is getting the angiogram to also get any other fundus photographs or red-free photographs or both, and if so, why?

DR. KIM: It's been a routine for our institution to get color fundus photographs as well as red-frees with every fluorescein angiography. We still do. Perhaps it's because color photographs are more like real life and easier to explain to the patients, although I don't find it helpful to the fluorescein angiogram.

DR. BRESSLER: You know, I think sometimes when I see the person at follow-up, I may forget from my drawing what was the extent of that hemorrhage or where all that fluid went. I think sometimes it is helpful, as well, to document what it looked like in comparison.

I also like the red-free photographs in addition. Sometimes that contrast of looking for subtle areas of fluid or areas where there might be blood against the red background of the fundus on the color fundus photographs is a little easier to see on the red-free, especially in this age of digital images, where sometimes that red just seems to saturate out in the picture.

DR. SUSAN BRESSLER: And honestly, the more the merrier. Even when we ask our photographers to do their best job and to give us their best quality, they don't always succeed. Our patients are older, they don't necessarily dilate as well as we would like, or they may have other media opacity, so the more images you have, the more likely you're going to have a quality pair, whether from the angiogram, the color photographs, or the red-free, that will give you the information you want.

DR. BRESSLER: I think that's true, and you never know which image won't be good until you're done and the patient comes back to the room, and that's not the time to obtain them again. So as long as they're sitting there, it takes only a few more seconds of work, and the result may be helpful.

Dr. Bressler, this patient has 20/80 vision and you've confirmed choroidal neovascularization on the angiogram. Do you then obtain an OCT of the left eye, and, if so, why? And if you get an OCT, if you had the luxury of getting either a spectral-domain or a time-domain OCT, would you choose one over the other? Would you get an OCT, first of all, and if so, why, and would it be time domain or spectral domain?

DR. SUSAN BRESSLER: I'll get the OCT on this eye with neovascular AMD. I didn't need it to make the diagnosis; that was made on the fluorescein angiogram that I had just obtained. The reason for getting the OCT is to have the baseline reference of the severity of the activity of the process before treatment is begun. Where is the fluid? Is it intraretinal or subretinal? Is of the pigment epithelium elevated? These are the markers of disease activity I'll be following on the OCT to determine how the person is responding to the therapy I initiate.

DR. BRESSLER: Dr. Kim, we got this OCT, you had ordered an angiogram so you'll be able to tell if there is any choroidal neovascularization in the right eye. You looked in that right eye before you sent the patient for images and all you saw were large drusen. Do you tell the person obtaining the OCT in the left eye to take it in the 20/20 right eye, which has large drusen but the patient has no complaints with the right eye?

DR. KIM: At baseline I get the other eye, as well. Sometimes we see some eyes with fluid that was not detected. I want to add to Susan's comment that pretty much all our OCTs are with spectral-domain.

I don't even know when was the last time we did the time-domain OCT.

With spectral domain OCT, I do see more intraretinal fluid and subretinal fluid, as well as some cases of pigment epithelial detachment (PED) are much better seen with spectral domain OCT.

DR. BRESSLER: I think we have good data now to show that you do detect more abnormalities and you have greater confidence in detecting those abnormalities if you have the luxury of having a spectral-domain OCT. Not that you can't take care of it with a time-domain OCT, and I would agree having that right eye information may add something that wasn't so obvious on the angiogram if the angiogram quality wasn't good enough to see.

Susan, here's an important question, you saw choroidal neovascularization; the patient is losing vision, is 20/80, and wants to manage it however you see best fit. You decide you will start treating it with an intravitreal anti-VEGF drug. Three anti-VEGF drugs have been shown to be beneficial in a variety of studies. In this patient, whose finances fortunately allow her to have coverage by Medicare and a copay of either of the three medications, so that the cost to the patient in this case — not necessarily to society or the insurance company —is the same no matter which you choose, which would you prefer to start with? Would you start with bevacizumab, Avastin, or would you prefer to start with either aflibercept or ranibizumab? I don't want to differentiate between those two, I want to ask Avastin versus Eylea or Lucentis, which of those two choices would you go with?

DR. BRESSLER: I think what you are really asking is what is my discussion with the patient. Because whatever I want may be an isolation of what the patient wants. I need to fully inform the person that, number one, although she has neovascular AMD, it is not the death sentence that disease carried a decade ago. We have several drug options to treat this disease, and all three are reasonable alternatives that carry a much greater prognosis for preservation of functional vision than we formerly associated with getting to this point of having neovascular AMD.

Number two, I would explain that there are three drugs, and the first thing that differentiates bevacizumab from the other two choices of aflibercept and ranibizumab is that bevacizumab is not FDA-approved for neovascular AMD because it was never subjected to the development and the clinical trial testing needed to seek FDA approval. In addition, bevacizumab isn't necessarily manufactured to the standards for drugs developed to be placed in the intravitreal space, so there is concern in clinical trial data about the systemic safety and maybe even the potential ocular safety. It would have to be produced by a compounding pharmacy, and their results are not as great overall as the systemic safety database that we associate with aflibercept and ranibizumab.

So because of my concerns about safety and some clinical trial evidence that the efficacy of bevacizumab, particularly in an as-needed regimen, may not be the same as these other two drugs, I would hope the patient would accept my recommendation to choose aflibercept or ranibizumab over bevacizumab, particularly since she, as a well-insured person, shouldn't have any financial barrier to following that recommendation.

DR. BRESSLER: Judy, Susan just recommended considering either aflibercept or ranibizumab because there were some safety concerns and she thought that there might be some stronger evidence for that. I thought we were told they were equivalent by the CATT trial; is that the headline but not necessarily the whole story? Or are the three drugs indeed equivalent?

DR. KIM: With equivalent dosing, ranibizumab and bevacizumab were similar in terms of visual acuity outcomes at one and two years. But PRN dosing wasn't as good as monthly dosing. I think that's important to note that as well, in addition to which drug she would be using.

At our institution we haven't had to worry too much about using a compounding pharmacy because our pharmacy draws it up. However, with the recent incidents in the nation, the wrong drug can be drawn up. So I do worry about that, human safety issue, not the drug safety issue.

I used to use Avastin and ranibizumab equally, but lately I'm switching most of my naïve patients to start with aflibercept, mostly because of the reduced burden of treatment that might be possible with aflibercept.

DR. BRESSLER: Susan, turning to you, Dr. Kim prefers, all else being equal, to consider using aflibercept because of the less frequent dosing in the

first year. If you were going to choose between aflibercept or ranibizumab, which one would you choose and why?

DR. SUSAN BRESSLER: Are we discussing a treatment-naïve person?

DR. BRESSLER: We are.

DR. SUSAN BRESSLER: Such as the patient you've presented to us?

DR. BRESSLER: We're saying for this patient who walks in at 20/80 and would like to be managed right now, we've heard some evidence to suggest some safety concerns about bevacizumab. With all else being equal, if costs are being covered, we're talking about only the monthly regimen with bevacizumab was shown to be equivalent to monthly ranibizumab in terms of visual acuity, but not necessarily PRN bevacizumab if we lean toward aflibercept or ranibizumab, Dr. Kim wanted to use aflibercept because of less frequent dosing. so I'm turning to you and asking whether you would start with aflibercept or ranibizumab and why?

DR. SUSAN BRESSLER: I wish it were a simple, quick answer. None of the questions you're posing truly are. As Judy noted, once we start talking about the drugs, we are also engaging in a conversation about dosing frequency, and so are we proposing to the patient ranibizumab on a monthly dosing schedule through at least one year? We might argue that's really through 24 months, but consistent dosing to provide the patient the greatest opportunity for vision preservation and improvement, referencing the CATT study? Or are we talking about using aflibercept only as the on-label dosing of three consecutive monthly exposures followed by q8 dosing through the first year, which amounts to eight rather than 13 injections if we were using ranibizumab monthly? Or are we really proposing that we're going to deviate from either of those dosing regimens and be completely PRN? And if we were going to consider being completely PRN, then at the end of the 12 months, no matter which drug we were using, it may boil down to exactly the same number of intravitreal injections.

I explaining all of this to the patient: do you want mandatory monthly, which I think yields the best results, with a similar drug or one that met noninferiority with aflibercept for eight doses, or do you really want to consider as needed? In the real world, if a patient says to me do everything humanly possible to preserve the greatest level of vision function, then it really does boil down to aflibercept on-label at eight injections over the year or the ranibizumab monthly, 13 injections over the year. I leave that to the patient to decide.

The patient frequently asks, one of these drugs has been around longer than the other and you have much more experience with that particular drug, perhaps five or six years. The other one is new, and you have maybe a year's experience at best. Sometimes that extra piece of knowledge makes patients choose one drug over another. But personally, I'm comfortable offering either.

DR. BRESSLER: Okay, so I like deciding that we know these will work and we can consider the patient's values regarding the safety and the frequency of dosing. Let me ask one other set of questions before we go to our break. Dr. Kim, you've decided you're going to treat this person and you're going to use aflibercept as you indicated. How do you choose what anesthesia you're going to use, how do you numb the area where the injection is going to go?

DR. KIM: We give a drop of topical anesthetic and we prep the eye with Betadine and so forth, but we also put cotton swab that is soaked with anesthetic and push on top of the area that I'm going to go inject as well. And I find that both the pressure and the cotton tip soaked with anesthetic provides extra anesthesia for these patients.

I have used subconjunctival anesthetic and some people swear by it and they still love it, but in the majority of cases I can get by with the way I described.

DR. BRESSLER: Susan, do you put povidone iodine, or Betadine, directly over the site where you are going to inject or do you just pour some on the eye, nonspecifically? And if you do put povidone iodine on the eye, how long do you wait at a minimum for it to dry before you inject?

DR. SUSAN BRESSLER: I do all of the above. I basically drown the eye in povidone iodine because I would like to make sure that there isn't a single organism still living on that ocular surface. There are times during my prep that I am copiously putting the Betadine in the quadrant that I am planning to inject, and then toward the end of the prep, I'll put a very

deliberate swab of povidone iodine directly at the site that I will be using.

DR. KIM: I agree with you, Susan, povidone iodine is the last thing that goes on the eye before that needle goes into the eye. I usually wait, as I'm preparing the medication, and some people say 20 seconds is necessary and so forth, but by the time I'm done preparing my injection it's ready to go.

DR. BRESSLER: It ends up being at least that 20 seconds. Judy, when you or someone you assign to draw up the medication from the aflibercept or ranibizumab vial, it comes with a cap. When that cap pops off there is a little rubber stopper, do you wipe that with alcohol before you insert your filter needle to draw up the drug or are you comfortable that it's sterile coming out of the factory when you pop that cap off?

DR. KIM: First, I always draw up the medicine myself, rather than have my technicians or nurses do it. Second, I also make sure that I flip the cap off without touching the seal; I do not use an alcohol wipe.

DR. BRESSLER: I think we don't have evidence that as long as you're meticulous about popping that cap off and not touching the rubber stopper, and the only way to know is if you do it, then we don't have evidence that you have to wipe that with alcohol. So I think that is worth mentioning.

Susan, how do you feel about drawing up the medication yourself or assigning someone to do that?

DR. SUSAN BRESSLER: I completely agree with Judy that I'm taking responsibility for this procedure and protecting this eye from endophthalmitis. I am not comfortable delegating somebody else to prepare my syringe and make sure that everything has remained sterile.

As careful as I believe I am in popping the cap from the bottle, I am not certain that I haven't contaminated something in the process. I am of the camp that does use an alcohol wipe on the rubber stopper. Interestingly, I just reviewed the labeling for ocriplasmin, where the label instructs you to wipe that bottle with an alcohol wipe. I was intending to pull the label for ranibizumab and see whether it's part of the label for that as well.

DR. BRESSLER: Often it's the standard practice by many pharmacies to indicate that if there is a cap and a rubber stopper, they recommend wiping it, letting it dry, but again, theoretically it's supposed to come out of the factory sterile. And we just don't have evidence that people who wipe it or don't wipe it have changed the incidence of endophthalmitis. Fortunately, the incidence is low, but you're right, it's not zero, and that may be something we have to look into in the future.

Judy, do you use any pre-op or post-op antibiotics or both when you have treated these patients?

DR. KIM: When we began doing injections, we did use both pre-op and post-op antibiotics, but when the Diabetic Retinopathy Clinical Research Network data showed that it was not necessary, we went cold turkey with no antibiotics pre or post and it has not changed our incidence of endophthalmitis.

DR. BRESSLER: I think with several case series, not only from the network but some other retrospective series, we can probably say we don't have any evidence that giving antibiotics topically after the injection decreases your risk of endophthalmitis. So more and more people are having comfort with this.

DR. KIM: I think people also have to realize that long-term use of antibiotics can overgrow some resistant bacteria. These injections are going to be continuous and chronic, so we need to be mindful of that. Also, the cost of these antibiotics should play a role for the patients.

DR. BRESSLER: Susan, do you check the pressure after the injection, and if so, why and when would you check it?

DR. SUSAN BRESSLER: I don't formally check the pressure in terms of applanation or tonopen, because I believe the less the eye is touched right after an injection, the more it decreases the opportunity for an infection. I do want to make sure that the eye is perfused, so I do look for a second with an indirect ophthalmoscope to see perfusion of the optic nerve.

I know alternatively I'm probably just as secure if all I do is check that hand motion acuity is there, and I may be changing to that in the near future. But there is just something that makes me more comfortable by looking in that eye for a second to

see that the nerve looks healthy. That makes me more comfortable to have that patient leave.

DR. KIM: We published in 2008 that these patients pretty much all come down to a normal pressure definitely by 30 minutes, but many of them after 10 minutes. So we no longer have patients stay to get their pressures checked. I usually just check with counting fingers or hand motion. I have not used an indirect ophthalmoscope for these patients lately.

DR. BRESSLER: Susan, do you do anything differently with the injection, if the person is on aspirin or may be taking Coumadin for chronic atrial fibrillation?

DR. SUSAN BRESSLER: Not really. In every patient I generally try to avoid doing the injection exactly where I have a visible conjunctival blood vessel. In patients who are on aspirin or Coumadin I might really focus on that for a split second before I do the injection. But other than that, not at all.

DR. BRESSLER: We're going to break for a few minutes, and then talk about our retreatment regimen after we've initiated our therapy.

BOB BUSKER: And we'll return to Dr. Bressler and his guests in just a moment.

Hello, I'm Bob Busker, managing editor of eOphthalmology Review.

eOphthalmology Review is a CME-certified program presented by the Johns Hopkins University School of Medicine. Volume 2 of the program features Dr. Neil Bressler in case-based discussions with leading retina specialists, presented as both podcasts and downloadable transcripts.

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Thank you.

BOB BUSKER: And we return to Dr. Neil Bressler.

DR. NEIL BRESSLER: Thank you, Bob. We're going to come back to our case now, I'm here with Dr. Judy Kim from the Medical College of Wisconsin and Dr. Susan Bressler from the Johns Hopkins University School of Medicine.

We've been talking about a patient in whom we've initiated aflibercept or ranibizumab treatment for choroidal neovascularization. This patient had 20/80 vision in her left eye, subretinal hemorrhage, and thickening of the retina.

Now the patient comes back to you. Susan, I'm going to ask you first, the vision has improved to 20/50 in just a month. Do you get a follow-up OCT, a follow-up fundus photograph, or a follow-up fluorescein angiogram, or do you get all three? Or do you get no imaging at all?

DR. SUSAN BRESSLER: I get the full battery of imaging. Is it solely for academic interest that I've obtained these, or will it really affect my management of the patient?

What is affecting patient management is my determining whether there is still disease activity. Of course, none of this is relevant if the patient and I have already decided to do mandatory dosing, either monthly with ranibizumab or three consecutive monthly doses with aflibercept, and then a q8 regimen. If we had already made that decision, I might forgo any of these images and only do the images on, say, a quarterly or an every-four-month basis through the first year to give me a better handle on how the eye might be responding anatomically. But it wouldn't necessarily affect my management if we had made the commitment to mandatory dosing.

But let's say the patient and I have decided to do an as-needed dosing regimen. Then I'll certainly get these images to guide my decisions. Usually a month after treatment, most patients still show disease activity, in which case probably the noninvasive OCT would have been sufficient to confirm that, yet I'll still get an angiogram, because it's satisfying to me to see how that lesion complex started to respond on the angiogram.

DR. BRESSLER: Dr. Kim, do these images affect your management in the patient a month later, when she had improved to 20/50?

DR. KIM: I do not get a fluorescein angiogram or color photographs or red-free at the one-month visit. If I have decided to do three consecutive monthly injections, I may not even get OCT. However, I do get OCT, first, to see how the patient is doing and also to show the patient she is improving. I see OCT as an educational process as well as a motivational process, because I know this is going to be a long-term disease treatment, and any encouragement we can give to patients will help them come up better.

DR. BRESSLER: Dr. Kim, let's say you did indeed get this OCT a month later when the patient improved to 20/50, and it looked better but wasn't normal. There is still thickening of the retina, and maybe there is even a little subretinal fluid. So you inject again and she comes back a month later, still at 20/50. The OCT looks exactly the same, so you inject again.

You got improvement after the first visit to 20/50 and the OCT improved. Then you gave two additional injections. It stayed at 20/50 and there is no further improvement. What are you going to do at that fourth month? Are you going to inject again or are you going to say, it's stabilized, so I'm going to stop?

DR. KIM: I will inject again until I see that there is no way this is going to dry up any further. But until I am convinced after a number of injections that there is no way, I will continue to inject, as long as I see intraretinal fluid or subretinal fluid. For many people three is not enough and you may need many more until you are convinced that it is not improving.

Susan, let's take a different scenario. You gave this patient two additional monthly injections. Now she comes back and for two months in a row has had no fluid in the retina that you can detect by OCT. There is no leakage on fluorescein angiogram, and she's 20/25. You've treated her three times, with improvement at the second month to 20/25 and then no further improvement after that additional injection. Now you are approaching the fourth month. You've seen no improvement from the previous month but no fluid, no leakage. Are you going to inject again? She's 20/25, so what's your decision about withholding treatment or continuing treatment?

DR. SUSAN BRESSLER: You're describing a patient who is having an ideal response, whose vision has improved substantially to a level that most of us would consider very excellent vision in the setting of neovascular AMD, and in every aspect of retinal imaging has no sign of disease activity, whether the color, the angiogram, and the OCT. A complete winner.

I will continue the monthly treatment on the patient until I am convinced that she has stabilized in each one of these aspects. If I've had enough visits to confirm the acuity has clearly plateaued, that it's been the same over, say, two to three consecutive visits, I think it's reasonable to re-explore with the patient the merits of PRN dosing over mandatory monthly dosing. So that she is involved in deciding where we may depart, we may decide together to depart from monthly dosing, and continue to monitor her monthly, so that if there is any evidence of an early recurrence in any one of these parameters — vision, angiography, or OCT — or clinical exam, we promptly resume the treatment.

DR. BRESSLER: Dr. Kim, let's say this patient has done very well, I'm going to suppose she has stabilized to 20/25 through a year. She was followed very carefully, say every eight weeks, and was treated with aflibercept in a fixed-dosing regimen. But now we're up to the second year, and I want to know how you might approach management in the second year. This person has been stable for three or four months, you're up to the second year, and you are not treating her for let's say at least the last eight weeks, but you've seen her every month and there is no worsening at all.

Do you ever extend follow-up beyond a month? Would you see her at six weeks or eight weeks or even longer? How would you approach that second year of treatment?

DR. KIM: Actually, in a patient who is totally dry and has vision as good as this patient's has become, I do treat and extend. Granted, there is no good prospective randomized clinical trial data, although the LUCAS trial might help us explain the efficacy in the future.

To me it seems like a nice balance between monthly visits but still PRN dosing, and monthly mandatory treatments where I can watch the patient and be able to inject as soon as there is a recurrence, but with treat-and-extend I can extend out as far as she tolerates and keep the eye dry. I do not think I am doing any disservice to patients by using the treat-and-extend modality.

DR. BRESSLER: We'll come back to that. Susan, I'd like to ask you, in the CATT trial in the second year, the people getting ranibizumab on a PRN regimen were still seen every four weeks. In the VIEW-1 and VIEW-2 trials, the people getting ranibizumab or aflibercept were still seen every four weeks. Do you follow all these patients who are being managed every four weeks in the second year?

DR. SUSAN BRESSLER: I do. Sometimes the patient may push back because they're elderly; somebody else is bringing them; they are imposing on neighbors, children, other relatives; and they start to feel guilty about all of these trips and people having to take off from work to bring them. So sometimes patients may feel that they are not interested in continuing to come monthly. When that surfaces I again reemphasize that in all of the studies that you just named, patients were monitored monthly. And that it's only with that level of surveillance that we can feel we are doing everything possible to maintain their improved vision function. If we start to stretch the intervals between those visits, they are putting themselves at some risk. That's something we'll reactivate in the interim that vision could be lost as a result of that reactivation, and I might not necessarily recover that lost vision.

It's easy sometimes for patients who are doing well to become more relaxed about having their visits. I think reminding them of those issues is key, but you know, real life does get in the way of the best medical care and sometimes we just have to relax what we're doing if that's the only way the patient can comply to a reasonable degree with our recommendations.

DR. BRESSLER: Judy, you like to consider sometimes extending the either treatment interval or the follow-up interval or both. Could you describe how you do that? Let's say in the second year of someone who's been treated, how you might either extend the time between treatments or just the time between visits or both?

DR. KIM: With treat and extend, if the patient is totally dry on OCT, then the next visit will be two weeks later than their previous interval, and each time they come, as long as they're dry, they still get the injection, however, the next visit becomes two weeks later than the current one.

The first year it's every four to six week follow-up and injection, but the second year, once they've been dry, I would give the patient an injection, and the next visit would be six to eight weeks. I do OCT at their next visit, and if it's still dry they still get an injection, but the next visit will be eight to 10 weeks. And I may extend up to 12 weeks, but it's rare that I would go any further than that.

DR. BRESSLER: So every 12 months you might inject if it is dry and then see them maybe 12 weeks after that?

DR. KIM: Correct, and it is amazing how some patients in some eyes can do very well with that. I do believe in customized, personalized treatment, because I know that some eyes need injection every month, but then I'm saving other eyes that could do well with injection just every three months. If they do have any recurrence as I'm extending out, they get an injection. The follow-up visit will be once again two weeks shorter, and this way I could sort of titrate their best interval.

DR. BRESSLER: And when it recurs, do they ever lose vision? Let's say you were spreading this out to 12 weeks and they call you urgently with a loss of vision just eight weeks later and you see that it has recurred and the vision dropped a couple of lines. If you inject then, do they always get the vision back or not necessarily, or maybe it hasn't happened?

DR. KIM: It's surprising to me that OCT seems to change before the patients say their vision has declined. As long as I'm managing them with OCT guidance, I do not feel that I'm getting irreversible vision loss. Some patients come in at eight- week intervals and say their vision seemed to start changing perhaps a week ago. In those patients I may reduce the interval.

DR. BRESSLER: Susan, would you inject patients and then extend out to six weeks and they're dry, inject them, and extend out to eight weeks, and they're dry, inject them and extend out to 12 weeks, let's say as long as 12 weeks?

DR. SUSAN BRESSLER: I'm definitely not in the treat-and-extend camp. As I was listening to Judy's discussion, I was thinking, okay, her patients have fewer visits but potentially more injections than the way I'm managing patients. My patients are definitely coming in monthly or striving to come in monthly, but they're really being treated only in the setting of disease activity.

That is just a difference in how we are all taking care of these patients, and I look forward to a study that really rigorously compares the treat-and-extend regimen as Judy described to a monthly visit and a treat on an as-needed regimen so we can fully learn what the risks may or may not be to the patient's final vision outcome when practicing one regimen versus another.

DR. BRESSLER: I'd like to end with two quick questions for you that may come up in these patients, although they don't always. The first is, Dr. Kim, we sometimes hear about a polypoidal choroidal vasculopathy pattern, or PCV. If you suspect such a pattern from perhaps the angiogram alone or maybe an ICG, do you treat the patient any differently from what we've discussed today?

DR. KIM: Actually, I just had a patient who had 14 injections with bevacizumab by an outside doctor but was not responding and was sent to me. We did an ICG and it was polypoidal. We did one treatment with photodynamic therapy. The lesion flattened out, the blood eventually dried up, and there was a significant improvement in vision. So with these patients I do photodynamic therapy rather than anti-VEGF therapy.

DR. BRESSLER: Susan, if the patient begins to develop some geographic atrophy of the retinal pigment epithelium, does that change all the management that we've discussed today?

DR. SUSAN BRESSLER: A patient receiving regular anti-VEGF therapy for documented neovascular AMD may develop areas of atrophy over time that I don't label geographic atrophy. If it's in the same location as previously documented neovascular AMD, to me that is atrophic scarring induced by the choroidal neovascularization. And I would expect it.

I think there's a new terminology for how lesions evolve after each form of treatment that we've ever developed, be it photocoagulation initially; submacular surgery, second; photodynamic therapy, third; anti-VEGF therapy, fourth; we learn over time how the anatomy evolves and responds to these treatments. So I am not labeling atrophic scarring geographic atrophy.

Now, can these patients in other locations of the posterior pole develop de novo areas of what I consider native geographic atrophy? Sure they could. And I consider that part of the AMD process rather than a result of my treatment. But the bottom line is, development of atrophy really doesn't factor into my treatment decisions about continuing their anti-VEGF therapy.

DR. BRESSLER: Finally, Dr. Kim, unfortunately this condition can be bilateral; people can develop the neovascular form of macular degeneration in both eyes. If you have someone who has what we described in this patient's left eye in each of their eyes, maybe it did not develop simultaneously, maybe it developed in one eye and then four months later developed in the other eye, and now you are treating both eyes. Do you treat both on the same day, or do you spread that out? How do you manage all of that?

DR. KIM: I have a long discussion with the patient about treating one eye at a time, asking whether they are willing to come back again for their second eye, or whether they want to have both eyes treated at the same time.

Some patients, because they are coming from far away, would rather have both eyes done at the same time, while others say there is no way I'm going to have both eyes poked. So those patients would come again one to two weeks after the first eye to get their second eye injected.

I can do both, and I'm comfortable doing both, but if I do bilateral injections, I use separate vials for each eye. I do separate prep, just as if I'm doing surgery, when I'm redraping the second eye.

DR. BRESSLER: We've had an extensive discussion today on our management of the wet, or neovascular, form of macular degeneration. We've been able to develop the appropriate diagnostic assessment for these patients, including the role of fluorescein angiography, the role of fundus photographs, and red-free photographs, the role of obtaining OCT when patients present with symptoms and signs that suggest the neovascular form of macular degeneration.

We've heard a lot about how we might apply some of the pivotal phase 3 studies that have looked at three different anti-VEGF medications for this, bevacizumab and ranibizumab in the CATT trial, ranibizumab in the MARINA and ANCHOR trials,

and comparing ranibizumab to aflibercept in the VIEW-1 and VIEW-2 trials.

I believe our knowledge is still lacking in this area. We have difficulty knowing how to follow these patients beyond seeing them every four weeks indefinitely. We have difficulty knowing how we might maintain their vision, but we've come a long way in trying to treat this condition, and we've certainly wiped out a lot of the blindness from it.

I want to thank both of you today for joining us and sharing your thoughts on how to evaluate these patients, how to treat them, and how to follow them in follow-up. I think it will help our listening audience who are trying to take care of their patients with macular degeneration.

Dr. Kim, thank you very much.

DR. KIM: Thank you, Neil.

DR. BRESSLER: Dr. Bressler, thank you again for sharing your thoughts with us.

DR. SUSAN BRESSLER: It was a pleasure.

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