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How Gene Therapy Is Designed to Work in Retinal Disease

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Dr. Vajzovic:
I'm Lejla Vajzovic. Here with me today, Szilárd Kiss. Gene therapy for neovascular AMD is on the horizon. Szilárd, how does this work, and how does it compare with intravitreal anti-VEGF injections?

Dr. Kiss:
Thank you, Lejla. The concept of gene therapy for AMD really relies on delivering the anti-VEGF gene and having the eye turn into a biofactory. So we're not replacing any gene. There's not genetic abnormalities that we're trying to fix as we do in other conditions. We're using the eye to make this drug instead of injecting it episodically.

When we think about a gene therapy broadly, we think about 3 things: what is the capsid being used? What is the route of delivery? And what is the gene that we're actually delivering? There are 3 gene therapies for wet AMD that are in late-stage trials. I'll start with ixo-vec. Ixo-vec uses an engineered AAV7m8 capsid that carries the gene for something akin to aflibercept.

You can deliver this in the office by an intravitreal injection. Once a patient gets an intravitreal injection, the gene for aflibercept is made inside the eye, and aflibercept is produced for potentially years following just 1 single intravitreal injection. So instead of a patient getting those injections, the eye makes it itself.

Sura-vec is slightly different. Sura-vec uses an AAV8 vector that requires a subretinal delivery. In this case, a patient is taken to the operating room, and a subretinal bleb is made. The vector then transduces the cells and produces a transgene something akin to ranibizumab. Following that delivery, the eye makes ranibizumab once again for years to come.

And finally, 4D-150 is another intravitreal delivery of something akin to aflibercept and, in addition, an RNAi. This particular gene therapy for wet AMD uses a capsid called R100. This is allowed to be delivered in the office following intravitreal injections like we do for other therapies. Similar to the 2 previous therapies I described, 1 delivery allows the eye to turn into a biofactory to produce the molecule and the transgene, obviating the need for repeated injections or at least decreasing it significantly.

Now, when we think about certain considerations as these therapies can potentially come onto the market, you know, we've got to think about the target in terms of how we deliver it. Is it in the office by an injection? Is it the operating room? And there's also a suprachoroidal program that uses sura-vec.

Vector exposure: You know, the body can be exposed to more of the vector via intravitreal injection as opposed to subretinal delivery. But the procedural complexity is obviously very different, with subretinal being a little bit more complex having to take patients to the operating room. Then steroid prophylaxis comes into play really in the intravitreal delivery because of that exposure to vectors.

So the ocular biofactory is on the brink. Instead of injecting every 4 weeks, 16 weeks, or every 6 months, it has the potential for many

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patients to be one-and-done and the potential to significantly decrease that treatment burden by producing anti-VEGF in the eye.

Dr. Vajzovic:
Thank you, Szilárd, for going over some of the gene therapy options coming down the pipeline, so to speak, in investigational clinical trials. I think you nicely highlighted really the anatomic targets in terms of intravitreal subretinal approaches, and what does that mean in terms of vector exposure, steroid prophylaxis, and just in general procedure complexity. I think we all will agree that monitoring, after these, will have certain implications as well, but ultimate goal is to really provide long, durable treatments and minimizing need for recurrent injections.

Well, this has been a great discussion. Stay tuned for our next episode, where we'll take a closer look at the gene therapies for treating neovascular AMD. Thanks for listening.

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