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Addressing Current Challenges & Unmet Needs in Hemophilia B

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:
Welcome to *Clinician's Roundtable* on ReachMD. I'm your host, Dr. Jennifer Caudle, and joining me today to take a look at the treatment challenges and unmet needs for patients with hemophilia B is Dr. Michiel Coppens, a medical specialist in the Department of Vascular Medicine and Hemophilia Treatment Center at the Amsterdam University Medical Centers. Dr. Coppens, welcome to the program.

Dr. Coppens:
Thank you very much.

Dr. Caudle:
We're happy to have you today. But before we dive in, Dr. Coppens, let's start with a high-level overview of hemophilia B. Just how prevalent is this disorder?

Dr. Coppens:
Yeah, I think I'm happy to say even that hemophilia is a pretty rare disorder. And regulators like the FDA or EMA in Europe or typically label hemophilia as what we call an orphan disease, acknowledging the fact that it's pretty rare and that it's pretty hard to do decent studies into registration of new products in that disease area.

Hemophilia is what we call an X linked disorder, which essentially means that genetically, women are carriers but do not really have a disease. And men really are the ones who have the severe forms of the disease.

Then zooming in on hemophilia, we have two main forms: hemophilia A, which is a shortage deficiency of the coagulation factor protein number VIII; and hemophilia B is the deficiency in number IX. If you look at the prevalence, about one in seven and a half thousand males will have hemophilia A, which is about 80 percent of hemophilia patients, and about 1 in 40,000 patients will have hemophilia B which is about 20 percent. The USA has about 332 million inhabitants, let's say 50 percent of those is male. So essentially, you would have about 20,000 hemophilia A patients in the USA and about 4,000 hemophilia B.

Crucial is the severity of the disease. About 50 percent of patients have what we call a severe disease, meaning that they have absolutely no circulating Factor VIII or Factor IX. That's the severe phenotype leading to spontaneous bleeding and most of the disease burden. The rest is a much milder and most of those patients do not have spontaneous bleed, but mostly bleeds after traumas or during procedures.

Dr. Caudle:
Thank you for that. And with that background in mind, that let's zero in on treatment. What can you tell us about some of the available treatment options for patients with hemophilia B?

Dr. Coppens:
Yeah, well, the principle of therapy is actually pretty simple. These patients miss a protein, so treatment would logically exist of replacing that protein. However, that isn't as simple said as done. Before any treatment was available hemophilia really most often was a fatal disease. I have a beautiful example of a case series from 1937, a time where there was no treatment for hemophilia of 113

hemophilia patients and their causes of death. And it really shows some trivial for dying like a nosebleed, like a tooth extraction, like a circumcision. And overall 70 percent of those patients did not reach the age of 15. And only 7 percent of patients went beyond 40 years of age.

So treatment really is replacing the missing protein and that's usually based on donated human plasma worked up into concentrates; bags that really only contain the protein of interest. And with that treatment it became possible to twice-weekly self-inject intravenously that protein to prevent spontaneous bleeding. And I think that was a crucial point in the treatment of hemophilia because I think that has mostly taken out the fatality of the disease. But it also means that the emphasis right now is more about preventing joint damage than anything else.

Well, after these factor concentrates, we now are derived from a human plasma, we have seen a shift towards recombinant products partly inspired by the HIV pandemic, but also the availability of human plasma around the world. And nowadays, we really have started to manipulate these proteins essentially to extend their half-life, which means to keep the protein longer into the circulation, making it possible to inject less frequently. And I guess nowadays, the standard would really be once weekly infusions or once every two weeks. But still, I would say it still requires frequent infusions in the order of magnitude of about 50 per year. And maybe that's the final point that we need to improve upon in the near future.

Dr. Caudle:
And you mentioned some of the details about these therapies. Can you expound on some of the primary challenges and limitations of these therapies?

Dr. Coppens:
Yeah, I guess it's still frequency of intravenous injection. I think do not underestimate the burden of intravenous infusions. That's a bit more than a subcutaneous injection for example, insulin in diabetes. That's really, well, a more intricate procedure. So essentially, anything that requires intravenous administrations should be considered burdensome.

And I think the other point that's really important, that's joint damage still occurs. And what you need to bear in mind, if you give treatment, let's say twice weekly essentially, before your next infusion, your factor level will be at its lowest. And that could be around more or less 5%, or even somewhat lower. And we really know that that's the time where you are most vulnerable for bleed. So I think if you're speaking in terms of where we would want to go, I think we would want to lift the overall factor levels to near normal levels. And that's where we could probably abolish joint damage all together.

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. Michiel Coppens, about common challenges in hemophilia B care.

So Dr. Coppens, now that we've reviewed the treatment limitations that we often face, let's turn our attention to the patient. You did mention a little bit about the frequency of treatments. But, what other and additional kinds of impacts do these treatment options and the disease itself have on the patient?

Dr. Coppens:
We need to acknowledge, and that's what we see in our patient. That sometimes when we overlook when we talk about our patients and about the progress in therapies that have been made, is that a lot of hemophilia patients avoid high-risk activities. And that means that certain professions essentially cannot be chosen or are probably not a good choice for patients with severe hemophilia. That certain sports participation let's call it American football, for example, would probably not be too wise for a patient with hemophilia.

And I think, as I said before, don't underestimate the impact of having to use intravenous infusions. Some people really have needle phobias, which makes each and every single infusion a true burden. And we know from practice, that a lot of patients, well and quite a number of patients, are not able to adhere to the treatment regimen they are put on. And essentially, the reason is not because they don't care. Let's say if it was a completely burden-less treatment, I don't think we would see any adherence problems all together.

Dr. Caudle:
Understood. And as a quick follow-up to that what would you say are some of patients biggest unmet needs when it comes to their care?

Dr. Coppens:
In my country and probably also the USA there's plenty of access to care and access to factor concentrates. But do realize that there are many parts of this planet where there is no access for patients to factor concentrates where hemophilia is still a poorly treated disease. But even in the most advanced, economically sound countries, there still is a need to self-inject, which ideally, we would like to abolish.

Dr. Caudle:
Now, with all that being said, Dr. Coppens, what key criteria do we need to meet in order to achieve an optimal therapy for our patients that can help address those challenges and unmet needs?

Dr. Coppens:
I think, ideally, we want to structurally move up their factor level activity to a higher level at maybe to a normal range or to a near normal range. And to achieve that without any intravenous injection.

But essentially, the only gene therapy is maybe the one that may fit that profile fully.

Dr. Caudle:
And before we close, let's take a look at the future of care. Dr. Coppens, what impact would that kind of optimized therapy have on our patients with hemophilia B?

Dr. Coppens:
Well, the future will be looking very bright. However, do not underestimate also the stringent follow-up that is strictly needed after gene therapy. There is quite a lot to monitor. And, for example, in the first three months after gene therapy, you would be needing to come into hospital weekly for blood sampling. And some patients may need to go on steroids to prevent liver reactions. However, when you reach that three-month point, and everything has gone well up to that date, you could actually be pretty close to the ideal situation. But I always say there are some long-term unknowns which need an answer in the next year.

So first of all, would be how long would successful expression of gene therapy last? Could that be years? A few years, maybe a decade? Could it be decades? Could it be lifelong? And basically, we don't know yet because there is not sufficiently long follow-up.

Last year, a report came out of a patient who had liver cancer about a year after gene therapy for hemophilia B. So that was pretty important, whether or not that liver cancer could have been caused by the gene therapy. And I think ultimately, it was shown, pretty convincingly, that it was unrelated to the gene therapy, but it really highlights that you always need to have an eye out for long-term very rare side effects and that we always need to do the proper follow-up for that.

Dr. Caudle:
Understood. And with that future perspective in mind, I'd like to thank my guest, Dr. Michiel Coppens, for sharing his insights on treatment challenges and the future of care for patients with hemophilia B. Dr. Coppens, it was wonderful having you on the program today. Thank you for joining us.

Dr. Coppens:
Thank you. My pleasure.

Announcer:
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