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Insights on the Potential for Gene Therapy for Hemophilia: An Inside Look at the Clinical Trial Experience

Announcer:
You're listening to *Clinician's Roundtable* on ReachMD, and this episode is sponsored by CSL Behring Medical Affairs. Before we begin, please note that gene therapy for hemophilia B is currently under clinical investigation and is not approved by any regulatory authority for therapeutic use. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
Factor replacement therapy has been the most common treatment for hemophilia B. But like any other treatment, it's not always the best option for our patients. But now, thanks to recent research efforts, gene therapy has become a growing area of interest, which is why today we'll be getting a behind-the-scenes look at the clinical trials that are exploring this treatment approach.

Welcome to *Clinician's Roundtable* on ReachMD. I'm your host, Dr. Jennifer Caudle and joining me today are Dr. Robert Klamroth and Dr. Richard S. Lemons. Dr. Klamroth is Head of the Department of Internal Medicine Angiology and Coagulation Disorders and Director of the Comprehensive Care Haemophilia Treatment Center at the Vivantes Friedrichshain Hospital in Berlin, Germany. Dr. Klamroth, thanks so much for being here today.

Dr. Klamroth:
It's a pleasure to be here with you.

Dr. Caudle:
And Dr. Lemons is a Professor in the Department of Pediatrics at the University of Utah School of Medicine and Chief of the Division of Pediatric Hematology/Oncology at the University of Utah Huntsman Cancer Institute. Dr. Lemons, welcome to you.

Dr. Lemons:
Well, thank you for this opportunity to join you and to share my experiences in management of hemophilia B.

Dr. Caudle:
So, to start us off, Dr. Lemons, can you tell us what factors might cause you to transition a hemophilia B patient from factor replacement therapy to gene therapy?

Dr. Lemons:
Certainly. I think there's a wide range of patients who would be suitable candidates for transition from factor gene therapy. In particular, patients who are highly motivated to improve their quality of life and who are compliant with their current therapy and those that find that prophylaxis with factor can be burdensome and who are looking to have a safe, effective and, more convenient treatment. Patients who are very active in their lifestyle, whether it's at work or outside of work would be ideal candidates, as well. And potentially, gene therapy would offer an opportunity to have a near-normal level of factor and allow them to engage in activities that perhaps they aspire to, but they are limited and cannot do at least on the schedule where they would like to do them. So, anyone who's highly motivated to and would be compliant in terms of follow-up and seeking medical care, should that be necessary, could be ideal candidates for gene therapy.

Dr. Caudle:
OK. And as a quick follow-up to that, why is AAV vector platform used to deliver gene therapy to these patients?

Dr. Lemons:

So, there are two main viral vector systems that are currently in use for gene therapy across different disease entities : multi-viral system which can accommodate a very large segment of DNA, but the AAV vector is the most commonly used, and there are several reasons for that. There are different serotypes of the adeno-associated viral vector system. There are ones that are more trophic for different organs within the body. There are some that have been identified and are known to go specifically and target the liver, which is where the ideal

target organ is for expression of factor. The AAV vector can accommodate a significant portion a set block size of DNA. So, for factor IX, for example, the entire factor IX gene can be put into the AAV vector and accommodates it very well. For very large genes, one has to truncate or take portions of gene, but for factor IX, it's a smaller gene than some other factor genes and it can really serve in its entirety in AAV.

One can think of the AAV vector as a messenger or carrier; it transports this factor IX gene into the bodyit targets the liver, goes into the liver and then is transduced in the liver. It doesn't integrate to a large extent within the liver but it is episomal and it uncoats and is able to produce the factor IX gene product, the protein, which then can circulate in the body and restore factor IX levels. So, AAV is a commonly used vector. It's safe. It does not cause human disease as it's used as a viral transport. One can really think of it as really a transport vehicle; it's like a car that transports the factor IX gene and it goes selectively, targets into the liver and uncoats the other AAV serotypes that target other organs such as the heart. But the nice thing about this AAV vector system is that it targets the liver, goes for the liver, uncoats and produces a factor IX gene product.

Dr. Caudle:
So, with all of that in mind, let's switch gears a bit and focus on clinical trials that have investigated the use of gene therapy in hemophilia B patients. Dr. Klamroth, what eligibility criteria is used to select appropriate patients?

Dr. Klamroth:
For the gene therapy trials there was some criteria for patients to include in the clinical trials. I think first of all, motivation is very important because, you know, that participation in a clinical trial for hemophilia and gene therapy is a lot of work for patients and investigators. There are regular blood controls, you have to monitor treatment very closely in order to avoid any kind of liver reaction and starting immunosuppression. So, motivation is crucial. Adherence is crucial. Of course, because the factors inducing the gene in liver cells, liver health is a very important point. So, only patients with healthy livers without chronic infection can be included in these trials. Third, patients have to avoid any family planning in the first six months of the clinical trial and to avoid any drugs and alcohol in order to avoid liver damage.

Dr. Caudle:
For those of you who are just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm your host Dr. Jennifer Caudle and today I'm speaking with Dr. Robert Klamroth and Dr. Richard S. Lemons about gene therapy clinical trials for patients with hemophilia B.

Now, once enrolled patients have started to receive gene therapy, Dr. Klamroth, how do you monitor their response to this type of treatment? Is there anything specific you look for in these patients?

Dr. Klamroth:
Yeah, you all know that there are some effects on the liver and there can be some, kind of, immune reaction. And monitoring this immune reaction is crucial for the period after gene therapy because if you have a T cell response or some, kind of, immunologic reaction in the liver, then there's a possibility of losing expression of factor IX. So, monitoring of the liver enzymes, especially the ALT is crucial because if there is a rise in LAT, that might translate in a loss of expression, so we monitor LAT and factor IX and if there's a rise in LAT and maybe a drop in factor IX, that is indication for immunosuppression to void, the loss of expression of factor IX in these patients. And this needs to be monitored very closely in the first six months of treatment.

Dr. Caudle:
OK. And now before we close, I'd like to learn more about each of your experiences with gene therapy and let's start with you, Dr. Lemons. What has your overall experience been like and how do you think gene therapy might impact patient care?

Dr. Lemons:
So, my experience with gene therapy, particularly with hemophilia B, has been very successful in the patients that we've treated. Overall, within our institution, there's a large number of gene therapy trials that are ongoing. So, the institution has great experience with gene therapy for different diseases. Our patients with hemophilia B that have done very well.

One of the most dramatic things that I've seen in improving their quality of life in those that have undergone gene therapy for hemophilia B is their improvement and their functionality their pain in their joints, which is a common complaint or symptom for patients with hemophilia has improved dramatically as a result of the gene therapy.

Dr. Caudle:
And Dr. Klamroth, I'll give you the final word.

Dr. Klamroth:
So, the biggest question is that we cannot foresee how an individual patient react. If we look at the group of patients who were included in gene therapy trials we can say yes, there's factor IX impression, patients have zero bleeds, and they don't need additional factor concentrates iff gene therapy works well. But the factor IX expression is quite variable between the individual patients. If you have a good factor IX expression, then gene therapy will be a huge difference to other treatments because you don't need any treatment anymore, you are free of bleeds and you can live a life full of participation without thinking about your disease and without thinking about bleeds. And that is a great advantage of gene therapy. It's at least, for certain time for years in hemophilia B, a potential cure for disease.

Dr. Caudle:
Well, that's a great way to end our discussion and I'd like to thank my guests Dr. Robert Klamroth and Dr. Richard S. Lemons for speaking with us about these important lessons. Dr. Klamroth and Dr. Lemons, it was great speaking with you today.

Dr. Klamroth:
It was a pleasure for me to participate.

Dr. Lemons:
Well, thank you for this opportunity to participate in this discussion. I hope this has been helpful and hopefully we've been able to share the excitement of these future treatments of gene therapy for hemophilia.

Announcer:
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