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Personalizing Prophylaxis for Hemophilia A and B: A New Era in Treatment and Management

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Personalizing Prophylaxis for Hemophilia A and B: A New Era in Treatment and Management”, was developed through the joint providership of the University of Cincinnati and CORE Medical Education, LLC. and is supported by an educational grant from Sanofi US and Novo Nordisk, Inc.

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Dr. Russell:
While the life expectancy of patients with hemophilia has dramatically increased over the past several decades, the hemophilia population still faces unique challenges that will require appropriate use of effective strategies. Prophylaxis with standard recombinant factor requires regular intravenous infusion at least two or three times a week. However, recombinant factor VIII and factor IX products with an extended half-life are currently available and newer strategies are on the horizon. These therapies have the potential to address and individualize the needs of patients. Coming to you from the ReachMD studios in Fort Washington, Pennsylvania, this is CME on ReachMD. I’m Dr. John Russell. Joining me to discuss the latest in the management of hemophilia A and B is Dr. Steven Pipe. Dr. Pipe is a Professor of Pediatrics and Pathology at the University of Michigan. He also serves as Director of the Division of Pediatric Hematology and Oncology, Pediatric Medical Director of the Hemophilia and Coagulation Disorders Program and Director of the Special Coagulation Laboratory. Dr. Pipe, welcome to the program.

Dr. Pipe:
Glad to be here.

Dr. Russell:
Why don’t we start today by looking at the big picture, here. Would you give us a quick refresher for what the prevalence of hemophilia is and what’s the difference between hemophilia A and hemophilia B?

Dr. Pipe:
Sure, the hemophilias as a group are X-linked recessive bleeding disorders they all lead to spontaneous bleeding and bleeding following trauma or surgery. because it’s X-linked, it’s typically expressed in males, but females are carriers and they may also have symptoms. It’s characterized by deficiency of one of two clotting factors hemophilia A is caused by a deficiency of factor VIII and hemophilia B deficiency of factor IX. Hemophilia A is actually four times more common. Now, the overall prevalence in the United States this happens about one out of every 5,000 live male births. At least a third of these are spontaneous mutations and it effects individuals from all racial and ethnic groups and at any given time, we estimate that there’s about 20,000 males in the United States with hemophilia. Their clinical manifestations are typically bleeding into joints, we call this “hemarthrosis” but also into muscles, soft tissues and other locations. The classic long term sequalae that we’re trying to prevent in hemophilia is a debilitating arthropathy that results in chronic pain, muscle atrophy and loss of mobility. The other distinction between the two hemophilias is since the primary treatment modality that’s been used for decades is protein replacement therapy with either factor VIII or factor IX, there is a preponderance of an

immune response against factor VIII that's unique to the hemophilia A population. And upwards to 30% or more of patients with severe hemophilia A will develop antibodies against infused factor VIII and we call these inhibitors and they pose unique problems and special challenges for patients.

Dr. Russell:
Let's talk about management, Dr. Pipe. What is the current standard of care for the management of hemophilia A and hemophilia B and, and what are the current outcomes attached to these standards of care?

Dr. Pipe:
Well, bleeding into joints is actually the primary bleed pathology in patients with severe forms of hemophilia. Now, the joint space is narrow, it's fluid-filled, it has a fibrous capsule where the nerve fibers are primarily located and it has a thin, essentially single cell layer of what's called the synovium. the synovium in healthy joint is relatively avascular however, when you bleed into a joint, iron deposition that comes from the blood leads to an inflammatory environment that drives hypertrophy of the synovium, so we get expansion and proliferation of the synovial cells and with that, there's a neovascularization that then increases the risk for rebleeding of that tissue. So, this sets up this cycle of repeated bleeding, inflammation and hypertrophy of the synovium that ultimately starts to lead to degradation of cartilage, osteophytic overgrowth, osteoporosis and this is what results in the hemophiliac arthropathy with deformed joints, contractures, chronic pain. So, the only way out of this cycle is effective prophylaxis to prevent bleeding. Now if we look at how often would a, a typical patient bleed who has severe hemophilia, if they're not on some form of prophylactic prevention. Studies have demonstrated that the majority of joint bleeds are gonna be seen in those with severe deficiency of factor VIII or factor IX that's defined as less than 1% residual activity. But, what has been observed for many years is that patients who have moderate forms of hemophilia, so even having as little as 1 to even 3% of residual factor VIII or factor IX, actually moderates the disease and the risk of joint bleeding actually goes down substantially. And that was the impetus to introduce the concept of prophylactic therapy. So, today, the majority of the factors that are infused are recombinant forms of factor VIII and factor IX. And the, the targets for those prophylaxis is to give them regular IV infusions of those factors and then those factor levels in their blood will drop down as it gets cleared form the plasma, but we try to maintain the, the trough levels so they don't fall lower than that, say, 1 to 3% range. Now, we've learned in recent years that we can optimize that further by increasing the intensity of the prophylaxis and aiming for trough levels that are better in the 3 to 5%. Recent guidelines from the World Federation Hemophilia a- have actually advocated for that kind of optimization. There could be a new standard of care for prophylaxis, in which case we would be able to maintain trough levels that are in the mild range, so that's anything over 5%. But at present, we haven't had the right tools to get us there. Aspirationally, if we could get patients whose factor levels never drop below, say, 15 to 20%, it's possible we could abrogate joint bleeding, altogether. So, you had asked about, the outcomes from traditional factor replacement for prophylaxis. So, we have some insights from two important studies. The one is the U.S. Joint Outcome Study. This was a randomized controlled trial comparing patients who were on on-demand therapy, so they only received infusion to treat breakthrough bleeds and that they were randomized against patients who were on regular prophylactic therapy. This was initiated when they were young toddlers and then they were followed up to age six. And then at the end of that period, they had MRIs performed to look at the status of their joints. And what was concerning from that study was that there were MRI abnormalities that existed in joints that never had a clinically obvious bleed. So, these are patients and parents who never identified that that elbow or that ankle had ever had a bleed, yet there were clearly changes there. And so, the long-term follow-up from that had suggested that early prophylaxis was not sufficient to fully prevent joint damage. In another important study, the Canadian Dose Escalation Prophylaxis Study, patients were started at a less intense prophylaxis and then they increased the intensity of their prophylaxis based on how frequently they were bleeding. And soft tissue changes were detected in almost a third of the index joints, even though there was no history of clinically-reported bleeding. And then more so by MRI analysis, they could demonstrate the hemosiderin, a marker of bleeding into the joint was detected in up to a quarter of so-called bleed-free joints. Now, those US Joint outcome study cohort of patients were then followed in a continuation study A survey of young adults in the hemophilia in the U.S. looking at two cohorts, age between 18 to 24 and those between 25 to 34 these are, these are cohorts of patients who really should've been benefiting to our real push to prophylaxis over the last two to three decades and yet what these surveys have shown is that a significant proportion of these young men report joint pains the some of the time, or in up to 10% most of the time, and many of them have significant motion limitations indicating joint damage.

Dr. Russell:
So, doctor, what are the current limitations of the replacement therapies?

Dr. Pipe:
Well, if we look at, just factor VIII prophylaxis therapies, where patients have been observed closely in Phase 3 studies, if we look at all of the published studies for standard half-life factor VIII we can look at a measurement or a readout of how well they're controlled by something called the Annualized Bleed Rate or the ABR. And in across those studies, the rage of annualized bleed rates on prophylaxis is between just over 1 to up to 6 and if you look at the percent of participants who experience zero bleeds while on prophylaxis, range is

anywhere from 25% to 60%. We'll talk in a bit about some of the pharmacokinetically modified forms, of factor VIII, but even there where we have a longer half-life factor VIII, the mean ABR in those observed trials is between 2.9 to 4.7 with the percent of participants experiencing zero bleeds ranging between 38 to 45%. So, what's really happening with replacement therapy, what's the key limitation? So, when you give an IV infusion of factor VIII or factor IX, you get a peak right after that infusion. That actually takes them well into the normal range. However, there is a fairly rapid falloff of the factor level based on the clearance and the pharmacokinetic properties of that molecule. And it means that before the patient is ready for their next dose, their levels have actually fallen below what may be critical levels that are putting them at risk for bleeding again. If you modify the factor and you change its pharmacokinetic properties and make it into a longer acting molecule, we really haven't changed the paradigm because you're' still gonna get a peak it's gonna take you a little bit longer to get down to those critical levels, but if you're trying to stretch out the intervals between dosing, you're still gonna spend a considerable amount of time below critical levels, putting you at risk for bleeding.

Dr. Russell:
So, you talked about these significant limitations, what efforts are being made to overcome these shortcomings?

Dr. Pipe:
What we now called the standard half-life hemophilia therapies, for factor VIII, this requires regular prophylaxis of an infusion at least three time a week, if not every other day to maintain those target trough levels we mentioned at the beginning. For factor IX, it's got a little bit longer half-life, you could probably get away with two to three times per week. But the idea is that replacement product that had a longer half-life would potentially reduce the burden of prophylaxis by reducing the frequency of administration. We might actually also be able to achieve higher trough levels because if you keep the interval the same but you have a pharmacokinetic property with a longer half-life, your trough level will be higher before you get your next dose and that could improve outcomes. many long-acting recombinant factor VIII and recombinant factor IX molecules have received regulatory approval and there's ongoing development of additional agents, as well. Some of the strategies to do this include strategies to reduce interaction with clearance receptors. This is primarily through conjugating the factors. With a large molecule called polyethylene glycol or PEG. There's another key pathway that rescues the proteins when they get taken up by the cells and it rescues them from the intracellular degradation pathways and recycles them back to the surface and into the plasma through interaction with something called the neonatal FC receptor. This is actually how antibodies in our blood maintain a long half-life. So, to take advantage of this interaction with the FC fusion protein, you taka recombinant, portion of immunoglobulin, you fuse it to factor VIII or factor IX or you can also take the recombinant albumin and fuse that TO the protein and also take advantage of that recycling pathway. There are some additional strategies that have enhanced the interaction with the carrier protein for factor VIII and plasma called von Willebrand factor through different bioengineering techniques. However, these haven't really extended the half-life significantly to be qualified as an extended half-life agent. There's also been attempts to alter the glycans, the sugars that are on the recombinant proteins and that has some impact on the half-life in vivo but again not quite enough to consider them as true extended half-life molecules. If we look at the impact of these extended half-life agents in the clinical trials these studies were really neatly designed because we saw multiple different strategies of doing prophylaxis. We'll see in these trials what I would call traditional programmatic prophylaxis, so all patients get a fixed dose and a fixed interval typically this would be once weekly for the extended half-life factor IXs and twice weekly for the extended half-life factor VIIIs. We've also seen some pharmacokinetic-driven strategies where the patient's own pharmacokinetic performance of that molecule allows targeted dosing to a target trough level, and then a fixed interval for dosing. Or, what we call a phenotypic-driven approach, where the patient has started on a, particular dosing regimen, they're observed for a period of time to see how good their bleed control is and then they have the option to maybe stretch out the interval or if they have too much breakthrough bleeding, they can increase the dose or compress the interval. And then the other strategy we see here is what I would call a convenience-driven approach. So, this is seeing what's the longest interval you can get between your doses and still maintain prophylaxis. And, uh, all of these have been demonstrated, uh, in the clinical trials and it's really opened up, uh, a lot of interesting approaches for personalization of care.

Dr. Russell:
So, doctor, you mentioned personalization of care, what are some example of, of how these therapeutics can be used to, to individualize care and better outcomes for your patients?

Dr. Pipe:
Well, I think to best illustrate this, I'll walk us through a few cases that I think illustrate, how we've used personalization in the clinic.

So, this first case is a case of trying to overcome non-adherence. This was a 6-year-old boy with severe hemophilia A. He transferred to our center at age 3 after prior management with only on-demand infusions. And at the time we first saw him, he already had a left ankle target joint, which means he had that inflamed synovitis related to frequent bleeding. We placed him initially on a traditional, conventional recombinant factor VIII at 50 units per kilo every other day and the family was trained in peripheral venipuncture access for his infusions. But the family really struggled with adherence over the next three years. He had continued problems with hemarthrosis

into both of his ankles and mom was really managing infusions only about twice per week, so because of that, we placed him on a recombinant factor VIII FC, extended half-life factor VIII at 45 unites per kilo every Monday, Wednesday, Friday and he actually had complete resolution of this target joint bleeding. And when we looked at his 72 hour factor VIII activity, so that's his longest interval between doses, he actually had levels of factor VIII that were in the 5 to 7% range. So, we had moved him up into that mild range and I think that went along way to contributing to his improved outcomes. Now, there have been some studies on how use and switch to extended half-life factors can have an impact on adherence, and there's a type of calculation that can be made to look at what's called the medication possession ratio and this is calculated for each patient based on the total number of days of drug that are supplied to the patient and then looking at when they last had their prescription fill and when their next was filled and how many doses they have on hand. And from that calculation, they can make a determination of how well the patient is adhering to the prescribed regimen. And with some studies in this area, it's been shown that the extended half-life agents actually can substantially improve adherence as measured by this medication possession ratio. Second case is how to deal with new onset target joint bleeding. So, in this case, we had an 8-year-old with severe hemophilia, he was on primary prophylaxis, with a standard half-life recombinant factor VIII he was on 50 units per kilo every other day. His annualized bleed rate was typically about 1, so about 1 joint bleed per year. He had a 48 hour trough factor rate activity of about 2% which is in that range of traditional prophylaxis targets that we talked about. But now recently, he started having recurrent bleeding into bilateral elbows, about once a month, actually, and so we were concerned about what this would mean for his joint outcomes. Now this was coincident with him taking up competitive basketball participation. And on clinical exam, we could see that he had mild bilateral elbow synovitis, sort of some bogginess, swelling, increased warmth, all signs of that inflammatory synovial activation and he had some mild loss of range of motion. So, because of that, we transitioned him to an extended half-life recombinant factor VIII, same dose every other day, but now he was not having any further bleeds over the following 6 months and when he came back to see us in the clinic, he had had resolution of the prior clinical manifestations of synovitis and when I looked at his 48 hour trough factor VIII activity, it was actually 15% and this is probably why he was doing so well. So, we can do this kind of personalization we can aim for convenience by having these long intervals between dosing, but as this case illustrates, it's also nice to have the option to aim for higher efficacy by targeting higher trough levels. Now, the last caseis using pharmacokinetic tailoring. So, this was a 21-year-old man with severe hemophilia. He'd been mostly treated on-demand before he came to us and we started him on prophylaxis at 40 units per kilogram every other day with a conventional recombinant factor VIII. He was managing about three to five doses per week, but was continuing to have breakthrough bleeding. He had had evidence of target joints in his ankles and elbows. He was progressively having loss of range of motion and chronic pain and actually had some serious bleedings, enough that he had to be hospitalized a couple of times per year. So, we increased the intensity of his prophylaxis because we actually determined that he had a relatively short half-life that was unique to him. It was probably driven because his own endogenous von Willebrand factor levels, which is the carrier for factor VIII was actually on the lower end and that probably contributed to a short half-life. So, based on that, we transitioned him to a recombinant factor VIII FC molecule, he went to Monday, Wednesday, Friday dosing, he actually did so well, we were able to down-adjust his dose per infusion and we were still maintaining trough levels of about 8%. And on that regimen, on follow-up clinic visits, he was reporting no joint bleeds over about a three month period and he said his pain was now manageable for the first time. So, pharmacokinetic tailoring has really become an active form of personalization in our clinics. What you can do is you can take limited samplings from a patient post-infusion and there are population pharmacokinetic formulas that you can use to graph out their predicted peaks falloff, troughs, and then their next infusions. And you can adjust the numbers accordingly, you can increase the dose, or you can change the interval and look at the impact over the course of a week of what their factor levels would typically look like. Now, that has been operationalized through a really neat service called the Web-Accessible Population Pharmacokinetic Service or a WAPPS hemo-platform. And what this platform has done is it has used brand-specific population pharmacokinetic models investigators and clinicians have submitted real patient data to generate and validate the formulas for these population PK models and you can take as little as a couple of samples after a patient has been infused and plug it into these formulas and it will generate reports of an individual pharmacokinetic profile.

Dr. Russell:
So, there's some really great success stories. Looking ahead to the future, there's many new therapeutic innovations that have either been approved or under investigation. What are the differentiating features of these strategies?

Dr. Pipe:
If we look at what we've talked about so far with traditional factor replacement therapy, whether it's with standard half-life factors or extended half-life factors, what we've been talking about is this repeated pattern of an infusion. You get a peak level and then a falloff back to trough levels and again. So, you get this sawtooth pattern of factor correction. Now, that factor level that we measure in the blood plasma has a correlate with a hemostatic effect. So, the paradigm hasn't really shifted with the extended half-life factors, we've just changed the intensity of the prophylactic strategy. It does give us the option, to maybe maintain higher trough levels, but the newest strategy that's just been introduced to hemophilia is the use of non-factor therapies But here the principal is that we're not actually

replacing the missing factor VIII or factor IX protein, but these strategies correct hemostasis, clinically, Aspirationally there's the idea of doing gene therapy for hemophilia. Now, this is still in investigation, but the principal here is , instead of giving them a protein infusion, every other day, with a one-time treatment, we deliver a, a transgene that encodes for factor VIII or factor IX gets taken up by the liver the l- own liver cells start to make the factor VIII, or the factor IX protein and it reaches a steady state of production and clearance in that individual; now we have a steady state factor level, no more peaks and troughs and we, accordingly, we also get a steady state hemostasis. We've been talking about the replacement therapy era, the shift from on-demand treatment to prophylaxis to improve outcomes, the added tools of having extend half-life molecules, those extended half-life innovations have been built on the back of the innovation of recombinant clotting factors and the ability to bioengineer them. The non-replacement therapies, the only one that has been approved so far, is a substitution therapy. It's a memetic of factor VIII, so It's a unique treatment for hemophilia A. This is a bi-specific antibody that recognizes that recognizes factor IX and factor 10 and it bridges those two molecules together to advance clotting in the absence of factor VIII and so it's mimicking what the factor VIII molecule does as a cofactor in coagulation. This bispecific antibody 's character allows for really good bioavailability with a subcutaneous administration, so that's an advantage. It also has a really long half-life, so instead of the hours of half-life that we're used to with the factor products we're talking about a half-life that's approaching 30 days with this bispecific antibody, so that's a real game-changer with reducing the intensity of, of prophylaxis. The other strategies that are still under investigation are antagonists of the natural anticoagulants. So, what we're doing here is we're trying to rebalance the hemostatic system. So, if we think of a balance, if you like in the absence of factor VIII or factor IX all of the natural anticoagulants are still there in full force and so the balance tilts and it leads to bleeding in the patient. So, what we've been doing for decades is to rebalance by adding the procoagulants factor VIII and factor IX to achieve a hemostatic rebalancing, but it's also true that you can inhibit, or reduce the action of the natural anticoagulants and you can also rebalance and improve hemostasis, even without giving factor VIII or factor IX. Some of the strategies that are being looked at here are a small interfering RNA that knocks down anti-thrombin levels monoclonal antibody inhibitors that target something called tissue factor pathway inhibitors, and then a bioengineered serum protease that targets activated protein C. So, each of the natural anticoagulants of hemostasis can be targeted to rebalance the clotting system. There's a lot of activity in this area I like to use the coagulation cascade to sort of frame where all this activity is going. What we've talked about just now are the targets directed against the natural anticoagulants, so antithrombin tissue factor pathway inhibitor, activator protein C but there's still innovation going on trying to develop even more improved extended half-life agents. One thing we haven't talked about, I mentioned that factor VIII has a carrier in plasma of von Willebrand factor, so turns out that that has limited the half-life of the extended half-life factor VIIIs. Despite all those different innovations we talked about Pegulation FC fusion, etc none of them have been able to exceed the inherent half-life of the von Willebrand factor molecule because all of them still have to bind von Willebrand factor to be stabilized in plasma. So, there are some new innovations, particularly a molecule called BIVV001 which in a sense is divorcing the extended half-life factor VIII from the need to be stabilized by von Willebrand factor and that increases the ceiling so the half-life can actually be substantially longer.

Dr. Russell:
Well, finally, Dr. Pipe, how would you summarize a lot of the points you made today?

Dr. Pipe:
Well, if we think about factor replacement therapy, first some of the new innovations like I just mentioned are opening up the possibility to break through, this von Willebrand factor imposed ceiling on factor VIII half-life by divorcing factor VIII from the need to be stabilized by von Willebrand factor. We now have once weekly dosing possible for prophylaxis for the first time and actually even longer intervals for people who are on the extended half-life factor IX products. There is the possibility to even think about subcutaneous delivery of some of these longer acting factor VIII and factor IX forms. I mentioned pharmacokinetic guided or supported therapy. This is actually now, a formal recommendation within the World Federation Hemophilia Treatment Guidelines The factor replacement therapies give us a lot of flexibility because we can normalize hemostasis, as needed. So, a patient doesn't have to worry about, you know, what their trough levels is, necessarily. If they want to go out for a, a high intensity activity, they can infuse right before that activity and take their levels right back up to the normal range. Because the factor levels can still be measured in the blood plasma, we can offer routine monitoring and that helps us with personalization, guiding doses and intervals. Prophylaxis and breakthrough bleed treatments can be treated with the same product, and that's the other things that I like about the traditional factor placement therapies. The substitution and the rebalancing therapies we mentioned, they do have lots of advantages. These are typically given with fixed dosing either weekly, up to as long as monthly, so, that becomes a, a very easy regimen to implement for, for an individual however, most of them do not normalize hemostasis like we can do with factor; it's something sub-normal. They've presented all kind of lab monitoring challenges 'cause if you're not replacing factor VIII or factor IX, then you aren't measuring it in the plasma, either. It makes the- a challenge for personalization to optimize these kinds of therapies. There is a sense, though, with the use of these new therapies that the patients feel like they've been liberated from routinely having to think about their hemophilia all the time, and that's probably because of the steady-state correction that they get with these agents. However, all of them still have continued reliance on factor-replacement therapy, if they

have bleeding events or certain types of surgery.

Dr. Russell:
Dr. Pipe, it was great speaking with you, today.

Dr. Pipe:
Well, thank you for allowing me to join you and to talk about these exciting developments in the care of patients with hemophilia.

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