ADVANCES IN HEMOPHILIA: FROM JOINT HEALTH TO FVIII GUIDELINES AND THE CLINICAL INTEGRATION OF REBALANCING AGENTS

Segment 2: Guidelines for FVIII Levels

Speaker: Guy Young, MD and Steven Pipe, MD

Dr. Young:

Welcome to this segment on guidelines for factor VIII levels and how they inform treatment decisions in hemophilia management.

For decades, factor VIII levels have been central to how clinicians assess bleeding risk, design prophylaxis strategies, and evaluate treatment effectiveness. In this discussion, we're going to take a closer look at how factor VIII targets have historically been used in clinical practice, what the current guidelines recommend, and how new data are shaping expectations around higher trough levels, sustained bleed protection, and what that might mean for long-term joint outcomes.

So for this segment, I'm going to introduce Dr. Steven Pipe. Dr. Pipe is a Professor of Pediatrics and Pathology, and he's the Lawrence A. Boxer Research Professor of Pediatrics at the University of Michigan in Ann Arbor, Michigan.

Before we get going, I'm just going to state the learning objective for this segment. It is to assess the impact of factor-based replacement therapies on factor VIII levels according to various guidelines.

So the first question for you, Dr. Pipe, is factor VIII levels have long been central or key to how we think about hemophilia management. Can you briefly walk us through how clinicians have historically used factor VIII levels to guide treatment decisions?

Dr. Pipe:
Yeah, thanks, Guy.

Well, certainly factor levels have been central to clinical diagnosis going back decades. It's how we diagnose hemophilia, often with a prolonged clotting-based tests like aPTT and then eventually a specific factor assay, factor VIII or factor IX. But it's also how we assign severity. And so still going back over many decades, we define the expectations about clinical outcomes for patients based on their residual factor level. So severe is factor VIII or factor IX level of less than 1%, moderate is between 1 to 5%, and then over 5% is mild disease.

We also rely on factor levels to screen patients for inhibitor complications, and it's often the first way that inhibitors are picked up after a clinical presentation.

With regards to how we use factor levels in other aspects of clinical management of hemophilia, we use factor assays to do dose adjustments when patients are on routine factor replacement. We rely on factor levels during acute bleed management and, of course, during surgical interventions. And then, for a long time, we have been using pharmacokinetic-guided prophylaxis in order to optimize factor dosing.

So really, for several decades, factor levels have been central to everything that we do in hemophilia management.

Dr. Young:
Great. Thank you very much for that. So building on that, and I promise I'm not going to date us, but we are roughly the same vintage and started out around the same time, and I remember back then that we had targeted factor VIII trough levels with prophylactic therapy of around 1%. We felt okay if we're above 1% or 1% or higher, then we're happy with that. But the goalposts have shifted, and most recently the WFH guidelines have started to shift these goalposts. So can you talk about why we're increasingly considering higher trough levels of factor to prevent bleeding?

Dr. Pipe:
Well, as you said, you know, we have to go back to the early days of initiation of prophylaxis, and beginning with the Swedes and then in the Netherlands. It was the observation that patients with non-severe forms of hemophilia had less joint disease, and even having a few percent of residual factor VIII or factor IX was enough to significantly reduce joint disease and the risk of joint bleeding. And so natural history studies done over many years have really confirmed that.

And if you look at that traditional prophylaxis trough target that you were mentioning of, say, 1 to 3%, in some ways that was a practical application of monitoring trough levels, because at the time all we had were the plasma-derived factor products as well as what are now considered the standard half-life recombinants. And to have a reasonable prophylactic regimen of, say, three times per week or every other day, that was the targets that you could reasonably end up with in the 1 to 3% range.

But if we look at some of the large studies that have been done—and of course the key one would be the U.S. Joint Outcome Study—and that directly compared standard half-life applied prophylaxis to on-demand treatment of toddlers and then looked at joint outcomes. And of course that was a dramatic outcome in that study. It was a relative risk ratio of about sixfold for osteochondral damage in the on-demand group versus those who were on prophylaxis.

But when those toddlers were first evaluated at age 6, about 93% of the participants had zero osteochondral damage when they were initiated on prophylaxis compared to less than 60% if they were on demand. But those patients, both the early prophylaxis and then what would be called the late prophylaxis group, the entire cohort were invited to continue prophylaxis all the way up through age 18.

And disappointingly in that long-term continuation study, now only 2/3 of the patients who were in the early prophylaxis group are free of osteochondral damage, and there was further deterioration in the late prophylaxis group, where less than 1/4 of the patients had no evidence of osteochondral damage.

And worse, if you dig down into the MRI results from this study group, what became apparent is that the evidence of joint deterioration in joints that the patients or the parents swore had never had any overt bleeding in that joint. And so this raises this prospect of subclinical bleeding, and that's been reinforced now in multiple studies.

The Canadian Dose Escalation Prophylaxis Study looked at osteochondral outcomes in patients on that prophylaxis study, and they also found anywhere from 1/4 to 1/3 of so-called bleed-free joints had evidence of osteochondral damage. And then subsequent large prospective studies have highlighted that subclinical bleeding is a real phenomenon.

So I believe that that was a significant influence on the WFH recommendations to move toward higher trough levels, trying to get above 3 to 5%. And the natural history studies would support that if you could get patients closer and closer to the mild range, you could dramatically alter the risk for adverse joint outcomes.

The trouble then was to do that with standard half-life agents was really challenging. These were really aggressive protocols to get patients in those trough levels. So thankfully all of the extended half-life innovations that came in the early 2000s were allowing us to use fairly reasonable prophylaxis regimens, again, maybe two to three times per week, but in some cases still every other day, in order to drive up those trough levels. And that has resulted in improved joint outcomes for a number of patients.

Dr. Young:
Great. Thank you for that. And that's a great segue into this next question or topic, which is about the ability to reach and sustain these higher targets. Now we're talking here about 3 to 5% from the WFH, but you alluded to even higher targets in the mild range where we can probably abrogate even more joint disease. So maybe you can just briefly go through the different iterations of factor VIII concentrates that we currently have and what they can achieve for patients.

Dr. Pipe:
Sure. The extended half-life group of factor products are either agents that have conjugates added to them, like pegylation or fusions to proteins like albumin or the Fc portion of IgG, as well as some additional newer innovations which are driving even further sustained levels of factor in the plasma.

And when these became available initially in the clinical trials, if you look at the outcomes, they were a little bit better than standard half-life agents, but at the time when they did those trials, they were really aiming to reduce the burden of prophylaxis. And so you look at the regimens, they were typically twice-a-week infusions for factor VIII, maybe once a week for factor IX with the EHL agents. And in some cases they tried to extend that to 10 days or even 2 weeks with the EHL factor IXs.

But it became apparent that if we're really going to improve outcomes, we really need to raise those trough levels higher. And I think there's a very good study that you're familiar with, the PROPEL study. And what they did is they used a pegylated form of factor VIII which had enhanced pharmacokinetic properties, and they analyzed the pharmacokinetic performance of that agent and compared it to targeting two different factor VIII trough levels, either a traditional 1 to 3%, which would be called the reference arm, or a higher trough level. In this case, they aimed for between 8 to 12% in what we'll consider the elevated arm.

And the outcome from that study really supports that if you move those trough levels higher, you will get better outcomes. And if we look at one of the parameters they used, it was the proportion of patients who had zero bleeds while they were on the prophylactic regimen. And whereas those with the traditional targets had zero total bleeds in around the 40% range, those who were targeted to the higher trough levels in that 8 to 12% range, that proportion actually increased to about 60%.

And then if you look at the spontaneous joint bleeds, this is where it was really remarkable, where the proportion of patients who had zero spontaneous joint bleeds—sort of the

hallmark of hemophilia—was 85% bleed-free in the group that were targeting the higher levels.

Now, does everybody need a target of 8 to 12%? That's not clear. We do think higher is better.

Dr. Young:
Thanks for that. And so moving on, there is a relatively newer product that is essentially targeting these higher troughs. Can you talk about the novel mechanism of action or essentially the way that our newest factor VIII product, efanesoctocog alfa, basically builds into this sort of profile?

Dr. Pipe:
So what's really driving this particular innovation is the issue that factor VIII products, whether they're standard half-life or all of the EHL innovations, the pegylated products, the Fc fusions, they're all subject to a von Willebrand factor–imposed half-life ceiling. And what's happening there is these proteins are still primarily stabilized in the plasma by binding to von Willebrand factor, just like natural factor VIII is. And so the half-life can really never be any better than a traditional factor VIII–VWF conjugate. And if we look at the half-lives of any of the innovations that have led to an EHL form of factor VIII, their half-life is improved only about 1.3 to maybe 1.5 times the standard half-life equivalent.

So what the aim was with efanesoctocog was could we decouple factor VIII from von Willebrand factor and then through other innovations drive even longer half-life. And the way they did that is they started with the base Fc fusion molecule, and then they added a covalent linkage to a recombinant portion of VWF called the D'D3 domain. This is the domain of von Willebrand factor that really stabilizes factor VIII and protects it in plasma. And they linked that conjugate through Fc fusion technology. And then in addition they added a series of repeating hydrophilic sequences. These are natural amino acids that provide sort of a watery shield around the molecule. These are called XTEN polypeptides. And in that combination, what they were able to achieve is now a factor VIII product which has pretty much three- to fivefold half-life extension compared to standard half-life, and again a marked improvement over other EHL factor VIIIs.

And what's also unique about this product is it has sort of an altered pharmacokinetic profile, where instead of a rapid drop right after reaching peak infusion in the plasma, there is a more gradual decline over time. And in the adults who were in this study getting prophylaxis with just a once-a-week infusion of efanesoctocog, they still were able to maintain factor VIII levels that were in the non-hemophilia range, so above 40%, for around 3 to 5 days, depending on the individual.

So this concept of a high sustained factor level and what this could potentially do for joint outcomes is really interesting.

Now in the clinical trial, the results were pretty substantial. So they had patients who were on their traditional standard-of-care factor VIII prophylaxis on a lead-in study, and then they were switched to efanesoctocog. And what they saw on the prestudy of factor prophylaxis is a mean annualized bleed rate of about 2 to 3, which has been pretty typical for decades of follow-up in patients on factor VIII prophy. But with efanesoctocog, that dropped to 0.69, so showing that this altered pharmacokinetic profile and this decoupling from von Willebrand factor had a significant improvement in joint protection.

Dr. Young:
Thank you for that comprehensive answer.

So finally, on our last question is really about translating all this into practice with respect to, you know, pharmacokinetic optimization and then real-world considerations like the patient's lifestyle, adherence, treatment burden. So yeah, maybe if you can sort of summarize what we have available and how should clinicians individualize prophylaxis based on things like activity level, bleeding history, adherence, etc.?

Dr. Pipe:
Yeah. Well, I think we've always had a holistic view of our approach to comprehensive care for our patients. So we're concerned about physical health, about bleeding, about joint outcomes, but we're also concerned about their psychosocial well-being and about their quality of life. So when we're choosing the ideal regimen for them, we want to take into account all of those parameters.

Now, there are clearly objective variables that guide treatment decisions—what's the bleeding phenotype of the patient, what's their joint status, what's their treatment adherence, how good is their venous access—but also what's their lifestyle, what do they want to do, what do they like to do, and how do we have to modify the regimen in order to help them achieve that. So those are the objective things that we interact with them in the clinic.

And then on top of that, there's a number of subjective variables that I think are also important influences on treatment decisions—what's the patient's preference, how do they want to be treated, what can they deal with on a regular daily or weekly basis, what's their support network around them, what kind of chronic pain issues do they have, what's their experience with current and past treatments. And so taking that all together, I think gives us a much more holistic approach to how we manage patients, and this helps guide how we choose the individual regimens.

Dr. Young:
Alright, well, Dr. Pipe, thank you very much for that very comprehensive discussion about factor VIII products, factor VIII levels. And I think it's clear that our thinking about factor VIII targets has evolved over time, and as we get better and better products, it continues to evolve, going from really what's the minimum protective levels to providing factor VIII levels that can really optimize long-term outcomes but also give patients a better quality of life.

So thank you again for helping us walk through how clinicians can apply these principles in everyday practice.

Dr. Pipe:

Sure. Thanks.