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VOLUME 1 — ISSUE 8: TRANSCRIPT

Featured Cases: Proliferative Diabetic Retinopathy

Our Guest Author is Dr. Adrienne W. Scott, Assistant Professor of Ophthalmology at the Wilmer Eye Institute at Johns Hopkins in Baltimore.

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

- Apply the result of recent trials evaluating diabetic macular edema and proliferative diabetic retinopathy to clinical scenarios;
- Describe the rationale for use of anti-VEGF in the treatment of diabetic macular edema and proliferative diabetic retinopathy; and
- Determine patient characteristics that favor one treatment modality over another.

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to *Proliferative Diabetic Retinopathy* in the format of case-study scenarios for the clinical practice. This program is a follow up to the Volume 1, Issue 7 *eOphthalmology Review* newsletter — Proliferative Diabetic Retinopathy.

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Unlabeled/Unapproved Uses
The author has indicated that this presentation will include discussions off-label discussions of bevacizumab, ranibizumab, and triamcinolone.

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Adrienne W. Scott, MD has disclosed that she has no relevant financial relationships with commercial supporters.

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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 7, the eOphthalmology Review Newsletter on proliferative diabetic retinopathy. Our guest is that issue's author, Dr. Adrienne Scott from The Johns Hopkins University. This activity has been developed for ophthalmologists and retina specialists, and there are no fees or prerequisites for this activity.

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

- Apply the result of recent trials evaluating diabetic macular edema and proliferative diabetic retinopathy to clinical scenarios,
- Describe the rationale for use of anti-VEGF in the treatment of diabetic macular edema and proliferative diabetic retinopathy, and
- Determine patient characteristics that favor one treatment modality over another.

I'm **DR. NEIL BRESSLER,** course director of eOphthalmology Review. Here in the studio with us is Dr. Adrienne Scott, Assistant Professor of Ophthalmology at the Wilmer Eye Institute at Johns Hopkins in Baltimore, Maryland. Dr. Scott has disclosed that she has no relevant financial relationships with commercial supporters.

Her presentation today will include the off-label discussion of ranibizumab, bevacizumab, and triamcinolone.

Dr. Scott, welcome to this eOphthalmology Review podcast.

DR. ADRIENNE SCOTT: Dr. Bressler, thank you very much for inviting me to participate. It's my pleasure to join you today.

DR. BRESSLER: Our topic is proliferative diabetic retinopathy. In your newsletter issue, you reviewed new data about the effects of panretinal photocoagulation on the development of macular edema, the effects of anti-VEGF intravitreal injections on the progression of diabetic retinopathy, and the impact of several newer treatment approaches for diabetic macular edema, including intravitreal agents in combination with focal grid laser therapy.

What we would like to do today is focus in on how we might be able to apply some of that new information to our patients. So if you would, please, start us out with a patient scenario.

DR. SCOTT: Thank you, Dr. Bressler. I'll present a typical case we might see come into our clinics. This is a 55-year-old woman who is referred by her internist for her routine diabetic fundus exam. The hemoglobin-A1c measures 10%, with a blood pressure of 180/190 mmHg. She is visually asymptomatic. Best corrected visual acuity measures 20/25 in her right eye and 20/20 in her left eye. The slit lamp exam is quiet and unremarkable, with the exception of mild cataracts.

On dilated ophthalmoscopy of the right eye there is mild fovea-involving diabetic macular edema with some juxtafoveal lipid. There are moderate nonproliferative diabetic retinopathy changes throughout the posterior pole. The left eye shows no evidence of diabetic macular edema but also shows moderate nonproliferative diabetic retinopathy changes.

DR. BRESSLER: So when a patient comes in like this where you think there might be a little macular edema in the right eye and the left eye now shows macular edema, and there is moderate nonproliferative retinopathy, what additional testing do you do to evaluate these patients?

DR. SCOTT: On baseline exam, I like to obtain fundus photographs to document disease progression and to be able to follow the patient long-term. I'll also get an OCT, of course; this is becoming more and more

standard care for the evaluation of macular edema. Furthermore, for my diabetic patients, I often get a fluorescein angiogram, especially if it's the first time that I'm evaluating them. This helps me to better assess the status of their macular perfusion, again, to help me better understand what their visual potential and prognosis would be, and also to potentially assist me with any treatment; for example, if I were to initiate focal laser treatment, I find the fluorescein angiogram invaluable.

DR. BRESSLER: So in this case, the time to main OCT showed a central subfield that was just minimally thickened at 260 µm in the right eye; and the left eye, maybe minimally thickened, with a central subfield of 240 µm. The fluorescein angiogram showed an intact foveal avascular zone in each eye, but there were leaking microaneurysms in the right eye, which were about 50 µm from the very center of the retina. There were no leaking microaneurysms in the left eye.

How would you manage the patient at this point with those findings?

DR. SCOTT: Importantly, the first thing that strikes me about this patient is that her metabolic status is poorly controlled. I would make sure that I explained to her that the hemoglobin-A1c of 10% is too high to maximize her visual potential, and I would certainly engage in a discussion about decreasing her A1c level, as well as her blood pressure. I would certainly involve her internist in this information and this discussion.

Clinically significant macular edema is found only in her right eye at this point and certainly it is reasonable to initiate treatment; however, I am careful about initiating any treatment in a patient who is asymptomatic, especially given her excellent vision at 20/25.

Focal laser would be a potential option; however, the leaking microaneurysms that are very close to the fovea might increase our chance for scotoma formation after laser treatment. Also, anti-VEGF therapy is an excellent option. However, in the major clinical trials that we've achieved so far, patients who have vision level about the 20/30 to 20/40 level have been evaluated. We don't have very much evidence on patients with diabetic macular edema and 20/25 vision.
In this case I would strongly consider observation only with maximizing her metabolic status and ask the PC to see her again in about three months.

DR. BRESSLER: That sounds very reasonable in that this patient has no symptoms, is perhaps at the threshold of some thickening of her central subfield. The patient was observed, and now she comes back in three months and she still has no symptoms, and her visual acuity is still 20/25, slightly better than the best visions that were looked at in clinical trials, although in the large clinical trials evaluating anti-VEGF drugs, there was no finding that it worked better in worse vision than in better vision. So we don't know that you can't use this in 20/25 vision.

In any event, this patient came back and now her OCT central subfield has increased from about 260 µm to about 300 µm, a 40 µm increase. Since you were observing her at first, would you manage it differently now that she is worse?

DR. SCOTT: Dr. Bressler, since I see the patient getting worse, I would recommend initiation of anti-VEGF treatment at this time with either ranibizumab or bevacizumab, per the recent data given to us from the DRCR protocol eye and READ-2 and BOLT studies. Because I see the patient getting worse, even though she is still visually asymptomatic, I don't want to see her drop her vision at any point, especially if I see the disease worsening.

As you mentioned, we don't have the evidence of what the clear answer is in patients with excellent vision, but we do know that patients certainly can benefit, even if they do have excellent vision at baseline. There is a further benefit for this patient with initiation of anti-VEGF therapy, and that's that anti-VEGF therapy has been shown to decrease the progression of diabetic retinopathy.

DR. BRESSLER: So I think in this case if we were to start with that therapy, we have a lot of evidence, from what you said. Well thank you for presenting that case.

I think you brought another one. Please tell us what is the next case we'll discuss.

DR. SCOTT: Certainly, Dr. Bressler. The next case I have is a case of a 65-year-old man with type 2 diabetes who presents with complaints of decreased left eye vision. The hemoglobin-A1c measures 7%.

He has pseudophakia in both eyes and a glaucoma suspect.

Best corrected left eye vision measures 20/70, and the OCT central subfield measures 500 µm on time domain OCT. His foveal avascular zone is intact when viewed with fluorescein angiography, and there are several leaking microaneurysms directly at the foveal center. There are also micro aneurysms greater than 200 µm from the foveal center.

The patient also shows non-high risk characteristics of proliferative diabetic retinopathy in this eye.

DR. BRESSLER: This is a very common situation where we have someone walk in with impaired vision and quite a lot of thickening in the central macula, in this case 500 µm, even though there is no high risk peripheral retinopathy. What would be your approach to treating this patient with pseudophakia?

DR. SCOTT: I believe this is the perfect patient for initiative of anti-VEGF treatment. There is an added benefit of not only decreasing the diabetic macular edema, granting the patient visual improvement, but the non-high risk proliferative diabetic retinopathy may also regress with anti-VEGF treatment.

Other potential treatment options in this patient could be intravitreal triamcinolone injection, which the DRCR protocol eye ranibizumab laser study showed to be effective in decreasing OCT central subfield thickening and increasing vision in patients with pseudophakia.

The one caveat of steroids, of course, is the risk for elevated intraocular pressure; therefore, this might not be the very best choice in this patient who is being followed as a glaucoma suspect. I wouldn't eliminate this option totally in this patient; however, I would certain make sure that a primary ophthalmologist or glaucoma specialist were able to follow this patient with me concurrently as I was administering the triamcinolone treatments.

DR. BRESSLER: I think we have learned that in patients with pseudophakia, some people might consider combining focal grid laser with intravitreal corticosteroids, but as you said, the overall study did not show a benefit for all patients who are both phakic and pseudophakic. So when a subgroup analysis shows a benefit, we have a little less confidence. Also, the patients with pseudophakia weren't randomly assigned to one of several treatments, so there may be confounding variables that favored the intravitreal corticosteroid group in that particular subgroup analysis that perhaps would not have been found if a randomized trial were done on patients with pseudophakia.

I agree, very often these patients, even when they have pseudophakia, are started on anti-VEGF therapy. So when you start this patient or consider starting this patient on anti-VEGF intravitreal injections, are you concerned about the risk of perhaps cerebral vascular accident in this older patient who has diabetes?

DR. SCOTT: That's a great question, Dr. Bressler. I go with evidence that's been obtained from the major clinical trials thus far, and the systemic adverse events in patients treated with ranibizumab has been comparable to those seen in other large clinical trials for age-related macular degeneration, for example. The risk of systemic adverse events has been extremely low, and we do not have evidence that ranibizumab injection into the vitreous definitively increases one's stroke risk. Therefore, with more and more confidence, we're using intravitreal ranibizumab in patients, even in older patients.

DR. BRESSLER: Now I would like to go to what we had used previously for the last 25 or 30 years, and that is focal grid laser. Would you initiate this patient with just anti-VEGF therapy, and if so, when would you consider adding focal grid laser on top of that anti-VEGF therapy?

DR. SCOTT: Well, Dr. Bressler, I think this is a wonderful situation that we're in because we have so many different treatments and treatment options and combinations from which to choose. I certainly would lay out all of these options to this patient, given that my first preference is to treat him with anti-VEGF therapy.

Certain patients express trepidation about intravitreal injection and prefer to be treated with focal grid laser. We do know also from our studies, however, the visual benefit of focal grid laser has never shown to be as dramatic as that seen with ranibizumab, and this patient does have some leaking microaneurysms that are greater than 200 µm from the foveal center, which might make this patient a reasonable candidate for focal grid laser treatment.

DR. BRESSLER: I believe in the DRCR network trials they showed that patients who initiated anti-VEGF therapy but still had edema that was no longer improving on injections after, let's say, six months, might also get additional laser. And those eyes continued to have some improvement, so maybe that's a strategy we can consider in those patients.

Speaking of laser, this patient happens to have some proliferative retinopathy that you noticed, it just wasn't high risk, that is it probably wasn't extensive on the optic nerve or maybe there wasn't any preretinal hemorrhage. So when you see some proliferative retinopathy in someone with macular edema, maybe it's a tiny area of NVE, do you consider adding panretinal photocoagulation as well? How do you approach this patient who has proliferative retinopathy, it's just not high risk at this moment?

DR. SCOTT: This is a typical patient who would have the dual benefit from the anti-VEGF treatment. Anti-VEGF treatment such as ranibizumab has been shown to decrease the proliferative diabetic retinopathy characteristics, with the added benefit, of course, of decreasing diabetic macular edema.

Again, panretinal photocoagulation can be considered for non-high risk proliferative diabetic retinopathy or even severe nonproliferative diabetes retinopathy if there were perhaps an issue with patient compliance with follow-up appointments. I would feel more comfortable making sure that his diabetic macular edema were improved before I would consider initiation of panretinal photocoagulation.

I would also discuss the added benefit of potentially intravitreal triamcinolone for decreasing proliferative diabetic retinopathy, although intravitreal triamcinolone is not the ideal treatment as we'd previously eluded to given that patient's glaucoma suspect list.

DR. BRESSLER: So I think still today when we see proliferative retinopathy, even if we're giving anti-VEGF therapy, we might consider at some point adding panretinal photocoagulation. But I look forward in the future to finding out what the role of anti-VEGF therapy may be in these cases, and I think further study is ongoing.

With intravitreal corticosteroids, although they also decrease the risk of progression of proliferation, you still have the problem of causing cataract or increasing the chance of having problems from intraocular pressure.

That was a great summary of a challenging case that we typically see in diabetes, so we'll return in a moment with Dr. Adrienne Scott from The Johns Hopkins University.

DR. BRESSLER: Hello, I'm Dr. 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 Dr. Neil Bressler, course director of the program. Our topic is proliferative diabetic retinopathy. Our guest is Dr. Adrienne Scott, Assistant Professor of Ophthalmology at the Wilmer Eye Institute at Johns Hopkins.

We've been looking at how some of the new information Dr. Scott discussed in the newsletter issue can be applied at the bedside. So if you would, Dr. Scott, please present another case.

DR. SCOTT: Certainly, Dr. Bressler, thank you very much. A 40-year-old man is referred by his internist for a routine diabetic fundus exam. The patient is visually asymptomatic. The most recent hemoglobin-A1c measure is 6.5%. He has 20/20 vision in both eyes, but high risk proliferative diabetic retinopathy in his right eye with extensive optic disc neovascularization. His macula are flat without diabetic macular edema.

DR. BRESSLER: This, unfortunately, is all too common for people who have had diabetes for a long time They no problem with their vision and doesn't realize until someone examines them that they actually have high risk proliferative diabetic retinopathy, in this patient with a neovascularization at the disc which is extensive in the right eye. So how do you manage this patient who is asymptomatic?

DR. SCOTT: Dr. Bressler, this is a perfect candidate for initiation of panretinal photocoagulation. The diabetic retinopathy study told us that the risk of severe vision loss is certainly reduced when panretinal photocoagulation is administered.

Additionally, we're in a wonderful time where anti-VEGF treatment is also available, and I might consider treating this eye with high risk proliferative diabetic retinopathy characteristics with panretinal photocoagulation in combination with an intravitreal anti-VEGF injection, which may cause a rapid regression of his neovascularization.

DR. BRESSLER: When you decide, let's say, to just begin with panretinal photocoagulation — and let's put any additional anti-VEGF injections aside — how many sittings do you plan to do that in? Do you do that all at once with this patient, do you do it in two sittings, in three sittings, what do you recommend to the patient, and then how do you carry that out?

DR. SCOTT: I would certainly discuss with the patient what these clinical studies have shown regarding his risk of severe vision loss if panretinal photocoagulation is not introduced. I would offer him the option of either having the panretinal photocoagulation all in one sitting, or I might ask him if he can return for an additional visit, allowing us to break up the sessions of panretinal photocoagulation into two or more sittings to decrease his potential discomfort during the procedure.

Often, if there is any reason why the patient is unable to return for additional laser treatment, I am comfortable proceeding with the full panretinal photocoagulation treatment in one sitting. Studies have shown that there are not clinically meaningful differences in OCT thickness or visual acuity measurement when PRP is given in one setting versus PRP divided among four sittings.

DR. BRESSLER: I think it's interesting that you have emphasized that the person may come back for more than one sitting to help him tolerate the discomfort that might occur. But we really don't have evidence to suggest that if there is no macular edema at the start of the panretinal photocoagulation, doing it all in one sitting will cause any clinically meaningful increase in macular edema. That may not be true for the patient who already has both macular edema and proliferative retinopathy, but in those cases you might not only be doing panretinal photocoagulation and also considering an anti-VEGF therapy, as we saw in your newsletter.

Finally with this patient, are you concerned that if you were to add an anti-VEGF drug because perhaps the proliferation looks so exuberant you are concerned about whether the panretinal photocoagulation alone will be beneficial? We don't have any definitive evidence that adding anti-VEGF therapy might be better if you were to add it, so are you concerned about causing a rapid progression of any traction detachment? We often hear some of our colleagues discuss that.

DR. SCOTT: That's a great question, Dr. Bressler, that has been seen and certainly reported anecdotally in which the proliferative diabetic retinopathy rapidly contracts after initiation of anti-VEGF treatment, often within a day or so. However, we do not know in this particular patient if that might not have been the course of his natural proliferative diabetic retinopathy, regardless of any treatment.

I have also seen this happen to patients after panretinal photocoagulation in which the neovascularization regresses so rapidly it has also caused a vitreous hemorrhage or a traction detachment.

DR. BRESSLER: I think that's a great point. These cases where progressive traction detachment occurs after an anti-VEGF injection may have progressed. In

any event, they are often the very worst eyes where we're giving these treatments to begin with. So I think more information will be necessary to clarify that.

I think we have time for one more case, so please, Dr. Scott, please present the next case to us.

DR. SCOTT: Wonderful, Dr. Bressler. Here's a case of a 55-year-old woman who presents with complaints of decreased vision in her left eye. Her most recent hemoglobin-A1c measures 6.5%. Visual acuity measures 20/32 in the right eye, and 20/200 in the left eye. Her left eye has had multiple sessions of focal grid laser, as well as panretinal photocoagulation for high risk proliferative diabetic retinopathy in the past. She has bilateral pseudophakia and no known risk for glaucoma.

On optical coherence tomography, her right eye shows a few foveal cysts and a central subfield of 350 μm, while her left eye OCT shows extensive foveal cystic edema, with a broad epiretinal membrane in a central subfield of 600 μm.

DR. BRESSLER: This is certainly a challenging case because here we have marked decreased vision in the left eye, not only with extensive edema in someone who has had panretinal photocoagulation for proliferative retinopathy in the past and focal grid laser for diabetic macular edema, but also shows a broad epiretinal membrane that might be contributing to some of this thickening as well. How are you going to treat this patient?

DR. SCOTT: I would absolutely want a fluorescein angiogram here, in her left eye especially, to asses the status of the macular perfusion. If the patient has profound macular ischemia, her visual prognosis may be limited, and I would want to be able to counsel the patient as to what to expect visually. This patient may benefit from intravitreal anti-VEGF therapy, as the DRCR eye study did demonstrate a benefit for visual improvement and decreased OCT thickening with ranibizumab treatment, even if the patient has had prior focal grid laser treatment.

Intravitreal triamcinolone may also be an option in this patient with pseudophakia and no known glaucoma risk. What I would not consider is monotherapy with focal grid laser. It had previously been performed on her and is unlikely to provide substantial visual benefit in this situation.

DR. BRESSLER: In this situation where our greatest evidence perhaps may be to support the use of anti-VEGF therapy, is there a particular anti-VEGF agent you would start with in this case?

DR. SCOTT: Bevacizumab and ranibizumab are currently used as off-label treatments for diabetic macular edema, so there is no definitive right answer in this case. Both ranibizumab and bevacizumab have shown favorable results in improving vision and reducing macular thickness in eyes with diabetic macular edema; however, to date, ranibizumab has been more widely studied in the larger, randomized, controlled clinical trials.

At this point, I would be comfortable initiating treatment with whichever medication the patient and I decided upon. I would take into account her preferences and her financial status, and we would make the decision together.

Interestingly, an upcoming DRCR protocol is thinking about evaluating ranibizumab versus bevacizumab for the treatment of diabetic macular edema. So this may provide additional answers as to how best to treat such patients.

DR. BRESSLER: I think that information really will be useful, both for the individual and for society, given the large difference in cost of these two drugs.

So finally, let's say you started treating this patient with anti-VEGF therapy every month and now six months later the visual acuity remains somewhere between 20/200 and 20/20 in the left eye, and it looks like there has been absolutely no change to the edema, what other options you would consider? Would you consider, for example, vitrectomy in this case, and how would you approach that?

DR. SCOTT: That's a great question and it's certainly reasonable in this case to try, for example, an intravitreal triamcinolone injection. This patient would be ideal, given no known glaucoma risk in this case and the pseudophakic status. We would start potentially with an intravitreal triamcinolone injection, and if there were a favorable response with improvement in vision or decrease in macular thickness, we might consider a longer acting steroid implants in this case.

Vitrectomy is an interesting option. Vitrectomy with vitreomacular traction has been evaluated and it has

been shown to decrease macular edema; however, the visual acuity results have been inconsistent in such patients.

DR. BRESSLER: Well it's certainly a challenging case. This is one of those rare cases where we might then try intravitreal steroids when we have absolutely no response to an anti-VEGF drug, but then maybe it's something structural like the epiretinal membrane and we might even be going on to vitrectomy. So thank you for sharing such a challenging case.

Dr. Adrienne Scott from the Wilmer Eye Institute at Johns Hopkins, thank you again for participating in this eOphthalmology Review podcast.

DR. SCOTT: Thank you very much, Dr. Bressler, it has been my pleasure.

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