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VOLUME 2 — ISSUE 2: TRANSCRIPT

Featured Cases: Vitreomacular Adhesion and Macular Edema from Retinal Vein Occlusion

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

- Distinguish between new retinal vein occlusion treatment approaches and choose the most appropriate therapeutic option among observation, laser photocoagulation, intraocular steroids, and intraocular anti-VEGF therapies;
- Appropriately apply new therapies for vitreomacular adhesion abnormalities among observation, ocriplasmin, and vitrectomy;
- Discuss the evidence regarding systemic work-up for patients presenting with a retinal vein occlusion.

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to vitreomacular adhesion and macular edema from retinal vein occlusion, as reported from the 2012 annual meeting of the Retina Society Scientific Meeting in Washington, DC. 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 discussions of Avastin (bevacizumab), aflibercept, dexamethasone intravitreal implant, microplasmin, ranibizumab and triamcinolone for the treatment of macular edema from retinal vein occlusions and vitreomacular adhesion abnormalities.

Faculty Disclosures
Dr. Haller discloses that she is a consultant to Thrombogenics.

Updated: Dr. Sun discloses that she is a consultant to Abbott Laboratories and Novartis. She has received grants/research support from Genentech.

Dr. Neil Bressler has disclosed he has received grants/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, Ora, Inc., QLT, Inc., Regeneron, and Steba Biotech.

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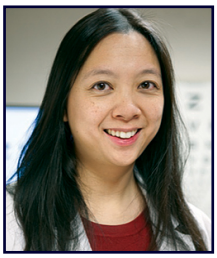

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⇩ PROGRAM BEGINS BELOW

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

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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 2 *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 Retina Society Annual Scientific Meeting in Washington, DC, 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. His spouse has served as a consultant for GlaxoSmithKlien and has received grants and/or research support from Allergan, Bausch & Lomb, Genentech, Lumenis, Notal Vision, Novartis, Regeneron, and Thrombogenics.

Today's topic is Macular Edema from Retinal Vein Occlusions and Vitreomacular Adhesion Abnormalities. Dr. Bressler's guests are Dr. Julia Haller from the Thomas Jefferson University Hospital in Philadelphia, and Dr. Jennifer Sun from Harvard Medical School.

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

- Describe the evidence regarding systemic work-up for patients presenting with a retinal vein occlusion;
- Evaluate retinal vein occlusion treatment approaches, including observation, laser photocoagulation, intraocular steroids, and intraocular anti-VEGF therapies; and,
- Appropriately apply new therapies for vitreomacular adhesion abnormalities, including observation, ocriplasmin, and vitrectomy.

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 Retina Society Meeting, are Dr. Julia Haller, chair of the Department of Ophthalmology at Thomas Jefferson University Hospital, and she is Ophthalmologist in Chief at the Wills Eye Institute in Philadelphia. Dr. Haller has disclosed that she is a consultant for ThromboGenics, Dr. Haller, thank you for joining us today.

DR. JULIA HALLER: Nice to be here, Neil.

DR. BRESSLER: Also joining me at the Retina Society Meeting is Dr. Jennifer Sun. Dr. Sun is an investigator in the Section on Vascular Biology at the Beetham Eye Institute at the Joslin Diabetes Center, and she also is an assistant professor at Harvard Medical School in Boston. Dr. Sun has no potential conflicts to disclose; Dr. Sun, thank you also for being a part of today's program.

DR. JENNIFER SUN: It's a pleasure to be here, thanks for having me.

DR. BRESSLER: Now regarding the off label or unapproved uses of drugs and devices I need to note that our discussion today will include the off label use of aflibercept or Eylea, bevacizumab or Avastin, dexamethasone intravitreal implant or Ozurdex, microplasmin or ocriplasmin, ranibizumab and triamcinolone for the treatment of macular edema from retinal vein occlusions, and for treating vitreomacular adhesion abnormalities.

Now we've had a lot of new presentations at the Retina Society concerning treatment of retinal vein occlusions and this is a very common problem, so I'd like to start with one of our patients.

So this is a patient who presents with macular edema that involves the center of the macula. Now the central subfield thickness on OCT is 425 microns in the right eye, and this person's visual acuity is decreased to 20/50 and there are dilated and torturous retinal veins and there's a minimal amount of dot and blot hemorrhages, but these are in all four quadrants of the retina.

This is a 70 year old man and it was judged to be consistent with a central retinal vein occlusion. And so when you have someone that presents with a central vein occlusion and macular edema, I'd like to know what your initial management might be, and specifically in this patient, Jennie Sun, the patient is phakic, their other eye is 20/20, there's no glaucoma problems that are suspected. The intraocular pressure is 14 and 16 in the right and left eyes, respectively, there is no iris or angular neovascularization in the right eye, and the decreased vision in that right eye has been present by the patient's recollection for at least a month, and the patient tells you they are having difficulty adjusting to this decreased vision in the right eye, especially when they're driving or they're reading.

So what do you do now with central vein occlusions in macular edema, do you observe them, do you do grid laser, do you consider intravitreal anti-VEGF medications or intravitreal corticosteroids? How would you approach this case?

DR. SUN: So, Neil, in these patients with central retinal vein occlusion and macular edema with visual impairment, I think that clearly the central vein occlusion studies show that grid photocoagulation was not better, necessarily, than observation. But fortunately, we do have excellent phase 3 clinical trial data for both intravitreal anti-VEGF and intravitreal corticosteroids that suggest that patients have better visual outcomes with both of these modalities. In particular, the intravitreal anti-VEGF agents.
So I would probably start in this patient, particularly since he's phakic, and has not had pressure problems, with the anti-VEGF treatments as a first line.

DR. BRESSLER: Dr. Haller, would you start with the same approach, what would you decide to do in this particular patient scenario?

DR. HALLER: Well I think it has to be customized to the patient and that involves a good bit of discussion. Now we have, with Eylea being approved two weeks ago exactly to the day, we have a number of different approved as well un – as well as nonapproved drugs for this type of situation. And I go a lot by what the patient tells me in terms of his ability to get in and out. We know with the anti-VEGF injection, you will be committing them to monthly injections, at least for a while, and that type of aggressive therapy may be more than, you know, there are 70 year olds who are pretty much like 50 year olds, and there are 70 year olds who are pretty much like 90 year olds. It depends how that person is looking at this situation, his other eye is very good. You do say that he is bothered by the eye so he is probably interested in having treatment rather than just letting it go.

But my tendency in a phakic person is to avoid steroids, at least at first, usually, and see how they do with an anti-VEGF injection. So I agree, I'd probably go with an anti-VEGF injection as first line here.

DR. BRESSLER: So Julia, let me follow that up, assuming you discuss it with the patient and they're very comfortable with starting with that treatment, do you then recommend to them or consider that they would be treated, let's say, every month for the next six months as was seen in some of the studies evaluating ranibizumab or aflibercept, or do you prefer that perhaps they start with a PRN regimen, you'll see how they're doing at each follow-up, based perhaps on their visual acuity and OCT? How do you handle the discussion recommendations to them for the first six months?

Let's say they tell you they really would have help from their friends of their family to come in as needed, what would you recommend to them?

DR. HALLER: I tell them the same thing that I tell the AMD patients, which is that most of the studies have been done with a strict regimen which involves monthly checks, but we don't know in any individual patient if that's absolutely necessary. But our tendency is to start out with monthly injections as sort of an induction phase, if you will.

In his particular case, he's not too thickened centrally, 425, his vision is still pretty good, 20/50, maybe he'll be very sensitive and respond quickly. But I usually say let's target three intravitreal injections once a month at least to start out with and then think about either the PRN protocol that you just suggested or

possibly a treat and extend type of approach once we get the retina thinned with the initial monthly injections.

DR. BRESSLER: Dr. Sun, do you sometimes use a PRN regimen at some point in the management of macular edema in a vein occlusion?

DR. SUN: There are certainly patients in whom I think I do end up using a PRN regimen. Generally, just as Julia does, I'll start with the q.1 month for 6 months, at least setting the expectation, because I think that's one of the most important things in managing the patients and it's much easier to set the expectation that they are going to have multiple regular injections and really drive home the point that they need to be compliant with follow-up on a regular basis. And then you can always pull back if you think they are doing extraordinarily well, the thickening goes away, the visual acuity improves to 20/20 or better. You know, in those cases I'm happy to discuss with my patients if there are lifestyle considerations or other issues why they might want to extend the follow-up period.

DR. HALLER: And I just wanted to echo the point you're making about expectations, I think that is so crucial, particularly in this disease which tends to be a chronic and we may – this morning there was a presentation looking at data from the Eylea studies in both the COPERNICUS and GALILEO trials showing that after that six months where by protocol everybody was treated monthly, they were switched over to PRN dosing in both of the studies. And what we saw there was that on average, in the second six months you could tell patients that on average, the median number of injections was only three. So that if they could make it through the initial period there was some hope that it would be onerous later on.

But as a caveat, although about 20 percent of people required 0 to 1 injections, there were a little bit more than 11, 12 percent, about 14 percent max in one of the studies where they required injections as much as four, five or six times, or even up to seven. So there are a subset of patients who do require more aggressive treatment and you don't know who that is going to be.

So when I'm trying to set expectations, I say, look, I am hoping in the second half of the year we'll be able to drop down to three injections or maybe even fewer, but there is a small chance you would need more.

DR. BRESSLER: You know, that is so important because we really only have very few studies so far in vein occlusion with macular edema to guide us as to what to tell the patients to expect. And we can't necessarily go by the diabetes outcomes in treating macular edema. I think we've seen very good data to suggest maybe by the third year you need one or two injections, we don't know if that holds for these vein occlusions and sometimes they come back, sometimes their vision won't improve, even though the edema may all go away.

Jennie, if you do decide to use the OCT, what do you consider, how do you determine if it's improving. Do you just look at numbers on the central subfield and say okay, that's better or how much of a number, or do you look at the morphology and compare it from one visit to the next and say, oh, there's less cystoid abnormality there. Do you use numbers, how much, and if so, do you use morphology as well or independently?

DR. SUN: These are all excellent questions, I use both, numbers and morphology. And so in general, if I'm looking strictly at the numbers guided by some of the literature I might say, oh, a 10 percent change in OCT central subfield thickness is something I consider a real substantial change from one visit to the next. But I really think that has to be evaluated very much in the context of the trend in how the patient is responding. And so a less than 10 percent change, either improving or worsening, in the context of an overall consistent trend in the same direction I think I consider very real.

And I do tend to, I think it is very important to not just evaluate the numbers that you get on the thickness maps, partly because when you look at the segmentation of the actual line scans, especially on the newer spectral domain machines, sometimes the machines draw the lines incorrectly and we see all the time patients where the numbers are artificially inflated or much thinner than you would expect and you can catch that if you go back and look at the line scans.

DR. BRESSLER: Dr. Haller, how about you, look at the morphology side by side, does that influence your interpretation in addition to the central subfield?

DR. HALLER: Yes, I completely agree that you need to look at the scans, too, and take with a grain of salt

what the machine is spitting out. Although I have to say I do like the newer software subtraction pictures where it shows you exactly what's improving or getting worse. And I should have mentioned earlier, one of the things I have an initial discussion with the patient about is their systemic health. So I am factoring in whether, you know, maybe they have out of control blood pressure.

When people come in my initial discussion is why did this happen to you and it may just be bad luck. You know, you have an anatomically tight outlet for your central retinal vein. But to the extent that their might be undiagnosed or treated diabetes, undiagnosed or treated hypertension, you know, we do want to make sure that we're on top of those. In the rare case where you have a bilateral vein occlusion, of course, you're looking for hematologic diseases like multiple myeloma or Waldenstrom's macroglobulinemia.

So when they're coming back I'm also trying to get a feel for whether, what the context is of their overall systemic health. But I am, I mean I'm pretty much locked into treating them once a month for the first three or four months, even if they don't seem to be getting a whole lot better right at first and having a response to it.

One of the things that we found when we were first doing the first studies of ranibizumab for macular edema and vein occlusions was that a few of the patients would come in a month later and they would tell you they did get better, but then they got worse again. And that's when we added to the protocol a one week scan and we found that some of the people with severe disease, of course, were getting better but it wore off after about a week. So that might impact, too, a little bit, what the patient was telling me, how they felt the course of their visual recovery was going as well as the morphology.

DR. BRESSLER: So let me switch gears a little bit with this patient and the management, I think it's been very helpful so far to know that we're going to start with some sort of intravitreal anti-VEGF perhaps in many of these patients and take into consideration the improvement and the expectations.

I'd like to go into sort of the side part of the retina, because this has been discussed in some of the presentations at the Retina Society this morning in terms of what you might get with visualization of the perfusion status based on wide field imaging.

So Dr. Sun, maybe I can go to you first and ask do you typically think it is helpful to visualize the periphery in such a case like this with a central vein occlusion and macular edema if you had such equipment to visualize it, in terms of either the fundus appearance or angiographic appearance, and how might you use that?

DR. SUN: Well I think, I do think that the peripheral visualization that we have the ability to get now with ultra wide fields from some of our newer imaging equipment modalities is extremely interesting. I think on one hand it doesn't really necessarily change my initial management of the patient unless I am looking for a new or active neovascularization in the retina that I might treat with panretinal photocoagulation. But for the purposes of treating the DME, I am not sure that the peripheral visualization will change that that much.

And I think that this is an area of real interest and ongoing investigation. So I think that over time we'll get better and better answers perhaps from studies that are in progress, looking to see are there parameters from looking at these ultra wide field angiograms so that we can tell if peripheral nonperfusion has additional predictive value in terms of looking at outcomes for these patients.

DR. BRESSLER: I think we may indeed update this next year or the following year. There are several studies going on right now to see if it really does influence the prognosis or the management and even whether you could add scatter photocoagulation to the periphery as to whether that would help. But we'll come back to that when we discuss what to do if the edema doesn't go away.

I'd like to still get another comment on that from you, Dr. Haller, in terms of visualizing the periphery and how you might approach that?

DR. HALLER: Well perfusion status, very much to Jennie's point, was something that was part of the topic today and also yesterday in some of the case reports, both in diabetes and in vein occlusion, so the two most common retinal vascular disorders. And very clear cut evidence emerging that anti-VEGFs and actually steroids, too, improve perfusion with treatment.

Mike Singer had an interesting case where he was able to document that with the anti-VEGF the perfusion

improved. When it wore off, the perfusion got worse again, so it went back and forth, and there seemed to be an area where the perfusion was never coming back and then an area where the perfusion stayed good, and then an intermediate zone where it waxed and waned. And one intriguing thing is how can you – how can you optimize perfusion in that mid zone.

Another one of the findings of the Eylea study was that the drug improved perfusion and that the nonperfused patients had as much of an improvement in vision as the perfused patient. So that was an interesting little clinical pearl in looking at the data because some of us tend to look at our nonperfused patients and say well we can try something but I don't know if it's going help you that much because you've got nonperfusion. So it was encouraging that the drug was of benefit in terms of visual acuity improvement even in the nonperfused group.

DR. BRESSLER: I agree, I think we want to treat all of them right now if we think that there is potential for improvement in their vision as we go forward. Well let's go back to our 70 year old here, they're still in the office this first time, we're still going to start with anti-VEGF, but the question is what if this patient has been taking good care of themselves, they're getting routine physical exams as part of their general medical care each year, are you concerned when they walk in that they need any additional systemic workup at this time for any systemic medical problems? So do they have to go back right away, they just had a checkup three months ago for high blood pressure, Dr. Haller, or diabetes, or maybe even less commonly, some coagulopathies? What do you do with this healthy, otherwise healthy patient?

DR. HALLER: I have to say that I'm much more of a total doctor than I used to be right out of my residency when I thought the eye, you know, I pretty much knew everything about the eye. So I'm more humble now and also I am more seeing the eye in the context of all of the other things that are going on.

Actually there was an interesting paper this morning looking at diabetic foot disease and how it possibly was an indicator for diabetic eye disease. And I think that speaks to that same point.

But anyway, when the patient comes in I do tell them that they need to be evaluated for high blood pressure and, and diabetes, and cardiovascular issues, in general. You know, I say you don't smoke, do you, you know, I say things like that. But we, what we know is that usually we don't find anything too much new, although – although it might be an occasion to tighten up their control.

So I usually do write a letter to their internist, I tell them it might be worth going back and just making sure that that blood pressure measurement that they thought was okay, really is okay.

And then the other question that always comes up when you're talking about this anywhere is what happens with a 30 year old or 45 year old, you know, is that, do you do a mega workup? And probably most of us do, are a little bit more aggressive on that patient, although very rarely does anything show up if it is unilateral disease. But we tend to look for inflammatory and other causes of, you know, occlusive disease in that young population.

DR. BRESSLER: Well I think the challenges there are do you find something that leads to some iatrogenic damage from some intervention versus you find something that you wouldn't have otherwise found. So we need more information going forward. So speaking about communicating with the physician, Dr. Sun, do you communicate with the patient's internist about this and if so, if the patient is not taking aspirin or other antiplatelet aggregation medications or anticoagulants, do you recommend that the patient's interest consider aspirin, antiplatelet aggregation medications or even anticoagulants, when they walk in with this central vein occlusion in one eye and macular edema?

DR. SUN: I definitely do communicate with the internist just to let them know that we found some sort of vascular event in the eye. I agree very much with Julia's approach to working up these patients. I think I particularly tend to be more aggressive in the younger patients and perhaps also in the patients that present with bilateral CRVO just to see if there's something systemic that we can identify.

In terms of aspirin and other anticoagulation strategies, I don't generally try to recommend as a matter of course that they should now start an aspirin of an antiplatelet agent. If they are on it already for other systemic reasons like a cardiac event or stroke, or TIA, you know, I certainly don't take them off. But I think the literature is not, has not shown a conclusive

benefit to aspirin and antiplatelet agents, and, in fact, there have been some reports, including a paper from Hayreh[1] last year, that suggested that perhaps patients with aspirin actually have a higher rate of visual decline and perhaps may have worse visual outcomes than patients that are not taking aspirin.

DR. BRESSLER: Sure, you might worry maybe you'll cause more bleeding or more thrombosis. Dr. Haller, if you do the same, you don't – you don't recommend that they start some antiplatelet or anticoagulant, what do you do when you get the referral from the outside ophthalmologist and the patient was started on aspirin specifically for their central vein occlusion, how do you manage that situation then if you don't recommend it initially, but now the patient walks in and someone else recommended it, even though as Dr. Sun said, we don't have any evidence to support that recommendation at this time?

DR. HALLER: Well that's always a delicate matter because you don't like to question the judgment of your referring physicians, but I usually tell people to get off the aspirin if they've just been put on it for that. And – and even more difficult I think sometimes is when you're speaking to the internist and when you tell them there is a venous thrombosis, they, to them a venous thrombosis is a deep venous thrombosis like in a leg and they are worried that a clot's going to break off and go somewhere. And it takes a little bit of education to say that this is as far as that clot's going, you know, it's already, it's already reached the end of the line and done the damage. So prophylaxing against it going further down the line is really not worth it.

But I usually tell the patient I would get off the aspirin and I try to write a nice letter complimenting the referring doctor on their care.

DR. BRESSLER: Excellent. So, Dr. Sun, let's just change our patient up a little bit here. I did present you a patient that had walked into us, but let's make believe they're not bothered by the vision. So they've had this central vein occlusion with macular edema for a month, it was picked up perhaps asymptomatically. Maybe they thought they needed to change their reading glasses, went to their optometrist, the optometrist looked in, saw some blood in the retina and doesn't know how long it's been there. The patient is, as we've said, 20/50 in the affected eye, they're 20/20 in their other eye, and you ask them, have you had any problem with driving, any problem with reading; no, they're okay.

They do notice it now that you tell them if they cover their left eye, but otherwise they're okay. Does that change your management, because we were starting this patient on an intravitreal anti-VEGF regimen, and it's a central vein occlusion?

DR. SUN: It is always amazing how many of our patients operate or feel like they're operating perfectly well with one good eye and one eye in which the vision is clearly down on testing. So really, if the patient is asymptomatic, it really does not change my medical recommendations for treatment at this point just because we know that the data shows that the visual acuity outcomes are much better with anti-VEGF treatment or even steroid treatment versus just observing.

So I would still recommend to that patient that they have, they begin the treatment with the knowledge that even if they are not feeling like it is functionally changing their life right now, perhaps, heaven forbid, something happens to the other eye, at some point they may become dependent on the vision in this eye and we just want to do everything we can to maintain and even improve that vision.

DR. BRESSLER: How about you, Dr. Haller, we know that if you wait six months from some of the trials which then switched people over from sham to injection their vision never caught up in a central vein occlusion from baseline, but we don't know if you wait a month or two. So do you also recommend the treatment or would you ever consider if they're asymptomatic seeing if perhaps within a month they start to improve on their own?

DR. HALLER: Well there is accumulating data that waiting makes a difference, and that six month, the six month crossover to which you refer in the CRUISE study, in the Eylea results that we discussed again today, that that's been reported before. And also in the Ozurdex study. So with steroids as well as anti-VEGF.

The numbers were great enough in the Ozurdex study which had by far the largest enrollment of any of the trials to actually do regression analyses and Yeh[2] and co-authors reported not too long ago that you actually could predict for each month of delay a certain number of letters of lost vision.

Now that's, you know, ex post facto analysis but it still, it was still pretty powerful I thought. So that's what I tell the patients, same as Jennie is suggesting, that data is strong that if you wait your vision will be worse. Having said that, it's the patient's decision and what I usually try to come down on is saying if you're still against it but willing to consider it, what about trying a couple of injections, the risk is low, see if by George you do notice an improvement and it does impact on your life, and if it does, then you might want to change your thinking about it. But if they're adamant, of course, I am not going to push anybody into an injection that might possibly cause and infection or some other problem.

DR. BRESSLER: Sure, and if six months is too long maybe they'll come back in a few weeks and maybe they will notice it or maybe it's worsening and they'll be more than happy to initiate therapy.

So, Dr. Sun, let's flip this a little bit, we'll say they are symptomatic again, it is bothering them, but they are pseudophakic in both eyes, they've been pseudophakic for four years already and now the question is same situation, but they are pseudophakic. Does that change your initial recommendation for an intravitreal anti-VEGF therapy or would you, in fact, make the first recommendation of intravitreal corticosteroids? Remember, this patient is going to go by what you recommend and remember, this patient has no evidence of any glaucoma or history of glaucoma?

DR. SUN: With the pseudophakic patient I think on the whole it doesn't necessarily change my general approach to use anti-VEGF as a first line therapy. It certainly lowers my threshold for suggesting intravitreal steroid, either as an alternative therapy early on, just because I know that cataract is not going to be an issue for them, and certainly cataract with repeated steroid use is an issue for many patients.

That being said, this patient doesn't have glaucoma right now, certainly if we give multiple injections of steroid or repeated steroids, glaucoma could become an issue for them and that is one of my main reasons I think for tending towards the use of intravitreal anti-VEGF rather than steroid.

DR. BRESSLER: Dr. Haller, how would you make a recommendation to this patient now that they are pseudophakic walking in?

DR. HALLER: A pseudophakic patient, particularly if there are any transportation difficulties, I would probably put the dexamethasone implant a little ahead of monthly anti-VEGF injections unless there was some other reason not to. I would also do that in somebody who was, who had had a vitrectomy or had very liquid vitreous from some other, for some other reason. Because, of course, the anti-VEGFs go pretty quickly out of an eye that's vitrectomized, so I think the steroid implant's the treatment of choice.

With the dexamethasone implant we know that at a maximum of six months we got about a 15 percent bump in pressure. Most of those were managed with drops or observation, and by six months the pressure differences, there was no difference in the sham versus the treated group.

So the dexamethasone implant, unlike triamcinolone, has a much better safety profile from the pressure standpoint.

DR. BRESSLER: Well and now you have the option which was not true in the dexamethasone implant studies to consider switching to an anti-VEGF. If you did, indeed, start with that and it seemed like it was wearing off in that particular patient by 60 days, or not getting the response –

DR. HALLER: Yeah, if you got 50 percent response but you think you could get a little more you can –

DR. BRESSLER: Although we have less evidence to support that. Okay.

And finally, let's go back to our patient one more time and then we'll talk briefly about follow-up before we go to our other case. And that is when these patients walk in as this one did, 20/50, macular edema, symptomatic, the other eye is fine, do you get a fluorescein angiogram, Dr. Sun?

DR. SUN: You know, I do not routinely get a fluorescein angiogram at this point in time. I think with the increased availability of the ultra wide field angiograms, I am much more likely to do so in the future. I think one of the issues I find sometimes with the CRVO patients is that if they have, particularly if they have a lot of intraretinal hemorrhage, it is very difficult to evaluate the perfusion or nonperfusion status given the blocked fluorescence from the intraretinal heme.

So again, I think over time it will be of interest to get the ultra wide field angiograms, but at this point, since they are not routinely influencing my treatment decisions, I don't necessarily get it.

DR. BRESSLER: Dr. Haller, last question about our follow-up of this patient. So we start an anti-VEGF regimen and the edema begins to go away, and then after five injections it doesn't go away any further, it seems to get stuck at maybe 300 microns, a small cystoid abnormality is there, the vision improved to about 20/32 but it didn't get any better than that. Do you just stop the anti-VEGF therapy, do you continue it, do you switch to steroids, do you add or substitute grid laser, what do you do for that person that they improved and then it just didn't completely improve in them? It happens.

DR. HALLER: Sure, it does happen and there are increasing case reports where people have tried different things. Usually they'll try one of three things, either switch anti-VEGF and now we've got Eylea approved so people may be switching to Eylea much the same way they were trying Eylea on pigment epithelial detachments and AMD that haven't settled down, but they always switch between Avastin and Lucentis. Or adding steroids, and there are some, a number of case reports where people seem to have developed a resistance if you will to anti-VEGFs and have been successfully given, for example, a dexamethasone implant with resolution of edema.

And thirdly, this is exactly where I so agree with Jennie's comments earlier about not always getting a fluorescein angiogram right at the beginning, especially with a blood and thunder type appearance of the fundus. But this is a case where I probably would get a fluorescein angiogram and just see if there might be more in the way of nonperfusion that might be stimulating, up regulating VEGF and causing part of the problem and then I would think about doing some focal scatter in those areas where the nonperfusion was.

And there was an interesting paper, the end of Mike Singer's[3] paper this morning talked about actually mapping out with wide field angiography the areas where the nonperfusion was and did not get better with the injections. And then he also showed an interesting suggestion for targeting that using the targeted Navilas laser where the, you draw into the picture the fundus image where you want to put the laser and then it scans around and puts scatter photocoagulation automatically based on those images.

DR. BRESSLER: Well really, that was a great discussion I think of many things that we think of when we are trying to manage macular edema and a central vein occlusion. It's been a rapidly moving field in terms of new information not only in the last year in the peer reviewed literature, but just at today's meeting in the Retina Society. So I thank you very much, and we're going to continue our discussion with some other cases in just a moment.

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.

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. Julia Haller from Thomas Jefferson University Hospital and the Wills Eye Institute in Philadelphia, and Dr. Jennifer Sun, from Harvard Medical School and the Beetham Eye Institute at the Joslin Diabetes Center in Boston. And our topics today are macular edema from retinal vein occlusions and management of vitreomacular adhesion abnormalities.

So I would like to get to our patient with an abnormal vitreomacular adhesion. Specifically, this is a patient in their mid-50s and they've been having difficulty with vision in their right eye probably for the past year or so. And now you're seeing the patient and the visual acuity is 20/50. And you look in and you see some fine glistening of an epiretinal membrane and Dr. Haller, there is only a small amount of wrinkling of the inner retina but it just doesn't look right to you and you get an OCT and on the OCT you can see some fairly prominent vitreomacular adhesion, it looks as if there is traction pulling up the central macular area with this 20/50 vision.

Now the patient's phakic. The other eye is 20/20 and there is no other ocular abnormality in that other eye. They have a posterior vitreous detachment in that other eye, it looks good. Their pressure is normal, it's 14 and 16 in the right and left eyes, respectively.

So if they have had this decreased vision for about a year, it's been bothering them more and more and you see this presentation, what do you discuss with the patient? Are you going to recommend continued observation, are you going to recommend trying intravitreal microplasmin, a vitrectomy, how do you approach this now in 2012/2013?

DR. HALLER: Well this patient sounds like they've got abundant reason to have decreased vision if they've got thickening to 500 microns centrally. And -- and so what I would tell this person is that either they live with the situation and it could well plateau right where it is and if they could put up with that, fine, or the traditional treatment would be vitrectomy, and since vitrectomy carries with it a small risk of infection, small risk of bleeding, small risk of retinal detachment and the certainty of cataract progression, that we usually save vitrectomy for a situation where the vision really is at least borderline disabling, where it's really, really impacting on their quality of life.

As an intermediary position, now that we have ocriplasmin available, they could also consider an intravitreal injection of ocriplasmin. We know that from the trial data with a single intravitreal injection, if the patient is like the patients who were in the study, 25 percent will get release of their vitreomacular adhesion. We also know that the group that did the best was that without significant epiretinal membrane. So a little bit of this depends on exactly what that epiretinal membrane looks like.

Now there was no significant downside, there was no harm done as far as we could tell if they did have an injection and it didn't completely work, so you could make the argument that it might be worth trying it and even though their chances are probably not as good as one in four, still if they did have separation then that would take care of the problem and no harm done. And if they didn't then you could go back to your initial discussion and start talking about did the risk of surgery, of vitrectomy, was it outweighed by the benefit considerations, do the standard surgical risk/benefit talk.

DR. BRESSLER: So I think this exactly gets to the mechanism of action that it can definitely release the vitreous adhesion but it is not necessarily going to do anything to cleaving that plane between the epiretinal membrane and the surface of the rest of the retina. So I think that is really important for our cases and exactly why this patient was so interesting.

Dr. Sun, you see a lot of people with diabetes and diabetes macular edema at Joslin and so I wonder what do you do when the patient walks in, we'll make it a little more complex, they have this presentation but they also have some dot and blot hemorrhages so there is mild nonproliferative diabetic retinopathy in both eyes, how do you know that this isn't some diabetic macular edema and the vitreous happens to be adherent to the fovea? How do you differentiate this diabetic macular edema thickening from vitreomacular adhesion thickening of the retina. This is not too infrequent, I think.

DR. SUN: I think you're right. I think we see a lot of patients in whom there is probably some components perhaps of each and there is central thickening. And the question for the clinician is to have some sort of judgment as to what the relative contribution of, say, the diabetes is versus the vitreomacular traction. And to a large extent it's a judgment call I think based perhaps on partly the appearance of the OCT and the extent of the vitreomacular traction you can see in some patients there is clearly an attached posterior hyaloid but it doesn't appear that there is that very focal adhesion that you see on other patients where clearly there is adhesion very centrally with a little tenting up of the retina right in that areas.

You may also be able to see, and a fluorescein angiogram may help you with this, too, for the diabetes cases there it is more a question of pure

diabetic macular edema than traction that the areas of swelling are really located around focal micro aneurysms that leak on FA. So I think it can be a difficult judgment call but there are patients in whom there also, there is a clear predisposition or a clear predominance of one pathology over the other.

DR. BRESSLER: And Dr. Haller, I'm going to make the case a little more complex in a different way. So let's remove the diabetic retinopathy, this patient does not have diabetic retinopathy, they had the presentation, as I described to you, but there is also substantial cataract. And you look in and you judge I think this cataract might be contributing to some of the decreased vision, as well.

I have two questions in that situation, how do you know that it isn't just the cataract, would you consider just removing the cataract and how would you decide whether you should start with ocriplasmin or go to vitrectomy when you have this cataract in the way? So let's, you know, let's ask the first question, how do you even judge how much vision might be decreased from the cataract versus this vitreomacular adhesion? I've seen people with vitreomacular adhesion and 20/20 vision.

DR. HALLER: Absolutely. And it's, it's just a variation of the same conversation you have with somebody who's got a little bit of epiretinal membrane in cataract because both of those can cause relatively minor degrees of visual disability and a little bit more can tip them over the edge. You know, they get to the straw that breaks the camel's back point and sometimes you really don't know if it's the cataract or the epiretinal membrane. If it's somebody that I've been following for a while and I see the OCT getting worse, worse, worse, worse at the same time as their vision, and their visual symptoms are getting worse, worse, worse, worse. Then I usually say, as far as I can tell, it is mostly the retina, because their cataract doesn't look that much worse.

More frequently it's somebody I'm seeing for the first time and so I don't have the benefit of graphing their, for their previous studies. And in that case it just depends on the individual patient, what their other eye is like, and a host of other factors. But what I usually come down saying is if I think there's a lot wrong with the retina and a lot wrong with the lens, you might consider a combined operation. If I don't, if it's not a slam dunk for me that both are big problems, then I'll often suggest the most low risk, high success procedure first which, of course, would be cataract surgery.

Now if we have the additional ocriplasmin option, then I'm probably going to suggest if I think the retina is a significant problem, that we try the ocriplasmin first, see what happens. It doesn't, we don't have any evidence that it makes the cataract progress. And you could argue that if you could get release of that vitreomacular adhesion, that the cataract surgery might be a teeny bit safer because we do know that the vitreous moves forward slightly after cataract surgery and it's possible, I think all of us have seen the occasional case where somebody, for example, gets a new macular hole after their cataract operation of has a traction progress.

So to me, the safest, least invasive thing to do in that situation where I'm not sure what is going on is go with the ocriplasmin injection and then probably think about the cataract surgery.

DR. BRESSLER: And I think this is the new component we have to consider which we would not have done previously when we didn't have ocriplasmin available.

What I would like to do now is quickly summarize our discussion today. So let's return to our learning objectives. The first learning objective was to describe the evidence regarding systemic workup for patients presenting with a retinal vein occlusion. And we discussed while we have no definitive evidence to indicate in an otherwise healthy person that a systemic workup may, indeed, find a cause related to the central vein occlusion that was discussed, there certainly is no reason to withhold recommending that all patients have good, general internal medicine exams and we should remember that these cases can be associated with high blood pressure, associated with diabetes, and let's be sure that, indeed, they have had all of their medical care taken care of.

The second learning objective was to evaluate retinal vein occlusion treatment approaches. Now this has really changed over the last several years. We now have several considerations including intravitreal anti-VEGF medications and several anti-VEGF medications that have become available. We have the option of starting every month with these medications or determining if we should use them in so called PRN

regimen. It's really changed the way we evaluate these patients now, we may not necessarily need a fluorescein angiogram to treat them. We may not necessarily use a laser in their macula at this time. And we describe how there is a role also for intravitreal corticosteroids, that these have been shown perhaps to have a role as well in the management of macular edema.

Our last objective was to appropriately apply new therapies for vitreomacular adhesion abnormalities. This landscape also may be changing as we have the availability of ocriplasmin, an additional regimen that now might be considered in the management of vitreomacular adhesion abnormalities, but to recognize that it's a very complex decision as to whether the vitreomacular adhesion abnormality is causing the visual acuity loss, to consider this treatment which may, indeed, be safer than vitrectomy, but needs to be – but needs to determine whether it's really the cause of vision loss when you might have cataract causing the vision loss or when you might have diabetic retinopathy also causing the vision loss.

So I want to thank Dr. Julia Haller and Dr. Jennifer Sun for participating in this eOphthalmology Review Podcast on macular edema from retinal vein occlusions and vitreomacular adhesion abnormalities.

DR. HALLER: Thank you, Neil, it's been a pleasure being here this afternoon.

DR. SUN: Thank you so much, it's been great fun.

DR. BRESSLER: Thank you very much.

BOB BUSKER: This podcast is presented in conjunction with eOphthalmology Review, a peer-reviewed, CME-certified program developed by the Johns Hopkins University School of Medicine for ophthalmologists and retina specialists.

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Thank you for listening.

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