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## VOLUME 1 — ISSUE 6: TRANSCRIPT

# Featured Cases: Neovascular Age-Related Macular Degeneration

Our Guest Author is Dr. Susan Bressler, The Julia G. Levy, PhD, Professor of Ophthalmology at the Wilmer Eye Institute at the Johns Hopkins University School of Medicine in Baltimore.

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

- Develop an appropriate diagnostic assessment of a patient presenting with symptoms of neovascular macular degeneration;
- Apply the results of the pivotal phase 3 studies of ranibizumab to eyes with choroidal neovascular lesions that are either predominately classic, minimally classic, or occult with no classic in the lesion composition; and
- Integrate the results of the CATT study into their clinical practice.

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to *Retinal Vein Occlusion* in the format of case-study scenarios for the clinical practice. This program is a follow up to the Volume 1, Issue 5 *eOphthalmology Review* newsletter — [Neovascular Age-Related Macular Degeneration](#).

### PROGRAM DIRECTOR

#### Neil M. Bressler, MD

The James P. Gills Professor of Ophthalmology  
Johns Hopkins University School of Medicine  
Chief, Retina Division Wilmer Eye Institute at Johns Hopkins  
Baltimore, Maryland

### MEET THE AUTHOR



#### Susan B. Bressler, MD

The Julia G. Levy, PhD,  
Professor of Ophthalmology  
The Johns Hopkins University  
School of Medicine  
Wilmer Eye Institute  
Baltimore, Maryland

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The author has indicated that this presentation will include off-label discussions of bevacizumab and ranibizumab.

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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 from Notal Vision, Genentech, Novartis, Bausch & Lomb, and Regeneron.

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Office of Continuing Medical Education  
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**DR. NEIL BRESSLER:** Welcome to this *eOphthalmology Review* podcast. *eOphthalmology Review* is presented by the Johns Hopkins University School of Medicine. This program is supported by an educational grant from Genentech, Incorporated.

Today's program is a companion piece to our Volume 1, Issue 5, the *eOphthalmology Review* Newsletter on neovascular age-related macular degeneration. Our guest is that issue's author, Dr. Susan Bressler from The Johns Hopkins University. This activity has been developed for ophthalmologists and retina specialists. There are no fees or prerequisites for this activity. The accreditation and credit designation statements can be found at the end of this podcast. For additional information about accreditation, Hopkins policies and expiration dates, and to take the posttest to receive credit online, please go to our website newsletter archive, [www.eophthalmologyreview.org](http://www.eophthalmologyreview.org), and click on the issue 6 podcast link.

Learning objectives are, that after completing this activity, participants will demonstrate the ability to:

- Develop an appropriate diagnostic assessment of a patient presenting with symptoms of neovascular macular degeneration,
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- Integrate the results of the CATT study into their clinical practice.

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I'm **DR. NEIL BRESSLER**, the course director of *eOphthalmology Review*. Here in the studio with us is Dr. Susan Bressler, the Julia G. Levy, PhD, Professor of Ophthalmology at the Wilmer Eye Institute at Johns Hopkins in Baltimore, Maryland. Dr. Susan Bressler has disclosed that she has served as a consultant for GlaxoSmithKline and has also received grants or research support from Notel Vision, Genentech, Novartis, Bausch & Lomb, and Regeneron.

Her presentation today will include discussion of the off-label discussion of bevacizumab and ranibizumab. Dr. Bressler, welcome to this *eOphthalmology Review* podcast.

**DR. SUSAN BRESSLER:** Thank you, Neil, for inviting me. I always think it's great fun to sit and talk with a colleague about managing some of our more challenging patients with neovascular macular degeneration.

**DR. NEIL BRESSLER:** And as you said, our topic today is neovascular macular degeneration. In your newsletter issue you reviewed some of the recent studies evaluating different dosing schedules for intravitreal administration of ranibizumab. In today's activity, I'd like us to look at how that information can be directly applied to our patients. So if you would, please, let's look at a patient.

**DR. SUSAN BRESSLER:** I think we can start with a very typical patient who presents to any one of our practices. Let's say we have a 75-year-old woman who we already know has intermediate age-related macular degeneration. In addition, she admits to a very lengthy smoking history and she has a positive family history of neovascular macular degeneration. She presents with a three-week history of both distortion and decreased clarity in her right eye. She noticed this when she developed a corneal abrasion recently in her left eye.

At the time of her examination, her visual acuity is 20/80 in the symptomatic right eye and 20/25 in her left eye, now that it's healed from the corneal abrasion.

**DR. NEIL BRESSLER:** What risk factors might this patient have to suggest that she may be progressing to an advanced phase of macular degeneration, specifically the neovascular form of macular degeneration, and indeed, are there any ways that this risk to progress could be decreased?

**DR. SUSAN BRESSLER:** Off the top of my head, this person has at least four risk factors for progressing to advanced macular degeneration, specifically, the neovascular, or wet, form of the disease. The number-one risk factor is the abnormalities that are present on a dilated fundus examination; namely, the presence of large drusen and pigmentary abnormalities.

If we already know that this woman has intermediate age-related macular degeneration, we're saying she meets these characteristics in some form or another. Let's say, for example, that the way she meets the

definition of intermediate age-related macular degeneration is by having large drusen present in both of her eyes. If that's the case, we know from the AREDS placebo group that her likelihood of developing neovascular AMD is about 26% over five years. In contrast, if only one of her eyes manifests the large drusen, she is still at risk, but the risk is substantially lower, about 6% over five years. But there is nothing we can do to change what's already in her eyes. She already has pigment, which is an additive risk factor to her drusen features. So the presence of pigment and drusen, we can't modify; we cannot lower her risk.

The second risk factor is her age, and although I'd like to believe that 75 is the new 55, age is a clear-cut risk factor, and again, we can't reverse that for her. And it's a very strong risk factor. For each decade over the age of 50, her risk is going up significantly.

Third is her smoking behavior, and smoking is the most consistent and modifiable risk factor for her to progress. I would certainly counsel her to stop smoking as soon as she possibly can.

Her fourth risk factor is her family history. Although we think of macular degeneration as being a multifactorial condition, we suspect that family history does play a role in many people, and unfortunately, we can't modify her genetics at this point.

**DR. NEIL BRESSLER:** So besides trying to stop smoking which, of course, would be great for lots of reasons, are there any other behaviors she could do that might reduce her risk of progressing to the advanced stage of macular degeneration? How do we detect this or what do we do to try and detect whether she is, indeed, progressing at any point in time?

**DR. SUSAN BRESSLER:** We think there is something she can do that will lower her risk, and that is essentially to adopt the recommendations of the Age-Related Eye Disease Study, which tested the use of high-dose antioxidant vitamins and minerals to decrease progression to advanced macular degeneration, specifically to the neovascular form, and simultaneously lower the risk of having moderate vision loss, meaning a loss of at least three lines of acuity on the eye chart.

So, for example, if she uses an AREDS type supplement, she can reduce her risk of anatomic

progression by a factor of about 25% over a five-year period. Simultaneously, she can reduce the risk of vision loss during that same period by a factor of nearly 20%.

In terms of how she monitors herself, we teach patients to monitor their central acuity, emphasizing that they need to do so in a monocular fashion on a regular basis. We tell them what they have to watch carefully for any decrease in clarity, development of a blind spot, or a warping of their image, distortion. And should they become aware of such a symptom, they should notify us as promptly as possible so that we can have them present as soon as possible after symptom realization to look for progression of disease.

In addition, we monitor patients on a regular basis, but unfortunately we really don't know the best frequency to monitor them, other than seeing them very promptly if they notice symptoms.

**DR. NEIL BRESSLER:** So we don't know when this patient really developed loss, because she noticed it when she had some damage or corneal abrasion to her other eye. So now she comes into your office and do you try to evaluate whether neovascular AMD really is the cause of her vision loss right now?

**DR. SUSAN BRESSLER:** Obviously I'm going to dilate the pupils and do a very meticulous examination of the macula. For me that means contact-lens biomicroscopy with the slit lamp, and I'm looking very carefully for fluid in or below the retina, blood in or below the retina or below the retinal pigment epithelium, and lipid in or below the retina. Simultaneously, I'm carefully evaluating the plane of the retinal pigment epithelium, looking for any areas of elevation. Some of this can be challenging, given that it's sitting within the environment of large drusen and pigmentary alterations to begin with.

I would complement this very careful scrutiny of the macula with a peripheral exam looking, of course, for any eccentric areas that suggest choroidal neovascularization, though likely not accounting for her symptoms. For me the diagnostic gold standard would be a fluorescein angiogram, complemented by color fundus photographs, where I am looking at the patterns of hyper- and hypofluorescence, assisted by a stereoscopic viewing system so that I can look for elevation at the level of the RPE and sort out where

I have leakage and what those patterns of leakage represent.

Now in this day and age it's also nice to complement this — and I do want to emphasize it complements the diagnostic maneuvers I have already suggested — I would like to complement this with an optical coherence tomography (OCT), and I would prefer to use a spectral domain instrument so that I can perform dense sampling of the macular region, looking for any evidence of fluid in the retina interstitial fluid or cysts on the retina, fluid below the photoreceptors, irregular elevations of the RPE, or deposits within the retina that might suggest lipid, or deposits below the retina that could be lipid or blood, as well as the less frequently observed findings of an intraretinal lesion of CNV.

**DR. NEIL BRESSLER:** Okay, so let's say this patient then, as I understand it, did get fluorescein angiography, and as I understand it showed that the lesion predominantly was indeed patterns of fluorescence of choroidal neovascularization. And not only that, the pattern was consistent with a lesion that was predominantly classic in nature, where over 50% of all the abnormalities of the lesion were classic neovascularization.

The lesion was about three disc areas in size, so what would you recommend to manage this patient at this point?

**DR. SUSAN BRESSLER:** I definitely recommend intervention. Without treatment, the odds of this lesion progressively enlarging, possibly bleeding, leading to fibrovascular scar and further loss of central acuity are all quite high. We have excellent phase 3 studies showing that administration of an intravitreal anti-VEGF agent, such as ranibizumab (as was employed in the ANCHOR study of predominantly classic lesions), when compared to what had been the standard of care at the time — photodynamic therapy with verteporfin for such lesions — the results for vision outcomes were superior when using this treatment.

We know that monthly mandatory treatment with intravitreal ranibizumab for the next 24 months facilitates the likelihood of her having the best levels of visual acuity. She would have a 30% to 40% chance of three lines or more vision improvement, and approximately a 90% chance of avoiding moderate vision loss over the two-year period.

Now we know from the CATT study that when monthly mandatory bevacizumab was compared to monthly mandatory ranibizumab, the results at 12 months were consistent with the predefined noninferiority limits. So if one would like to consider substitution of bevacizumab administered on a monthly mandatory schedule through the first year, this is a reasonable option, particularly if there are fiscal constraints in delivering ranibizumab, but one might have to have some discussion about differences in how the drug might be prepared and some potential questions that we have regarding systemic safety.

**DR. NEIL BRESSLER:** So this patient then was treated and it turned out she got six monthly injections; and by that sixth month her vision had improved to 20/50; she no longer saw distortion subjectively; your examination showed that there was no longer any fluid or lipid or blood in the retina; you did a fluorescein angiogram that showed just fluorescent staining of the lesion; you did an OCT, which no longer showed any thickening of the retina, any cystoid abnormalities; and there was no subretinal fluid.

I would like to discuss what you do at this point. You're six months into it, you don't see any sign of any activity, let's say. What would you do at this point in terms of ranibizumab? Would you continue it? Also, what would you do if the appearance hadn't changed after six months of bevacizumab — would you continue it?

**DR. SUSAN BRESSLER:** I couldn't fault anyone who said as good as she looks, we are just going to stay the course and continue the monthly ranibizumab at least through the first year. I think there is a slight suggestion that this still is the treatment regimen associated with the greatest benefits, as we look at a variety of studies.

On the other hand, it's also perfectly reasonable to digress now from that original treatment plan. She is doing phenomenally well, she's had vision improvement, and you have described anatomically something that looks completely inactive and we're going to presume that you've been doing serial OCTs, exams, and periodic angiograms, and you can demonstrate that every parameter has improved and has stabilized over consecutive visits. Given those circumstances, it is perfectly reasonable now to go to a PRN administration of the ranibizumab while still

adhering rigidly to monthly assessments. Because the goal is to pick up even subtle evidence of a relapse and then to resume treatment promptly should she relapse as you continue to follow her through a year. You also asked me, would it be reasonable to suggest if what I had been administering from day one was bevacizumab instead of ranibizumab, I would have concerns about going to a PRN regimen. My concerns emanate from the CATT trial, where bevacizumab on a PRN administration, given in the context of monthly assessments, did not meet the prespecified noninferiority criteria. We might sacrifice some vision outcome in the long run, were we to shift gears to a PRN regimen with bevacizumab.

**DR. NEIL BRESSLER:** My last question on this patient is, let's say you did decide that you could withhold treatment and she turns to you and says, you know, coming in every month is quite difficult, it's hard to get a ride here, it's hard to take off all that time, do I have to continue this, how long can I continue it? Is there anything I can do to have less frequent visits, be it ranibizumab or bevacizumab, or is there any other drug to consider?

**DR. SUSAN BRESSLER:** It's a difficult question and it's a real-life question. Certainly, our elderly patients are dependent on their caregivers for their transportation needs, and coming monthly and imposing on their working children is really problematic.

The problem is, these drugs probably do not have an effect that lasts beyond a five-week window. Certainly in the phase 3 studies of ranibizumab, the treatment windows were three- to five-week intervals, so we don't have any suggestion from those studies that the drug in real life works differently than the pharmacokinetics would have suggested it worked in the first place. In fact, there is evidence from a Diabetic Retinopathy Clinical Research Network Study of bevacizumab performed in the context of diabetic macular edema, in which the drug was administered at six-week intervals, but patients were watched with OCT three weeks and six weeks after drug administration. There was very definite evidence that the drug effect was significant at three weeks and almost universally absent at six weeks.

So we really don't have a suggestion that using agents at longer intervals will maintain our anatomic goals. We also know that studies such as PIER and EXCITE

used a fixed-dosing/reduced-visit schedule. These studies, EXCITE in particular, had an adequate control group of ranibizumab administered monthly, showing that these results, in terms of vision outcome, are inferior to monthly treatment.

So while our patient is frustrated, if she really does depart from our recommendation of the monthly visits, then at least with ranibizumab, it may be putting her long-term objectives at risk.

I'm excited about what might be on the horizon. Another drug, VEGF Trap-Eye, we hope will receive FDA approval and we hope will be available to us for use in the near future. It's my understanding that phase 3 studies of VEGF Trap-Eye have met noninferiority with ranibizumab administered monthly, with a reduced fixed-dosing schedule that would amount to eight visits as compared to 13, over a 12-month period.

**DR. NEIL BRESSLER:** That was a fascinating discussion of the challenges that come up every day with this common problem. We'll return in a moment with Dr. Susan Bressler to discuss another case from The Johns Hopkins University.

**DR. NEIL BRESSLER:** Hello, I'm Dr. Neil Bressler, I'm The James P. Gills Professor of Ophthalmology, Chief of the Retina Division at the Wilmer Eye Institute at The Johns Hopkins University and course director for eOphthalmology Review.

eOphthalmology Review is a CME-certified program presented by The Johns Hopkins University School of Medicine. eOphthalmology Review has two parts: a newsletter delivered by email and podcasts like the one you are currently listening to. Each presents current, concise, peer-reviewed literature reviews and commentary in areas of importance to ophthalmologists, retina specialists, and retina fellows.

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Welcome back to this eOphthalmology Review podcast. I'm Neil Bressler, course director of the program. Our topic is neovascular age-related macular degeneration. Our guest is Dr. Susan Bressler, Professor of Ophthalmology at the Wilmer Eye Institute at Johns Hopkins.

We've been looking at how some of the new information Dr. Bressler discussed in the newsletter issue can affect our treatment decisions. If you would, Susan, let's look at another patient case.

**DR. SUSAN BRESSLER:** Let's take the instance of an 80-year-old man who has previously lost central vision in his right eye from neovascular macular degeneration that developed about 10 years ago.

He had been managed with photodynamic therapy. He had received five photodynamic therapy treatments during a two-year course and recently an angiogram showed a staining lesion with 20/400 acuity, so he is solely dependent on his left eye.

His left eye has recently developed a subfoveal occult choroidal neovascular lesion, and he retains acuity of 20/30. This was picked up at the time of a routine office examination. He is not aware of any vision changes in his preferred left eye.

**DR. NEIL BRESSLER:** How would you manage this case then if he didn't notice much of any problem, would you initiate treatment or would you watch him closely?

**DR. SUSAN BRESSLER:** I think you really have those two choices. It is reasonable to observe him, but by observing him, we mean at very close intervals with very definite emphasis to him that he has to monitor his left eye, bringing to his attention that we're concerned that in the months ahead he may start to recognize symptoms, and that he should let us know immediately if he starts to question any discrepancy in his acts of daily living.

Now why is observation reasonable? We'll recall that most studies that explore new treatments for

neovascular AMD, when they enroll individuals with occult subfoveal lesions, they generally require recent disease progression. And recent disease progression often translates to a person having deterioration in level of visual acuity, or progression of CNV as determined by angiographic enlargement of a known CNV lesion, or blood associated with the process. In this we're just picking this up today. He doesn't have blood associated with his lesion, we don't have a history that this is growing, and we don't have a history that in its presence he's losing acuity.

One of three patients with his presentation can stay absolutely still for a couple of years, so it is reasonable to see whether he's in that third, rather than embarking on a course of monthly visits and monthly treatments that do on some occasions have some associated adverse effects. On the other hand, one could argue that intervening now lowers the chance that he'll have vision deterioration in what is the single eye that is allowing him to function as a relatively normal person.

So if you really want to safeguard in the long run, give him the highest probabilities of maintaining his function, then starting treatment right now is reasonable, as well.

**DR. NEIL BRESSLER:** Let's take two scenarios for this patient. Let's say you saw him on nine monthly consecutive visits and you did not treat him for those nine visits. Everything looked the same, the vision is still 20/30, he still has the same amount of fluid. Alternatively, let's say you treated him for nine monthly consecutive visits, and after those nine visits it still looks the same, his vision is still 20/30, he still has this same amount of fluid. In either scenario, what should we be doing at this nine months later time point?

**DR. SUSAN BRESSLER:** For me the situation is really the same as when he presented. If both he and I were comfortable with observation to begin with, then the fact that nothing has changed, he and I should still be comfortable with observation at this point.

Alternatively, if he and I felt that it was in his best interest to proceed with treatment nine months ago, at this point we could be patting ourselves on the back that we have prevented deterioration and he is functioning still at the same level he was nine months ago.

And we could take complete credit for that and presume that if we want to continue affording him the protection, we should continue with our planned treatment, since we still have signs of an active disease process. It may not be progressing, but it appears active, it's leaking on the angiogram, and it has some fluid on the OCT.

**DR. NEIL BRESSLER:** Now let's get to our last two questions on this challenging case. Let's presume he was followed even longer, monthly out through 15 months, and let's presume he was not treated and you were watching him very carefully when suddenly at that 15-month visit or a few days before he develops sudden vision loss, dropping to 20/200, and has a large, nine-disc area of hemorrhage. Or let's say you were treating him monthly, nothing changed for 15 months, and again suddenly at this 15-month visit or a few days before, despite treatment he suddenly develops subretinal hemorrhage, visual acuity dropping to about 20/200. Now how do we handle this lost vision, whether we had followed him carefully or whether we were injecting him monthly — what do we do now?

**DR. SUSAN BRESSLER:** You had multiple questions there. The first one was, had I been watching him for the 15 months and deferring treatment, and all of a sudden he came in with this bleed, well that is really a sad and unfortunate situation, and one that both he and I were trying to avoid. By watching him closely, we were hoping that if this lesion started to progress it would so with a slight enlargement on the angiogram, a little bit more fluid on the OCT, or maybe a couple of letters or a line of acuity decrease, or maybe even something more subjective than that.

It is rare, but it certainly happens that the first sign of progression can be a dramatic bleed. And it's because we all know that can exist, that many would have been in the camp of treating him up front, with the hopes that having adopted that approach, an event like this could have been avoided.

So now let's take the instance where we had been treating him and he still went on to a significant bleed. Well, in either scenario, I'm going to continue my treatment because I have yet to see that there is something better to approach an individual who has a predominantly blood lesion in the macula.

Note in CATT, the enrollment criteria were eventually broadened to include predominantly blood lesions

such as this. It makes up a minority, less than 10% of the participants, but we can extrapolate from CATT that treatment with anti-VEGF is still a reasonable option to decrease significant vision loss, as relatively few patients in CATT had significant vision loss.

In terms of whether we think there is still a possibility that the blood will clear over time and that vision might improve, I've certainly seen it happen. So just because he has this significant bleed does not mean that he is destined to have extremely poor vision.

So because this is his second eye, I'd be very aggressive, treating him monthly until there is no sign of any residual blood, no sign of residual leakage on an angiogram, fluid on clinical exam, or in the retina or below the retina on OCT before I would give up on trying to maximize his vision potential.

**DR. NEIL BRESSLER:** Fortunately, those events are rare, but not zero, so we hope they will be as few as possible.

Dr. Susan Bressler from the Wilmer Eye Institute at Johns Hopkins, thank you again for sharing these cases and your management approach in participating in this eOphthalmology Review podcast.

**DR. SUSAN BRESSLER:** Thank you, Neil, it's been a pleasure, and I think we have discussed two very genuine cases that are common to all of us who are managing these patients.

**DR. BRESSLER:** Thank you again.

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