Gene Therapy for Hemophilia - Pediatric Grand Rounds-8-8-2025-Meeting Recording

August 8, 2025, 12:29PM

1h 0m 21s

Kamat, Deepak M started transcription

Kamat, Deepak M 0:41

Good morning. It's 7:30 in San Antonio and it's time to start our grand rounds. Just a quick reminder that the CME code is in the chat box and we'll keep repeating it every 10 to 15 minutes. Please complete the evaluations at the end of the grand rounds.
It's my great honor and privilege to introduce this morning's grand round speaker, Steven Pipe, who is a professor and Lawrence A. Boxer Research Professor of Pediatrics and Professor of Pathology at the University of Michigan in Animal Ann Arbor, Michigan. He serves as a clinical consultant within the Pediatric Hemophilia and Coagulation.
Disorders Program and the Special Coagulation Laboratory. His clinical interests include bleeding and thrombotic disorders and congenital vascular anomalies. Dr. Pipe also directs a basic research lab investigating coagulation factor 8 and the molecular mechanisms of hemophilia A.
He has been actively involved in the clinical trials with now therapeutics for hemophilia, including gene therapy. He was the 2015 recipient of the Leadership in Research Award from the National Hemophilia Foundation.
He has served on the Board of Directors for the Hemostasis and Thrombosis Research Society as a Chair of Board of Directors for the American Thrombosis and Hemostasis Network, and most recently as Chair of the Medical and Scientific Advisory Council to the National Bleed Disorders Foundation.
Dr. Pipe, thank you very much for accepting our invitation and the floor is yours.

PS

Pipe, Steven (Steve) 2:18

Well, thank you so much. Really appreciate this opportunity to present to you all this morning. This has been the focus of both my clinical work and my research for approaching now about 8 years. And so I'm really excited to give you an update on how far we've come.
With what I think potentially is a definitive treatment for the the inherited bleeding

disorder hemophilia. So we're gonna talk about where we're at with gene therapy for hemophilia.
So just as a item of disclosure, I am going to talk about both approved products as well as some pipeline products and I've either served as a consultant to these programs or on steering committees.
And I've also been investigator on the clinical trials, but I have no personal stake in any of these products.
So let's just level set for everybody. So we are going to be talking about both Hemophilia A and Hemophilia B. This is the rare congenital bleeding disorders. It's the most common rare bleeding disorder that we look after in the.
Coagulation clinics course Hemophilia A is more common. It's about 80 to 85% of hemophilia cases and this is caused by a deficiency in clotting factor 8. Hemophilia B is the balance of about 15 to 20% of cases and this is caused by deficiency in factor 9 and.
Economically, these look very similar based on their severity. When we talk about severe forms of both of these disorders, these individuals have less than 1% of residual activity if they have a minimal amount of anywhere from 1 to 5%.
We consider them moderate disease and anything over 5% we call mild disease, but we pay attention to the clinical bleeding phenotype and that ultimately also defines the severity of the patient and.
This is important because severe hemophilia results in bleeds into the joints, the muscles, potentially internal organs, and it doesn't just cause acute complications, but it can lead to chronic pain and disability due to the chronicity of the repeated bleeding, particularly into the joints.
And so.
The standard of care for the severe hemophilia bleeding phenotype or for those who have non severe hemophilia but with a bleeding type that is needing of prophylaxis. This is the strategy that we use for patients and prophylaxis has been the standard of care to prevent bleeding now.
For more than 30 years.
Now to understand the overall burden of Hemophilia, if we if we think about the classical approach to prophylaxis, it was the need to replace the missing clotting factors, Factor 8 or Factor 9 in this.
Demanded administration by intravenous injections and because of the half-life of these products, this really was a pretty frequent injections and for a typical

hemophilia patient, they were doing IV infusions essentially every other day and this kind of demanding prophylaxis risks leading.
To poor adherence and it really reduces the overall quality of life for the patient.
Most important complications of the factor replacement era is that at least a of our hemophilia A patients develop an immune response against the clotting factor.
Eight and we can no longer use Factor 8 products and we have to use what are called bypassing agents, which I'll show you. This increases the overall treatment burden for care. It increases their cost, it increases mortality and these alternative agents really don't work as well as the original Factor 8.
Concentrates overall, despite even very good application of prophylaxis, we still see patients can be limited in achieving their physical, professional and social goals. They live their lives with sort of fear of breakthrough bleeds and over the course of decades.
Accumulating damage to their joints. And if we look globally, about 85% of the world has no access to any replacement products and certainly not prophylaxis. As far as access to treatment, approvals and accessibility does vary by region, but the overall high lifetime costs.
Really are a significant impairment to access to treatment globally.
Just to give you some perspective on clinical and humanistic outcomes, this is from a a study in the US and it looks at persons with Hemophilia B who are receiving prophylaxis. What what do we see if they are getting standard of care replacement therapy?
Well, we use a count of bleeding events that require treatment. We call this the annualized bleed rate or ABR. And if you look at the mean ABR for this population of patients, you see a number there of 1.73 now, so just under 2 bleeds per year while on standard.
Care prophylaxis that that may not seem like a lot, but those bleeds are a significant in their acute setting. But more importantly, that's two bleeds every year, every decade of your life and that has cumulative damage over time and what we see that about 20% of patients actually.
Actually report at least one target joint, which means they're having bleeding into the same joint at least two or three times in the preceding 6 months. And so you can see that despite this standard of care prophylaxis, A substantial number of patients.
Are still reporting target joints. From a humanistic outcomes perspective, using patient reported outcome tools like the EQ5DF5L score, we can see that particularly

in the chronic pain category.
Majority of patients are reporting significant on a regular basis impacting their quality of life.
So we've had a lot of advancements over the last 20 years or so. If we look at the currently available hemophilia treatment options, of course we have the Factor 8 and Factor 9 clotting factor concentrates. These have been available to us starting in the 1970s with plasma derived clotting factor concentrates.
Recombinant era started in the early 1990s. We had recombinant versions of Factor 8 and Factor 9. These unmodified early versions of the recombinant factors we now call the standard half-life agents, but with additional bioengineering innovations, we've been able to do things like.
Adding PEG conjugates to the recombinant proteins using technologies like FC fusion or fusion to albumin and what these have done have extended the half life of the factor 8 and the factor 9 to try to reduce the frequency of the infusion. So we now call these the extended.
Half-life or EHL factor replacements. I mentioned what happens if you develop an inhibitor to Factor III or Factor IX. You can no longer use those therapies. Well, we now have to use what are called the bypassing agents. We still really only have two categories of these. There's a plasma-derived agent called activated prothromic. Complex concentrate only one product that's available globally for that. There are two recombinant factor 7A agents which are available. These are OK for managing acute bleeds. You can get patients through surgery, but neither of them really. Have the kind of efficacy in routine prophylaxis to prevent bleeding. What's happened in the last approaching now eight years in the US is the availability of a factor 8 mimetic. This is a bispecific antibody and it mimics.
What the factor 8 molecule does so factor 8 bridges together factor 9A and factor 10 to drive the conversion of factor 10 to 10 A. So this factor 8 memetic as a bispecific antibody can also bind to factor 9A and factor 10 bridge the two together and. Help substitute for the factor 8 molecule. The beauty of this antibody is has a very long half-life. It can be administered subcutaneously, so liberating patients from the need for IV prophylaxis and the long half-life allows for really stretched out intervals of.
Prophylactic administration either weekly, every two weeks, or every four weeks. The challenge with this molecule doesn't normalize hemostasis, but it seems to give enough hemostatic protection that at least for prophylaxis, it's proven to be quite

effective.
But notably, this agent, because it looks nothing like the factor 8 molecule, this provides effective prophylaxis whether you have an inhibitor to factor 8 or not. And so this has now become the dominant choice of prophylaxis, at least within the US and much of the.
World.
So if we look at the current prophylaxis regimens, where are we limited? Why are patients still accumulating bleeds overtime? Why? Why is it still leading to joint disease in subsequent decades? Well, it has to do with the if we look first at the factor replacement.
Here's a typical regimen on the right of a patient right after they give themself an effusion. They can take their factor 8 levels right up into the normal range, but because of the relatively short half life of either the standard half life or even the extended half life agents.
Their levels in the plasma continue to drop over subsequent hours and with standard half-life agents, you drop drop down to levels which are approaching where you might be at risk for bleeding events. And so the typical regimen on a standard half-life agent would be every other day.
Dosing. So you see this repeated sawtooth pattern and even with the extended half-life factor 8, this really only stretches out the interval, but it doesn't change the paradigm of how the hemostatic protection looks. And if we think about these levels of protection, you can see that depending on the activity the patient.
Patient wants to participate in how that correlates with where their factor level is over the course of the day or a week can impact their risk for bleeding. So you know, if they're doing relatively sedentary activities most of the time, then maybe they're OK when their levels get down under, say, 15%, but.
weekend.
If they want to take on more aggressive activity or in our adolescents or young adults, if they're participating in sports, these target levels for where they need to be to prevent bleeding need to be substantially higher. And so navigating these demands for where your levels need are needed for protection versus the.
Prophylaxis coverage that's derived from the factor replacement, you can see where the challenge is. And if we think about the non-severe persons in our clinic, which are about half of them, they still can have a risk for bleeds, but generally they have not been on prophylaxis.

So what about the factor 8 mimetic emesizumab? Well, we think that this protection level is probably in the range of of about 10 to 20%. There could be, you know, some variability on an inter-individual basis. This is enough to provide prophylaxis against. Breakthrough joint bleeding, but isn't necessarily going to prevent all bleeds, particularly with aggressive activity. The nice thing about the factor 8 mimetic is instead of the peaks and troughs of factor replacement, you actually get a steady state level that's maintained throughout the week.

So if we look at our expanding options for prophylaxis, we've talked about the factor replacement therapies. The factor rate mimetic emacizumab is what we we call the first non-factor replacement therapy, but there are additional agents that have just been approved.

In the last couple of years, actually, we call these the rebalancing agents, and they're called that because they actually don't substitute or replace the missing factor 8 or factor 9. What they do is they target the natural anticoagulant pathways of coagulation.

So you might remember some of your regulatory molecules like tissue factor pathway inhibitor, antithrombin and activated protein C These all regulate coagulation and they are the brakes of coagulation and if you knock down the activity or the.

Levels of those natural anticoagulants, you can actually thrombin generation and so we actually have approved agents which now target those anticoagulant pathways.

So that sort of brings us our conversation for today, which was, well, what about a definitive treatment? What about a?

A one time treatment that would be able to allow for continuous expression of either Factor 8 or Factor 9 and be able to liberate patients from this prophylaxis and hopefully prevent bleeding, hopefully for a lifespan.

Now, gene therapy is really a umbrella term. It covers both genetic therapies as well as cellular therapies. The approved therapies to date for hemophilia are in vivo gene therapies, which I'm going to show you. And this is where we're taking a gene and actually delivering it.

To the liver and allowing the liver, which is a natural production organ for clotting factors, allow the patient's own liver to make Factor 8 or Factor 9. But there are additional investigational therapies in gene editing, both in vivo and ex vivo, and then actually the first.

Patient in Hemophilia was just dosed with a cellular therapy. I'll tell you about that at

the end.
So let's just summarize the factor replacement therapy error for for hemophilia. So if we think about this intravenous administration of these clotting factors, we have a measurable factor level with these peaks and troughs, but we also have a corresponding hemostatic protection that goes.
Along with those factor levels, the extended half-life therapies stretch out the interval, but they don't really change the paradigm. We've come to identify certain target ranges for where we want patients to be for effective prophylaxis. But the challenges are peaks and troughs exist here really are not.
Physiologic, they can be inadequate for overall bleed protection. It's a demanding administration schedule. And of course we mentioned the challenge of inhibitor development to the infused proteins. Well, what about the non factor therapies? Well.
What you can see here is although these provide a steady state hemostatic protection, it's not, it's not in the non hemophilia range, it's probably in the mild hemophilia range. But since we're not replacing Factor 8 or or Factor 9 with these agents, there's no measurable level.
So to a certain degree we're measuring the level of the non factor therapy, but we're not actually able to measure a factor 8 or a factor 9A molecule. The clinical data shows that these really do provide effective prophylaxis. It's a more stable hemostatic effect.
It's definitely improved convenience by being able to do subcutaneous instead of these can be used for persons with hemophilia with or without inhibitors. And actually those rebalancing agents I showed you are quite unique because they're cross-platform. So here we can use the same agents for Hemophilia A.
Phylia be with or without inhibitors, but there's still some challenges with these newer agents. There is a risk of thrombotic complications. These require some specific risk mitigation as well as monitoring to ensure that we don't tip patients into a thrombotic state.
And we don't have the same long term data as well as the predictability of individual responses. What's the potential that gene therapy could offer? Well, really the potential is to sort of harmonize the best of the clotting factor concentrate era and the non factor therapies.
We're aiming for steady state correction of hemostasis, hopefully in a range that at least overlaps or is sustained in the near normal or the even the non hemophilia

range. But we also now have the opportunity to have a measurable level. So if your liver's expressing.
8 or factor 9 I can measure that level in the plasma. It should be steady state and I know what kind of correlate that should be for hemostatic protection. And as it stands today, gene therapy is the only therapeutic intervention here that can really deliver this.
So what is the platform that came to the clinics? We have been studying hemophilia gene therapy for more than 30 years and it's the adeno-associated viral vectors that have proven to have the safety and the efficacy that we're looking for.
So these adeno associated viruses are non pathogenic viruses. We're really just using the capsid proteins of these viruses. There's no there's no viral genes remaining that are used in these vectors rather.
Inside the capsid, we package the transgene, which includes either Factor 8 or Factor 9, as well as some regulatory elements so that it will transcribed and allow for expression in the liver. So packaged viral capsids are.
Delivered through a one time treatment event in the outpatient setting. It's infused over about one to three hours and afterwards that's when the magic happens, as they say. So what happens after infusion? Well, these viral vectors get recognized by receptors.
On the hepatocyte, they get taken up by endosomes, and then because of the biology of these AAV vectors, they're able to escape the endosomes so they don't get degraded, and they're able to deliver the transgene to the nucleus.
There, the transgene predominantly remains episomal, and it basically turns into a circular piece of DNA that's capable of associating with the transcriptional machinery.
And then what happens is we get a message that then gets translated into a.
Protein in the secretory pathway. We're basically recapitulating expression of either factor 8 or factor 9 into the plasma and from this one time treatment event, these episomes can remain within the cell for years and years and continue to provide.
Template for expression of factor 8 or factor 9 and we end up with the steady state levels we're looking for. So what are we trying to achieve with gene therapy for hemophilia? Well, certainly we want to reduce bleeding events. We want to reduce the overall burden of their reduce the anxiety.
Of risk for breakthrough bleeding, if they are able to come off prophylaxis, will reduce their need for clotting factor concentrates, which is the primary cost of managing hemophilia and ultimately want to improve their quality of life, them to

have protection from bleeding and liberated from prophylaxis.
So they can just live their lives and all of this is achieved by increasing the factor 8 or factor 9 levels. So there's been a number of clinical trial programs that have been active over recent years and we've been able to participate in several of these.
Both for Hemophilia A as well as Hemophilia B. A few things you can note here some different manufacturing proteins. Some of these vectors are are packaged in in human embryonic kidney cells. Others are packaged inside.
A insect cell platform. Because of the size of the AAV capsid, the full length factor 8 doesn't fit inside of these vector capsids. So what you see is all of these programs use a truncated form of factor 8. This is still a.
Fully functional form of Factor 8, but it's what's called AB domain deleted or truncated form of Factor 8. For the factor 9 transgene, we really had an amazing innovation that came from a family of patients. A family in Padua, Italy was identified who had a.
Clustering of thrombotic episodes in their history, and it turns out their factor 9 levels were multiple hundreds of percent, anywhere from 400 to even 700% levels of factor 9. And it turns out that they had a single point mutation in their factor 9 gene.
So this is called the Padua mutation. Well, this mutation has now been incorporated into the approved therapies for hemophilia B gene therapy. And so now we get an advantage of a expressing a factor 9 molecule that's anywhere up to six to eightfold more potent.
Than the the original factor 9 AV comes in a number of different serotypes. This is the the mix of the proteins on the capsid and these have numbers. Some of these are natural AV capsids, others are are bioengineered to improve different aspects of their behavior.
And so with all of this mix, what we see is a real wide range of dosing that is used in the clinical trials and it's anywhere to about a 200 fold range of dose that is administered to patient and that has some implications for some of the.
Some of the adverse events and consequences of these infusions. Another important thing I want to point out here is we all get exposed to natural AV. This is a non pathogenic virus in the community and we.
Can develop antibodies against AAV. These antibodies that we develop naturally can cross react against these AV vectors. And in the early days of developing this technology, what we observed is that.
Even having some low levels of pre-existing immunity to would preclude the efficacy

of the gene therapy. Most of these programs screen their patients pre-existing antibodies against specific AV capsid and if you.
Have.
A certain level of these antibodies, you are not eligible for this therapy. The one platform that has been able to dose and get an efficacy despite pre-existing immunity is this one program here from from CSL and I'm going to give you a little bit of the data.
Not all of these programs have moved forward. There's one here that was actually approved by the FDA, but the company decided not to pursue marketing. But if you have a chance to review this article in the New England Journal of Medicine, there's six-year follow-up from this study showing the safety and efficacy. So even.
Though it's not going to be marketed, it's still important to our learnings about safety and efficacy of gene therapy in this population. So first one I'm going to talk to you about is the approved therapy for hemophilia A. So this is Veloctico gene Roxaparvec.
This is using a AV 5 vector to deliver this truncated form of factor A. Now this was studied and this is still to date. One of the largest phase three programs in hemophilia was studied in adult men who had severe to moderate severe hemophilia up to a level of 1%.
Factor 8. They had all previously been on Factor 8 prophylaxis and so they all participated for the most part in a lead in study so that we could see what their factor consumption was and what their degree of bleed. So basically what their annualized bleed rate was while they were on standard care prophylaxis.
They all then received a single event treatment event of the Veloxicogene Roxaparvec, and we've now followed these individuals for five years to track all of these types of bleeding events.
So this is what we observed with the factor expression. There definitely was a very early and then rapid expression of factor 9 well into the the normal range. So the non hemophilia range begins at about a level of 40% factor 8 activity.
But there was this slow decline of the Factory 8 level over subsequent years.
There was concern here whether these patients may ultimately even lose their expression, but what we've observed now over multiple years is the stabilization for the most part in the mild hemophilia range. And actually in the last three years we've seen very little decline in the mean levels.
So we're still in mean levels of around 24% and this has been highly effective for

prophylaxis for these patients. If we look at the distribution, there's still a wide variability of where patients land as far as their steady state expression, but overall. Here in year five, 87 participants remain in the mild or in the nonhemophilic range, and there's only a small number of patients who've had to resume prophylaxis. If we look at the hemostatic efficacy, they've demonstrated durable protection from bleeding, remember.

All of these patients came off prophylaxis after their one-time treatment event and they've now gone multiple years and you can see that reduction through year five in annualized bleed rate and notably almost 80% of the participants have had zero treated bleed.

After being followed for five years after this treatment, obviously because they are no longer doing regular prophylaxis, look at the number of infusions they had during the lead in phase. This is number of infusions per year on prophylaxis and now again a 93% reduction in infusions.

Fusions over five years and almost 2/3 of the participants have never needed a factor 8 infusion over five years of follow up. So if we look at all of the factor 8 programs, there is this tendency to have much higher levels in the first year, a decline over subsequent.

Years and then maybe a plateauing and this has had some impact on the uptake as well as the approval of the therapy. There are, you know, there's obviously a costly therapy and some countries have evaluated this trend and said, you know, we're not sure we want to pay.

You know, you know a couple $1,000,000 for this treatment if we're not going to get, you know, a lifetime of expression from this therapy. If we look at the break even point for cost effectiveness expression for at least five years, certainly.

The cost effectiveness is dominant for for gene therapy, but you can see that this pattern or trend has had an impact on how this has been perceived in in different geographies. Most of the participants through five years remain off prophylaxis 82 almost.

Just over 81% have remained off prophylaxis through the end of year 5 and notably because of this plateauing from year four to year 5, there's only been one additional participant who resumed prophylaxis in this last follow-up year. So we think this is probably going to remain stable for many years to come.

So what about the approved factor 9 therapy? So this this is a this is a Traneco gene, desaparvivec. It was studied in the Hope B phase three trial. This included adult men

with.
Severe to moderate severe hemophilia up to a factor 9 activity of 2%. Recall that this uses this point mutation in the factor 9, which boosts the activity of the factor 9 by about 6 to 8 fold and it's really the same.
Strategy as what you saw with Velocticogene. So patients after screening were followed for at least six months in a lead in period on their standard of care continuous factor 9 prophylaxis that captured all the baseline data and then they received their one time.
Treatment with the Traneco gene. Now I mentioned that all trials to date except for one have excluded patients who had neutralizing antibodies to the AAV. Turns out that there was an early phase of this program.
Where some patients had neutralizing antibodies and still had evidence of efficacy. So we did a small phase 2B study. We dose 3 patients who were all positive for neutralizing antibodies to they all had excellent efficacy.
So we decided for the phase three program to measure their pre-existing antibody levels, but we didn't exclude them. So they were all dosed and brought into the trial and then we've followed them now over. It's approaching five years actually.
So here's where we are with the factor 9 activity levels over time. Now differentially compared to the Hema trials, the levels of factor 9 expression have been very stable from year to year. So you can see the the the mean levels here still quite a bit of spread or just.
To.
Of the factor 9 levels, but from year on these have been very stable and at least at the four-year time, 98 of the participants have been in at least the 1/3 of the patients are actually solidly in the non-human.
Fully arranged. So as you can imagine, this should have a significant impact on bleeding. And if we look at all bleeds, spontaneous bleeding and particularly bleeding into joints, this through a year 4 is approaching 0.
And notably, again in this trial, 60% of the participants have experienced no joint bleeds over four years post treatment with a Tranecogene. And of course, since they're all liberated from prophylaxis.
Marked reduction in factor 9 infusions and in factor 9 consumption as you would expect. There were two participants in this study who were non responders. One had a very high neutralizing antibody titer, probably at the 98th.
Center.

That we would find in the community and he was a non responder. So there may be some limit to what the neutralizing antibodies can be. And there was another individual who started to have an infusion reaction during his infusion and his infusion was interrupted and he only got 10% of the dose. So it's not it's not unreasonable.
To expect that neither of those participants would have a response. But other than that, of the other 52 responders, only a single patient has had to return to a factor 9 prophylaxis, and that happened about 30 months following infusion. So a lot more predictability with this factor 9 program.
To offer to patients when they're considering this. So if we look at the summary, what we can say is that we're seeing durable factor 9 activity at therapeutic levels, marked reduction in factor concentration usage, reduced bleeding rates compared to prior standard of care factor replacement therapy.
And overall acceptable safety and I'll show you a little bit more about this. So we do have to be careful in how we present this and how we communicate this to patients because there are some issues.
Although it's great to think about a one-time treatment event, you come in for your outpatient infusion and you get infused and then stop prophylaxis. You don't have to worry about your hemophilia anymore. It's it's not exactly like that. There are significant post-infusion monitoring requirements. All of these gene therapies that are approved require at least a week.
Weekly visits for several months and then there are long term monitoring aspects that we continue to do. Some of it's because this is still the early days of gene therapy, but we also need to learn we're targeting this therapy to the liver, so liver health over the long term.
Obviously is important. I mentioned at the beginning that we all get exposed to AAV. So not only can we develop pre-existing immunity that might preclude the ability to get this therapy, but another observation from the clinical trials has actually been a particular challenge.
So between week about four and week 20, we commonly see a elevation in the liver transaminase levels. These can. These are generally low level elevations. They're completely asymptomatic. There's no liver dysfunction associated.
With this, but when this was observed in the early days of gene therapy, this seemed to be a biomarker of a liver toxicity from the vector that's driven by the patient's own immune system. And we think what's happening is after the AV capsid.

Delivers the transgene into the nucleus. The cell then degrades the AV capsid and those proteins are then presented by MHC on the surface of the liver cell and if the immune cells.
Basically recognize that as a foreign antigen, T cells can get activated and you get a T cell driven lymphocyte response directed against the hepatocyte and we think this is driving this low level transaminase elevation.
The risk here is that this targets and eliminates those hepatocytes and if those cells are lost, the transgene is lost and expression is lost. And indeed in the early trials we saw this transaminase levels started to go up, factor levels started to drop and then without any intervention.
the factor expression could be completely lost. So uh back in around 2011 with one of the early factor 9 trials, they tried to suppress this immune response with oral corticosteroids. So basically patients were put on oral prednisone and actually there there was some evidence that maybe this was able
To improve the transammonitis and salvage the factor expression. So how often do we see this? Well in the factor 8 trials, this has been very high, anywhere from 50 to almost 90 of the patients developed this transammonitis and had to be treated with this.
Course of immunosuppression. I have to say this is a significant dissatisfier for the patients. These are high doses of steroids, usually starting at either 60 milligrams, as high as 80 milligrams per day, and then, you know, sort of a cascading wean over anywhere from 8 to 12 weeks.
So highly likely that the Factor 8 patients would need to undergo this immunosuppression, much less so with the Factor 9 therapy. We don't know why, but it hasn't happened as frequently in the Factor 9 trial. So this is what's driving the the post.
Infusion monitoring requirements. We start monitoring for this within the first few weeks after dosing, and then patients have to get blood draws about every, you know, at least once weekly, sometimes twice weekly, with a readiness to start the immunosuppression if needed.
The other thing from a realistic perspective, we have to present to patients, I showed you the wide individual variability, a patient who says, you know, I I want to get gene therapy, I want to have normal levels. Well, I I can't really deliver that for them, or at least with confidence.
There are some patients who are going to end up, you know, in the low mild range,

some may be near normal, some well into the normal range. And in some cases we've seen quite high levels, multiple fold above the upper limit of normal for factor levels.
For the most part, this has been without consequence. There is some drift down over time, but I've seen in some of these trials with factor levels that that are, you know, 4 to 700% actually. So patients have to go into this therapy knowing that we can't predict exactly where their level is going.
To land.
Now, the first therapy was approved two years ago. Another one was approved last year. So we're now sitting with both an approved gene therapy for Hemophilia A as well as Hemophilia B. And now what we've been trying to navigate is how do we? Deliver a a system of gene therapy delivery in in the US setting and there's both a patient journey as well as a a journey for the center as well so.
I showed you the landscape of treatment. We've got a real panoply of therapy, some that are, you know, highly effective. And how do go through a shared decision-making process with the patients to determine whether gene therapy is right for them or should they continue on some of these other prophylactic strategies once they make a decision?
For treatment, we have to go through some liver health screening. In some cases, we're also evaluating the neutralizing antibodies to make sure they're eligible and then they actually will receive the gene therapy well when we move from the. Clinical trial setting to the clinical delivery, we're working with different people. We're now no longer working with our investigational pharmacies. We're now working with our clinical pharmacists. So there's new people that have to get a handle on how to. Receive and reconstitute these gene therapies. And then we're also working with sometimes new teams of subspecialists to follow these patients over the long term. So what's been interesting is whether every center really is going to be able to take on this strategy of gene therapy delivery. And this is probably more well developed in the EU than it is here in the US, but I do have some examples both from the clinical trials.
Setting as well as commercially where this has worked and so centers are now evaluating whether they want to be a supervising coordinating center, whether they are going to serve as a dosing center or in some cases they may send patients to a dosing center.
For the one time infusion, but then come back to their center and then they will do

the balance of the follow up. As it turns out, just this past year I sent one of my patients to Indianapolis for their dosing because we weren't quite ready to do a commercial patient at our center. So they just went there for their day of infusion and then I've done all of his follow up afterwards.
So this this coordination of care amongst the centers I think actually can work well since we're now dealing with legacy issues with our hemophilia patients who had a history of hepatitis C back in the day and now we're doing a liver targeted therapy, we're having increased.
Increased engagement with hepatologist for management of these patients and then because of ongoing questions related to the immunosuppression protocols, even there's been consideration of adding immunologist experts into this field as well.
So if you're going to work between a dosing center and a follow-up center, there are some things that we have to coordinate together. So where are the regular lab measurements going to be done leading up to the gene therapy and then where are they going to be done afterwards? How are you going to manage the travel between the dosing and the management center?
And then where are you going to get the labs after they've received their gene therapy? Some key questions that you have to coordinate together is OK, well, when is it safe to stop the factory replacement therapy? How do we ensure that we're going to?
Be able to detect as early as possible any increase in the transaminases and then what's the plan in place for the immunosuppressive therapy. What we do at our center is we try to make sure that whatever lab we're going to use for monitoring post-infusion, we've already done pre-monitoring labs at that.
Same lab. So we have a good comparison. You'll note that actually transaminase levels can vary quite significantly between labs. So we try to do these at the same place. We also send them home from their infusion prescription for the Prednisone. So it's in hand if we see an elevation of trans.
Aminases, we can get them started on the Prednisone right away. We're still measuring anti AV neutralizing antibodies in everybody. It's just the one approved therapy for factor 9 where they can still be dosed.
We are doing liver health assessments, both pre as well as post, and we're also trying to make some recommendations to them about how to maintain good expression over a lifespan. And that means really advising to curtail their alcohol intake. Our preference is abstinence.

But certainly we want to avoid any sort of regular alcohol intake or binge drinking. We have to make them wary of anything that would be leading to fatty liver or liver fibrosis, and they also have to be careful about other concomitant medications.
We do want to track bleeding events and in some cases patients have to sort of relearn now in the post gene therapy when they have pain in a joint, is it bleeding in a joint or is it, you know, chronic pain because of legacy bleeding issues. So there's sometimes there's some adjudication of bleeding events to help.
US know whether they're they're having breakthrough bleeding or not, and all of this is requiring clear communication between the patients and the centers.
You might have heard in the news that there've been some disappointment of the uptake of these treatments commercially. They've been out now for two years, at least for one of them. And I think some of this is some uncertainty about the long-term efficacy and safety. This is particularly true for the heme aging.
Therapies, some challenges with clinic resources and institutional barriers. This has certainly been been true at my place and making the flip from clinical trials to commercial delivery has actually been very challenging at our center. There's still challenges with reimbursement. There's just some insurances that are just not willing.
To pay for this therapy and we've had continued amazing innovation with new therapies current as well as in the pipeline. And there still may be a lack of understanding of this complex therapy that is contributing to the low uptake and so continued communications like this and trying to educate every.
Everybody about gene therapy, I hope will help us overcome some of these hurdles. Just talking about switch from clinical trials to commercial. Well, you know, clinical trials are fully funded. The research and the medical teams are fully compensated. Institutional administrative costs are paid. Pharmacy procurement and processing is all.
Done by the investigational pharmacy, patient travel and expenses are often reimbursed. It's a controlled environment. The commercial teams may be completely different from the clinical trial team. So making this flip is challenging. Our colleagues in transplant seem to have been able to do this with CAR T-cell.
Therapy moving from the clinical trials. We're hoping that we can follow on some of the learnings that they've had to ensure that we can do this efficiently. So where do we look to the future? Just just to wrap up here, there are other viruses that can be used to deliver genes. There's at least one.
Hema program that is looking at using alternative viruses like a lentivirus. We have

already initiated the first gene editing using CRISPR Cas 9 in coordination with AV technology.
And in this example, we are targeting the factor 9 gene to be integrated directly into albumin locus and then have the albumin promoter driving the expression of factor 9. The first patient was just dosed with this ex vivo gene therapy using B cells. This is a really.
Fascinating protocol where the patient undergoes apheresis. B cells are collected, they go to the manufacturing facility, engineered ex vivo to express factor 9 using a CRISPR technology and then those cells are differentiated to long lived plasma cells and in.
And infused autologously back to the patient. And so I think you wanna look to the data for that trial as it moves forward. And then finally to avoid some of the immunologic challenges we've had with the AV technology, there's still considerable investment in non viral gene.
So different types of lipid nanoparticles to basically do what the vectors are doing to deliver these transgenes to the liver without the need for using a viral vector system. The the CRISPR based gene editing is capable of transducing both the dividing and the non dividing cells. So I mentioned at the beginning, you know we see some loss of expression over time. The immune response that causes the liver toxicity could take out cells once you've lost those.
Those hepatocytes with the episomes, then there's no continued expression. And if there's any liver cell division, then you will lose those episomes. They're not passed to the to the daughter cells. So this is part of why in vivo gene editing is being explored, because we can now.
Transduce into the cells, directly integrate into the DNA, and that would allow for persistent expression, even with cellular division. And this opens up the possibility that maybe years from now we'll be able to do this exact type of gene therapy in children and not just adults.
Still some unknowns related to CRISPR technology, but these will come with time as we follow on with the trials. So what I want you to remember from today, the pros of gene therapy, it's a single infusion event.
But it's not a set it and forget it type of type of approach. You do have to have significant post infusion monitoring to ensure that you have a good outcome from this. We are able to achieve steady state hemostasis. Patients for the most part are liberated from prophylaxis and.

There's an annual cost savings for these patients because they're no longer using regular factor replacement. Some patients are currently ineligible. We're not treating children yet. Neutralizing antibodies are still a barrier for most. We don't know whether this therapy will induce factor inhibitors. It's never been observed in.
In the approved trials and approved agents to date, but there's at least one trial that did have a factor inhibitor that was induced with this therapy. There are both known and unknown risks, questions about long-term safety and durability and certainly the high initial cost is still posing a challenge.
challenge in in some locales as well as even within the US with payers. So thanks for the opportunity to share and I'll be looking forward to taking any questions.

Kamat, Deepak M 54:08
Thank you Dr. Pai for that wonderful, wonderful presentation on gene therapy for hemophilia. We already have a question in the chat box. What is the eligibility lower limit for gene therapy? Is it age 18 or older?

PS

Pipe, Steven (Steve) 54:21
Yeah. So with the approved therapies, the phase two trials were all conducted in adults and you know for a new platform of therapy that makes sense. Really the the principle biology is when is the liver mostly done growing so that we don't have to worry about cell division leading to loss of vector over time.
And we think probably early adolescence is probably the lower limit with the AV technology. So as it turns out, we've just launched the first adolescent study with Tranicogene. This is the factor 9 gene therapy and those patients hopefully will be dosed.
Over the course of this next year. And so we're going to collect data in under eighteens for that trial and actually they're prioritizing enrollment of patients who are in the age 12 to 14 category to try to get that data.

Kamat, Deepak M 55:16
Thank you. There's another question. Obviously these products are very complicated to produce. Is there any hope for cost reductions in future your predictions?

PS

Pipe, Steven (Steve) 55:26
Yeah. Well, no, this is a good point. I I I can't really speak to the cost of the

manufacturing. There are significant challenges in in the consistency of of the production and of course.
The complexity of what I showed you of that whole AAV mechanism of action, you want to make sure that all of the specifications are, you know, right on target to ensure that you get consistent outcome. I I I hope that new technologies will will lead to improvements. I I think I'm hopeful that.
Some of these non viral approaches actually may be beneficial and hopefully that will potentially reduce the the costs overtime.

Kamat, Deepak M 56:17
Why is there so much unpredictability? Like you said, you cannot really tell first, yeah.

PS

Pipe, Steven (Steve) 56:21
Yeah, I, I, I, I think you know really is a black box after the AV gets taken up by the padocyte, all the inter individual variability that determines how efficiently the the episomes circularize in the nucleus and the expression, et cetera. So yeah, it's.
It's an unfortunate aspect of of of that. I hope that with new technologies, I think that the thinking is that with the gene editing platforms where we're targeting to a specific locus and then getting driven by the endogenous promoters, I think there's some hope that we will narrow the variability.
So we'll have to wait for the results of that trial to see if that's been achieved.

Kamat, Deepak M 57:05
Has any of the patient received more than one gene therapy that the levels drop down and then?

PS

Pipe, Steven (Steve) 57:08
Yeah. So what happens is, yeah, So what happens is after you've received AV once, your antibody levels are so high after receiving this vector, it essentially cross reacts with most of the other vectors. But it's interesting you mentioned that because I told you that the Etranoco gene is the only.
One that has allowed patients to be dosed even with pre-existing antibodies. So they now have an they're going to have an open protocol where they will allow patients who've been dosed on prior gene therapy failed to get a response with that therapy. They will then screen them.

For the neutralizing antibody to a Traneco gene and then they're going to allow them to be dosed and see if they can get some efficacy. So this may be the first example of the ability to redose.

Kamat, Deepak M 57:59

There's another question. Why do you think the one company, despite FDA approval, decided not to do future studies cost are there?

PS

Pipe, Steven (Steve) 58:08

Yeah, well, you know, they submitted their own explanation for that. Some of the one of the lines in in the press release was that the community didn't seem as interested in gene therapy anymore.

There's now been multiple editorials written from the community to state that that almost certainly is not the case. And I I outlined some of the challenges related to the uptake of commercial gene therapy. I think all of those are are are valid.

But ultimately, this is a race. This is a race of technologies, new therapies, new pipelines that are continuing to innovate and provide effective therapies for prophylaxis for patients, and those are being presented.

In shared decision making with patients, I still think gene therapy delivers what no other therapy has been able to to date, but it's still an individual decision that we reach. So I think that company had some other issues. They had another gene therapy program that kind of.

Imploded and I think they just kind of decided as a company to move away from gene therapy. So I don't think I would take from that that the community has lost enthusiasm for gene therapy. It's still a vibrant part of our of our treatments going forward.

Kamat, Deepak M 59:36

Thank you, Doctor Pipe. Any other questions, comments for Alder Pipe?

I don't see any. Dr. Pipe, thank you very much for educating us on gene therapy. I really, really enjoyed your presentation. Thank you all for attending this morning's run round. I'm going to conclude. Have a wonderful Friday. We'll see you next Friday. Thank you, Dr. Pipe, again.

Pipe, Steven (Steve) 1:00:06

Yeah. Thanks so much. Yeah. Have a great day.

Kamat, Deepak M stopped transcription