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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

On the Horizon: Strategies for Surgical Success of Durable Anti-VEGF Delivery in nAMD and DME

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Dr. Awh:
The quest for durable anti-VEGF suppression has led to tremendous developments in our field. Now we are on the forefront of new technologies to bring to the office and to the operating room. Today, we're going to talk about some of these.

This is CME on ReachMD. I'm Dr. Carl Awh, and I'm pleased to be joined today by Dr. Peter Campochiaro. Peter, welcome.

Dr. Campochiaro:
Thanks Carl. It's great to be with you.

Dr. Awh:
Great to have you, too. Let's get right down to it. There's the Port Delivery System [PDS] with ranibizumab and some gene therapies in clinical development. These have the potential to provide long-term effective VEGF suppression. Can you give us a brief overview of these strategies?

Dr. Campochiaro:
Sure, Carl. The Port Delivery System is an implantable, refillable reservoir that provides continuous delivery of ranibizumab into the vitreous cavity. Its basis is diffusion down a concentration gradient from the implant into the vitreous cavity. And pharmacokinetics have shown that there are therapeutic levels throughout an entire 6-month interval in between refill exchanges. So it's really an extremely reliable delivery platform.

A gene therapy involves intraocular injection of an adeno-associated viral vector that expresses an anti-VEGF protein so that retinal cells continuously produce the therapeutic protein. RGX-314 is an AAV8 vector that expresses and anti-VEGF Fab that's very similar to ranibizumab. It's being tested by 2 routes of delivery: subretinal injection and suprachoroidal delivery.

ADVM-022 is an AAV vector that was developed by David Schaffer at UC Berkeley by directed evolution and it expresses aflibercept. It has reduced binding to the internal limiting membrane compared to most AAV vectors and so it penetrates better into the retina, and it's being tested by intravitreous injection.

Dr. Awh:
Thank you, Peter. You know, this is a very exciting time to be a retina specialist and, again, to be a retina surgeon. To hear more about the things we'll discuss today and other developments in the field, you can check EyeHealthAcademy.org.

Peter, we've both been involved in the clinical trials of the Port Delivery System. There's definitely a learning curve both to the

implantation of the device and the refill. Can you take us through some video and a description of the implantation procedure?

Dr. Campochiaro:
Sure, Carl. You know, at the beginning of the case, a 27-gauge infusion cannula is inserted, but it's not turned on. The first key is to take good care of the conjunctiva and Tenon's capsule. A peritomy is made in the supratemporal quadrant with a radial incision near the horizontal meridian, and then dissection is done along the scleral surface trying to keep Tenon's attached to the conjunctiva. The second key is hemostasis. And episcleral vessels are cauterized so that there's no bleeding near the sclerotomy site. Then the third key is to make a scleral incision 4 mm posterior to the limbus that is exactly the right size: 3.5 mm. if the incision is larger than that, it can lead to instability of the implant. So first of all, you should measure throughout the procedure, and if it is larger, a suture should be put in to make sure the opening is exactly 3.5 mm. The sclera is incised to expose the pars plana and then it's treated with laser photocoagulation using long duration overlapping burns going back and forth several times to completely char the pars plana. And then usually there's some oozing of fluid to tell you that the endpoint has been reached. The PDS is then inserted into the wound and rotated gently until it pops into place. The fourth key is to never turn the infusion on when the wound is not plugged to avoid vitreous prolapse. And usually the infusion is not needed, but if they eye is soft, it can be turned on once the wound is plugged with the PDS. That facilitates insertion. And after insertion, the PDS is gently tamped down to make it flush with the sclera to minimize protrusion.

Dr. Awh:
Thanks, Peter. Yeah, as with all new surgical techniques, we're continually refining our understanding and our abilities.

Let's look at some videos now that point out how important meticulous handling of conjunctiva and Tenon's is when we're doing the implantation procedure.

This surgeon intended to bury the knot, but the knot will end up at the entry point of the needle bite, not the exit. It's apparent that this entry point is quite a bit back from the limbus. Surgeons are instructed to bring conjunctiva and Tenon's capsule to the limbus. Even this non-buried bite is made too far back from the limbus. These sutures resulted in a peritomy edge which is well back from the limbus.

The exposed sclera visible at the end of the case is even more apparent postoperatively as conjunctiva often retracts after surgery. This case highlights the importance of bringing both conjunctiva and Tenon's capsule fully to the limbus or even slightly overlapping the limbus.

Next is a case that really bothers me. The surgeon makes the entry wound too close to the cut edge of the peritomy. Even though the implant is nicely seated, its optimal location would have been closer to the base of the peritomy. But because the implant is too close to the edge of the peritomy, these sutures end up overlapping the implant flange. The reason this case particularly bothers me is that it was one of my first cases in the LADDER study. Because the wound closed easily and without tension, I finished the case thinking things would be fine. However, here's what happened: conjunctival erosion. Since this case, I've always made sure to place the implant close to the base of the peritomy and take a better bite of sclera with my first limbal suture.

Here's another example of conjunctival erosion. Many surgeons use a traction suture to help position the eye during the implantation procedure. This surgeon decided to use the same suture to close the peritomy. This resulted in the apex of the peritomy flap being pulled away from its original location, leaving a wedge of exposed sclera. Additional sutures were placed, but you can see the tension on the tissue in this area, while the edge of the peritomy on the other side of the first suture is slack and droops away from the limbus. This case demonstrates the importance of that first suture to close the apex of the peritomy. It should be correctly positioned with no obvious tension on the conjunctival flap.

Finally, here's an example of a very nice closure. First, note that the implant is placed near the base of the peritomy flap. The surgeon is careful to get a good bite of sclera, conjunctiva, and Tenon's capsule. It's important to bring both layers to the limbus and to place as many sutures as necessary to ensure good closure with no exposed sclera. Because the implant was inserted close to the base of the peritomy, the sutures end up far from the implant. There's no visible tension on any part of the closed peritomy. The image on the right is a typical successful post-op appearance.

These cases demonstrate the importance of meticulous attention to closure of conjunctiva and Tenon's.

For those just tuning in, this is CME on ReachMD. I'm Dr. Carl Awh, and joining me today is Dr. Peter Campochiaro. Today, we're talking about innovative techniques for delivering durable VEGF suppression in neovascular AMD and for diabetic macular edema.

Dr. Campochiaro:
Carl, we've talked about how the Port Delivery System is implanted. The other important feature is that it's refillable. Can you tell us how the implant is refilled and how frequently that needs to be done?

Dr. Awh:
Well, in the phase 3 ARCHWAY study, we are refilling the implant at 6-month intervals, sooner if necessary. However, in the phase 2 LADDER study, many patients were able to go much longer than this between refills.

The important thing for doctors to understand is that this is not an intravitreal injection. It is really an exchange of the contents of the Port Delivery System. It's critical to use a special dual-lumen needle with a special refill syringe. We can see in the video that being perpendicular to the PDS is important. The syringe and needle is pushed into the PDS through the hub. As fluid is pushed into the PDS, the old fluid is removed. So it's an exchange, not an injection. To approach the PDS from a perpendicular angle is quite important. It actually tends to take higher magnification and possibly more lighting than for a standard intravitreal injection.

Peter, with such a long duration of effect and such a long time between refills, how should we interpret small amounts of fluid that we may see on OCT in patients with the PDS?

Dr. Campochiaro:
That's a really important question, Carl, because the situation is different with sustained delivery of ranibizumab compared to intermittent injections. The sustained delivery results in constant coverage and so there can be some fluctuation in the amount of fluid, but small fluctuations really are not of great clinical significance because there's constant treatment on board.

Dr. Awh:
Thank you.

Let's move on to gene therapy. There are 2 delivery strategies being considered for RGX-314. Peter, can you walk us through those strategies?

Dr. Campochiaro:
Sure, Carl. Now subretinal injection of vector is done in the operating room after vitrectomy and induction of the PVD if one's not present. It's reasonable to take your time when positioning the needle. And you can use various cues such as the shadow of the needle. When the shadow comes together with the tip of the needle, that indicates that you're at the retinal surface. Another indicator is when you can indent the retina and then pull back until it's right at the surface of the retina. Here you see the bleb being raised. And it's important to keep the needle perpendicular and to keep the tip within the bleb and slowly inject and draw back slowly and avoid any horizontal movements of the needle that can enlarge the retinotomy.

Now, for suprachoroidal injection, this is done with a microneedle injector. After administration of proparacaine and 5% betadine, a caliper is used to measure 4.5 mm behind the limbus and a 900-micron needle is positioned perpendicular to the surface and slowly advanced through the sclera with gentle pressure on the plunger. While the tip of the needle is within the sclera, there is resistance that prevents any injection. As soon as the needle tip passes into the suprachoroidal space, there is a release of resistance, which allows the injection to begin. So this video shows an IR [infrared] image which illustrates the spread of the vector into the suprachoroidal space. You see the difference in temperature is that blue, and it spreads in the suprachoroidal space.

Dr. Awh:
Thank you, Peter. That's really very exciting. I think the Port Delivery System and these gene therapy approaches are great illustrations of how ophthalmology and retina, in particular, remain an amazing blend of both medicine and surgery. It will take the skill of the surgeon combined with these tremendous breakthroughs in drug therapy to bring these benefits to our patients.

In the last few minutes, let's discuss how we see these potential new durable anti-VEGF approaches impacting our practices. Peter, how do you see yourself bringing this into your practice?

Dr. Campochiaro:
Well, I anticipate that the PDS will be approved for patients with neovascular AMD later this year. And I expect that uptake will be pretty rapid. Initially, it'll be used for patients who are requiring frequent injections, perhaps every 2 months or less. Patients will probably be seen a week after implantation and a month after implantation to make sure there's good conjunctival cover, as you stressed, and no other complications. I think patients will also be seen maybe 4 and 5 months after the implantation to make sure that there's no large or substantial increase in macular fluid which would prompt an early refill exchange.

I think after 2 cycles, refill exchange cycles where patients go the full 6 months, I think most of those patients will just come in every 6 months for a refill exchange. However, it's important to educate patients regarding potential complications that would require an urgent, unscheduled visit. And I anticipate giving out my cell phone number and asking patients to contact me if they have any issues such as a red eye, pain, or any sort of discharge.

I think we need more data to see how gene therapy will fit in, but I don't see the PDS preventing future innovations. There are still

physicians who have concerns about potential retinal toxicity from sustained suppression of VEGF. The PDS will eliminate those concerns and show the retina community that sustained suppression of VEGF is really the best way to treat neovascular AMD. That will stimulate innovation to find new ways to achieve that sustained suppression, including gene therapy.

Carl, what do you think?

Dr. Awh:
Well, as usual, Peter, I have very little to add to what you've said, other than I probably won't give people my cell phone. But if you don't mind, I might give them your cell phone number.

Well, that's all the time we have today. I'd like to thank the audience for joining us and, Peter, thank you very much for spending this time with me.

Dr. Campochiaro:
Thanks for having me, Carl.

Announcer:
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