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Gene Therapy for Hemophilia B: Assessing Long-Term Safety and Efficacy

Announcer:
You're listening to *Clinician's Roundtable* on ReachMD, and this episode is brought to you by CSL Behring. Here's your host, Dr. Brian McDonough.

Dr. McDonough:
Welcome to *Clinician's Roundtable* on ReachMD. I'm Dr. Brian McDonough, and joining me to discuss new four-year post infusion data for etranacogene dezaparvovec in patients with hemophilia B is Dr. Doris Quon. She's the Medical Director of the Hemophilia Treatment Center at Luskin Orthopaedic Institute for Children in Los Angeles. Dr. Quon, thanks for being here today.

Dr. Quon:
Glad to be here.

Dr. McDonough:
Let's dive right in, Dr. Quon. What's the significance of the HOPE-B trial on etranacogene dezaparvovec in the treatment landscape for hemophilia B?

Dr. Quon:
Well, etranacogene dezaparvovec is the first gene therapy that was approved for hemophilia B, and it was based on the HOPE-B clinical trials. And what does that mean? Gene therapy offers to patients with hemophilia B the potential to have reduced or eliminated bleeding events, sustained bleed protection, and increased long-term factor IX levels. It offers the ability to decrease their treatment burden and the potential to eliminate or reduce prophylaxis through a one-time infusion. And what is prophylaxis? Well, prophylaxis is regular infusions of factor IX for severe or moderately severe hemophilia patients. The severe or moderately severe hemophilia patients can develop spontaneous bleeding, and in order to prevent that bleeding, they need to take regular infusions. And so having this one-time gene therapy with etranacogene dezaparvovec will give them higher factor levels, so they may be able to eliminate their need to take factor on a regular basis intravenously. So it decreases their treatment burden through this one-time infusion of the gene therapy. And ultimately, I think that it would improve their quality of life.

And finally, this is not always thought about, but the long-term impact, or economic impact, could be a financial benefit because it's—again—a one-time infusion, and normally patients will take their regular prophylaxis infusions on a weekly basis.

Dr. McDonough:
Now, if we zero in on the new four-year data, what were the findings on annualized bleeding rates in these patients?

Dr. Quon:
So what they found was that there was about a 90 percent reduction in their bleeding rates. So what was unique about the HOPE-B trial was that the patients, before they got the gene therapy, were able to log their bleeds and their factor use, and then we were able to do a comparison. So a before and after, if you will. So after the infusion, we found that all bleeds—spontaneous bleeding, as well as joint bleeds, which are sort of the hallmark of hemophilia bleeding—70 to 90 percent of the bleeds occur into the joints in the patients with severe or moderately severe hemophilia. And so all the bleeding, spontaneous as well as the joint bleeds, was reduced, and about 70 to even 85 percent of the bleeds were reduced compared to before they took etranacogene. And in terms of the joint bleeds, they went down significantly, and about 60 percent of the patients experienced no joint bleeds over the four years. So I think that's a really good impact on the bleeding—their annualized bleed rate.

Dr. McDonough:
And as a quick follow-up to that, was there any difference in annualized bleeding rates across participants who are NAb positive or negative?

Dr. Quon:
The therapy was effective in patients with pre-existing neutralizing antibodies, so there were no major differences that they were able to really discern between being neutralizing antibody positive or negative in my understanding.

Dr. McDonough:
For those just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm Dr. Brian McDonough, and I'm speaking with Dr. Doris Quon about recently released four-year data on etranacogene dezaparvovec for hemophilia B.

So if we continue to explore the efficacy findings, Dr. Quon, what should we know about endogenous FIX activity levels over time?

Dr. Quon:
The four-year data demonstrates the durability of the factor IX activity levels and then the impact on the ability of factor IX expression to provide a suitable hemostatic protection when patients were able to discontinue their prophylaxis. So I talked about stopping their prophylaxis; about 94 percent of the patients who were in the trial were able to stop their prophylaxis. They found that there was a very stable expression of factor IX over the four years. And what we're seeing is that the vast majority—about 98 percent—have been able to maintain their factor activities in that mild-to-normal range, if you will. So mild is at least five percent or higher. And you have to understand that these patients had severe hemophilia and were one percent or less. So in the study, they had to be—to be participating—two percent or less. So they were able to increase their factor levels to at least five percent or higher. And one third of the patients had factor levels that were in what we consider sort of non-hemophilia range, so 40 percent or better. So some of them even increased to the normal range. So even along with this increase in the factor levels, what we expect to see is good protection from bleeding, and that's what we were seeing. As I said, there was a huge reduction in their annualized bleed rates.

Dr. McDonough:
And what can you tell us about the 4-year safety data?

Dr. Quon:
My understanding is that there were no new safety signals in the four-year data. In the clinical trials, we saw some immediate effects during the infusion—what we called infusion-related reactions—and those resolved themselves. The biggest adverse event that we saw was the elevation of liver function tests, specifically what we call the ALT. And that increased in and needed treatment in about 16 to 17 percent of the patients. Some patients maybe had a headache, but no new safety signals were seen in the four years of data.

Dr. McDonough:
As we approach the end of our program, Dr. Quon, how might these new findings impact hemophilia B care?

Dr. Quon:
Like I said, the safety data is very good. There are no new signals in the four years. The efficacy is really good. And right now, the product has only been approved for adults greater than 18. I think, based on this, they might be able to move it to, maybe, older adolescents. The gene therapy is a liver-directed therapy using what we call adeno-associated virus 5. And we believe that the liver is mature enough to have a good outcome from this maybe starting around age 12, and so for adolescents between age 12 and 18 who are currently not eligible, perhaps we can start thinking about moving down that age, because they could really benefit from something like this. So that's something to think about.

But I think that it shows that the gene therapy for hemophilia B is safe and durable, and it works. We increase the factor levels, and as a result of the increased factor levels, patients have bleed protection. They're not bleeding, as we see from that 4-year data. And it decreases their burden of treatment. They don't have to do their weekly infusions anymore. And so I think that ultimately will increase their quality of life from decreased treatment burden and bleeding.

Dr. McDonough:
With those potential impacts in mind, I want to thank my guest, Dr. Doris Quon, for joining me to share the newest data on the etranacogene dezaparvovec in patients with hemophilia B. Dr. Quon, it was great having you on the program.

Dr. Quon:
Thank you for having me. I enjoyed being here.

Announcer:

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