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TRANSCRIPT - GR 03 07 25 ***"Updates on Treatment in Hemophilia"*** guest speaker Louise Man, MD, University of Virginia

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Internal Medicine Grand Rounds

- Good afternoon, everyone. It's my pleasure to introduce our panelist today from Saint George's University of Chicago and then went on to complete her Internal Medicine Residency. She is now an associate professor. She is currently working on establishing Gpa. As a multi-center interventional study.
- She believes in the philosophy that practicing medicine and art rather than the science which has been reflected in her new every single year, and on a personal note with the low one.
- Good afternoon, everybody. I'm really excited to be able to provide you updates. I'm also glad it's today, and not in one month, because there might be an FDA approval in about 2 weeks. So it's a good thing it's today and not after Formula One. My talk really features a patient's perspective. I think it's actually wonderful for us to have some education for us.
- Patient's perspective on the things we talk about here. I have no relevant disclosures. Sadly, I am not a pediatric hematologist, so my perspectives are tied towards adult care.
- I will mention when there's pediatric studies involved. Some generic names are impossible to pronounce. You guys can take a crack at this one. So I'm going to use the word Octavian. Instead of that one.
- I will focus on medical management today, mostly because if I schematically depict who is involved with the care of patient, with hemophilia, there are actually a lot of people. And I'm but one piece of the puzzle, and I just don't have enough time to recognize all the aspects of management appropriately. So today, my focus is on medication management.
- These are the objectives which you guys read earlier. I'm going to review clotting factor concentrates both standard and extended half-life. I'm going to review non-factor hemostatic agents, which is very exciting and very novel, and maybe in 10 years they won't be considered novel anymore. And I will also discuss gene therapy. I will review Aav factor, gene therapies.
- There are 3 FDA approvals, and there's maybe some future different directions as well. And again, last, but not least, we're going to hear from a patient directly. So some terminology for basic review hemophilia A is the deficiency of clotting factor 8. Hemophilia B is deficiency of clotting factor 9. I will not discuss hemophilia C. It's a very different disease, and we'll not discuss it today when I use the word prophylaxis or prophy. For short, I'm talking about routine chronic therapy for prevention of bleeding, and that is because this applies to individuals who are at very high risk for spontaneous bleeds. When we talk about on demand, we mean treating prn when I use the word factor. I'm talking about clotting factor concentrate. I'm talking about factor concentrate and concentrate. They're all synonymous for all purposes of my talk. Factoring is a verb. You'll see when we discuss treatment

inhibitors. We talk about antibodies that people develop to clotting factor concentrates. But that is a complication of their treatment with congenital Hemophilia. I won't be discussing acquired Hemophilia.

- So if you don't mind just raise your hand if you have attended any talk about hemophilia treatment.
- Okay, this half the room I asked to show up. It's really interesting, because in the last 15 years there have been so many development. If you look at this long journey to get here, it has been a really long journey. I mean, about 70 years ago people discovered Ffp, and then in the 19 sixties, people discovered cryo. But it really wasn't until the 19 seventies that people could be treated at home. They had to go to the hospital for treatment and that comes in the form of the dry dry factor concentrates.
- And then, in the 19 eighties factor was cloned for the 1st time, but around that time we discovered we give patients other things besides factor, and that is hepatitis. And HIV, not good. And shortly thereafter viral inactivation methods were developed fairly quickly. And then in the 19 nineties, you had 2 factor, 8 products become available. Then a factor, 9 product become available in the late 19 nineties.
- And then in the last 15 years, I've lost track of how many things come out when so we had our 1st human therapy trial in the early 2 thousands, then you have non concentrates. I mean what the heck is that right?
- You have 3 FDA Gene therapies, and then you have 2 anti-tising agents approved in the last 6 months. I mean, that is an amazing, an amazing time.
- Strategic error. I am not reviewing the clotting cascade. I am not doing that. That is just not smart. The purpose of this slide is just to show you that up until very recently all of our treatments to treat Hemophilia centered on how to replace what was deficient. That's all. We did cryo fft factor, different forms of factor, all of it is geared towards replacement.
- So this is our treatment paradigm. Until very recently if you have mild distance, you present with meeting with injuries or with surgeries. And you're treated on demand on demand. You get a factor, because that's what the person is following. Okay disease is very interesting because it's a range of one to 5% clotting factor levels. But people can present a number of ways they can present with bleeds only with injuries, or they can actually bleed spontaneously.
- So there's a term that actually, we use that's called moderate severe for people who may have moderate levels. But they actually have very high risk of spontaneous bleeds. Patients may be treated with factor prophylaxis, or they may be treated on command.
- This is a table. I don't expect you guys to remember all these medication names. But it lists several quantity concentrates.
- And what's interesting is that these factor concentrates. These are their brand names and their generic names. This is a half-life range of these factor products. This is the prophy dosing for somebody. So, for example, cavaltry's half-life is 12 to 14 h for adults, and it's dosed 2 to 3 times a week. The half-lives of these medications are all shorter in pediatric patients. So you have to factor much more frequently as a kid for an adult the larger the individual, the longer they hold on to their factor. So if you look, you can factor as little as twice a week on a regular basis. Or you might need to factor 4 times.
- This is a slide, just to remind you guys, there are still plasma derived factor concentrates. We don't recommend using plasma derived factor. You can use

recombinant for people who live in developing countries that might be what they have, and they might need to be using plasma derived products.

- This is a table at top to summarize, to list the recombinant factor, 9 products. These are standard halfway product and observation. Protein is either once, weekly or twice weekly. If you have hemophilia these, this table summarizes factor 9 still available. But again, these are common and when possible.
- Okay, so some of you guys have a box. If you guys have
- 30 or clean hands, you guys can open up, it's not gonna go to a patient. We're gonna open up the box.
- And if you're sitting in a group. Okay so what does it mean? The patient has to factor right? This is actually very interesting. When I was a house guy, I never ever saw something like this. So factor reconstitution. If the patient don't factor.
- They keep it at home, either in their fridge or at Room 10, and if they refrigerate it, they take it out of the fridge. It has to stay out and stay at Room 10. It should never be frozen. When you open the box. You have a vial adapter. It's a white powder. You have a pre-filled syringe sometimes, or you might have to draw it yourself, and you have a vial adapter, and you should have alcohol pads. You should clean your hands.
- Okay, take the step out of class. You pop the top off. You should clean it with alcohol, secure the vial adapter onto the vial. Once you secure it, you attach the plunger rod to the middle of the syringe, and when you attach the syringe it sort of falls into the vial. You should gently swirl it around, and that actually is reconstitutional factor.
- So, however, if Dr. Mann said, we need 4,000 units 3 times a week, and you got 1, 2,000 vial. You got 2, 1,000 from the specialty pharmacy, and you'll have to reconstitute 2, 1,000 2,000 to make your 1,000 dose.
- So you have to do this multiple times for each dose you have, and once you've reconstituted, you gotta grab all your supplies that you need butterfly needle tourniquet. I don't know how many people swing with the tourniquet here. You have your factor in your syringe, so if you drew up multiple vials, you might have a fairly fairly large amount of volume. Here's a tourniquet potentially use your dominant arm to start accessing the non dominant arm to slow Id, push over 10 min, clean up, get a band.
- So that picture I showed you is one type of factor product. There are other types of factory products. This one, some of you have a kind of a glass vial, and it's got a two-sided vial adapter. There's a dill ring up here. There's a factor down there. This is actually harder to use, because one side might split into the other once they are a vial. There's like a nozzle here in the middle, and we draw out the factor once you constantly this is one specific factor product. I wanted to show you guys that the diluent volume varies depending on the vial size. So if you have a 2,000, you would use a 5 ml. Serial water diluent for this one, but you would use a 2.5 ml. For Diluent of 2 5,500, or 1,000.
- So if Dr. Mann told you 4,000, you got to do 2, 1,000 and a 2,000. Draw them up together and give yourself that, and that's from one dose of factor.
- Oh, yes, and right after you reconstitute. You gotta make sure you use it right away, or if you don't use it within 3 h, you should probably close out sometimes 4 h, depending on.
- Oh, that's pretty tiring, just for your walkthrough, and I'm not doing it. So this is a treatment schedule for someone who is a standard factor of 8 concentrate. This is

their treatment schedule. This is their calendar, no matter what they're doing in their life. Surgery, no surgery bleed, no bleed. This is what they're doing.

- And if you're if you have Hemophilia B, and you're self treating with a factor, standard, half life factor 9 concentrate. You're either treating twice a week or every week for the rest of your life, for as long as you're alive.
- So the question is, that's a lot. Can we do better? So this table lists the extended half-life factor 9 8 concentrates. Excuse me, and if you look at the factor half-live, and you look at the package, insert dosing. You'll notice that the dosing is typically twice a week, sometimes every 4 days between 2014 and 2019, everything was essentially twice a week at minimum. And then in 2023, the FDA approved Altuvio, and this is an only once weekly factor of 8 concentrate on hemophily.
- These are the different technologies used for a lot of that.
- And then, starting in 2014, you had extended halfway back the concentration weekly every 10 days, every 14 days, maybe so once a week.
- So this is a lot better. Right? So you have every other day, potentially or twice a week, or once we could have Hemophilia B, and then you factor twice a week, and then every 7, 1014 days. If you have hemophilia. B, so that's if people stick with factor. But again. That's indefinite therapy, and that doesn't include if you have a bleed, if you have a surgery.
- I just gave you a bunch of tables with a lot of different drug names on them. So the question is, how do you decide what to treat your patients with? Right well? The World Federation of Hemophilia does not have a specific recommendation for one factor, product over another. Recombinant is preferred as a provider. We would much prefer our patients get treated with extended half-life concentrates over a standard half-life. For obvious reasons.
- I tend to say, patients historically don't love the switch factor. They get admitted with a bleed. They don't really love to be treated with something different than what they're using at home. So sometimes we would say, there's a minor contribution that we pick what's in our hospital patients. They are very well connected. They're very knowledgeable about their disease. They've talked to industry. They've talked to other patients. Some of these patients are on clinical trials, but once the drug is approved, they'd like to stay on that therapy once they've tried it out themselves. Family preferences. If you're a mom, and you've got 3 boys with Hemophilia. Do you want a different specialty pharmacy? Do you want a different rep for each boy? Do you want a different drug for each child?
- Probably not. We're not supposed to share medications. But if you ran out of factor for one child and the other one has the same factor. You're going to use that one to get them out of a jam right? How do you monitor factor?
- It is a gold standard to use pharmacokinetic assessment to tailor prophylaxis to a patient. This involves the use of population. Pk, software. You pull data from across the world across patients across different centers, and you try to accumulate the best specific information you have on that factor concentrate.
- So Roxio is a probably the most widely available Pk assessment tool for Hemophilia, 829 centers across the world use it, 15,000 different patients. And these are the different factors that have been used for modeling the most data obviously on lactate and advate, and a dynavate here in camultry and then for Factor 9 products. You have the most data on alcoholics, which is an extended havoid medication.

- So this is a sample of data that we collected on our patient, who is taking factor with eloting prophylaxis twice a week. As time has gone on, this patient has had labs drawn at various times random times, peaks and troughs, and this has been entered into his profile. This is your plasma. Concentrate on your Y-axis, and this is your time on your X-axis, and his treatment plan has been entered in. So he is on 4,500 units every 3 and a half days. Yes, he does. Morning of one dose, and then he does. Pm, the other dose.
- What this model can tell me is that if I enter in his treatment plan at 1 h, his peak is 123% factor, 8 levels at 24 HI can tell that he is at about 51% by 48 h, 24%. He bottoms out at 10 and a half percent.
- This is actually really cool. There is a patient portion of this app, so as the provider, I can see his profile, I can look at his infusions. But the patient can download this app log, bleeds, log treatment infusions, and also see what his current factor level is. So you can kind of. Ask the app what your current factor level is to know what it is real time factor. How do we dose factor? How do we now know how to dose factor. Well, there is not one right way to skin the cat, but the World Federation of Hemophilia published guidelines on factor replacement for surgery and breakthrough bleeds. So, for example, this is for hemophilia a. This is for Hemophilia B. If I am taking a patient surgery. But if I'm managing a patient perioperatively, I could dose him to 80 to 100% pre-OP, or I can dose them as low as 60 to 80%. Pre-OP. These are the post-OP factor, level recommendations. And this is for minor surgery. This table actually lists also how to treat breakthrough bleeds so joint bleeds. Iliopsoas bleed intracranial bleed throat and neck bleeds, gi bleeds. This is how to treat patients. And this is using factor. This is published by World Federation of Hemophilia.
- So what are the advantages and disadvantages of factor. Well, it's fast. You can fine tune it, you can monitor it, you can repeat dosing if you need to, and you're monitoring it. So you won't overdose unless you so choose to.
- What are disadvantages in factor oops. You have to have id access. Some people need a port, especially when they're younger ports can get infected. It's relatively frequent still. So if you're doing standard half life product you're doing every other day cost how much this factor cost. This is always very interesting for a 70 Kilo adult with severe hemophilia am factor, prophylaxis. It's roughly 1 million dollars per year. Every year. They're alive. High burden of treatment yes, future direction. Maybe we could extend half-life of these drugs even further. We're really stretching the bounds of science. It's kind of amazing that you can even factor twice a month if you have Hemophilia B. But stay tuned. There may be other developments there. So enter non-factor hemostatic agents. So, as I said up until very recently, we've just been focused on replacement of what's missing.
- Sure there have been attempts to rebalance Hemostasis in the setting of factor deficiencies. So in blue you have coagulation factor mimics or memetics, and in the orange you have natural anticoagulant knockdown. And you're trying to antagonize those things. So Mecizumab was approved by the FDA in 2015, and then in the last 6 months, we had 2 approvals for similar drugs, Marstazumab and Concizumab.
- Mecizumab or Hemlibra. It is a bispecific antibody to activated Factor 9 and factor 10. So it mimics the role of clotting factor 8 without being active. Itself. So it's not a replacement. It's a memetic. And it's a monoclonal antibody. It was 1st in class. And again FDA approved in 2018. So it's actually been out for several years now. And it's these were the earlier studies done for hemophilia, a severe disease, adults as

well as kids with and without inhibitors, and this table summarizes the studies wanted just to highlight a few things. The dosing is once a week, every 2 weeks, or every 4 weeks, and a couple of things, the adult doctors in the room.

- One of the things that was that came to light in the 1st clinical trial with this medication was, there were actually 5 patients with Tma or Thromboembolic events.
- These were actually all in people who were receiving high dose of Pcc. Because they had inhibitors. So they were being treated with bypassing agents, and the 5 who developed these side effects were all being treated with high doses greater than 100 units per gig in a 24 h period and in the Haven 2 study there was actually one person who developed an anti-drug antibody and it resolved, and there were no further antidote antibodies in the remaining 2 clinical trials. So this medication was, FDA approved at the end of 2018 following that these were pulled analysis. This was a pulled analysis that was published in 2021 looking essentially at safety, profile, long-term, follow-up, annualized bleed rates, which is a very common outcome in Hemophilia studies annualized bleed rates, how many bleeds you have in a year annualized bleed rates were about 1 1 and a half, very very low, and again, nobody who was treated with lower doses of bypassing agents had Tma or thrombotic events and then, in 2022, and 2023, the Haven, 5 and 6 studies were published looking at the Asia Pacific region, as well as interestingly, people with moderate or mild Hemophilia a. So before it was always severe, hemophilia a not moderate or mild. So this was the 1st study done with moderate or mild disease, and no online events and very low annualized rates.
- So what does this drug entail? So I'm going to pass this around. And you guys can look at it you know.
- So these come in actually a couple different dose files. There are 6 of them 4 of them can be drawn out together. 2 of them can't be mixed with the other ones, but they can be drawn up together so the gray and the diagram can be drawn together. The other 4 have to be can be drawn together. So you have to sterilize the top of your vial, draw out the fluid with a transfer needle, a filter needle switch over your needle to a treatment needle, and then you can administer sub with a fairly small needle abdomen 25.
- Okay, this is the treatment regimen for emesizumab. You have a high dose weekly for 4 weeks and your maintenance. So what is indefinite therapy can be once weekly. It could be every 2 weeks, or it could be every 4 weeks.
- Okay, so if you are an 80 kilo patient and you have severe hemophilia A, you draw up about 1.6 CC's of this medication, and you administer it. Sub-q. Weekly for 4, and your maintenance could be as low as 0 point 8 Ml. Subq. Every week, 1.6 every 2 weeks, or it could be 3.2 every 2 weeks and if you have a bleed on top of this, you can treat with fat.
- What are some of the issues we have with emesizumab. Well, there's some very interesting effects that this medication has. It impacts your ppt, it shortens it.
- It increases your clotting factor assay. And it's an interference. It's not an actual increase, and it interferes with your ability to measure. For inhibitor of tigers. Chromogenic assays are not affected, and thromboostography is not affected, so these are the results from an actual patient who came in for routine follow-up. His Ptt. Was 21.7 seconds it was short, so I knew he was inherent with his therapy. The factor 8 looked to be 600, except it's actually still less than 1% chromogenic acid.

- So in terms of lab monitoring, the only thing I can really follow on my patients is the Ptt. To see if they're adherent or potentially. If they've developed an anti-drug antibody, the Ptt. Would be prolonged. I've never diagnosed an anti-drug antibody with the half-life is roughly 27 days. So if your patient stops this up to 6 months later, their lab can still be affected.
- So this is actually a problem, because I think when people show up and they get labs. People actually think they're they're fine. They're not bleeding because we've got 600% clotting factor. That's not true. So it's a game changer, the burden of treatment is less.
- Some patients don't actually like it. They actually hate the sub-q part of administering them. They're saying it burns. I'd rather just keep my Iv. I can't feel anything over my Iv anyways right over my vein. Anyways, the clinical trials for emesizumab actually showed improved quality of life and better joint improvement in joint pain.
- My observation is that people with mild joint disease might experience this, but people with severe joint disease, they usually don't have that much improvement in their pain. Consider this for people who have difficulty with Iv access monitoring. It's very, very difficult, because we just talked about this. If someone had hemophilia A and they were being taken to a major surgery, you would normally factor them up to 80 to 100% pre-OP. But if you have emcizumab on board and you're checking your factor levels, your factor levels don't tell you anything because you already know your patient has less than 1% clotting factor. So there's a lot of issues with, how do we know how we safely manage people through surgeries? What if they have a hip replacement and you give them a lot of factor. Can they develop a Dvt. The answer is, yes, they can.
- So checking factor levels does not help factor management. You're a little bit using your discretion as a provider when you're managing patients perioperatively and then on the flip side of the clotting cascade. You have 2 anti-tiffb agents that were approved by the FDA in the last 6 months. Marsdazumab and Pencizumab.
- So, Tifp, let me go back. Tifp is a tissue factor pathway inhibitor. It is an anticoagulant protein, because it prevents formation of Thrombin, and it's an Igg monoclonal antibody. But there was a relatively large phase. 3 study.
- They looked at adolescents and adults, Hemophilia, a severe Hemophilia, a and moderate, severe, severe Tmp. With and without inhibitors, they observed them for 6 months on whatever their treatment was had a 12 month treatment phase and then a 16 month extension phase and they looked at annualized lead rates. In the end they only enrolled people without inhibitors. So this drug is actually only approved for people without inhibitors, mostly adults, fewer adolescents. Look at the annualized rates across the board. If you compare it to routine prophylaxis. Annualized lead rates down to 5 and on demand treatment annualized lead rates down to 3, and on the extension phase, 16 months later annualized lead rates were 2 to 3.
- No deaths, no thrombolic events. 23 people developed anti-drug antibodies sucked up a lot, but for the most part. He went away approved, and so approved last year for tumorphilia A and B without inhibitors.
- It's a pre-filled pen. You just have to stick yourself package, insert warnings and has not been evaluated with major surgeries. We don't know what to do. If you have a major surgery, they consider recommending discontinuation and resuming at post-OP, but there's no recommendation on when to resume it. Post-OP. So those of

you in the audience are familiar with monoclonal antibodies. What happens if you stop a monoclonal antibody immediately. What happens? Nothing. It's still on board right.

- If you have an acute, severe illness, we don't know what to do. Maybe you could consider stopping your marse and math, for now we don't know exactly. The kids study is studying Marse and math in in children.
- And then I have a Cousin Act was approved not too long ago and it's also a monoclonal antibody, and it binds to the K 2 domain of of tiff p explorer. 7. Study compared concip prophylaxis with no prophylaxis, adolescents, and adults, Hemophilia A and B with inhibitors. This is the 1st clinical trial for hemophilia b with inhibitors. Just to point that out.
- During the earlier parts of this study the FDA put a pause on this clinical trial. Why, 2 arterial and 3 venous thrombotic events. Yikes.
- So the trial resumed after dose, continuation after dose, attenuation of completed which I will review with you in a minute. But the clinical trial was paused. There was actually a separate study ongoing that was also paused.
- This trial design is a little hard to understand, but I'll just kind of briefly remove this all. There are 4, 4 arms, 3 of these are treatment arms. One of them is no treatment, and this is randomized, 2 to one. This is no treatment, and this is treatment. But these 2 are randomized. And then group 3. You have patients who were brought over from the earlier phase studies for Concizumab, and then Group 4 is people assigned to treatment. So not randomized. 3 were treatment one. There's no treatment, and in the end they enrolled 91 adults and 42 adolescents, and they found that the annualized bleed rates for Group One. No. Prophylaxis for consist, the annualized bleed rates were 11.8 group 2. Randomized treatment was 1.7 groups, 2 through 4 annualized bleed rates were close to 0.
- Then they did the same study, similar study design, but in people without inhibitors. And again this study was paused, due to the thrombotic events and very low annualized bleep rates for people with hemophilia and bleed.
- So this is, consider that I only have one, and I'm so thankful to the pharmacist who talked to the drug Rep in order to get this. So you guys can pass this around. So it kind of looks like an insulin pen.
- There's 3 different dose pens. It's pre-filled. You actually just need to dial it to the dose that you need to administer. You put a new 32 gauge needle every day, and you administer this. But this drug is daily.
- There's a loading period, and then you treat for at least 5 weeks, but no more than 8 before you check plasma, concentration levels of concizumab, and then you dose escalate. If your concentration is low and you dose if your concentration is high. So the adjustment that they made when the FDA paused, a clinical trial was they allowed for dose attenuation. When people have very high concentrations of concizumab.
- The people who developed the class, by the way, were people who are had higher concentrations of this drug on board.
- Okay? So the George site is a pediatric site for this particular population as well.
- So when we talk about non-factor hemostatic products. There's 3 now. So we have emesizumab, which is a bispecific antibody to factor 9. And it's sub-cute every week every 2 weeks or every 4, and it's for Hema only with and without inhibitors, and these come in vials and then you have Marcizumab, and you have concizumab both anti. 10 P.

- These, this is weekly, and this is daily. They feel tense, so maybe just much easier in terms of being able to get ready, for these are all prophylaxis. These are not appropriate on demand treatments. We actually saw a patient in clinic about less than 2 weeks ago. He was taking emesizumab on demand because he just didn't want to do factor, and then thought like, maybe he got some good disease control with emesizumab. And then so he said, I'm going to just take it when I need to. The problem is, it doesn't work that way. You can't take a long acting medication on demand. You will not get any relief of your pain, and you will not get any treatment for your disease.
- There are a lot of unknowns as great as these medications are, and as exciting as they are. We don't really know how to treat wetness for disease. I worry because my adult patients have a lot of thrombotic risk obesity, a lot of joint disease. Maybe they're sedentary cardiovascular disease. And I worry because I worry that if they have a bleed and there's medication is new. I worry a little bit that I don't know exactly what the best way to treat them is. And our adult patients, they need things like hip replacements, knee replacements, cardiac surgery, thyroid biopsies.
- I don't want to overdose, and I don't want to underdose them either. Future optimal dosing. Maybe some of these dosing strategies will change, and maybe again we'll find out more about kids below the age of 12.
- And again, I'm so glad I'm not getting this talk in a month, because in a month there might be a new treatment out there. There's a which is a small interfering Rna molecule, and it is once a month future direction for other non factor. Ideas is enhanced quality factor 5 and enhanced quality factor 10 being looked at for rebalancing of hemostasis.
- So what about gene therapy. I feel like there was like a some sort of rep called and asked for a statement on how I feel about Gene therapy and Hemophilia.
- There are 3 FDA approved gene therapies for Hemophilia. They are all in vivo treatments. What this means is you have a normal or a variant factor producing copy of factor 8 or factor 9. It is packaged into a viral. Vector these are all Aav 5 vectors to this at this point in time it's a single peripheral. Iv infusion done in an infusion center, not in the hospital.
- The viral vector. Is taken up by the nucleus of the hepatocyte. It sits as an Episome so not integrated into the patient's DNA, but sits outside of it, but because it's been taken up into the nucleus. Hopefully, you have protein synthesis and production of your clotting factor 9 and 10, what are some challenges or some issues with gene therapy?
- There's a fairly high percentage of patients who have pre-existing Aav antibodies. So we do not think minus one clinical trial. That showed that it was okay. We generally worry about this. We worry about a lot of side effects as well as ineffectiveness with gene therapy. If people have pre-existing antibodies hepatotoxicity, the number one concern for aav gene therapies in hemophilia right now they're approved only for age 18. There's concern that for pediatric patients, their livers are still growing. And so you probably have inefficacy as a potential problem. If you are administering something that's taken up, but then the cell is still radically dividing cost. If it fails, I'll talk about cost in a second price tag for these is anywhere from 2.5 to 3.5 million dollars for one inclusion. And if it doesn't work you can't try another. Aav gene therapy.
- Okay? So this table summarizes all the gene therapies that are FDA approved. There are 2 for Hemophilia B, and there is one for Hemophilia. A. I will point out

some very interesting observations. So after a single infusion factor 9 in these patients with severe Hemophilia B increased by 36% at 6 months and 34% at 18 months.

- The 4 year data just came out a few weeks ago. The mean factor, 9 activity for these patients treating therapy, 37%. They have mild disease. They're only treating on demand with factor if they even need to.
- Price tag 3.5 million dollars. One dose.
- Okay, bet has hemophilia B, gene, therapy factor of 9 levels, 27% 62% of patients had lft elevations on steroids for durations ranging from 23 to 165 days. This is actually a very small number. I can't explain why a very small number percentage of patients had lft elevations treated with corticosteroids. And then Broctavia chemotherapy mean levels, 41%.
- And then 4 year data, 75% of patients still had 0 treatment 4 years after one treatment, 2.9 million dollars.
- So what is the role of gene therapy? I mean high risk, high reward. But it's actually not that expensive? If it works, we're talking about lifetime expense, not that expensive if it works. Okay. So all of this is in vivo gene therapy. The next frontier of gene therapy may be ex vivo gene therapy, where you take stem cells out of the patient, engineer them, and do the gene transfer outside of their bodies and then re-infuse them after you do bone marrow conditioning.
- So New England journal published this 3 months ago, 5 participants, adults had a lentiviral vector F factor, a Transgene treated with myeloablative regimen conditioning. That's like the atomic bomb version of you. Put it off in the bone marrow set off an atomic bomb. Let that person's cells you know the the transfer gene in graft. They treated them with factor while they were severely cytopenic, all of them engrafted, and look at these patients. 5 individuals no lead after gene therapy follow so far for 1214 months so gene therapy, high processing high single cost, high reward dosing is interesting. So viral vector dosing is weight-based. And the question is, if you give really high viral vector doses, you might get really good factor expression. But you might get a lot of toxicity as a trio. We still don't really know how to handle a pre-existing aav immunity. We just tell those people. They're not eligible for gene therapy for the most part, except for hemogenics, and then toxicity remains a concern.
- Exevo gene therapy. The question is, if you have some good alternative treatments who would sign up for gene therapy?
- Right? So this is actually our treatment paradigm. Now, if you have mild disease factor on demand. You can still take factor, or you could actually use emesizumab. If you have hemophilia A, if you have moderate disease, those options are still available, and if you have moderate severe, you're going to go into this route for Mezumab, and possibly Gene therapy. So this treatment landscape looks a lot different than it did 25 years ago.
- We've been through a lot to get here, but this is an explosion of availability of the treatments.
- It takes a village or 2. So we actually have 2 comprehensive disorder clinics. We're trying to consider ourselves as a lifetime clinic, like all your care at Uva pediatric comprehensive Clinic Drusel, who's sitting right there in the red if you have any questions for her pediatric team, and then the adult team. And then, of course, the army of people who take care of our patients when they get admitted. And that's you guys, thank you.

- And a genetic counselor is an educational consultant on our pediatric side, so based in village. And it's an exciting time to be a classical hematologist. So with that, I'm going to get help with my friend Keith, who's going to give us some perspective on treatments.
- This is for you. Yes, bye, bye, you guys will hear me.
- Hi, Keith, thank you for coming. Thank you. No, thank you for making time for us. You have no relevant disclosures. Can you tell the audience a little bit about yourself? Yeah. So I'm 52 years old. I was diagnosed with Hemophilia birth. My grandfather, on my mother's side, had Hemophilia, he was born in the twenties, so his treatment availability was dramatically different than what I've been able to enjoy in my lifetime. He passed away at 54 years old, due to a hemorrhage in his brain. So in his lifetime there was no treatment other than a blood transfusion up until close to his death. It wasn't until after his death that they discovered Ffp. And cryo so dramatically different outcome for patients with Hemophilia we saw the timeline, and it's what what has happened in the last 20 years. 30 years is is dramatic compared to what people before experience. I have approximately a 6% factor level without any treatment. But clinically, I do tend to have more bleeding than a mild patient that I'm categorized. So one of the things that's been interesting in my lifetime is figuring out the best treatment regimen for me specifically as a child. The concept was we would treat on demand. We wouldn't just do any prophylaxis, and it wasn't until recently. I think that's coming up in another slide that we've done that consequentially
- I've had some significant bleeds and wear and tear on my body, due to having hemophilia specifically as a child. I remember a lot of issues with oral bleeding like, if I'm losing teeth, or if I had an injury, I used to just as a typical child. I would like do things, and then, if I
- I would bite my tongue a lot like I don't know why, but like that would cause a bleed that was difficult to treat. I also developed some knee problems as an adolescent. I had some injuries in middle school that required some knee surgeries.
- Basically, I was told when I was like 10 years old, you're going to need a knee replacement by the time you're 20 years old. But of course we want to delay that as much as possible. Because what am I going to do with knee replacement at 20? What do I do when I'm 40? So I did finally have a knee replacement at age like 47, which has been life changing.
- Also, I've had some other issues downstream because of my knee problems. I've had ankle problems. I've had to have my ankle fused a few times because it didn't form union. So that's been a challenge.
- Also, I've had one weird sort of event, sort of later in life with just suddenly I became tachycardic. I go to the hospital, find out I'm super anemic. I didn't have any symptoms of bleeding that I could determine, and it's still kind of unknown, but we think probably it was some sort of gi bleed. I had a cold, probably coughing too much. Maybe enough bleeding was going on that it wasn't really detectable, but over time
- created a situation that I needed a blood transfusion.
- And if you don't mind me asking Keith, why were you admitted for 2 months after a thigh bleed right? So when I was in high school. We all had the beloved gym class and me having already 2 arthroscopic surgeries on my knee, probably shouldn't have been participating in gym at all. But this is kind of the challenge of being a child. The school doesn't really necessarily understand what you should and

shouldn't be doing, so I was instructed to jog around the track, and I guess just probably that motion of having your knee and running probably strangely caused a bleed in my thigh to the point where I was like bent over, and I was using factor concentrate at the time on demand, and it just took several weeks to for that bleed to resolve and physical therapy. I needed just to straighten out my body again to be able to walk normally. So my middle School high school years. I didn't spend a lot of time actually in school. There was always something knee surgeries or this strange bleed. After that I didn't have to go back to Germany. Yeah.

- So in my childhood the treatment for me was cryoprecipitate before Factor concentrates were developed in the like late seventies. I believe so. I was born in 73. So the pretty much easy way of getting treatment for factor was, if I wasn't going to the hospital for factor, I was eventually able to start getting factor at home at around age 5, when we talk about the cost of factor. This was one of those early battles with convincing insurance companies that it's cheaper for you to allow patients with Hemophilia to treat at home than paying for a hospital visit or an emergency room visit every time you have to leave, and one of the things that facilitated that was the evolution of back, or concentrate over cryoprecipitate. I remember I grew up here in Charlottesville, so I remember trips to the Blood Bank at the Barrington Wing, where we would have, I call it. It was like orange juice. I mean this massive quantity of cryoprecipitate that was required for bleed. Eventually we were able to get the concentrates talked to my dad because I was trying to remember where it came from, and at the time it came from Mcd. So there was some partnership going on here in Virginia between the 2 hospitals. Once we had the factor concentrate at home. That was much easier, because now you're as a patient in control of treating your Hemophilia. You don't have to call the doctor every time you have a bleed to figure out what you need. And it's based on those guidelines that you talked about. We know what our levels are based on our dosage. And so that kind of helps you manage that at home
- I did start after like prior to my knee surgery that I had when I was 45. So I started the Xantha, which is one of those extended half life. But it's not completely like the the long acting factor. That's when I actually started prophylaxis, because at that point it was sort of more of the standard of care, and I realized that I could really manage my life a lot better if I kind of have a sense of of knowing what my faculty level is.
- So early life. We talked about going to the blood bank. I never
- It wasn't difficult for me for my father. He was the primary person that would give us factor. I have a brother, too, I forgot to mention. I have another brother that has Hemophilia. My mother has a sister that also is a carrier, but both of her sons did not get Hemophilia so for us it was pretty easy for me, for my dad or myself to get a baby. It wasn't difficult. I didn't ever need a port, and as a child, even though I had significant bleeding events it was sort of not a daily occurrence. So I think, accessing my vein. Wasn't that that difficult. I do remember.
- I started self infusing probably like as a teenager, probably like 12 or 13, probably close before high school. But right around that time.
- I'm I think, for the most of the time, until I was like much older, pretty much. We would stick to the same arm. In sort of this part of the arm. But quickly as I was starting to do this myself, and more frequently, it occurred to me that I probably should switch and try different veins in different arms, and and luckily I am left-handed. But it is. I'm pretty able to switch and use both arms.

- That's not that difficult. Do you think that's true for most people? I don't know. I would say maybe not. I know my brother probably not.
- And as a sort of flip side. My brother would say that he's the type that actually sort of avoids giving himself factor, even though he's also in prophylaxis. So I don't know how compliant he really is. Yeah. And so that's part of the challenge here. I remember as a child, and we kind of get into this later. I think, too of avoiding again. I didn't need factor constantly, like every every couple of days, but you know, once a month or so I probably need factor, and I remember running away and hiding from it, because it's like, even though I knew it would make me feel better. I still kind of avoided doing it. And so when we talk about some of these treatments that are available now it, it opens up a new sort of dynamic of if I had a child, how would we treat them? But let's see.
- So tracking, I'm really anal about tracking even before the app which which I love. I I think I'm only one of the few. I don't understand why, but I've always documented everything. And so I have physical log books. I have composition books where this is an example of when I had my knee replacement so obviously for the knee replacement, I have factor multiple times a day for multiple weeks. And so you can see sort of the progression of the dosing twice a day every 12 h, and then once a day, and then later out into almost a month after surgery, doing it on the days that I would have physical therapy. So even before I was doing prophylaxis, I always knew that. Okay, if I'm going to do something really that could have more risk or have more likelihood of creating a bleed, then I would go ahead and give myself. So this is an example of what I do now.
- I'm taking tractor every 3 and a half days, so I go back. And this is an example here with a bleed where? Okay?
- So here these are just my usual prophy doses 8 Pm. 8 am. 3 and a half days later. And then here, I realize, okay, I just did some work outside, and I bashed my finger with the hammer because I have the app, which I'll show you in a minute. I can know what my factor level is and say, Okay, is this going to be all right on its own? Or do I need to give myself a little booster dose? And so here I decided I was at 22% when it happened. So I might as well give myself 1,500, knowing that in the next day and a half I would be getting a full dose of my regular protein dose. So with the app, I can see what my level is at any point. So these are actually screenshots from from my app.
- And on this particular time. This was prior for me before I gave myself my usual protein dose. So the app is telling me I'm about 9%. I don't have a slide, showing what it is after. But as soon as I do the dose, I'm like at 1, 53%, or 148%, the level. One of the things that's interesting about the dosing of this is that even though my prescription is for 4,500 units, what I get from the pharmacy might be 10% plus or minus what that is. And so it's all based on what they have available. And the lots are strange, like you don't ever have a vial that has an exact dosage. It's some weird combination of that. So this is an example here with that lead that I have when I bash my finger. So the app lets me document the bleed. And this was my level after I gave those 1,500 units. So I was pretty confident that that was high enough level to take me to my next toast.
- So this brings up a conversation that Dr. Nan and I have had recently with my own treatment, and that is with the advent of the new non-factor treatments. And one of the things that I wanted to understand is, if that would be a good match for me now

as an adult, which makes me think about how I would treat if I had a child with Hemophilia as well.

- One of the things that I would definitely do which is different from how I grew up was, I would definitely want my child to be on prophylaxis growing up with on demand treatment. Even if you're not that severe, you're going to develop arthritis in your joints. You're going to have damage to your body. That may not be that apparent when you're a child, but as you get older they'll definitely be apparent. And so, for sure, if I had a child with Hemophilia, I would want them on prophylaxis treatment in terms of what I would do and what I'm allowed to do when I was a child. I wasn't allowed to do much of it. I couldn't play sports, I couldn't. I didn't really spend a lot of time at friends houses. My mother was very protective and obsessive about that. My brother, who was older.
- Who clinically didn't believe as much as I did, was allowed to do some of these things as a child, a little bit of stuff like he could play soccer. He went to Cub Scouts or something like that, but I think by the time I was those ages my mom was like, I'm not gonna be able to listen to that and that's good and bad. But one of the things that's dramatically changed. My life now, as an adult is being on prophylaxis. Now, I feel like I can do things like if I want to go hiking if I want to go, you know.
- Do some late sporting activity. I feel like I'm relatively safe in doing those things. What would you choose for a treatment. How would you feel about sub-q treatments versus trying to PIN down a child for Iv access? Yeah. So obviously, a sub-q treatment once a week for a child would be a blessing.
- I'm still kind of on the fence, because I keep changing about that, because even for myself, I was inquiring about those medications. And what frightens me as an adult taking those non-factor treatments is if something happens. If I do have a trauma, if I'm in a car accident, if I need surgery, do we really know how to treat that without treating my factor too high, and risking the clot, especially with other co-conditions. We, as adults, would have, such as the cardiovascular issues or other things. With a child, I would be a little less afraid of that, because, as the parent. I could make sure if I'm in the emergency room I could tell the physicians there that my child is on a non-factor product, or I could educate the er doctors, which happens a lot when you have hemophilia so I would be a little less concerned, even though I do worry about the testing ability. Like, if the child goes into the emergency room or anyone into emergency room, we really want to know what their factor level is. We don't know. And the test that you could do to get that you know, detailed test isn't available at the hospital. So yeah how do you feel about Gene therapy. Gene therapy, I think, sounds very exciting when we talk about the cost of that. We kind of balk at 3 million dollars.
- I'm spending over a million dollars a year as it is just doing prophylaxis. So in a perfect world, where, you know, we had either a single pay or health system, or a company that you're going to stay with, that could realize the benefit of that cost reduction. Obviously 3 million dollars is not a lot compared to my whole life being over a million dollars. I mean one of the things that's been interesting with the evolution of some of the laws, with health care is, you know, a person with hemophilia, when we used to have a maximum policy of a million dollars would get rid of that pretty quick. So yeah, I would do it in a heartbeat. I think is without question. I mean, I guess if you could screen and make sure beforehand that I'm not gonna reject it, you know, that might be really useful. Yeah. So yeah. And so

there's a question about industry and things, you know, for I personally have not been subject to harassment by industry.

- I think the choices of products have been more on my terms of what is available. What's gonna work the best for me? Like, Dr. Man said. You know, we get very set in our ways when we have something that works, and we can rely on it. We can be relatively sure of the outcome. We like to stick with that product so. And I think Hemophilia is rare enough that there's not a wide marketing team, you know, to the world. You're not seeing commercials for these products on on the news, although I do enjoy reading about them. And one of the things that happens when I learn about a new product is, I obviously talk to Dr. Mann about it and try to figure out if that's a good match for me.
- But yeah, I don't personally think that, you know you don't have a lot of undue influence.
- And then, lastly, any anything you would like someone in the audience to know? Or Yeah, I guess you know one of the things that I've encountered, you know in my 52 years of life is that
- I realize that hemophilia is rare, and I realize that this might be the only time that you guys are hearing about it in terms of like in the future you may never have a patient that has hemophilia, but if you do a don't panic, you know, because as scary as it does sound, it's really not that scary, I mean I when I had surgeries, you know, I've been hospitalized and moved hospitals because they were afraid of of doing my gall bladder surgery.
- It's very well managed and controlled. If you know what you're doing. If you know the factor products. You know what the levels are. You know what we need to do a certain surgery, and also just to, if you do encounter a patient. Listen to what they say, because they know more about it, and how their body works, and you know I know before my arm gets swollen. If I have a bleed. I could feel that it's coming, and I think sometimes I've been in situations where
- I know that I have a bleed and I need treatment, but if a doctor examined me, they would think, you know. Obviously no one's going to deny me treatment, but at the same time they'd be like he was fine to me. Nothing's really going on. I don't. So I think the challenge is just to be open-minded and understand that
- that we know what we're talking about when we earn.
- Thank you. Thank you so much for your time.