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## Hemophilia Patient Cases: Managing the Challenges of Inhibitors

Announcer:

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Your host is Dr. Jennifer Shu.

Dr. Shu:

When it comes to treating hemophilia, we're faced with a lot of challenges, which instantly become more complex when patients develop an inhibitor, and since this occurs in about a third of hemophilia A patients, knowing the various management considerations becomes essential.

This is CME on ReachMD, and I'm Dr. Jennifer Shu. Joining me today to review some hemophilia patient cases is Dr. Shannon Meeks, a pediatric hematologist at Emory University in Atlanta, Georgia.

Dr. Meeks, welcome to the program.

Dr. Meeks:

Thank you.

Dr. Shu:

So let's just jump right in here. Our first case is a 3-month-old boy who was diagnosed with hemophilia A. Since there's a family history of severe hemophilia, including a brother who had a high titer inhibitor his mother was understandably nervous about her second child developing an inhibitor as well and when coming to the clinic, she had lots of questions about treatment options and if there was anything she could do to prevent an inhibitor from forming.

Dr. Meeks, can you give us an overview of the risk factors for inhibitor development in hemophilia A patients?

Dr. Meeks:

Sure, Dr. Shu. There are actually multiple factors involved in inhibitor development in hemophilia A patients. The primary driver is severity of disease with severe disease having a higher risk of inhibitor development than mild to moderate disease. Within patients with severe disease, there are both genetic or patient-related variables as well as environmental or treatment-related factors.

Dr. Shu:

Great. And can you expand a bit more on both the patient-related and treatment-related variables behind inhibitor development for these patients?

From the genetic or patient-related variable standpoint, the Factor VIII mutation is very important—also, race and ethnicity. We know that African-Americans are almost twice as likely to develop inhibitors, and there's a report of increased incidence among the Hispanic population as well. Family history of inhibitor is an important risk factor, and there have also been other immune response-related genes

shown to influence this inhibitor development. Within the genetic mutations, the type of your mutation actually plays a large role in development with multi-domain deletions having the highest rate, upwards of 70%, while missense mutations have a much lower rate, closer to 20%.

There are also environmental or treatment-related risk factors, such as early intense Factor VIII exposure, as well as thoughts that immune stimulation at the time of factor exposure may play a role—the thought here being that Factor VIII may be recognized as dangerous if it's encountered during periods of heightened immune response.

There's also been some change over time with how frequently we test for inhibitors, and that frequency of monitoring has played a role in seemingly more inhibitors being diagnosed, but that's probably just the frequency of testing.

The other environmental or treatment-related risk factor that's been a big topic of debate of late is the type of Factor VIII product. So there are 2 primary types of Factor VIII products, recombinant and plasma-derived, and there have been 2 recent studies, the RODIN study and the SIPPET trial addressing this.

Dr. Shu:

Let's focus on the types of Factor VIII products and how this factors into patient risk.

Dr. Meeks:

Okay. There are a couple of different broad categories of Factor VIII products. The first is plasma-derived. These are variable purity and they have different amounts of Von Willebrand factor content depending on which product it is. There are also recombinant products. These are produced in mammalian cell culture systems. They have high purity and no Von Willebrand factor. There are first-, second- and third-generation products that vary in cell culture media components and stabilizing molecules.

In terms of historical data of inhibitor development, if you take many studies over many years, plasma-derived Factor VIII averaged out at about a 14.5% inhibitor rate while recombinant Factor VIII was higher at 31%. If you remember back, we talked about the frequency of inhibitor testing potentially playing a role in these differences, as most of these plasma-derived Factor VIII studies are older than the recombinant Factor VIII studies.

Dr. Shu:

Do you have a good sense for why different Factor VIII products transmit different risks for inhibitor development?

Dr. Meeks:

We have some ideas, but many of these are primarily hypotheses at this point in time. So, again, there are different screening protocols over time, which have made a difference. Also, Von Willebrand factor and the presence of it and the affinity of Factor VIII for Von Willebrand factor is thought to potentially play a role. There are also differences in Factor VIII structure, and many of these play out as post-translational modifications. These post-translational modifications are cell line specific and are crucial for protein function.

Dr. Shu:

Backtracking a bit here, you mentioned earlier the RODIN study done in Europe, Israel and Canada. Can you talk some more about that study and its findings?

Dr. Meeks:

Sure. The RODIN study is a multicenter cohort study, again out of Europe, Israel and Canada. It's prospective and observational. So between the years of 2000 and 2010, they investigated 574 previously untreated patients, or PUPs, with severe hemophilia A. The median age was 4.6 years. And they followed these patients while collecting data up to 75 exposure days or until an inhibitor development following either plasma-derived Factor VIII or recombinant Factor VIII infusions. This study was published in an article in the New England Journal of Medicine.

When they looked at a comparison of adjusted relative risk between factor products, their primary aim was to compare all recombinant to all plasma-derived products, and when they did that, they saw that there was no difference in inhibitor rates between the products. However, they also did a subsequent analysis looking at individual generations of products within the recombinant Factor VIII category, and here they found a slightly higher risk of inhibitor development in the second-generation, full-length factor products.

There are some limitations of the RODIN study, and they are frequently debated in the community. One, the comparison between generations of recombinant products was not a part of the original study design, and the choice of products was decided by the provider; therefore, it was not randomized, and there was some concern that there might be some center bias in terms of what products were chosen. In addition, 72 of the patients that were enrolled were not able to be analyzed.

Dr. Shu:

And at the time of the RODIN study, there was also the SIPPET trial, right? What were the results of that?

Dr. Meeks:

Right, so the SIPPET trial was ongoing at the time of the RODIN study, and the SIPPET trial was a big deal in the hemophilia community. It was a multicenter, international, randomized, controlled, open-label trial. It compared plasma-derived Factor VIII products and recombinant Factor VIII products with the primary endpoint being frequency of inhibitor development.

So, when you look at the results from the SIPPET trial, the cumulative incidence of inhibitors for recombinant Factor VIII was 44.5% with 28.4% high titer, and in the plasma-derived category, the cumulative incidence was 26.7% with 18.6% high titer. From the SIPPET results, Factor VIII was associated with an 87% higher incidence of inhibitors than plasma-derived with a hazard ratio of 1.87. For high titer inhibitors, the rate was 70% increase with a hazard ratio of 1.70. Subsequent analysis showed no difference in inhibitor rates on the second-generation products with this analysis being done as a direct result of the RODIN study.

There were some limitations to SIPPET as well. One, minimally treated patients were recruited along with previously untreated patients. High rates of inhibitor development were seen in both groups. And although an international design in the study, the majority of the patients were enrolled from 2 countries. It also didn't investigate any of the newer extended half-life Factor VIII products. So in the Factor VIII product field, the recombinant products have been relatively similar over the past many years until we got extended half-life products, and in the last 3 or 4 years, we've gotten new products that have some different structural properties.

Dr. Shu:

So to come back to our first patient case of the 3-month-old boy with severe hemophilia A, what are the main takeaways for risk assessment and next steps?

Dr. Meeks:

In terms of our 3-month-old boy that we started out with in the case, there are a couple of things that we should know. One, we know that there are genetic and environmental risk factors at play in his risk of inhibitor development. Given that he has a large gene deletion as well as a family history of his brother having an inhibitor, he will also be at very high risk for inhibitor development.

Dr. Shu:

If you're just joining us, this CME on ReachMD. I'm your host, Dr. Jennifer Shu, and joining me today is Dr. Shannon Meeks from Emory University to review some complex hemophilia patient cases.

So now let's move on to our second case. This is a 13-year-old boy with severe hemophilia A and a high titer inhibitor who comes to the clinic having failed standard immune tolerance. He's been on bypassing agent prophylaxis for many years but continues to have regular breakthrough bleeding, and his activities are limited because of that. His parents have a lot of questions about immune tolerance induction and other new products that are potentially available for him.

Looking at this generally to start with, what are the treatment strategies you would recommend for this patient?

Dr. Meeks:

So, when we talk about our treatment strategies for patients with inhibitors, I like to break them into 2 different things. One, the acute management, we have to stop the bleeding, so we have to develop a treatment plan to stop the bleeding if it occurs. But there are also long-term strategies. One, we need to figure out if we can eradicate the inhibitor through immune tolerance, but we also, while we're eradicating that inhibitor, need to prevent bleeding with some sort of prophylaxis.

In terms of the treatment of bleeding, our goal really is to replace what's missing, i.e. Factor VIII, but for patients with inhibitors that don't respond to Factor VIII, the mainstay of treatment is bypassing agents. There are 2 bypassing agents currently available and used. One is recombinant Factor VIIa, or NovoSeven, and one is activated prothrombin complex concentrates, aPCC. Brand name is FEIBA.

Dr. Shu:

Let's zone in on bypassing agents, such as recombinant Factor VIIa and activated prothrombin complex concentrates.

Dr. Meeks:

So the bypassing therapies for the treatment of bleeds definitely have pros and cons. So if we start with our aPCCs, the pros are the half-life is relatively long at 8 to 12 hours; usually, we can get by with 1 to 2 doses per day for most bleeding and 3 times per week for prophylaxis. The cons really are it's a plasma product and it's a large volume, which can be a reason not to infuse or challenge to infusion for some patients.

In terms of the recombinant Factor VIIa, it's a small volume of a recombinant product, making it very easy to infuse. However, the half-life is short, every 2 to 4 hours, and every 2- to 4-hour dosing is needed for major bleeds. It's given on a daily regimen for prophylaxis.

Dr. Shu:

I'm sure this is a question you get a lot, but between these types of bypassing agents, is one considered the better option?

Dr. Meeks:

So there was actually a study called the FENOC study, which was a prospective, randomized, crossover study of a comparison between these 2 products to treat joint bleeds with the primary endpoint being control of bleeding at 6 hours. The results showed similar efficacy. About 80% of bleeding episodes responded to treatment, but there was more discordance than anticipated between the 2 drugs. We often get reports from patients and family that one drug seemed to work for a while or seems to work better in one situation and the other drug works better in another, so it's an ongoing discourse back and forth with the patient and the situation to pick which one would work best in a given situation.

Dr. Shu:

If we switch gears to focus on prophylactic treatment, what are the developments on this front?

Dr. Meeks:

So in terms of prophylaxis, we know for patients without inhibitors that prophylaxis really is the standard of care, so we really have extended that over into our prophylaxis for our patients with hemophilia and inhibitors. Knowing that complete prophylaxis or complete prevention of bleeding may be a lofty goal in these patients, we still try. So, if we use our activated prothrombin complex concentrates, there was a randomized, prospective, crossover study at 85 U/kg on 3 nonconsecutive days per week. And not surprisingly, both total bleeds and joint bleeds were reduced in comparison to patients not on prophylaxis. A similar randomized prospective trial was done with 2 different doses of recombinant VIIa. Either 90 or 270 mcg/kg were given every day and again saw decreased bleeds in both of these prophylaxis groups.

Dr. Shu:

I understand that there is a new potential treatment that can be used. Can you tell us a little bit about that?

Dr. Meeks:

So we do have 1 relatively new agent to the field of inhibitor patient prophylaxis, and that would be emicizumab, or Hemlibra. This is a bispecific antibody that binds to Factor IXa and Factor X and acts in similar mechanisms of Factor VIIIa. It's a once-a-week, SQ injection, and the FDA approved it in late 2017 for prophylaxis in adults and kids with inhibitors.

The studies are ongoing in non-inhibitor patients as well. The studies have been named HAVEN 1, 2, 3 and 4. HAVEN 1 was the initial study in adults with inhibitors and was published recently in the New England Journal of Medicine, and this study showed that when you compared patients on emicizumab prophylaxis to no prophylaxis, there was about an 87% reduction in bleeding events. So they have also shown data, although it's not been published in manuscript form, at multiple conferences about similar bleeding reduction rates in patients with—kids with inhibitors as well as patients without inhibitors. However, some of the initial enthusiasm for some of the HAVEN 1 data was tempered some with some adverse events that we saw.

So in terms of our HAVEN 1 results, there was a reduction in bleed rates for these patients while on emicizumab. However, there were also some serious adverse events. Five patients on the HAVEN 1 trial had thrombotic events or thrombotic microangiopathy events. When they did an evaluation of these events, all of these patients had received on average a cumulative amount of activated prothrombin complex concentrates in a 24-hour period of more than 100 U/kg while they were receiving their emicizumab prophylaxis. A change in protocol was developed, and no further serious adverse events of this nature were seen in more than 350 patients treated in the emicizumab development program after the modified treatment plan was introduced. There is a black box warning on the package insert for emicizumab because of these serious adverse events.

Dr. Shu:

Coming back to the treatment strategy of eradicating inhibitors, can you reiterate for our audience why we want to keep this top of mind for hemophilia patients?

Dr. Meeks:

Yes, so in terms of eradicating inhibitors, we know patients with inhibitors have increased morbidity, and while bypassing therapy is effective, it's not as effective as Factor VIII. It's more difficult to perform elective surgical procedures. And not only is treatment more challenging, but prevention of bleeding is often more challenging as well. These inhibitor patients also have increased costs because of a wide range of utilization of their healthcare system and the cost of these treatment products. In terms of mortality, in 1983, we actually had a report of increased mortality in all patients with inhibitors, but more recently there have been—differences in mortality in patients

with inhibitors or without inhibitors have been somewhat inconsistent.

Dr. Shu:

So, how specifically should a care team go about eradicating the inhibitors? Is this where the family's interest in immune tolerance induction comes into play?

Dr. Meeks:

Yes. Now, immune tolerance induction is how we go about trying to get rid of the inhibitor or at least to get the inhibitor to a point that the patients are responsive to Factor VIII treatment. So immune tolerance induction is regular infusions of Factor VIII. Classically this has been done with either recombinant or plasma-derived Factor VIII. Although, we'll talk a little bit later about some newer protocols using some of the extended half-life products. For the regular ITI, historically we've either given a low dose at 50 U/kg 3 times a week or a high dose at about 200 U/kg per day.

There actually was an international immune tolerance induction study run by Dr. Charlie Hay and Dr. Donna DiMichele that compared these 2 regimens, but it had to be stopped early because there was more bleeding in the low-dose arm. Immune tolerance induction is not easy. It requires a very compliant patient and family, and we actually may need some sort of indwelling central catheter for venous access. About 60 to 70% of patients will respond to immune tolerance induction.

Dr. Shu:

What about the other 30% or 40% of patients who don't respond? Are there other options if the initial immune tolerance induction attempts fail?

Dr. Meeks:

Yes, so immune tolerance induction is usually done for a prolonged period of time, so often times patients will start with up to 2 to 3 years of immune tolerance induction with whatever product they were on when they developed their inhibitor. And then, if that wasn't a plasma-derived product, we often will then switch them to a plasma-derived product for another couple of years.

If that doesn't work, we have a couple of things coming down the pipe as relatively new that we now can try. One is ITI, or immune tolerance, with extended half-life products. There are some hypotheses that modifications to the Factor VIII may help tolerize to Factor VIII. And there was a case series recently of immune tolerance with Factor VIII Fc where the Fc portion of this molecule is hypothesized to potentially help tolerance. So for patients like this one who have done tolerance attempts with recombinant and plasma-derived, immune tolerance with these extended half-life products are always an option.

We can continue now with non-Factor VIII therapy. Some patients who have their bleeds well controlled on bypassing agent prophylaxis may elect to stay on bypassing agent prophylaxis and not do another immune tolerance attempt. And now, as of late last year, we also have the option of bleeding prophylaxis with emicizumab. With either of these options, if we had to have treatment of bleeds, the option there would be bypassing agents. In the past we often used immune tolerance induction with the addition of immunosuppressive agents. However, the utility in patients with good bleeding control on their bypassing agent, or now emicizumab therapy, limit this as an option really for those who are still having significant bleeding despite our available agents.

So in terms of Factor VIII Fc for immune tolerance, Manuel Carcao and colleagues recently published a retrospective analysis. This was an analysis looking back at how patients have been treated at 10 US and Canadian centers. And within those 19 patients, we had both first-time immune tolerance patients and patients who were refractory patients who had failed previous immune tolerance attempts. For the first-time patients, 6 of 7 had high-risk features to begin with, and at the time of this report, 4 of 7 were tolerizing or were tolerized in an average of 7.8 months. In terms of the therapeutic benefit for patients who have failed previous immune tolerance episodes, there were 12 of these patients on this trial, and there was definitely evidence that some patients were able to see a fall in their Bethesda titer as part of this regimen. We will see as time goes on and we get our next look at these patients about whether or not these immune tolerance success stories continue.

Dr. Shu:

And again, just to put this in context to our patient case, how would you respond to the parents' questions regarding treatment options for this 13-year-old with severe hemophilia A?

Dr. Meeks:

So for this patient I think we can honestly tell the family that there are 2 new options that they can consider. One would be immune tolerance induction with the Factor VIII Fc products, which has shown some promising evidence that it might help a subset of patients like this patient who have failed other immune tolerance attempts. We have to keep in mind though that this is a retrospective analysis and so the data overall is limiting. The other option would be to consider going on emicizumab therapy for bleeding prophylaxis. A majority of patients had very minimal bleeding on that agent. And then on top of that agent, there are people starting to talk about

potentially combining emicizumab with immune tolerance.

Dr. Shu:

Dr. Meeks, before we wrap up, do you have any closing takeaway messages for our audience?

Dr. Meeks:

Well, I think it's a very exciting time to be in the field of hemophilia and inhibitors and an exciting time for patients who have dealt with inhibitors for a long time. We, for the first time in a while, have a couple of new options for patients who really felt like their options had been exhausted except for just sort of figuring out how to live with bleeding and their inhibitors, so I think as the next few years come along, that we'll have a lot more answers to how these new therapeutic options will fit into treating patients.

Dr. Shu:

Well, we've covered a lot of ground on best approaches for managing hemophilia patients and how to respond when these patients develop inhibitors.

Dr. Meeks, on behalf of ReachMD, I would like to thank you for sharing your insights with us today.

Dr. Meeks:

You're welcome.

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