



Canadian Hemophilia Society
Help Stop the Bleeding

PODCAST SERIES

HEMOPHILIA GENE THERAPY – FROM DREAM TO REALITY

EPISODE 14

FOUR PEOPLE DESCRIBE THEIR EXPERIENCES WITH HEMOPHILIA B GENE THERAPY

PARTICIPANTS

Daan Breederveld, Netherlands; Stephen Brown, Canada, John Curley, U.K.; Brian O'Mahony, Ireland

HOST

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Intro 00:00

This is HEMOPHILIA GENE THERAPY - FROM DREAM TO REALITY, a show coproduced by the Canadian and Irish hemophilia societies. Here's your host, David Page.

David Page 00:16

Good morning, afternoon or evening, wherever you are in the world. Welcome to this video / podcast co-produced by the Irish Haemophilia Society and the Canadian Hemophilia Society called Hemophilia. Gene Therapy - From Dream to Reality. Over the last several years, gene therapy for hemophilia B has become a reality. Some received it through clinical trials. Others received it after marketing authorizations and reimbursement approvals in their countries. Today, we will talk to four of these people. Our ultimate question to them is, "Are you happy you made the decision to receive gene therapy? Why or why not?" Let me introduce our four guests: from Canada, Stephen Brown; from the Netherlands, Daan Breederveld, from the U.K., John Curley; and from Ireland, and my colleague in this production, Brian O'Mahony. So first I'd like to ask each of you, in turn, where you live, what you do for a living, your age, and whether you received gene therapy in a clinical trial or after marketing authorization. And we'll start with Stephen in Canada.

Steven Brown 01:19

Thanks, David. My name is Stephen Brown. I'm 50 years old, and as David said, I'm in Canada. I'm in Burlington, Ontario. I received gene therapy close to six years ago as part of the Pfizer clinical trial.

David Page 01:32

And Daan in the Netherlands.

Daan Breederveld 01:34

Hi, Daan Breederveld, from Amsterdam, close to Amsterdam, living in a small village. I work as a company doctor, occupational health physician, and part time carpenter. And I received my gene therapy in a clinical trial, a phase three trial, six years ago, CSL Behring.

David Page 01:51

Thanks, Daan. And over to you, John.

John Curley 01:55

Hello. I'm John Curley. I'm a welder in Portsmouth Dockyard. I live on Hayling Island. That's a little island next to Portsmouth, and I'm 55 years old, and I had my gene therapy six years ago as well.

David Page 02:09

It was a clinical trial, John?

John Curley 02:11

Yes, a clinical trial.

David Page 02:12

I guess it would be. The market authorizations have only been in the last year or two. Finally, Brian.

Brian O'Mahony 02:17

Hi David. My name is Brian O'Mahony. I'm the Chief Executive of the Irish Haemophilia Society. I'm 67 and I had my gene therapy as part of the HOPE-B clinical trial five and a half years ago.

David Page 02:28

I'm going to ask each of you, in reverse order this time, to explain how you came to the decision to take gene therapy. More precisely, what were your goals in choosing this treatment over factor concentrate prophylaxis? What did you know beforehand about the risks and benefits? Who did you talk to in making this decision? And do you think you had all the information that you needed to make that decision? So we'll start with Brian.

Brian O'Mahony 02:53

That's several questions in one. Look, I'm probably somewhat different because I was following the science on this for many years, and as CEO of the Irish Haemophilia Society, I was also responsible for encouraging many of the companies to come to Ireland, to look at Ireland as a potential site for clinical trials. And we organized meetings with our members for them to discuss this and to look at the trials that were coming forward. In the course of looking at all the trial data, I became convinced that for me personally the benefit risk ratio of taking part in one of the trials was positive. So I decided I would do this. I suppose my decision drivers were ... I liked the idea of stopping prophylaxis. I was hoping to diminish the amount of chronic pain in my damaged joints. I wanted to be more active physically. And also, frankly, I wanted to see what life was like without having severe hemophilia. In terms of my goals, I was fully aware that I could set my own expectations, but they may not be met. Having said that, I was hoping for a factor IX expression somewhere between 20 and 60%. I wasn't really looking for 100. I was hoping it would last for at least 10 years. And as I said, I was hoping to have decreased chronic pain in my target joints. So who did I speak to? Somewhat different than many. My family trusted my views on this, so we didn't have a lot of conversations about this, but I had quite a few conversations with clinical colleagues and friends around the world, because, as you well know, David, here we have a large network of colleagues who work in this area. So I talked to a lot of people, some people who thought it was a good idea for me to do this. Some thought it was a bad idea, and I listened to all opinions and then made my own informed decision.

David Page 04:29

So you had access to a lot of information. John, perhaps that wasn't your case. Can you tell us about your decision-making process, the drivers, your goals?

John Curley 04:38

I was a bit isolated in the Portsmouth area. I never grew up knowing any other hemophiliacs or what they did. It wasn't until probably about 20 years ago that they asked me to go up to Basingstoke to a proper hemophilia

centre to meet a woman called Savita. Savita Rangarajan. Did everyone know her? And she was the head of the hemophilia centre there. She asked me to do some clinical trials for her. She always said, "Look, John, if anything comes like any cure comes along, you'll be first in line if you do this stuff for us." So I did loads of trials anyway. I always had full confidence that I wouldn't be killed or die. So I did loads of trials, and it was all fine. And then she just said, "Oh, there's a one called the HOPE-B actually come up, would you like to do it? It's a cure." I didn't ask anyone or query. I just said, "Yeah, I'll do it." I just didn't want to be a hemophiliac. Just wanted to be like a normal human and it all just went smoothly, and it all just went fine. Yeah, I never had any worries at all.

David Page 05:37

As a welder, did you have some goals, perhaps, improving your health so you could continue in that kind of very demanding job.

John Curley 05:44

The main thing was hiding it all the time. Only a few people knew I was hemophiliac in the dockyard, because the majority of them didn't know it existed. Because obviously, years ago, there was the HIV and hepatitis thing and all that. And so you had to hide it. I wouldn't have got any work otherwise, so I was always sort of like hidden. So part of the reason was that as well: so I'm not a hemophiliac anymore. So that was one of the reasons. I suppose it did affect me. Sometimes I get bleeds into my elbows. or I think, Oh God, you know, mate, it will stop all that, which it did. I was never on prophylaxis. By the way, no one had ever offered me prophylaxis. It was just as and when I got hurt. So the thing was, I didn't want to be a hemophiliac. I wanted to just get on with life, and it worked. I had full confidence in everyone; I don't know whether I shouldn't have.

David Page 06:30

Two very different perspectives. There's one, very well informed. Another one, trusting that it would work out. Daan, where do you fit in in that picture?

Daan Breederveld 06:40

Well, somewhere in between, because I think it's very rare that you're so well informed as Brian is. But being a medical doctor myself, I was, of course, not on top of the science around gene therapy, but I did follow it since the 90s, actually, since they were experimenting on mice and dogs, and I dreamt, when I was in elementary school, I told the teacher—everybody around me wanted to be a fireman or a policeman—and I said, I want to be a professor who will invent a pill against hemophilia. So yes, I was also dreaming of a life without hemophilia. But then again, things went so slow that I didn't think that it would be for me in my life. And then my physician pointed out that there was a phase one trial. Then my kids were very small, and I just .., the risks and benefits were not in favor of joining the study. And then it was about 2018 that he asked me and said, "Well, there's now a new study, and they've changed things a bit. It's in favor of the results. We think we've seen preliminary results, and they seem very good. Would you like to join?" Because this might be your last chance of having even gene therapy, because maybe it will not be reimbursed in the Netherlands, because the population is so small in our country that actually, I'm very sorry to say that he was right, because it wasn't reimbursed one month ago by the Dutch government. So I just thought, This is my last chance. I have to go for it. And then it took me half a year to really decide on going forward. And I knew about the risks. I knew I might have to take prednisone if my liver enzymes went through the roof. But I didn't mind that, because I've also had interferon treatment for my hepatitis C, chronic hepatitis C infection. And I thought, well, prednisone can't be any worse than taking interferon for one year and a half. So let's do it. And it took around four to six months to decide on. I consulted my physician. He provided me with articles, scientific articles, and I shared the results with my wife, with my children, with my father, who's a physician as well, so well informed, I can say, but also depending on my physician.

David Page 08:47

Did you have some goals in terms of improving your health or having perhaps better outcomes than on factor IX prophylaxis?

Daan Breederveld 08:54

I didn't really think in percentages, but I knew that the preliminary results were about well, tens of percentages that you could rise. And I thought, well, if it would be 10% that would be enough. Clinically, I had less than one. So I was a severe hemophiliac, and I would be very grateful to have around 10-20% and I'm, well above that now. So I haven't taken any prophylaxis since 2019.

David Page 09:19

And Steven Brown in Canada, what was your whole process leading up to gene therapy?

Steven Brown 09:26

Similar to Daan, I was approached about joining a trial much earlier. I think it was one of the phase two trials, and same reasoning. I had a new son, and at that point in time, it was just not the right time for me, given that the science was still a little new, and the risk with my new son. When I was approached again to do it, it was one where I didn't have to make a decision right away as part of the trial, because there was a lead-in into the trial. So it gave me an opportunity to really start getting involved in it. I'm really close with the doctors at my hemophilia clinic. I also ... Dan mentioned it as well ... one of the reasons why I wanted to do it is that my day job is as a health economist, getting market access and reimbursement. And I had literally said that to my hematologist. I'm like, this might be my only chance to actually receive this, because I do not know what the market authorization will be. Canada did authorize it, From my understanding ...

David Page 10:22

it's not reimbursed yet, though.

Steven Brown 10:24

No, it's not reimbursed yet, but it's gone through ... and I really just talked it over with my wife. I am a little bit more knowledgeable. I also have a PhD in molecular biology, and going through all of that, I had always said that hemophilia B, hemophilia B specifically, was like the poster child for gene therapy, small molecule, you just need to get it exposed in the blood, and it can have a great impact. So there was part of me that just having a PhD, going through the time since Dolly the sheep was cloned, actually receiving gene therapy myself, was, you know, kind of the cool factor. There is the part of me also that I'm very appreciative of all the older hemophiliacs that went through all the trials in the past, to get things like the long-lasting and recombinant factors that we did. And I felt it was a little bit of my duty to try to take that opportunity as well as I do have a son. He's very active. I'm getting into that old age, and it would be nice to stop, slow down some of the damage in my joints so that maybe I can be a little bit more active in the future. That was kind of my rationale.

David Page 11:28

Staying with you, Steven, how was the day of infusion? Was it a big deal?

Steven Brown 11:33

It was a huge deal. It was the first time in Canada that they had done this, and just the red tape to handle an infectious product was a lot of work. It took a lot of collaboration with a lot of different groups, including, like the pharmacists, the research labs as well the hematologists and clinic. When I was there, everybody's all gowned up, masked. I'm here sitting in a T-shirt waiting for it. And I think there were a lot of people that came down to see me that day. I have lots of great pictures. One of my old hematologists came down to visit because it was seen as a very ... a breakthrough, crossing that line of offering a potential cure. I use the word cure very, very loosely here, but, yeah, it was a big deal.

David Page 12:18

Daan, a big deal for you in Holland?

Dan Breederveld 12:20

Actually, taking the decision was a big deal. And then after I took the decision, I knew I was entering a process I could not stop, and I didn't want to stop, and it was more of a big deal for my treatment team, actually, because they were all dressed up in suits and masks, and this was before Coronavirus. So we weren't used to that yet, and it was crazy, but I was just there sitting in my T-shirt as well and just enjoying the scene and took the shots and lay down for half for an hour. And then they told me, "Oh, you can go for a walk in the hospital. You can have some lunch and just return in half an hour, 45 minutes, and then we'll see how you're doing." So yeah, it was relaxing. Sometimes it was the most uneventful day of my life, but life changing.

David Page 13:03

John, how did it go for you? On dosing day?

John Curley 13:06

No one told me it was infectious. They just said, "Oh, it was like a builder. And they said, Oh, John, on like this day, can you come in and we'll inject you." And I went, okay. They give me an injection on the arm, but it was like a clear fluid. My wife was there, and I didn't know it was like dangerous or anything. Was it infectious? Was it? I think a couple of people might have had gowns on or something, but they put a drip in my arm, and it took about an hour to infuse. I say, I don't know what I was expecting to happen, like a big marching band or something, come out. I don't know, but it just went smooth. And they said, Oh, once it was done, I said, Oh, is that it? And they went, yeah. And then I'd go and sit in a room next door, lie down on the bed and after about two or three hours, they said, Oh, it'll be all right. They said, Oh, you can go home. It was totally uneventful. It was an event. And then it was uneventful, I don't know, I don't know what I was expecting, but it took about maybe three weeks to actually start to build up the clotting factor. I think I'm probably the least educated here, and I don't know if ignorance is bliss, but they didn't tell me a lot, I just go, okay then and it but it worked. Everything they said would happen, happened. So I was pretty fine with that. I always had confidence in them, but I suppose it took half a day total. I had to drive to Southampton, put a drip in, lie on a gurney, took about an hour, and then I got out, went to another room, lied on the bed, and then yeah, told to go home. Yes, well, fine. And then, obviously, every other week I used to come back for a blood test and that, and it's, yeah, it's all pretty simple. This all went exactly how they said it would. So, you know, yeah, brilliant and uneventful.

David Page 14:41

So Brian, I guess you were a bit more prepared for your experience?

Brian O'Mahony 14:45

Just to be sure, John first. John the gene therapy vector, was not infectious. It's attenuated virus. It doesn't cause any infection. It's harmless. It's just a delivery vehicle, really, for the piece of DNA. No, look, I would agree with what Daan said as well. It's quite an eventful day in terms of potentially life changing, but it's also very uneventful. It's very boring. In fact, you go and they set up an intravenous drip. This takes about an hour, an hour and a half. You sit for a couple of hours, and then you go home. Now, I was the first person in the hospital to get any sort of gene therapy, so I was quite relaxed. But there were nurses, research nurses, doctors, all gowned up. There was the hospital director, the research director, their PR team were outside. There was a crash team in case something went wrong. So I was quite relaxed until I see about 20 people outside. What's going on here? Having said that, I'd made it clear I was also going to speak publicly about this, so hence I give them permission for their PR team to be there. No, it was very uneventful. You know, you get the infusion. They're just watching to make sure there's no sort of infusion reaction. And then it takes an hour, an hour and a half, you stay for a couple of hours, and then you go home. Now, I did find when I went home that night that I was kind of emotionally drained, because it was an uneventful clinical procedure. But intellectually I knew this is a big deal. This is a potentially life changing day, so I was tired that night when I went home, just from the sheer importance of the event.

David Page 16:13

Let's move on to the follow-up, because the follow-up is a bit different. It may be more of a big deal than the dosing day. Brian, how did that go for you? In terms of the rigor of all the testing in the six months following the administration?

Brian O'Mahony 16:25

The first three months are especially onerous because you're going in once a week, every week for three months. And in fact, I decided to go in twice a week and have some extra transaminases done twice a week, just to make sure that that was all stable.

David Page 16:40

What's the purpose of the of this frequency?

Brian O'Mahony 16:42

Daan mentioned that you might have to take prednisone when the gene therapy goes to your liver. Quite understandably, in some people, the liver reacts and gets a bit inflamed. It doesn't really cause any serious liver damage, but that inflammation can kill off the gene therapy in the liver cells where it has taken hold. So it's very, very important, if your liver enzymes start going up at all, that you spot that straight away, and you start steroids. The protocol was once a week. I actually went in twice a week to do that. It was quite funny in the sense, because in the lead-up period, which was quite long, about six months, I was doing a lot of negotiation with the research person about which days I'd come in for follow-up tests, and I was still trying to squeeze in some of my work and travel abroad, and then, of course, all that went away, because a week after my gene therapy, covid happened, so there was no travel for two years. So in one sense, covid made it easier for me to do the follow-up, because you couldn't go anywhere. On the other hand, it made it more difficult, because at a time when everybody is avoiding hospitals, you're constantly going to hospitals. I have to say, they managed it extremely well by bringing me into a non-clinical area, but certainly with a clinical trial, the follow up is more intense than with licensed gene therapy. But even with licensed gene therapy, there's quite a lot of follow-up. So that's something that has to be factored into your life. You have to think, okay, if I'm going to do gene therapy, hopefully in the longer run, it will free a lot of my time from dealing with the centres. But in the first year, it certainly does not do that. You'll probably never be in the centre as often as you are on the first year after gene therapy, because there are a lot of visits: first three months, every week, then every month, then every six months after the first year. So it gets much easier after the first year, but the first year, you certainly have to plan that, and you have to plan how that's going to be done, where the blood is going to be taken, and so on, so forth. That's really, really important to factor that into your work, college life at the start.

David Page 18:31

John, you're a welder. You live on an island. Was the follow-up easy for you, or was it really a challenge?

John Curley 18:36

Yeah, funny enough, I was working for a private company. I work for the government now, but I was working for a private company, and it was way better. I said, look, I'm doing some experimental stuff. I said, oh, it's really top secret. I said, I'll have to disappear off a couple of hours a week. Are you okay with it? And there they said, Oh, they used to say, like, make sure you clock out. I didn't. But they say make sure we clock out. And they said that's fine by us. So, yeah, it didn't. It used to take me probably an hour to get there and blood tests, and then it's no big deal. I didn't think it was a big deal, considering what I received, as Brian said, once a week, had to go there. I don't know it's for three or six months for blood and urine samples and things like that, but I never, ever thought was a big deal. Do you know what I did used to like? They used to text me, "Oh, John, your blood level, your clotting factors, are gone up to like, 20%." Then it was 25%, then it was 30%. Yeah, I used to get all excited about it. Oh, and when it started to get up around about 45-50%, I started to get a bit concerned. And I was going, "Oh no,!" "It's all right, you know, you'll be right. Don't worry. We've got things in place." Because I thought, bloody hell my you know, have a heart attack, but no, it all worked out fine. I think it stopped at around about 55% and it has been that, but it fluctuates actually between 50 and 55% for the last like four years,

maybe. And it was all really fine. It all just went really smooth, exactly what he said would happen, happened. And I go back now once every six months. Don't have to, but they asked me, would I, and I said yes, so once every six months, I go for a ultrasound scan and a blood test, and that's it. It's no big deal. There's no hardship on me. And now it's fine. It's a small price to pay for what you get.

David Page 20:15

And Daan, how was your experience post administration?

Daan Breederveld 20:18

I fully agree with John here. It's a very small sacrifice, also considering, well, what if the gene therapy would not succeed? Then I would, well, at least contribute with all the blood samples to more knowledge about the gene therapy and what would make it more successful. And yeah, it was exciting for me to see my levels go up. But actually, even before I had my first blood tests done or communicated to me—I didn't know my levels actually—I think it was eight or nine days after my gene therapy. I fell down on a concrete floor. I tried some nasty toy of the kids, which was spinning on an electro motor. I shouldn't have done it, but I tried it. I tried to ride it, and then I fell down on my left hip, and everybody around me just scared as hell, because normally this would mean I would ride off to the hospital and need to treat myself with product and things like that. And I said, Well, this is nice. Let's see what happens. And I didn't treat myself. I didn't have a hematoma or a bleed ... nothing. So I knew it was successful. That was really the proof of the pudding, so it was great. And yeah, my levels went up till 20, 22% and then after a year and a half, they went up further, until the 42 I'm at now. So I'm very, very happy with that.

David Page 21:38

Steven, was your experience somewhat similar?

Steven Brown 21:40

Somewhat similar. I will be the odd man out. My experience was a little bit not quite as positive. So again, part of the clinical trial much more involved. So was going back to the hospital. I think 24 hours, 48 hours, I think 72 hours. The slowly tapered blood work was twice a week. When I stopped going to the hospital frequently, they had a mobile phlebotomist come to my house to do the blood work twice a week. That was not the greatest experience. The first few times took three hours because they were trying to process samples in my house. And I was like, "This can't continue because I have to go to work." Also, I did have a liver response, so I did get put on prednisone, which changed things quite dramatically. I knew about the risks of the prednisone. I don't think I fully appreciate what the dose of prednisone would do ... more from, my mental health perspective: massive insomnia and I just didn't really feel like myself. So I appreciate all those people that have been through prednisone. It's very, very hard. Layered on top of that was covid. So there was a big concern about me being on prednisone beginning with covid. So they tapered me quite quickly, probably quicker than what the protocol said and I had to re-dose back up, not to the full amount afterwards.

David Page 23:01

How long were you on prednisone?

Steven Brown 23:03

I started prednisone, I think probably around February, and I think I finally got off of it sometime in the summer, July, August, so about six months total by the time because I got tapered and then back up.

David Page 23:20

How did your wife find that?

Steven Brown 23:22

She loved it because as part of my prednisone manic phases, I kind of nested and I organized and cleaned. Because I don't know what that's about, but that was a thing when you can't sleep at 2 a.m. just this urge to

clean your cupboards and organize everything into this neatness. It was a little bit more involved. And then the mobile phlebotomist, it turned out, didn't really matter, because once covid hit, the mobile phlebotomist actually ended up with a centrifuge on my dining room table and would process samples for four hours until delivery on the opposite side of my monitor as I worked, because all the places for them to do that externally were now shut down. So it was very different, a little bit of a different experience. I do agree, though, it's very cool to see your levels go up. Mine dropped again a little.

David Page 24:07

Let's get to that. The big question, how did things turn out in the end, not only in terms of levels, but also in terms of how your joints feel and how much you're bleeding?

Steven Brown 24:16

My levels started to fluctuate around 25%. They have dropped now down to about 15% since then. So I am definitely in the category of a mild hemophiliac. I have had bleeds, now. Granted, the majority of the bleeds have been in very bad target joints and have resolved very, very quickly. But in terms of joint health and just general health overall, I don't know if I can say it's just a placebo effect that it's given me confidence, but I went from looking into having an elbow replacement in my left elbow to now I can curl 25 pounds. It took a long time to get there, but I am in better shape now than I have been in my entire life. Unfortunately, it does not reverse the damage of my really bad joints, but I think it's helped me prolong how bad they are. So yeah, that's where I'm at.

David Page 25:09

And Daan, what's been your result, both in terms of levels, but in terms of overall health?

Daan Breederveld 25:16

I'm actually feeling relieved and free, not depending on product or pharma anymore, and keeping in mind that, well, indeed, we had the HIV and the HCV period. And although all the products we use now are recombinant, you can never be sure. And you know, if the factory had been in Ukraine, we'd have had a big problem in Europe. So that's a real relief, knowing that you're going to survive in a jungle is actually quite a nice feeling, or you can die from something that normal people would also die from. But in terms of joint health, I didn't have any joint damage. I was very lucky. And at the same time, I had my first muscle rupture in a tennis tournament two years after my gene therapy, because I ignored the pain, and I stretched, and I stretched, until I looked in the mirror. I thought, Oh, what's this? There's a dent in my muscle. So I tore my pectoral muscle. So that was quite, quite odd.

David Page 26:12

Did it hemorrhage as well.? Did it bleed as well?

Daan Breederveld 26:15

It was a bit bluish and greenish, but it didn't count.

David Page 26:18

It doesn't protect you from everything in the world.

Daan Breederveld 26:22

No, exactly. But in that sense, I had to get to know my body again in a way, where the limits are, because normally, a bleed would prevent me from going further. And now I thought, well, this can't be a bleed, so I'm just, it's just a cramp and I'm just going on. So that's new, but it's all luxury problems. I would say I'm totally relieved I took it.

David Page 26:45

John, you, you've already mentioned that you gained quite a good level around 50%. Have you seen a difference in terms of your joint health and your overall health?

John Curley 26:54

I had weak ankles. That was about it. They used to tell me you get micro bleeds. I didn't know this, but sometimes you get sore. I don't know. Then they said, "Oh, that's because you used to get micro bleeds." I think it has improved. I think, as Daan said, psychologically as well, just the traveling and things like that, it feels so much freer. I used to be a keen cyclist, and I've actually, I think my hip, my left hip's wearing out now, so it's looking now I might have to have a hip replacement. I don't know how that's going to go, but no, as concerning the rest, I've not had a bleed. I've not had anything. I'll say there's been a couple of times I've actually cut myself, and I've been amazed that it stopped, watching it just stop, and I was like, wow, bloody hell, you know, so my wife's over there, comfy. I've not had any bleeds at all, have I? No, no. Not one bleed, not one thing's gone wrong. So, you know, it's pretty good. So if I have to have a hip replacement, I don't know how that's going to go, maybe they have to give me some extra factor or something. I don't know, but they're looking into it. They're going to see but no, it's just positive. I've got nothing negative to say. I mean, honestly, if I there was a thing negative, you know, I would tell you. There's been nothing negative at all about this whole thing from start to finish. So it's been bloody marvelous. And you know, I hope other people can experience it. Because, you know what? I'd say, half of it was probably psychological, just that, as Daan said, the freedom it releases you from constantly watching whether the pavement is uneven or if there's a sharp object about. It releases you from that. So, yeah, just absolutely fabulous. The whole thing.

David Page 28:23

Brian, you're, you're a bit older than the others, and maybe your joints were not in quite as good a shape. How have you seen things after gene therapy? And then tell us what your levels you achieve?

Brian O'Mahony 28:33

Well, before gene therapy, I had a knee replacement, an ankle fusion, elbow surgery, quite a lot, quite a lot of existing joint damage, which, of course, does not reverse. Now, my factor levels have been very good, between 50 and 65%. And right from the start, it's been very good. So certainly, my joints feel a little better. I put that down to in the first two years after gene therapy, the time since my knee replacement, and also not traveling, and getting into a better exercise routine because I wasn't traveling because of covid. I had two bleeds in the last five and a half years, two minor bleeds. I also had factor for a couple of steroid injections. And I also had a brain lesion, which required a very lengthy surgery. The brain lesion was not due to the gene therapy; it wasn't linked. And in fact, the amount of factor I used for a 12-hour brain surgery was quite small, but no, I've got no treatment remorse, no regrets. I think it was the right decision for me to take at the time. I don't regret it. I started to think it's been nice to be free of prophylaxis. It's been nice to be able to travel without bringing factor with you. I probably don't have the same degree of psychological freedom, as John or Daan mentioned, because, of course, my job is hemophilia, so I'm spending less time on my own hemophilia, which means I'm spending more time on others'.

David Page 29:50

What's the one thing that surprised you most in this whole voyage and this whole journey?

Brian O'Mahony 29:55

Two things. One, after the first three months of the clinical trial I did become iron deficient, and that was actually because of the sheer volume of blood they were taking every week. So that's something they need to factor in, that you can get iron deficiency. The second thing was, a year after the trial, I was up in the Dublin mountains with my wife and children doing some hill walking, and I was up on a low stone wall, and I slipped and fell onto some rocks and nothing, no bleed, nothing. Like Daan falling off the children's toy. That's quite a bizarre and very nice experience. I could tell very quickly this was not going to bleed. And I've had a couple of incidents like that since. I was in Vienna last month. I turned around after leaving a building and I whacked my

shin off a low concrete bollard which was stippled so it gashed my shin and then knocked me off balance, so I fell hard on concrete and hit my shoulder and my hand and my knee, and my knee was sore for two days. I put an ice pack on it. It wasn't a bleed. It was just sore, and that's fine. No bleed. So that's a strange feeling for all of us who've grown up with severe hemophilia to see a situation where 100% you would have needed immediate factor and you don't need factor.

David Page 31:09

John, what surprised you most about your journey?

John Curley 31:11

Probably more the psychological side. When they said, this will work, John, we're really confident it works. John, this will work. So I was pretty confident. So the psychological effects on me, I think that's what surprised me the most. As Brian said, traveling, not having to take injections with you, and the freedom of just, you know, I don't have to make sure it's a hospital near me, or a fridge, or that side of things. That's what surprised me the most, how much it actually really influenced my life, even though I didn't want it to, it did. But yeah, so no, just the freedom, the psychological freedom, to just, you know, do what you want, obviously without being stupid. But yeah, that's what's great about it for me.

David Page 31:51

And Daan. What surprised you?

Daan Breederveld 31:53

It's more or less in the same freedom category. I think, before I had gene therapy, I could not forget. I had to be thoughtful all the time. I always thought when I engaged into new situations, okay, what would do this to my hemophilia? What's the nearest hospital? What would happen if I ... Worries in the background and now I can forget. I may forget. And that's it, it feels so rich and so privileged. I'm grateful.

David Page 32:25

Steven, any surprises for you?

Steven Brown 32:28

Not a surprise, because I think everybody else has already said the answer. It's a weird feeling, going from a severe hemophiliac wondering every ache and pain is a bleed going now to wondering, is that even a bleed, or is it something that I can go on and ignore, and as others have echoed, that you can, you know, sort of push through and worry about later. It's a very different feeling. I didn't think I'd be in my 50s and my major health problems right now are not my hemophilia, it's my allergies. It just goes to say I see my allergist more than I see my hematologist, and in fact, I had to treat for a procedure recently, and my son came in the room; he was 12 at the time. He was like, What are you doing? Like he had never seen me treat, even though, when he was younger, I would be treating frequently for my hemophilia. So it is a very weird feeling to go having something that is always omnipresent in your life to now, not so much, and it's been a little bit of a learning because it's not a cure for me, it's going from a severe to a mild. So now trying to live my life as a mild hemophiliac with all my learnings from a severe.

David Page 33:37

Thanks to our four guests for a really stimulating discussion, and we hope for our viewers and listeners that it succeeded in making gene therapy for hemophilia a little bit more real and understandable. And to learn more about gene therapy, we invite you to tune in for the other episodes in this series Hemophilia Gene Therapy - From Dream to Reality, and above all, for those who are interested and eligible for gene therapy, it's important to talk to your primary medical provider or your hematologist to better understand if gene therapy is right for you. Thanks and see you next time.

Signoff 34:10

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