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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 volume 1, issue 1, of the eOphthalmology Review newsletter, "Diabetic Macular Edema."

Our guest faculty today is the author of that first issue, Dr. Jennifer Lim. She's from the University of Illinois at Chicago. This activity has been developed for ophthalmologists, including retina specialists.

There are no fees or prerequisites for this activity.

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

- Describe treatment options for diabetic macular edema according to the results of phase 3 clinical trials investigating anti-VEGF therapy for diabetic macular edema,
- Enumerate management options for patients with coexisting diabetic macular edema and proliferative diabetic retinopathy, and
- Discuss management options for patients who have co-existing diabetic macular edema and cataract.

I'm **DR. NEIL BRESSLER,** course director of eOphthalmology Review. On the line we have with us today Dr. Jennifer Lim, Professor of Ophthalmology and Director of the Retina Service at the University of Illinois in Chicago and the Department of Ophthalmology and Visual Sciences with the Illinois Eye and Ear infirmary in Chicago, Illinois.

Dr. Lim has indicated that she has received grants or research support from Regeneron, Genentech, and Allergan. She has also served as a consultant for Quark and has received honoraria from Genentech and Regeneron.

Our presentation today will include references to unlabeled or unapproved uses of bevacizumab and may include references to unlabeled or unapproved used of intravitreal corticosteroids.

Dr. Lim, welcome to this eOphthalmology Review podcast.

DR. JENNIFER LIM: Thanks, Dr. Bressler; it's my pleasure to be here today and to participate in this program.

DR. BRESSLER: Thank you very much. Let's look now at how we can apply current knowledge in treating diabetic macular edema from a case study perspective. So if you would, please tell us about our initial case.

DR. LIM: Our first patient is a 70-year-old man who presents with persistent diabetic macular edema in his right eye after having had 3 prior focal laser treatments for diabetic macular edema. Those treatments were spaced 3 to 4 months apart. Currently his visual acuity is 20/100 and he has 1+ to 2+ nuclear sclerosis. His OCT shows a central subfield thickness of about 300 microns at this point.

DR. BRESSLER: So we have a gentleman who is phakic, and you told me he has some vision loss. I don't know how much of that is from prior damage because of his macular edema, and his retina is somewhat thickened. As you said, his central subfield is 300 microns. Maybe, had he never had focal/grid laser, it might have been even thicker, but we know it's thickened right now.

My first question to you, when you see a patient who has had laser and still has some diabetic macular edema, do you typically get a fluorescein angiogram in these cases, and if so, what are you looking for on that angiogram?

DR. LIM: I typically do get a fluorescein angiogram initially, and there are several reasons for doing that. One of the first, obviously, is to see whether there is actual leakage and whether the leak, if present, comes from active macular edema, as opposed to, say,

ischemic edema. Also we want to see the extent of the laser treatment and whether an untreated microaneurysm is still in place.

DR. BRESSLER: So when you see that his retina is thickened and the fluorescein showed there was indeed leakage from microaneurysms and retinal telangiectasia in the areas of thickening, do you also look at the OCT for any morphologic abnormalities, besides just looking at the central subfield thickness?

DR. LIM: Yes. The OCT is very helpful for looking at the vitreoretinal interface, specifically looking for vitreomacular traction, which, as you know, Dr. Bressler, can also cause the retina to have edema. Another reason I look at the OCT is to see whether there is any evidence of an epiretinal membrane, which can cause traction on the retina and can also lead to edema. These areas of either VMT or epiretinal membrane can sometimes be hard to see clinically, but they can be elucidated by the OCT.

DR. BRESSLER: So let's say in the case you presented, this person with 20/100 vision has thickening of the central subfield. How would you go about treating him if the OCT showed no substantial epiretinal membrane, no obvious vitreomacular traction? Do you think all of the thickening is what we would consider typical diabetic macular edema? How do you go about treating that these days?

DR. LIM: These days, using the results that recently came out from the Diabetic Retinopathy Clinical Research Trial, I would consider using an anti-VEGF, either with laser up front with more later if there is room in this case; or perhaps use anti-VEGF monthly, for at least 4 treatments, see how the patient does, and then perhaps later add laser at about 24 weeks.

The other option to consider is steroids. In a patient with 20/100 vision, I would probably shy away from that because the patient already has a cataract, as I mentioned, 1+ to 2+ nuclear sclerosis, and I wouldn't want to aggravate that with steroids in his case.

DR. BRESSLER: Now let's say in this case we did decide to initiate an anti-VEGF therapy, you gave the person an injection of ranibizumab, and you were prepared to see him after a month. You might, as you said, add focal/grid laser, or you might wait to give focal/grid laser after you see whether the response was good.

As I understand it, the outcomes were similar, whether someone started with focal/grid laser at the same time they started with anti-VEGF therapy, or whether they waited to see a good response with anti-VEGF therapy, and then add the focal/grid laser let's say almost 6 months later. Is it correct that you could probably get similar outcomes in the first year, whether or not you started with the laser right away?

DR. LIM: That's absolutely correct, Dr. Bressler. DRCR results showed a change of an approximately 8- to 9-letter gain mean change at 1 year for the group with prompt laser versus the group with deferred laser. For that reason, we're still working out the timing of when to add the laser and whether laser is actually needed.

In the group that had deferred laser, approximately 70% who started with ranibizumab alone never needed laser at 24 weeks.

DR. BRESSLER: Are you concerned at all if this person had, for example, a myocardial infarction or a cerebrovascular accident, or stroke, let's say 2 years ago, because many people with diabetes indeed do have a history of these morbid conditions?

DR. LIM: That's a good point to consider; however, in all of the studies that have been done, there really is no safety signal for using ranibizumab in the DRCR studies at this time.

If a patient has had a recent stroke, however, I might defer ranibizumab if the stroke was within 1 or 2 months, then use laser first, and then possibly use ranibizumab a little later. But again, the data still have to be worked out further for that. I just want to emphasize that no safety signal has been seen in the studies to this point.

DR. BRESSLER: My last question on this case is, let's say you do initiate an anti-VEGF therapy at 4-week intervals, and you find after 4 or 5 injections that the retina is no longer thickened, neither clinically nor on the central subfield of the OCT. If you withhold treatment at that point, when do you see the person in follow-up? Are you concerned that the edema might come back? How do you approach it once you withhold treatment?

DR. LIM: I do very close follow-up of these patients, and I'll see that patient back in another month. And sometimes, yes, the edema will come back and I'll reinitiate therapy. But say I see the patient in another

month after withholding treatment for 1 month and they are still dry, then I might consider stretching the interval to perhaps 2 months and then see them back again, repeat the OCT, and repeat the clinical exam.

My threshold for retreatment is very low. If I see any evidence of thickening on the OCT and the vision drops with that, or even if the vision doesn't drop significantly, but is not, say, 20/20, I'll reinitiate therapy with ranibizumab.

DR. BRESSLER: I think this approach has been adopted recently by many people who are following patients very carefully over the first year. I think this is why many patients have been told, it took a long time for your retina to become thickened in the center, but now we have to treat it monthly until it is no longer improving, and then watch very carefully for edema to worsen or recur, and resume treatment if it does recur.

I believe the studies found that on average, 6 treatments were given in the first 6 months, but only 2 to 3 in the second 6 months, and then only 2 to 3 in the second year. So this is a little different from choroidal neovascularization in macular degeneration, where we fear that by stopping, we might lose some vision permanently. Here I think we've learned that a little thickening, perhaps that we pick up watching carefully, as you said, might be amenable to then resuming treatment. So I'm hoping this will be helpful.

Thank you for presenting that case. Now perhaps you could present another case where we discuss the management of diabetic macular edema.

DR. LIM: This next patient is a 29-year-old woman with 20/50 vision, a clear lens, and a central subfield thickness of 300 microns.

DR. BRESSLER: So in this very common scenario — and let's assume this patient has not had laser treatment previously for diabetic macular edema — how would you consider managing this case with some mild impairment of vision, 20/50, and definite thickening of the central subfield on OCT?

DR. LIM: Well, as you know, Dr. Bressler, the DRCR used ranibizumab in real patients whose vision was worse than 20/32, so technically she would have fit into that study. But clinically when I see these patients and their vision is still relatively good, the central subfield is mildly thickened, and they have never had laser, I would still consider focal laser treatment, especially in a young woman.

First, she could become pregnant. Anti-VEGF during pregnancy is not entirely studied at this time, so that might be consideration. Another consideration is that with relatively good vision like hers, although the risk of endophthalmitis is very small, less than 1 out of 1,000, I wouldn't want to risk that with this relatively good vision. It wouldn't be an incorrect choice to use ranibizumab; it's just a matter of risks and benefits in this young patient.

DR. BRESSLER: I think that is a very good point. Even though we learned that anti-VEGF therapy for diabetic macular edema gave superior results overall for one group compared with another group getting focal/grid laser, that doesn't mean that we still cannot consider focal/grid laser. Indeed, I think about 30% of the people who got focal/grid laser had improvement, and less than 15% had substantial worsening. So we have gained another treatment, but it doesn't mean we cannot consider certain features of a patient, as you just explained in this patient, that might make a physician want to use focal/grid laser in one case but perhaps consider anti-VEGF therapy in another.

Let's say in this case that you did decide to apply focal/grid laser Can you tell me where exactly you place these laser spots?

DR. LIM: I do my treatment based on fluorescein guidance. First, I would shoot a fluorescein. Obviously we had already done an OCT, and I would treat the microaneurysms I see. Then in areas where there is diffuse leakage, I would put a grid treatment into that area so that I had a nice pattern of treatment wherever the retina is thickened.

DR. BRESSLER: If you see microaneurysms in areas that are not thickened, even though you can detect them on the fluorescein angiogram, would you tend to observe those or would you add laser to areas that are not thickened?

DR. LIM: In general, we want to treat the thickened areas based on the ETDRS. So if we see a microaneurysm in a totally flat retina, there is no treatment guideline for treating that area. In that case, I might not treat it. If it's a juicy aneurysm, we might consider it, but in general, no.

DR. BRESSLER: Now let's go back to our patient and let's say another physician, and the patient's needs or wants led to the decision to initiate anti-VEGF therapy with ranibizumab. The initial injection is given today, and the patient calls you back the next afternoon and says she is having a lot of pain in her eye. How do you handle the management of someone who calls back 24 hours after the injection and says she is beginning to get a lot of pain in the eye?

DR. LIM: I think it's imperative to tell that patient that she must come in right then and there and see you, or if it's the middle of the night she could see your fellow or resident at the university. But she really must come in as soon as possible. And I would tell her that the worst possible thing, of course, that it could be, is endophthalmitis and because of that possibility, if she doesn't come in she could lose her vision permanently without treatment.

You know, of course, it could be other things. Perhaps the Betadine is irritating her and she is getting some corneal or conjunctival irritation, or perhaps she even has a corneal abrasion, but we really have to rule out the most devastating possibility, which is endophthalmitis.

DR. BRESSLER: And finally with this case, related to the concern of endophthalmitis, I think we have to warn every patient every time they are getting an injection. The risk may be 1 in 1,000 injections and given that we give these people perhaps 10 injections over a year or 2, the risk in a person may be 1 in 100, but regardless, the risk is not zero.

What do you do on the day of injection with respect to any topical antibiotic drops? Do you give any? Do you consider giving them? How do you approach the use of topical antibiotic drops?

DR. LIM: I personally do not use topical antibiotic drops on the day of the treatment, but I am very meticulous in cleaning off the lid area, not necessarily rubbing the lashes, but cleaning the lid margins carefully with the Betadine, and then putting Betadine through the conjunctival area where I am going to inject, flushing that out, and then putting a swab right on the spot where I'm going to treat the patient. I wait at least 30 seconds to allow the Betadine to kill off the bacterial flora in that area.

I send patients home on antibiotics. I'll tell them to use whichever antibiotic I choose, 4 times a day for 3 days. There really is no data to support the use of that other than common clinical practice, which even now in 2011 is changing. Some people may or may not use antibiotics. But I think really the crucial thing here is the pre-treatment aseptic technique and cleaning the lids and the conjunctival area.

DR. BRESSLER: I think those are very good points.

DR. LIM: I did want to add one thing, and that is, I do use a sterile lid speculum to open up the eye during the injection. I also use the drape or gloves, although probably the crucial part is using a lid speculum.

DR. BRESSLER: I see. I think we have learned that meticulous attention to antiseptic technique, to make sure that needle is sterile, the drawing up of the drug is sterile, and there is antiseptic like povidone iodine over the spot where you inject, may really be key to preventing endophthalmitis. And as you said, there is no strong scientific rationale to give any antibiotic drops afterward, because it doesn't concentrate in any sort of effective way in the vitreous, so many people, as you said, are not giving any antibiotic drops now, and I think that's a reasonable alternative.

I want to thank you for discussing that case. We'll return in a moment with Dr. Jennifer Lim from the University of Illinois Eye and Ear at Chicago to discuss our next case.

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.

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For more information on registration, to receive eOphthalmology Review without charge, or to look at archived issues, please go to www.eophthalmologyreview.org. Thank you very much.

DR. BRESSLER: Welcome back to this eOphthalmology Review podcast. I'm Dr. Neil Bressler, course director of the program. Our topic today is diabetic macular edema, and our guest is Dr. Jennifer Lim. Dr. Lim is Professor of Ophthalmology at the University of Illinois in Chicago, with the Illinois Eye and Ear Infirmary.

We've been looking at how some of the new information that Dr. Lim discussed in the newsletter issue can be applied at the bedside when we are treating patients with diabetic macular edema. So Dr. Lim, if you would, please present another case for us to discuss.

DR. LIM: Our next patient presents with 20/200 visual acuity and has a 2+ to 3+ nuclear sclerotic cataract and diabetic macular edema in her eye.

DR. BRESSLER: So when you have a patient who has substantial cataract, yet you can still see perhaps on clinical exam and even on OCT that there is substantial diabetic macular edema, how do you coordinate whether to treat the diabetic macular edema, whether to take the cataract out, or do both within a short period of time? How would you approach this case with respect to those management problems?

DR. LIM: First and foremost, when I treat patients with diabetic macular edema and a cataract, I want to get that diabetic macular edema under control. So as long as the view allows me to, I'll treat the diabetic macular edema first, and once that is under control, I'll refer the patient for cataract surgery. Of course, sometimes that's not possible, and if your view is not good enough to safely treat the patient, I would refer the patient first to have the cataract out and then promptly treat them after their cataract surgery.

DR. BRESSLER: Now let's take a very typical approach where perhaps you initiate an anti-VEGF therapy. You started monthly ranibizumab in this case because you learned that's an excellent treatment that is actually superior to focal/grid laser on average for people who present with diabetic macular edema.

So you have started your monthly treatments and the edema is starting to go away, but it's been 4 or 5 months and it's still not all gone and the cataract is getting worse. So you and the patient decide that even though the edema is not all gone, I really need to function by removing that cataract. So you refer the patient to a cataract surgeon. How do you time your continued intravitreal injections, while at the same time you are having this person see an ophthalmologist for cataract surgery?

DR. LIM: I think it's key that you continue the treatment of that patient, but you also want to make sure you don't jump in too soon after the surgery to allow the wound to heal. So although there really is no data on this, I usually will give them about two weeks after the cataract surgery, then see them and start treatment again by week 3 or so.

That said, the DRCR, the Diabetic Retinopathy Clinical Research Network, is studying whether preexisting macular edema worsens after cataract surgery.

DR. BRESSLER: I know after two years in one of the diabetic retinopathy clinical research network studies of DME, about 14% of patients who received ranibizumab injections had cataract surgery, and I'm not aware of any distinct wound problems that were reported. So maybe you're right that there is really no obvious clinically relevant effect on wound healing and we just have to have the cataract surgeon treat it as they may.

Now let's say, the patient does have cataract surgery and you are still following and treating the edema, and right before the cataract surgery the retina central subfield on OCT was 280 microns. The patient comes back to you a month after the cataract surgery. It's been a month since you last injected, because the surgery was done soon after your injection, and the retina is 400 microns in the central subfield. Suddenly for the first time there is a substantial increase.

How would you manage that? Would you get a fluorescein angiogram or just continue your injections? What do you do with that sudden increase in thickening after cataract surgery when you have been treating diabetic macular edema with an anti-VEGF drug?

DR. LIM: I think that's a very realistic scenario, and I don't get too excited by it. Because after cataract surgery, as you know, you can induce cystoid macular edema. Inflammatory cytokines that can contribute to macular thickening are released. And even in patients who aren't diabetic, there are cases of subclinical macular edema.

I think perhaps the surgery exacerbated the edema that was present before, so I would just go ahead and treat them as I was beforehand.

DR. BRESSLER: Now my final question in this case is, let's say you did treat it and the edema has improved, but it's not all gone. It's been a year and you've been treating and getting rid of most of the edema, and now the capsule becomes opaque so that you or the cataract surgeon is considering a YAG capsulotomy. Anything special we should consider as we continue these anti-VEGF drugs in the setting of a YAG capsulotomy?

DR. LIM: I have done that in my patients, and I don't believe there is anything unusual to consider in these patients. I would just go ahead and do the YAG laser, and then continue my anti-VEGF injections as before.

DR. BRESSLER: Thank you very much for discussing this complicated situation where we have to coordinate both the treatment of diabetic macular edema and consider cataract surgery.

I believe we have time for one more case, so Dr. Lim, I would like to ask if you have another case you can present to us in the management of diabetic macular edema?

DR. LIM: I do have another case. Our last patient is 40 years old and he complains of recent floaters and blurred vision in his right eye. On exam, he has clinically significant diabetic macular edema, but also NVD with fronds emanating off the nerve and multiple areas of neovascularization elsewhere in his right eye.

DR. BRESSLER: This is a different case. Now we not only have to consider treating diabetic macular edema, but at the same time deal with proliferative diabetic retinopathy. When you have both of these situations, how do you approach the management of both the DME and the proliferative diabetic retinopathy?

DR. LIM: Before the anti-VEGF, I would do PRP to treat the PDR, as well as put in focal at the same sitting. I think it's crucial not to forget that we really must treat the PDR, and at this point PRP is the proven therapy for that.

So for this patient, I would put in the PRP and consider either focal laser treatment at that time or use an anti-VEGF that will treat not only the macular edema but will also have an effect on the PDR.

Currently there is a protocol in the Diabetic Retinopathy Clinical Research Network that is looking at this use of anti-VEGF with PRP for eyes with PDR and macular edema versus using focal laser and PRP alone without the adjuvant anti-VEGF. We'll know the answer to that a few months down the road.

DR. BRESSLER: When you put the panretinal photocoagulation into the eye, do you put all the spots in at once for 360 degrees, or do you break this up into several sittings?

DR. LIM: I personally put all of my spots in at one sitting. A study by the Diabetic Retinopathy Clinical Research Network looked at eyes that had no macular thickening but did have proliferative diabetic retinopathy that required PRP. Investigators in that study gave the PRP either in 1 sitting or in 4 sittings, and at 16 weeks later, there was a slight increase in the macular edema in the eyes that had single-session PRP. But at 1 year, there really wasn't any difference.

So long-term, doing either 1-session PRP or 4-session PRP really doesn't affect the incidence of diabetic macular edema at 1 year in retinas that were flat beforehand. So I go with 1-session PRP.

DR. BRESSLER: Of course, as you emphasized, those eyes did not have diabetic macular edema, as the current case does, so I agree with you that we have no strong evidence to say we're going to seriously worsen the DME in the long run. I think someone could choose either approach until we get more information

about how much diabetic macular edema is worsened, perhaps, in the presence of PRP.

My next question deals with adding the anti-VEGF drug when you have someone, as you described, with some neovascularization at the disc and elsewhere. As you described it, there was no obvious tractional component in this eye, and yet it does have proliferative diabetic retinopathy. Are you concerned that the anti-VEGF drug may in some way cause more traction in this case and cause a traction detachment of the macula?

DR. LIM: In this case I'm not concerned by that. There is no existing traction retinal detachment. Cases in the literature have looked at progression of traction retinal detachments caused by fibrosis after administration of an anti-VEGF, but even in those cases it's a pretty rare event. Also, in the DRCR protocol that is looking at the use of anti-VEGF in eyes with macular edema and PDR, I believe to this point no cases of progression or development of TRDs have been seen in such eyes.

DR. BRESSLER: So again, these are very good points to emphasize. We do know that when you have substantial traction detachment with or without anti-VEGF injections, the person, unfortunately, is at high risk of having progressive traction detachment. That's why we often go on to operate on those eyes.

But as you said, at least for the cases enrolled in the Diabetic Retinopathy Clinical Research Network, we have little if any evidence to suggest that ranibizumab injections caused progressive traction detachment of the macula.

I want to go to one final question in this case. Let's say you did get some resolution of the proliferative retinopathy and some of the macular edema as going away, but it's not all gone, and now the person walks back with a complete panretinal photocoagulation, yet the vitreous separates and causes some vitreous hemorrhage in the absence of any additional retinal neovascularization. How would you manage that new vitreous hemorrhage while you are still trying to treat the diabetic macular edema, assuming you can still see that the retina is attached?

DR. LIM: Assuming the retina is attached, the OCT can still be taken, and you can see how thick the macular area is, I would consider using an anti-VEGF. Now obviously, if the hemorrhage is too dense and you give it a month to clear but you still can't see in, I would consider doing a vitrectomy, sooner rather than later, to clean out the eye so we can continue to treat and manage the patient, and follow with OCT.

DR. BRESSLER: Thank you very much for discussing this challenging case and all the cases for our podcast. This has been Dr. Jennifer Lim from the University of Illinois at Chicago and Director of Retina Services at the Illinois Eye and Ear Infirmary. Thank you for participating in this eOphthalmology Review podcast.

DR. LIM: Thank you, Dr. Bressler, it was really fun to have this discussion with you for these patients with diabetic macular edema.

DR. BRESSLER: Thank you again.

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