THE RIGHT TREATMENT FOR THE RIGHT PATIENT: INTEGRATING NOVEL THERAPIES INTO CLINICAL PRACTICE

ALAN E. MAST, MD, PHD

Dr. Mast: Welcome to Part 1, *The Right Treatment for the Right Patient: Integrating Novel Therapies into Clinical Practice*. I wanted to start this presentation by just showing the cover page of this article which is the World Federation of Hemophilia 2020 Guidelines for the Management of Hemophilia.

So, what these guidelines proposed is that prophylaxis is the standard of care everywhere for hemophilia. So, for patients with severe hemophilia A or hemophilia B, especially children, the World Federation of Hemophilia recommends regular long-term prophylaxis as the standard of care. When prophylaxis is not feasible, episodic, on-demand therapy is essential treatment for acute hemorrhages but will not prevent long-term joint damage.

Start early. The World Federation of Hemophilia recommends early initiation of prophylaxis prior to the onset of joint disease and ideally before the age 3. The goal is to prevent all bleeds. For patients with hemophilia A or B with a severe phenotype, which may include patients with moderate hemophilia, the World Federation of Hemophilia strongly recommends that patients be on prophylaxis sufficient to prevent bleeds at all times.

So, we wanted to start this presentation again, just to say this is what the standard of care is. But now we want to go to why are new hemophilia therapies needed. And so, the current standard of treatment, which is the replacement of deficient factor VIII or factor IX, with recombinant or plasma-derived factors, usually requires regular IV infusions two to four times per week using the standard half-life factors.

The extended half-life factors reduce the frequency of infusions, but IV prophylaxis is still needed one to three times per week. And this frequent IV treatment is inconvenient and even distressing, particularly for infants, young children, and their parents or caregivers and comes with increased risk of infection.

Lack of compliance comes hand in hand with difficulties of administering treatment. In addition, inhibitory antibodies occur in approximately 30% of people with severe hemophilia A and 10% of those with hemophilia B. And these inhibitors render standard treatment ineffective, making patients more prone to severe and disabling bleeding.

Treatment to eliminate inhibitors is costly, invasive, and has a high failure rate of approximately 20 to 40% in hemophilia A and 70% in hemophilia B. Administering bypassing agents like recombinant factor VIIa or activated prothrombin complex concentrate is costly, invasive, and requires good venous access.

Now, I just want to go over the evolution of hemophilia treatment. And way back in the 1930s, hemophilia was treated and was first recognized that plasma was as effective as whole blood transfusion at that time. And then in the 1960s, it was recognized that cryoprecipitate can be used to treat hemophilia, and that could be a lyophilized factor that was used at home as well.

The problem with these therapies is that they became associated with viral transmission, would include hepatitis and HIV, and that led to the new methods, the solvent detergent treatments of these products to virally inactivate them. And, but it also within the hemophilia community, led to a lot of emphasis on getting safer and safer products; and that led to the cloning of the factoring, factor IX genes and the approval of recombinant factor VIII and factor IX products for treatment of hemophilia.

Then later in the 2000s, the randomized clinical trials for prophylaxis were performed and showed that this was the best method of treatment. This was then followed by the development of the long-acting hemophilia agents, and then the factor VIII-mimetics, gene therapy, and the rebalancing agents that inhibit natural anticoagulants.

So, this slide reviews the data that led to the World Federation of Hemophilia recommending that prophylaxis is the standard of care. The red bars are the on-demand treatment bleeds per year, and then the blue bars are the number of bleeds per year that the patients had once they were on prophylaxis. And you can see that it's greatly reduced. The third study on the right side of the slide shows that full-dose prophylaxis is superior to intermediate dose prophylaxis for these patients.

So, and now I'm going to talk about the factor VIII-mimetics and just to briefly describe their mechanism of action. You can see in the top left part of the slide you have factor IXa on the left side and then factor X on the right side. In the middle is factor VIIIa. Now what factor VIIIa has to do is it acts as a co-factor to bring factor IXa in proximity with factor X so it can activate factor X in the coagulation cascade. And when you're missing factor VIII or factor IX, you have hemophilia, and this process doesn't work.

So, what the factor VIII-mimetics are is they're a bispecific monoclonal antibody which are demonstrated in the bottom left-side of this slide. And one arm of the antibody binds to factor IXa, and the other arm binds to factor X. And in this way the bispecific antibody mimics factor VIII and brings factor IXa and factor X together so that the factor IXa can activate the factor X, even in the absence of factor VIII.

So, there have been two bispecific antibodies developed to date. One is emicizumab, which is approved by the FDA in 2017-2018. This is an effective subcutaneous drug that has flexible dosing regimens and a long half-life. It has decreased the treatment burden, especially in patients with inhibitors; and it's been shown to have long-term safety and efficacy established in the HAVEN studies.

There is also a second bispecific antibody that mimics factor VIII that's currently in Phase 3 trials. It has been reported to have approximately 15-fold higher potency than emicizumab and is effective at preventing bleeds in patients with hemophilia.

So, I want to introduce the next target for hemophilia treatment, which is called tissue factor pathway inhibitor or TFPI. And TFPI is an anticoagulant protein in our body that influences both the intrinsic and extrinsic pathways of the coagulation cascade which are diagrammed here.

So, how TFPI works is it is an inhibitor of tissue factor, factor VIIa, which is the proteins that activate the extrinsic pathway. And so, in the presence of TFPI, the tissue factor VIIa complex cannot directly activate factor X; and instead, the tissue factor VIIa complex is now activating factor IX to factor IXa, which is how it, why hemophilia proteins factor VIII and factor IX are required for hemostasis.

There is also more recent data showing that a form of TFPI inhibits prothrombinase of the coagulation pathway, so you can see that TFPI is effectively blocking both the extrinsic, both the extrinsic pathway and the common pathway. And so, and what it does is it does this at very early stages of blood clotting; and I like to say that TFPI is a, "you didn't really mean that" protein.

So, a normal patient or normal people without hemophilia, TFPI is there to prevent procoagulant stimuli or low level procoagulant stimuli from becoming a major intravascular thrombus. However, in a hemophilia patient, if you remove TFPI, then you can have these smaller procoagulant stimuli lead to a blood clot because now you can reopen up the extrinsic and common pathways to generate fibrin.

So, one of the ways to think about hemophilia and TFPI and how it works is that hemophilia requires two components. One is the absence of factor VIII or factor IX. This is what we traditionally think about, but it also requires the presence of TFPI to cause a bleeding disorder. In the absence of TFPI, patients with hemophilia would not bleed, at least according to this, these understanding biochemical mechanisms as a blood clotting pathway. And so, I want to, and that's why inhibitors of TFPI are being developed to treat hemophilia.

So, the next slide shows that there's different types of TFPI, because TFPI's an alternatively sliced protein. And this diagram here shows TFPI-alpha, which is a soluble heparin-releasable form of TFPI that's present in plasma, platelets, and extracellular matrix. And the inhibitors of TFP-, the antibodies to inhibit TFPI both bind to what's called the second Kunitz domain, which is the middle structure by the factor Xa of this diagram; and these antibodies block factor Xa from being inhibited by TFPI. And in doing that, they also greatly dampen the ability of TFPI to inhibit tissue factor, factor VIIa and prothrombinase.

There's another form of TFPI called TFPI-beta which coats the endothelium of our body, and the antibodies also bind to this form of TFPI as well. And so, it's important just to understand that, where TFPI is in the body, how these antibodies work, and then you understand, better understand the mechanism of the drug's action.

And a simple thing to remember is that it, these antibodies bind to the second Kunitz domain and block TFPI from inhibiting factor Xa. However, you could hypothesize that the main mechanism of action of these monoclonal antibodies is to block the TFPI-alpha forms, which are present in plasma or platelets and will accumulate at a site of a hemorrhage; and, therefore, blocking TFPI activity locally is really how these antibodies are thought to work.

So, just to summarize, by blocking TFPI to treat hemophilia is a strategy that's being pursued. Is one, it releases early inhibition of the extrinsic clotting pathway to restore thrombin generation. It works equally well in hemophilia A and hemophilia B. It works in patients with inhibitory antibodies against factor VIII or factor IX. It's allowed subcutaneous administration for bleeding prophylaxis, and now two monoclonal antibodies that block TFPI activity have recently successfully completed Phase 3 trials.

And one of these antibodies is called concizumab, and it was studied in the Explorer trials. On the left was the Explorer 7 study where patients with hemophilia A or hemophilia B with inhibitors were studied, and it was clear, you can see – compare the black bar to the purple bar – that the use of concizumab greatly decreased the annualized bleeding rate in these patients.

And then the Explorer 8 study examined patients with hemophilia A or hemophilia B that didn't have inhibitors. And if you look down under the ABR, the annualized bleeding rate, the median bleeds in the hemophilia A and hemophilia B patients were approximately equal to that observed in the patients with inhibitors. However, the mean bleeds were higher in this study at 3.9 or 6.4, and that is because there were a couple people remaining in this study that had very high bleeding rates. They weren't, essentially weren't responding well to this drug. But most of the patients did respond well to this drug.

The other antibody being developed is called marstacimab, and it was studied in the BASIS trials. And on the left side, the, a graph is showing patients that were previously being treated with on-demand therapy; and that's the six months OP rate. You can see their mean bleeding rate was on here 40 bleeds a year. And when they started on the marstacimab, it decreased 91.6% to way fewer bleeds; and that was retained in the long-term follow-up.

And on the right side of the slide, you can see where there, they treated patients who were on routine prophylaxis with marstacimab; and it again decreased the number of annual bleeds by about 35.2%, which was maintained in the long-term extension part of the study.

To summarize sort of the anti-TFPI monoclonal antibodies in development for hemophilia, with or without inhibitors, concizumab was assessed in the Explorer trials. It has been approved in Canada for patients with hemophilia B with an inhibitor. It's been approved in Japan for patients with hemophilia A or hemophilia B with inhibitors, and it's currently under FDA review in the United States; and it's dosed subcutaneously once daily with a custom pen.

And marstacimab was evaluated in the Phase 3 BASIS trial. It's undergoing regulatory review in the United States and European Union, and it is dosed once weekly using subcutaneous dosing.

So, the next target that's being developed for treatment of hemophilia is antithrombin, which is being developed, a drug called fitusiran is being developed. And fitusiran is different than the monoclonal antibodies I described earlier. It's a siRNA. So how this drug works is it actually intercalates into your hepatocytes and decreases the amount of antithrombin that's synthesized by the liver cells. And so, you can see on the left side of this slide, when you're being dosed with fitusiran, the antithrombin III level in plasma drops to about 20% of what it is before a treatment is started.

So fitusiran has been studied in three trials that are called the ATLAS trials. They're described on this slide, and it has very similar efficacy to the anti-TFPI antibodies where it reduces annualized bleeding rates to, you know, one to two per year. And this works in patients with or without inhibitors as shown in the various graphs on these slides.

The next target that we want to talk about is activated protein C, and so activated protein C is an anticoagulant protein that degrades, is a protease, and it works by degrading factors Va and factor VIIIa. And so, what this SerpinPC protein does is it's a protein that inhibits the activity of activated protein C. And it, so, again, this is a different mechanism of action than the previous drugs I've described. It's not a monoclonal antibody, and it's not knocking down the expression of a protein. Instead, it's infusion of a new protein that's been genetically altered or modified to specifically inhibit activated protein C.

And what this slide shows is if you can slow the activity of activated protein C, you'll increase the activity of factor Va and factor VIIIa in the, in the body or in the plasma; and that allows more prothrombinase to assemble that can generate more thrombin and then produce a blood clot.

So, this slide shows the results of a Phase IIa study of SerpinPC. It was performed in patients with severe hemophilia A or hemophilia B with and without inhibitors. And again, similar to the anti-TFPI and the anti-thrombin drugs, there was a 93% median reduction from baseline in total annualized bleeding result. And so, and with no severe adverse events related to this drug over 2.8 years.

And the figure on the right side of this slide shows individual patients and how their bleeding rate changed when they were started on SerpinPC. So, the gray bars on the left side of the forest plot indicate each individual patient's bleeding rate before they started on the drug, and the blue bars on the right show their bleeding rate after they started the drug. And you can see that most of them responded well to the treatment; but there were, again, a few that didn't respond well to this treatment.

So, it's a, it's a fun time to be involved in the hemophilia field right now because there are lots of innovative treatments being developed to meet patients' clinical needs. And what I went over today is there's now extended half-life factors that reduce number of injections and lower treatment costs. There are factor VIII-mimetic therapies that reduce number of injections and provide a subcutaneous route of injection as well as better cost-effectiveness ratio, including long-term treatments. And then there's the rebalancing agents that either use siRNAs to knock down antithrombin expression or monoclonal antibodies to inhibit TFPI or a new protein to inhibit activated protein C. And these all can be given subcutaneously and hopefully will also result in a better cost effectiveness ratio over the long term.

All right, so with that introduction of the different new agents that are being developed to treat hemophilia, I wanted to present the following case discussion. EL is an 18-year-old male with moderate hemophilia B who has been experiencing sporadic bleeding episodes which have led to chronic pain and limited mobility. Despite receiving prophylactic treatment with clotting factor concentrations, EL continues to have breakthrough bleeds, impacting his daily activities and quality of life. He reports increased pain and difficulty walking, as well as limitations in performing his usual activities. EL expresses a desire for more effective treatment options to better manage his hemophilia and improve his overall well-being.

EL has been on prophylactic treatment with recombinant factor IX concentrates for several years, but he has experienced suboptimal control of his bleeding symptoms. He has also tried adjunctive therapies, such as anti-fibrinolytic agents and physical therapy, with limited success in preventing bleeding episodes.

So, Dr. Wheeler, I'd like to ask you how would you manage this patient?

Allison P. Wheeler, MD, MSCI: So, Dr. Mast, I think the first thing I would need to know is a little more information about this patient. He hasn't been doing well on recombinant factor IX concentrates, but has he been on a standard half-life product, or has he considered extended half-life products? In using extended half-life products, if he is using them, is he aiming for fewer injections; or could we consider him taking an extended half-life product with increased frequency to maintain a higher factor trough?

If he wants to stay with factor products, I think exploring some of these options and talking about different factor troughs, potentially considering some population PK or pharmacokinetic studies on him to try and maximize his factor therapy is, you know, definitely an option. And there are a lot of patients who prefer factor products as their prophylaxis.

I think another thing to consider with him and at this point it would require clinical trial involvement, if he lives in the United States, would be some of the therapies that you discussed, either the anti-TFPI or anti-thrombin molecules at this point would definitely be something that could provide great prophylaxis for this patient.

And then, finally, if he really is sick of treating and wanted to consider something like gene therapy, which we haven't really talked about today, I think after, you know, a careful discussion about the potential benefits and the potential downsides and what's required of him in that setting, that could be a discussion as well. So, a lot of options for him. As you said, it's a really exciting time to be taking care of patients with hemophilia right now.

MANAGING THE DIVERSE ACCOUNT OF ADVERSE EVENTS WITH TREATMENT

ALLISON P. WHEELER, MD, MSCI

Dr. Wheeler: We're going to start now with Part 2 of this program, *Managing the Diverse Account of Adverse Events with Treatment*. So, adverse events are an important part of any clinical trial. And the adverse events that have been reported with hemophilia treatments that are currently under investigation have been both reassuring and something that have required a little bit of investigation.

So, the most common adverse event that we've seen is injection site reactions; and these are usually mild and resolve with some technical changes to how patients give themself the medications. Obviously, there are concerning adverse events that we need to keep watchful eye for: allergic reactions that can occur when given any drug and can occur either immediately or develop over time as somebody is exposed to a drug more.

And anytime we're giving a new medication to somebody, we worry about inhibitor development. And as inhibitors would develop in patients with hemophilia receiving a prophylactic treatment, we would look for increased bleeding tendencies or complications. And so, monitoring for inhibitor development and having this at the forefront of one's mind as you think about your patients is really critical.

The novel prophylactic agents that we've seen, and that Dr. Mast described early, also had the concern for thrombotic events. With these medications, the mechanism of action is decreasing natural anticoagulants in various ways that were described carefully in the previous section. And with that, you could imagine there's the potential for thrombosis or potential for clinically deleterious events in terms of clot development.

So, looking for signs of symptoms of deep venous thrombosis or pulmonary embolism, particularly in individuals with preexisting risk factors for thrombosis is going to be very important and has been important throughout the clinical trial program. In addition, there needs to be careful assessment for risk-benefit of each prophylactic agent for each individual patient. So, we need to educate both patients and caregivers about the signs and symptoms and adverse reactions and provide guidance to them on when to seek medical attention.

So, let's talk a little bit about what happened during the clinical trial programs. During the concizumab clinical trial program, there were three patients with thrombotic events that resulted in a pause in the Phase 3 clinical trial. The first patient was a patient with hemophilia A who did not have an inhibitor. This patient was between 40 and 50, 45 and 50 years old and had multiple thrombotic risk factors present at baseline. This patient experienced like an acute myocardial infarction.

There was a second patient with hemophilia A, between 40 and 45 years old, who also had thrombotic risk factors at baseline. And this patient experienced a DVT, PE, and superficial thrombosis of the vein.

These two patients together had risk factors that are concerning for increased risk of thrombosis, specifically obesity, lower leg edema, hypertension; and the other patient had a history of smoking, hypertension with occasional use of ACE inhibitors, increased blood pressure at screening, increased inflammation, and occasional chest pain for about a month preceding the thrombotic event. In addition, each of these patients received factor VIII in the setting of bleed concerns at the time of their thrombotic events.

The third patient was a patient with hemophilia B with inhibitor. He was 20 to 2-, 25 to 30 years old. He had obesity, hypercholesteremia, and multiple removals and replacements of a central venous access device, which is a thrombotic risk factor. He ended up experiencing a renal infarction, again, in the presence of factor product replacement for concern of a bleed.

These three patients caused the study to pause in March of 2020, and it was during that pause that there was an evaluation of each of these patients and the development of a risk mitigation strategy to prevent thrombotic events as the trial was ongoing. The risk mitigation that ended up resulting from these three thrombotic events was, again, due to an assessment of the clinical review as well as nonclinical data and an increased understanding of how concizumab interacts with factor concentrates in plasma.

Based on this, these results, there was a pharmacokinetic profile on each of the patients; and there was population pharmacokinetics that allowed modeling to understand where each patient was in terms of their concizumab level at the time of thrombosis.

In addition, there were thrombin generation studies that were done. These studies used plasma that was spiked with either concizumab alone or concizumab in combination with recombinant factor VIII, recombinant factor IX, recombinant activated factor VII, or activated prothrombin complex concentrate. And you can see on the right side of this graph the thrombin generation studies. In all these graphs, the dark blue lines are the thrombin generation for no concizumab but the presence of each individual factor. And the green line is the combination of concizumab and the individual factor.

And visually, I think it can be appreciated that there is an additive but not synergistic effect that is seen when these, when concizumab is combined with an individual factor product. So, the risk mitigation

strategy that came from all this investigation was, one, decreased factor dosing to the lowest approved factor dose when a patient does have a mild or moderate bleed. And second, a dose adjustment that happens as a mandatory part of everyone receiving concizumab treatment.

Jumping to the next slide, we can see that the concizumab levels were titrated at visit 5 of the study after the study restarted. Visit 5 occurred four weeks after starting concizumab, and you can see that everyone was started on the middle dose of 0.2 mg/kg. And if a patient's concizumab level after four weeks was less than 200 nanograms per mL, the patient was increased to 0.25 mg/kg dosing of concizumab. Alternatively, if the patient's concizumab level after four weeks was greater than 4,000 nanograms per milliliter, the patient's dose was decreased to 0.15 mg/kg. And anywhere in between 200 and 4,000 nanograms per mL, the patient remained on 0.2 mg/kg dose.

Transitioning to the fitusiran clinical trial program, there were also a number of thrombotic events that resulted in pausing of the clinical trial. These eval-, the valuation of these clin-, thrombotic events occurred in October of 2020; and again, similar to the previous discussion, resulted in a risk mitigation strategy.

So, the five different patients who experienced thrombosis, thrombotic events on fitusiran, were first a patient with hemophilia A with inhibitor between 30 and 40 years old. This patient actually had previously experienced a deep venous thrombosis which was not identified at enrollment and would have been an exclusion criterion for this study. In addition, the patient had a number of thrombotic risk factors: Type 2 diabetes, obesity, and tobacco use. Further, this patient had an antithrombin activity of less than 10% at the time of their thrombotic event.

The next patient was a patient with hemophilia A who was greater than 60 years old. This patient had well-controlled HIV, hepatitis C, and had prostate cancer and was status post-radical prostatectomy. This patient also had an antithrombin level of less than 10% when they had their thrombotic event, a cerebral infarct.

The next patient was a patient with hemophilia A with inhibitor between 20 and 30 years old, and he had suspected thrombosis involving a spinal injury and, again, had an antithrombin activity of less than 10%.

Patient with hemophilia B with inhibitor, who was also 20 to 30 years old, who was receiving concomitant bypassing agents, specifically recombinant factor VIIa in excess of a current bleed as part of management guidelines in the fitusiran studies. This patient had an antithrombin level of 10 to 20% and experienced an atrial thrombosis.

And finally, there was a patient with hemophilia A who was 20 to 30 years old who also had concomitant use of factor concentrate in excess due to current bleed management guidelines. This was actually a very complicated case of a patient who was misdiagnosed and was being treated for a subarachnoid hemorrhage but in reevaluation had a cerebral venous sinus thrombosis. And unfortunately, this patient did have a fatal outcome. They also had an antithrombin activity between 10 and 20%.

So, what happened with the fitusiran risk mitigation strategy? The first thing that happened was they really began targeting a more specific antithrombin activity of greater than 15% but less than 35%. Based on fitusiran's mechanism of action and the observed antithrombin activity of less than 10% in clinical

trial participants with a reported vascular thrombotic event, this antithrombin activity goal was modified and created as a target for risk mitigation.

This strategy is based on all patients initiating with a starting dose of 50 milligrams every two months and then having their antithrombin activity checked. If the activity is greater than 35%, they are dose-escalated. If their antithrombin activity is less than 15%, then they are dose deescalated. And you can see that this happens twice for each individual patient to target that range of 15 to 35%.

Just of note, based on population PK modeling, about 88% of patients will require either 0 or 1 dose adjustment. So, even though this is a fairly complex dosing scheme that requires careful attention, most patients are not going to have a lot of changes.

In addition to the dosing regimen, patients on fitusiran also had a factor dosing recommendations for breakthrough bleeding. This is actually also a fairly complex program that requires both understanding of a recommended single dose of factor product at the lower end of the treatment range when somebody experiences a mild or moderate bleed but also careful considerations of when and how repeat dosing should occur. So, it's very important for any provider taking care of somebody on fitusiran to really understand these bleed management guidelines.

For situations that require higher doses of factor or more frequent administration such as multiple repeated doses, the clinical trial recommendation was that study monitors, as well as clinical advisors, were a part of the discussion to really prevent the excess use of factor products only when somebody was having a severe or life-threatening bleed. In addition, the fitusiran clinical trial program recommended that antifibrinolytics should not be used in combination with factor concentrate or bypassing agents while somebody's receiving fitusiran.

So, where does this leave us? Dr. Mast did an excellent job of talking about the efficacy of each of these new novel therapies; and I've just discussed with you some of the potential adverse events and some of the nuances that need to be considered when taking care of a patient with hemophilia in this new era of novel therapy.

It's really important when you're talking with patients to include them in this process and to really have this process be shared decision-making between a provider and a patient, provider and a patient's caregiver, or any combination of people who are contributing to a patient's care. We need to really seek information from our patients and understand what their goals are, understanding where their decision-making is. We need to then initiate treatment and then really reevaluate that treatment in those, both the short term and long term to make sure that we're reaching these patients' goals and that the patient is still happy with the choice that they made and the choice that you made together.

We used to really just have factor replacement and previously really just standard half-life factor replacement for our patients. But now we have the potential to include our patients in clinical trials; we have factor replacement, both standard and extended half-life for our patients; we have nonfactor therapies that have been described today; and we haven't described gene therapy at all, which is another consideration for our patients.

There are different considerations for patients with and without inhibitors as many of these nonfactor replacements can be given in patients with inhibitors and provide prophylaxis and efficacy in that setting.

There becomes a lot of questions about where immune tolerance induction fits into the discussion and where do bypassing agents fit into the discussion. So, a lot more to think about and a lot more to discuss with our patients and really understand where they are and what's important to them so that we can help them make the best choices and have the best therapy to treat their hemophilia.

So, as we integrate novel therapies into clinical practice, it's important that we understand the mechanism of action of these therapies and how they work. We need to be able to understand and discuss each medication focusing on safety and efficacy. We need to understand and implement risk mitigation programs. We need to use data to inform treatment decisions and even consider clinical trial enrollment in patients who are maybe more complicated or just want to contribute to the clinical trial programs. We need to educate both our patients as well as the comprehensive care teams, and we need to really work on shared decision-making with our patients.

Okay, with all this in mind, let's go through another case study discussion. So, this patient, DS, demonstrated persistent bleeding after circumcision. And it was at this point that he was treated with silver nitrate. He was sutured, and subsequently after determining that he had a factor IX activity of less than 1%, he was treated with concentrated factor IX recombinant product. This stopped his bleeding and introduced him to our hemophilia treatment center.

He initially did exceedingly well for the first 14 months of life. He had no bleeding concerns and then presented with a left buttock hematoma after falling on a wooden toy and, again, was treated with recombinant concentrated factor IX in just a single dose.

He then fell when he was 16 months old, and he came into the ER, was retreated, was treated with recombinant factor IX, and demonstrated hives after his infusion. It was after this point that he was assessed more thoroughly and was determined to have a factor IX inhibitor of 4.9 NBUs. This wasn't surprising because he really didn't respond to the factor IX initially, but he did respond very well to repeated doses of recombinant factor VIIa at 90 mg/kg.

When he was 17 months old, he had a port-a-cath placed with recombinant factor VIIa support and immune tolerance induction therapy was started with a recombinant factor IX product. He, at first, demonstrated some irritability with his factor infusions; but this improved with slowing the infusion and also giving him some antiallergy medication.

He then continued to do fairly well. At 21 months old, however, his inhibitor persisted; and he was started to develop proteinuria and urine protein to creatinine ratio was concerning for some membranous neuropathy. This is not unexpected with factor IX ITI therapy, but it did result in discontinuation of his ITI therapy; and he was started on recombinant factor VIIa three times a week for prophylaxis. And again, he did fairly well for a little while.

At 25 months old, he did come in with a severe buttocks hematoma, was treated with recombinant factor VII; and at that point he was transitioned to prophylaxis daily given the severity of that hematoma.

At 29 months, he had a spontaneous right knee hemarthrosis, again was successfully treated with recombinant factor VIIa. But then at 32 months old, he developed a severe spontaneous left calf hematoma which was not responsive to recombinant factor VIIa despite fairly aggressive treatment. He subsequently required a PCC, prothrombin complex concentrate, to be given to resolve this bleed.

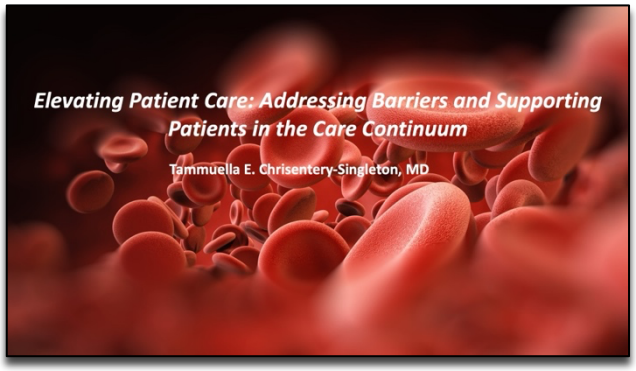
And I think as you can appreciate, while this patient did really well initially, despite the presence of his inhibitor, as he was getting older, his bleeds started to become more frequently; and they started to be more severe. So, the question is, what options do we have for this patient, still very young and a factor IX inhibitor with decreased response to his bypassing agent treatment?

Okay, so, Dr. Singleton, what do you think our options are for this patient?

Tammuella E. Chrisentery-Singleton, MD: You know, this is, this is pretty complicated, right? This is, this is a very, very challenging patient. Right, you've gone through, I mean tolerance. You're still having significant difficulty. With a patient like this, I would think that you would have to start to explore all of the available options.

Dr. Wheeler: Well, and I think that's really what we did. We did look at all the options with this patient. You know, as you can see, we were using one recombinant factor VIIa product for him, which is the one that we had on formulary. But we now have two on the market, and so we shifted him over to the alternative recombinant factor VII product after using prothrombin complex concentrates in the hospital to treat his bleed.

In addition to that, probably starting around 21 months old, maybe 25 months old, we started talking to this family about the potential for being involved in a clinical trial. And for this patient with severe hemophilia B and an inhibitor, the rebalancing agents that we've been discussing today, the anti-TFPI and antithrombin molecules are really the only options that were available to him. So, after a lot of discussion about what it means to be in a clinical trial, about the unknowns, the potential risks, and what's happened throughout the clinical trial programs, this family did elect to start a rebalancing agent and continue on a clinical trial in the hopes that their child would have the best prophylaxis possible.



ELEVATING PATIENT CARE: ADDRESSING BARRIERS AND SUPPORTING PATIENTS IN THE CARE CONTINUUM

TAMMUELLA E. CHRISENTERY-SINGLETON, MD

Dr. Chrisentery-Singleton, MD: So now we are going to have a chance to talk about elevating patient care. That would be the ideal thing, right, to address barriers and to try to figure out how we can support patients in the care continuum.

So, we certainly have an appreciation, as we take care of patients, that needs vary across the lifespan. So, when we're caring for hemophilia patients, from birth to diagnosis, we certainly have concerns. So, if we know that there's a family history, we're on alert. But then the family has to come to terms with the diagnosis. Following that, we have a very detailed conversation about the available treatment options and really a shared decision-making exercise to conclude about exactly what the treatment of choice would be.

As we move forward into early childhood, we have concerns, constant worry about possible accidents. What would be considered to be normal childhood trauma can be a significant concern in patients living with hemophilia. So, we have conversations and detail and anticipatory guidance about possible ways to avoid trauma. We also talk about when to infuse, how to infuse, providing a lot of support in terms of those infusions and maintaining an open line of communication.

We also have a focus on supporting the entire family unit through this process. Now, moving into one of my favorite periods, we move into adolescence and early adulthood. So, there's a growing need for independence, so this is a time where we're shifting into that transition period where teens and young adults are taking on more responsibility, not just learning how to self-infuse, knowing how to self-infuse, understanding a medication regimen, understanding what therapies they're on, understanding what decisions should be made and could be made and becoming a part of some of those decisions.

Now adolescents and young adults can have challenging consequences or challenging things that they face that result in consequences because a lot of young adults and teens just simply want to fit in. They don't want to feel different. So, having in-detail conversations during this period is particularly important and understanding if additional family support or support for the teen and young adult in terms of just having conversations about what's happening and how they feel about it may be incredibly important.

We may certainly have adherence challenges during this time, and that is the time not to stop support but add support. But maintaining that sense of independence while we're doing that, so a huge focus on that transition but still providing significant support.

Now, as we enter adulthood, there are a lot of changes that take place in terms of careers and jobs and what those demands actually are. We have adults who have very physically demanding jobs. We have adults that may have increasing responsibilities associated with those jobs or careers. And so, we have to take into consideration the entire patient in considering a treatment plan. We also have to recognize that during this time the risk-benefit ratios become increasingly important because of increased responsibilities associated with being adult.

And then finally in the later years, as we enter our, our older age, there are issues that are, that, that naturally happen as we age but, but can become more enhanced when you're living with hemophilia. So, joint damage and hemophilic arthropathy would be one of those. Associated comorbidities with age, cardiovascular disease, and how would one manage that in the face of hemophilia? Decreasing activity and making adjustments for that decreasing activity and, again, enters that joint decision-making or shared decision-making between the adult and the provider.

So, we are aware of barriers in terms of treatment for all of our patients, but barriers to treatment certainly remain for patients living with hemophilia, not to, not the least of which would be financial barriers that can be associated with therapeutic options, with care. Patients can have limited access to comprehensive care centers, depending on where they live. So, we certainly have patients that may live in a state where there's not a comprehensive care center, or we may have patients that have to travel many, many hours to get to the comprehensive care center.

Again, I mentioned transition before. Transition is incredibly important. That transition between pediatrics and adult care is incredibly important, not just to deliberately focus on it but sometimes to

recognize that there may not be an adult provider to transition to and an additional plan may need to be put in place.

Cultural and language barriers are incredibly significant, and it's important that we recognize those to make sure that we are really delivering the best care possible and, of course, inviting the patient to participate in that shared decision-making process.

Now, I mentioned before with transition that we may have some issues with adult providers. That is certainly a barrier in terms of having providers that are available that have a significant amount of experience in terms of treating patients with hemophilia and, of course, generally having limited resources can be a significant issue.

Now, with our hemophilia patients, because most of the therapies are intravenous or subcutaneous, there can be a perception in terms of a highly perceived burden of treatment, both for the patient and the family. We also know that there are issues associated with bleeds and bleeding symptoms. Again, many patients have problems with venous access issues, maybe not knowing how to infuse, having difficulty infusing from a peripheral access standpoint. And, of course, prophylaxis can certainly be viewed and is and can be very time consuming for patients; and that can certainly contribute to adherence issues.

So, within those barriers, I mentioned transition to care. So, transitioning from pediatric to adult care is probably one of the most significant barriers. It's one of the most significant barriers because we have issues that surround social and behavioral factors. There are other barriers and concerns that are associated with a system that are, that's in place; so, I mentioned having fewer adult-trained providers, adult hematologists that are available, especially in certain areas of the country, can prevent, present a significant barrier to that transition from pediatrics to adult care.

Many patients lose insurance coverage. We can have poor coordination between pediatrics and adults. We can even have challenges within a center where there's a continuity of care because we treat both pediatric patients and adult patients, but if we don't have a deliberate plan, if there's not a systemic process for that transition within the center, we can still have significant challenges.

Low reimbursement can be an issue within the healthcare system. But overall, we know that we can have significant issues and significant failure in this transition that can result in patients living with hemophilia that have more morbidity, more problems, can also relate to an increased death rate in some patients when appropriate care is not available.

So, associated with this, we know, again, that when you transition from being a child into being a young adult and into adulthood, adherence decreases as a patient ages. So, again, that support system, having that additional support is incredibly important.

Adolescents should gradually assume responsibility. Treatment adherence, again, is a key challenge. And having a comprehensive care center available for patients so we have a formal transition program is incredibly important to try to make sure that we avoid the failure in transition that can result in significant problems for patients.

So again, what are some of the strategies that we could use to address this transition to adult care? I mentioned that even when we have patients that are cared for from pediatrics into adulthood at one

center, it's still incredibly important to have a structured transition plan. If you are a pediatric center, having a relationship with an adult center so that you have that structured transition plan that doesn't start at age 18; it actually starts as soon as the patient enters adolescence. So, you have structure with each year, gradually introducing concepts in a very structured way.

You want to make sure that this transition plan and a patient's success in this plan is monitored. We want to have assessments that are in place to determine the patient's readiness to move onto the next phase or stage because that can be, and should be, a very individualized process. With this individualized process, we want to provide patients with individualized support. Again, we want to provide extra support. You would think, it's almost counterintuitive, that as a patient ages that they would require less. But in reality, during this period of transition, patients require more support. When switching again to a self-treatment option that may be beneficial for the patient considering a specific circumstance, that pa-, that patient may require more support.

How about a patient who's moving away from home for the very first time, losing some of that intense parental support? What's needed to support that patient? Should an alternative treatment option be considered? Again, that individualized transition plan with individual, individualized support.

So, in terms of assessment tools, they can be very valuable, determining that readiness. There are various milestones that can be used, including HEMO-milestones, the HEMO-Milestones Tool. Again, assessing outcomes, determining what indicators are important for readiness, understanding if there are any changes in bleeding rate and providing anticipatory guidance in terms of what you should do if you have increased bleeding when you're away from home and college or if you have moved away and taken a new job.

How to interface with the emergency room or hospitals. Admissions. Emphasizing the significance of adherence now that you're on your own, time between visits, when you should be seen. A lot of things should be covered, and it's important for us to recognize that there are really no defined or definitive systematic approaches.

So, a comprehensive care team is incredibly important to the transition process. The continuous assessment of patients when they're in the transition period is incredibly important. Understanding the barriers that are in place.

So, this is one of my favorite things to talk about in terms of barriers. As we look into examining health disparities in hemophilia care, now admittedly if you're anything like me, as soon as you hear the word disparity, you may automatically think ethnicity, race, or culture. But within hemophilia care, examining health disparities actually covers a vast sort of area of topics or a huge amount of concerns, not just race or ethnicity; but stay tuned and let's take a look at some of the things that we need to consider when we're thinking about health disparities in hemophilia care.

Now this is one of my favorite illustrations as well, when you take a look at equality versus equity. So, if you have three people that are of different heights, if you're doing something that's equal, you provide them with the same size box. But you can still see that there's an issue here because the shortest person still can't see over the fence. When we consider the concept of equity, that's considering where you are

as an individual, meeting the patient or the person where they are so that they have an opportunity to have the same access to care.

So, now that we've kind of laid the foundation in terms of equity versus equality, let's take a look at a few of the issues that I think are incredibly important in our quest to make sure that all patients living with hemophilia have true access to care.

So, we know historically that hemophilia patients or females in hemophilia were technically, were usually just called carriers. So, because of that, women with bleeding disorders have been underdiagnosed and certainly underrecognized. For every man living with hemophilia, there are approximately 1.5 females that are carriers. So, at least a third of those women who are known to be carriers have low factor levels. I didn't say anything about symptoms, but I said low factor levels. Women should make up about 30% of patients living with hemophilia.

Now, hemophilia in most women that are, that fall into the car-, carrier category are technically those mild-to-moderate patients. But again, that's hemophilia. So again, women should make up approximately 30% of patients living with hemophilia. The World Federation of Hemophilia reports only 3.5% being women, again, addressing the issue of underrecognized and underdiagnosed.

Well, what are some of the issues? Again, some of the issues involve that "carrier" stigma. So, carrier doesn't imply or doesn't equal, again, low factor levels. Hemophilia is hemophilia is hemophilia. A low factor level should be a low factor level in hemophilia, male or female. But again, research has primarily focused on men living with hemophilia.

von Willebrand's disease is also more common than hemophilia and affects a lot of women, and a lot of women can have hemophilia with the presence of low factor levels that are associated with their carrier status. A lack of knowledge and empathy is certainly present surrounding symptoms that women have with bleeding, especially with menstruation.

So, the diagram to the left indicates just some of the issues that can be associated with women and bleeding that can be associated with menstrual cycles. So, bleeding can be stigmatized as just being something that's normal, but it can be incredibly excessive in women who are living with hemophilia.

Patients and providers are often completely unaware of what would be a "normal period," and a lot of education is needed there. Again, bleeding disorders are un-, underrecognized and underdiagnosed; and resources that are often dedicated to men and conditions that men live with are not necessarily as available for women who may have the same diagnosis. So again, it's a lack of knowledge that contributes to underdiagnosis and it being underrecognized. Let's take a look at the next slide.

So, again, concentrating on healthcare barriers and equity and equality, we just reviewed some of the concerns surrounding women. Well, there are also concerns surrounding racial and ethnic disparities in patients living with hemophilia. So compared to White patients, non-Hispanic Black patients are less likely to receive prophylaxis, less likely to be on home therapy, and have a two-fold higher frequency of inhibitors despite having similar genetic mutations.

Additionally, immune tolerance induction is also less likely to be successful. It's also less likely to be started or utilized in patients who are Black and especially those who are Black and non-Hispanic. Black

and Hispanic patients, again, are underrepresented in hemophilia trials, just generally speaking. So non-White, and especially Black patients, can have worse outcomes; and this is reported across the board in every metric study due to systemic inequities and certainly not just biology.

So, patients living with mild and moderate hemophilia are certainly less likely to have spontaneous bleeding but have bleeding, nonetheless. So, what you see on the left is a very familiar diagram, and it's indicating that joint bleeds increase as factor levels decrease. And joint bleeds decrease as factor levels increase. So, although there is a difference in terms of the annual bleeding rate in a patient that's living with severe hemophilia compared to a patient who's living with mild to moderate hemophilia, bleeding exists.

As you can see, that even as we approach 5%, 10%, 15%, when looking at this very familiar diagram, bleeding rates decrease; but again, bleeding is still there. So, because patients who live with mild to moderate hemophilia have fewer bleeding epi-, episodes and are less likely to have spontaneous bleeding, sometimes in those patients bleeding episodes can be very difficult to identify.

In addition to that, healthcare providers may not recognize the complaints that are associated with bleeding. They can also have significant issues and challenges with a, a bleeding diagnosis or a bleeding episode being diagnosed. So, it can usually be recognized pretty late.

The overall diagnosis of a patient, especially those who are living with mild hemophilia, can be delayed; and it's often not recognized until patients are living at, or at a very older age.

So, as we have just discussed, a lot of the, the barriers that can be associated with accessing care for patients living with hemophilia, right, we talked about women. We've talked about mild-to-moderate patients. We've talked about patients that have challenges because of ethnicity or race.

Now we'll shift and talk a little bit about accessing the quality of life for patients living with hemophilia. Like how do we make these assessments? Well, assessment tools are incredibly important. So, the Haem-A-QoL questionnaire is a validated tool that's specifically dined, designed to assess the quality of life in individuals living with hemophilia.

The HJHS, I'm certainly very familiar with that. It took a long time for me to learn how to do that. But this is used to assess the joint health in individuals living with hemophilia. It's an objective tool; and it may not capture the broader quality of life concerns, but we can certainly have so-, some insight into joint status.

The World Health Organization Quality of Life questionnaire is a generic quality of life assessment tool, and it may not address hemophilia-specific concerns. But it is certainly something that we should be aware of.

And followed, finally, the Functional Independence Measure. This is used to assess functional independence and activities of daily living and is not specific to individuals living with hemophilia. So, assessing the quality of life of patients living with hemophilia and knowing what tools are available to us is incredibly important.

So, in an ideal world, what would we like to see for patients that are living with hemophilia? Well, this is one of my favorite illustrations in terms of health equity leading to a functional cure. So, we certainly want more for patients living with hemophilia than just having an improved quality of life in terms of participation and activities of daily living. We also want an improvement in terms of minimal, just having minimal joint impairment. We also want to have the ability to engage in low-risk activities and have freedom from spontaneous bleeds. But in an ideal way, we would also like to see patients live with a more unrestricted lifestyle, leading all the way to an optimal health and well-being state with normal hemostasis.

So, this is a case that I think is perfect to align with our discussion. So, AK is a 17-year-old with severe hemophilia A with a history of inhibitors. He's currently on a non-factor therapy prophylaxis, and he's received comprehensive care at a pediatric HTC since he was since he was adopted from a state orphanage in Brazil when he was around six years of age.

He developed a high titer inhibitor after starting prophylaxis replacement therapy at age six when he came to the pediatric HTC, and he has a history of chronic hemophilic arthropathy in his bilateral ankles. So, he has a very strong support system in place; but as he approaches his 18th birthday and high school graduation, he and his family face the daunting task of transitioning from pediatric care to adult care.

So, he's planning to get a job while training to become an electrician, so it's important to think about his career choice. Additionally, his family has struggled with financial instability, and they now need to move closer to the father's new job, which makes the HTC about a five-hour drive away.

So, with some of the things that we've discussed, what are some of the challenges that you guys see here; and how would you address them?

Dr. Wheeler: Well one question I have, Tammy, is he going with his family? He's training to become an electrician, and they are moving. So, what's the dynamic there?

Dr. Chrisentery-Singleton: Absolutely. So, for now, and I'm chuckling sort of as I say this, he can't afford to move out just yet. I have young adults at home. Yeah, so I'm very familiar. So, he can't afford to move out just yet. He will be with the family five hours away. So, there was no consideration of where he was going to be other than that.

Dr. Wheeler: Okay, and my next question is with dad getting a new job, is he still covered under their insurance? And will his nonfactor product be covered by this new plan?

Dr. Chrisentery-Singleton: And voilà, enters yet another concern. So, the answer is we're not sure. We don't think that he's going to have coverage with the dad anymore. And so, we, as a part of his transition plan, are actually preparing well what would be the next steps in that transition and advising him and going to school and advising him about what the state options are and advising him about any programs. So, there are a number of issues here across the board, including getting him ready for transition.

We have cultural considerations, right, because this is a patient who was originally from, from Brazil. He is going to be physically separated by a great distance from the HTC, and there are only very small community hospitals from an emergency room standpoint between their new location and the HTC.

So, there's significant challenges here that we have to think about, but we have to have a very collaborative approach with the HTC, with our social workers, with all of our staff to uncover all of the obstacles and needs that he may have as an individual.

Dr. Wheeler: I'm just going to throw one more in there, Tammy, because I think it's really important, and it's talked about so much with our subcutaneous nonfactor products on the market. Does he know how to self-infuse? And is that skillset a feasible skillset for him to obtain at this point, knowing that he's going to be so far from an HTC and maybe even a hospital that would be willing to give him his factor replacement?

I think I can flip a coin and get a yes or a no from a smaller community hospital whether or not they'll, they'll infuse for a patient. So, that's definitely a topic you want to discuss with this family.

Dr. Chrisentery-Singleton: Absolutely. Absolutely, and you get the gold star for the day because that by, by far, is at the top of the list of some of the challenges that we face with this particular patient. And he does not know how to self-infuse, and so we are actively setting up a program to try to support him in that effort.

So, this has brought us to the conclusion of our program, and there are a few amazing things that I think we've covered today. We certainly understand that there are multiple challenges that exist within current hemophilia treatments. We know that we have challenges and barriers that include inconvenience, adherence issues, inhibitory antibodies that can develop, and the need for trough levels, etc.

Emerging therapies with novel mechanisms of action such as rebalancing agents – a few are noted here – are certainly important in terms of patients that need a lot of these newer products with newer and novel mechanisms of action for enhanced and improved efficacy, safety, convenience, and choice.

Safety integrating these novel therapies will take careful patient selection and risk mitigation strategies to make sure that we reduce any events that could occur, especially thrombotic events.

An individualized approach is incredibly important when we are treating hemophilia patients. So, individualized care, a team-based care approach with that shared decision-making can certainly help to address biases and barriers to optimize hemophilia treatment for all of our patients.