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Adverse Event Mitigation in Gene Therapy for nAMD

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Dr. Kiss:
I'm Szilárd Kiss. Here with me today is Carl Regillo. Carl, multiple anti-VEGF gene therapies are on the horizon for neovascular AMD. How safe are these treatments? Who should be getting them?

Dr. Regillo:
Let's start with safety. I can answer that right off the bat. Where we stand now in phase 3 testing, we're seeing actually very good safety across the board with all the programs. So what are the programs? I know we've talked about this. The way I think of it, or I'll categorize it, is there's 3 companies making 3 gene therapy products being tested for wet AMD, but 4 programs. And the reason why there are 4 programs is because 2 programs are intravitreal, and 1 product is being tested both subretinal and suprachoroidal. Why does it matter? Well, it definitely changes the side effect or adverse event profile and the safety. So there's pros and cons to all these approaches.

There's not 1 perfect way to deliver gene therapy. So what are the adverse events or side effects that have been seen? Well, when you inject an intravitreal gene therapy intravitreally, you can expect, if you didn't put on any steroid prophylaxis, you can expect inflammation up front early on, and potentially even later on. But we knew that. So intravitreal, we have to suppress inflammation. Inflammation has actually been seen in clinical trials, especially higher doses. It is dose-dependent. So going from phase 1 to phase 2 into phase 3, we've been able to fine-tune the dose of intravitreal gene therapy, that is, with both ixo-vec and 4D-150, to optimize efficacy and minimize the inflammation or breakthrough of inflammation through a course of prophylactic corticosteroids in the form of steroid eye drops, mainly difluprednate. For subretinal gene therapy, the sura-vec injected in the subretinal space requires a vitrectomy. So side effects or adverse events can be related to doing the surgical procedure, and that includes retinal tear, detachment, endophthalmitis. And retinal detachment actually has been seen. From the product itself in the subretinal space, it's actually very well tolerated. It's immune privilege for the most part, and we're not seeing inflammation other than what you see in a typical vitrectomy. We don't see it later on or presumably from the gene under the retina per se. But at higher doses, you can see significant RPE changes, and it can be quite dramatic and severe. In this program, we're injecting the gene product in the peripheral retina. So if you're going get RPE changes, tends to be peripheral retina. If that happens to occur in the macula, if the RPE changes occur in the macula, and it has happened at higher doses, it can affect the vision. There's been vision loss. So that's a potential, quite severe adverse event, with subretinal gene therapy. And then suprachoroidal, you do get inflammation. It tends to be anterior in nature. It tends to be on the eye wall at the site of the injection, so you can get episcleritis, localized scleritis, and anterior chamber inflammation, anterior chamber cells. And so that program, with the varying doses as it's gone up in dose, has required topical steroid prophylaxis.

Going a little deeper into the steroid prophylaxis, we've learned you need a long course. Now into phase 2 and 3, typically what occurs with intravitreal gene therapy in the protocols is you start with topical difluprednate at 4 times a day starting before you do the gene

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therapy, and then you carry on with a very slow taper, typically over around 5 months, give or take. And that usually does the trick as long as the dose is at an appropriately low level, enough to give good efficacy but not too high to get breakthrough inflammation, while you're tapering the steroid or later on after you've tapered off the steroid. And so far, so good. At the doses being used in phase 3, it has been very well tolerated both during the prophylaxis and very little recurrence thereafter. But we'll know more when the phase 3 program reads out, of course. For subretinal, there have been modifications in the surgical approach to minimize the pigmentary changes by lowering the dose and also to minimize the effects of the pigmentary changes by injecting it further away from the macula, typically inferior retina. And then suprachoroidal, we talked about steroids again being used topically for a given period of time to help suppress the inflammation that can be seen. So inflammation—and keep in mind with inflammation also means the potential for elevated intraocular pressure. So that also needs to be considered.

In regarding who may benefit, certainly the people you think of first will be the patient getting frequent injections, but it's important to realize they should also be good responders.

So good response, but the need for frequent injection to help decrease treatment burden and get better long-term vision outcomes.

Dr. Kiss:
Thank you. So efficacy is going be the key, but we need to make sure these therapies are safe. For the intravitreal approaches, it's really a dose-dependent inflammation in the eye controlled by steroids. For the subretinal approach, it's really around the pigmentary changes and peripheral retinal thinning.

Well, that's all the time we have for today. Coming up, we'll discuss some of the tips and tricks for administering these gene therapies, so stick around.

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