Canadian Hemophilia Society
Help Stop the Bleeding

PODCAST SERIES

HEMOPHILIA GENE THERAPY – FROM DREAM TO REALITY

EPISODE 15

SHARED DECISION-MAKING

PARTICIPANTS

Dr. Pratima Chowdary, U.K.; Dr. Davide Matino, Canada; Brian O'Mahony, Ireland; David Page, Canada

HOST

Sarah Ford, Chief Executive Officer, Canadian Hemophilia Society

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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, Sarah Ford.

Sarah Ford 00:15
Welcome to the video podcast series HEMOPHILIA GENE THERAPY - FROM DREAM TO REALITY. I'm Sarah Ford, CEO of the Canadian Hemophilia Society, your host for today's podcast. Over the last several years, gene therapy for hemophilia B has become a reality. Some received it through clinical trials, and others received it after marketing authorizations and reimbursement approvals in their countries. Each of them had a difficult, life-changing decision to make. They needed to fully understand the potential benefits and risks, and the physicians responsible for their treatment needed to be assured that they were providing fully informed consent to the therapy. This process is called shared decision-making. To talk to us about shared decision-making, we have invited four people, two physicians and two people with hemophilia, one who has received gene therapy, and another who would consider it. I would like to bring our first guest to introduce herself. Dr. Pratima Chowdary, please introduce yourself and where you're coming from and your involvement with gene therapy.

Dr. Pratima Chowdary 01:14
Thanks, Sarah, thanks very much for inviting me for this video podcast. I'm a consultant hematologist at the Royal Free Hospital, London, and I've been involved with gene therapy for almost 15 years of my consultant journey. It started very early on with the gene therapy trials, and now I'm quite actively involved with the licensed products.

Sarah Ford 01:35
To begin, could you describe the process you go through with your patients before coming to a decision on gene therapy?

Dr. Pratima Chowdary 01:43
It might be easier if we start with the currently licensed products, because I think the way we do the discussion around the clinical trials is quite different compared to how you would engage in a discussion in terms of when a product is licensed. Typically, I think most of the patients are well known to us, so we know that they have been

established on the treatment. More often than not, it would be a factor therapy. And some of these patients now will be going on to non-factor therapy. We would introduce the option to them in their routine clinical review and say, “This is a new treatment that is now available in the NHS.” And then we would ask them if they want to know more about it. And then I think typically, I would say two out of three patients would say, yes, they want to know more about the treatment. Typically, in the first instance, I try and explain to them the mechanism of action and what the therapy might offer as a benefit. So I typically have a session one, and then the session two would be more about going in depth of what this treatment might mean. And the third one is going through what I would call the fine print, so that they feel that they've been adequately counseled.

Sarah Ford 02:51
So how do you typically test or better understand people's understanding of the benefits and risks involved in this type of decision?

Dr. Pratima Chowdary 03:00
So maybe if I start again in terms of what are the aspects of the treatment, I would cover in what I would call a stage one, stage two, stage three. So we've started calling this the three-stage consent in the UK, and this is something we described in detail in the UK CDO guidance. I think the first step, as I mentioned, was to explain to the patient that a new treatment is available. We then go on to talk about what are the benefits of new treatment. Typically, I would say to the patients the advantage of gene therapy is that they could stop their regular intravenous infusion if it is successful, which we would expect in the majority of the patients. I would then explain to them how the treatment works. I've tried to simplify it into more of a 30 to 60 second kind of explanation, where I say that a normal gene is packaged and then delivered into the liver cell, and the packaging material actually knows the post code which is the liver, and this packaging material is something we pick up from nature, which is a virus coat, and then the gene is then deposited into the cell, where it could actually give the messages for the production of the protein. I think this becomes very important, because you need to then explain to them what are the challenges. Typically, we don't need to go in depth about the mechanism of action, but remembering that we have to explain to them about the limitations the mechanism of action becomes very important. We also then go on to say that whilst it may not be for everybody, but we want to offer it to them and see if they might be eligible for the treatment. And also I caution them that this is something, if it's successful, we still need to see them, because I often find their desire is not to want to maintain hospital contact. So I get in my message up front saying, even if they stop prophylaxis, we would like to monitor them for the long term, and if they're still interested after this three-to-five minute discussion or a short education session, I give them the patient information booklet, and I say that there is no rush to make a decision. But if they're interested, they can call us and let us know that they would like to go on to the next stage or they could let me know at the next clinic review. Going on in terms of what I would do in terms of stage two, I would explain to them what I would expect for an individual patient. I would go on to say that the level could be anything between 5 to 50% but I translate to them, what does it mean in terms of a day-to-day practicality? I think that's very important. I have found because what does it mean to have 12% versus 18% versus 22%? So again, I talk to them in terms of the fact that: can we stop prophylaxis? and will they not require treatment in the context of a bleed or minor surgery? and the requirement for treatment in the context of major surgery? I also then talk to them about the fact: how long will we expect to see the treatment effect? and that again, in terms of the fact that there is this uncertainty, but we have data for up to 10 years now, and we can say that it would last up to 10 years. I think the most important thing is to express to them the variability in expression. And that is why I focus in terms of what does it mean for them, in terms of day-to-day practicality, because that then moves away from the excessive emphasis on the factor level. I then go on talking about the uncertainty around the long term safety, and this is where it becomes important for them to understand how the transgene, or the functional copy of the gene, is placed into the liver or into the nucleus, and where it is actually sitting, and how are the random things that can happen because of what we do not know, or we know from wild type infection, but there is a desire for us to maintain long term surveillance, so that if a random event does happen, we are able to pick it up. So that is typically the stage two, and this is where I also would talk about the fact that when they're given gene therapy, there is a possibility that their body might react to the virus, and that is what we would expect from our immune system, and therefore, the need for what I would call intense surveillance in

the first six months. I often use the terms like you will see as “more often than necessary in the first six months,” or “we might adopt you for the first six months,” just they so they understand the amount of involvement that we might have, and they might be fed up with us. And if I may progress, then I think if they're still interested, then we go on to stage three. We again reiterate the intense monitoring that is required. We talk about when is the right time for them to have gene therapy. For example, if they have a major change in their career or a life circumstance change in terms of getting married or a baby on the way, we would say it might not be compatible because of the time commitment. We allow them to plan ahead so that they are there and they have the time to see us regularly. Then we also explain to them how we would monitor the immune response to the gene therapy, and it might require treatment with steroids, and potential effect of steroids. We also then talk about the practicalities in terms of lifestyle changes. For example, one of the things we found is, if you are in marketing, the requirement to go out for evening meals and a little bit of alcohol and all those kinds of things in terms of the impact. And this is often at stage three is the place where we go through the do's and don'ts so that they understand what they're committing to. And once they are happy, we then say, are they ready to go into the next stage and have the infusion?

Sarah Ford 08:38
Thank you very much for that. I'd like to introduce our next guest, Brian O’Mahony, who is the CEO of the Irish Haemophilia Society. Brian, would you like to introduce yourself?

Brian O'Mahony 08:50
Hi, Sarah. My name is Brian O'Mahony. I'm the CEO of the Irish Haemophilia Society, former president of WFH and EHC. I have severe hemophilia B, and I took part in a gene therapy clinical trial five and a half years ago.

Sarah Ford 09:03
It's great to have you on here today, and we wanted to get your perspective on shared decision-making and the process that you went through as a patient in this process.

Brian O'Mahony 09:12
I suppose it was slightly atypical, because of my work with WFH and EHC, and with the society, I'd been following the science of gene therapy for many years, also encouraging companies to come to Ireland and consider Ireland for participation in their clinical trials. So I think I was much more knowledgeable about gene therapy than the standard patient. Having said that, when I decided to take gene therapy, there were a number of reasons. I like the idea of not having to take factor nine prophylaxis regularly. I like the idea of possibly having a decent duration of factor IX expression, which might decrease chronic pain and target joints, which might allow me to increase my activity. I also wanted to lead because at that point, nobody else had taken gene therapy in Ireland, but I thought this through very, very carefully at the time.

Sarah Ford 09:58
Do you see similarities between your decision-making process and those who will now be doing this for an authorized product that's coming to market?

Brian O'Mahony 10:07
I think there is a difference, as Pratima said, between clinical trial and a licensed product. In a clinical trial, the informed consent process is more rigorous. You're dealing more with the unknown. For example, when I took part in the phase three trial, the information I had was on three previous patients. If you're taking a licensed product, you have information on 54 patients in the phase three trial, so you're dealing with less information. It is more of an unknown scenario. Having said that, I think in both the clinical trial scenario and the licensed scenario, it is quite a rigorous, and should be quite a rigorous, informed decision-making process. I very much like Pratima’s point about three separate visits, and I believe there should be an interval of time between them for people to think this through and not make a hasty decision, to think through all the potential ramifications.

Sarah Ford 10:54
You have the pleasure to work with a lot of different patients within your community, and as you mentioned, also around the world. Do you see varied and different attitudes by patients towards shared decision making process, or are there commonalities between their expectations of shared decision-making processes?

Brian O'Mahony 11:11
I think shared decision-making has come into vogue in hemophilia primarily because of gene therapy, but now, of course, it's also being applied to all the other therapeutic options, which is the right thing to do. Having said that, when you talk to patients about gene therapy, in my experience—I've done a lot of workshops—you get a range of possible responses. Some people are definitely not interested. They're very happy with the current therapy. They're very happy with the current quality of life. They see no reason to take gene therapy. Others are definitely very interested. They want it. And what you have to do there is almost slow it down and make sure that they go through an informed decision-making process and fully consider that. Many are unsure and they need the information and the stages and the discussions and the meetings. And I think there's a role there, not just for the hemophilia treatment centres who'll be giving the gene therapy, but also for the patient organizations in providing basic information. And then many people are in a wait-and-see mode. They're interested. They're looking at this. They're seeing that there's a licensed gene therapy which is widely available, another which is only available in three countries. But they're looking at this, and they'll probably wait a couple of years to see what the real-world evidence is.

Sarah Ford 12:17
Thank you very much for sharing your perspective, Brian. We would like to welcome our next guest, David Page, who has a different perspective.

David Page 12:26
Hi, Sarah, yeah, thanks for that introduction. I have not received gene therapy. I am considering it perhaps in two different ways. It's not yet available here in Quebec, where I live. It's not reimbursed yet, but it may be in the next while. So there may be a possibility to receive a commercial product, an approved product. And there's a possibility of being involved in future clinical trials. There are other gene therapies in hemophilia B in development. So to me, those are somewhat different approaches to the shared decision-making process. As Brian said, when it's an approved product, you have a lot of information. So you know exactly how many people end up in the normal range or in the high mild range. And you know … you can really expect to have very few or no bleeds whatsoever … and how many people may not get a good expression of factor IX and have to remain on prophylaxis. So you have that information, and you know that's something you can discuss with your hematologist. In a clinical trial, especially in a phase one clinical trial, you have a lot of unknowns. You don't know what that level of expression will be. You don't know as much about the side effects. I'm actually a caregiver now as well as a person looking for treatment, and so I can't really afford to be laid up, to be unwell for a long period of time, and that's a possibility with side effects of this therapy, especially one which is less well known. So I really have to find out about those risks. And I'm not sure to what extent—maybe Dr. Chowdary can talk about this—how much you can reveal to patients in those early clinical trials about the results in the, say, in the first three patients, how much of that is confidential. As a patient, I'd like to know as much as I can. I guess, one other element for me, I think, having been a teacher for many years … it's good to teach, but you also have to test whether your teaching has had an impact. Have people understood? So I think asking patients to retell what they've understood so as a physician, you really know that they've taken in the information, considered it and understood it. So I think almost like a test phase should be somewhere in that shared decision-making process,

Sarah Ford 14:33
From your perspective as a patient advocate, but also as a person with the lived experience with hemophilia B, what are you looking for from the doctors or physicians or healthcare professionals that are involved in the shared decision-making process? What for you is an ideal situation in terms of how they present this conversation to you as a patient

David Page 14:53
In a clinical trial setting, I'm hoping that they are very close to the investigators and can give me as much information as possible so I can make my decision. As a patient, you reserve the right to say no at the very last minute. You can revoke consent right up to the last minute. So I would want my physician to be informing me. You know, in those many months before the administration, you go through an observation period, there's the antibody testing period. So there's a lot of opportunities to learn from your physician as he or she is learning as part of the investigating group. So yeah, I want a lot of transparency with my physician. When it's an approved product that's a bit different. We have a lot of data. And there, I think, Dr. Chowdary has really laid out those processes very well, and they have to be multistage, from an exploratory process, to thinking about it to the point where you're drilling down and looking at those risks and benefits in a very concrete way.

Sarah Ford 15:53
Thank you very much. I'd like to introduce our next guest, Dr. Davide Matino. Dr. Matino, please let us know your background and your experience with gene therapy treatment.

Dr. Davide Matino 16:03
Yes, I'm Davide Matino. I'm one of the adult treaters at McMaster University, and we do not have experience with commercial gene therapy in Canada. We have been involved in the clinical trials, so we have, been the site that has been involved with the majority of the gene therapies given so far, at least in Canada, both for hemophilia A and hemophilia B, but only in the context of clinical trials. That's our experience.

Sarah Ford 16:33
Thank you. What's your approach? Typically, when you're starting the shared decision-making process with your patients, how do you normally begin the conversations, and what process do you typically follow for shared decision-making?

Dr. Davide Matino 16:45
You know, I agree with Pratima in the sense that this is a multi-step process but of course, in the context of the clinical trial, you follow whatever is the standard for the clinical trial context, so both from the ethical point of view, from the sponsor's point of view, the informed consent that you have available. But I would say that in general, what we've done is that we've made aware our patients of the possibility to participate in these clinical trials. For those that were interested, we had conversation regarding, what is the trial? What's the reason for the trial? what's the objective? What's my role in the trial? And any other questions that the patients may have. They typically think about it, and then they come back with, an interest or not in the trial that we have up and running in the centre. If there is an interest about the trial, then they come back. They can review the information. They are given the information from the research coordinator, and after that, we go back and ask if they have further questions, or if they need time to think about it, what is the timeline for the clinical trial. Because, you know, sometimes they only have three months' time or six months' time, or whatever, right? So they need to know what's the timeframe. And for those that decide to pursue this option, very often, there is an observational phase, right? So they do not go straight into treatment. They enter the observational phase. And while they're on the observational phase of the study, they can still think about it. And very often, there isn't a short time; it's not a week or two weeks, it's months. So they can actually have more questions, they can come back and ask for more information. And that's typically, you know what happens. In fact, we have four, five or six conversations before the actual dosing day. And when we will have this available for everyone in the commercial setting, probably we will follow a process that is similar to what Pratima was telling us, that it's maybe less structured in the sense of the clinical trial structure, but still allows plenty of time for discussion, decision, thinking, before actually going for it.

Sarah Ford 19:02
When you're looking at gene therapy as a treatment option versus other therapies that can be stopped if they're showing any safety issues or ineffective, how do you approach decision-making, or shared decision-making

conversations with your patients in that context of comparing gene therapy to other therapies that are currently existing and available for them?

Dr. Davide Matino 19:23
I would say that process is similar. The main difference is that, as you mentioned, it is irreversible. Once you've received the product, you cannot go back. And in one sense, this is what you expect from gene therapy. You want that to be permanent, even though it's like long term. But I wouldn't say l permanent at this point in time, but yes, that's the main difference. So everyone that is thinking about gene therapy needs to know that at the present time, this is a one shot. It's a decision that you cannot take back, and it might impact in the future, the possibility to receive another treatment is … It's impossible. It's just that, at the moment, it seems that our capacity to give a second single treatment is made impossible by being in reaction against the vector. So it doesn't mean that it won't change in the future, but for what we know today, it's a decision that might impact them, for the foreseeable future in different ways. So that's the only part really that is different from the other products or other approaches to the shared decision-making process, at least in my view.

Sarah Ford 20:31
Thank you, Dr. Matino, what I'd love to do right now is considering we have two physicians and two patients as part of this discussion, really speaking to each other, addressing what we would like the different considerations to be on the table. So David and Brian, from your perspective, what is most important thing that you would like physicians to know as a patient when going through the shared decision making process? We'll begin with Brian.

Brian O'Mahony 21:02
I think Parliament laid out the answer in the sense that I think it's really important to have a couple of discussions with a patient. I think three is a good number, not one. I don't care if somebody comes in, they're very enthusiastically wanting gene therapy. That's not something you should do in one discussion. I think it should be two or three at least. And also, they should have some discussions with the patient organization, If they're involved. It really does need to be a fully informed decision. They need to consider all the pros and cons. I think we all want to avoid any sense of treatment remorse. You don't want somebody coming back to you in years time saying, I wish you hadn't persuaded me to do this. The person must make a fully informed decision themselves. Okay?

Sarah Ford 21:41
Thank you. David Page, what are your thoughts on this?

David Page 21:45
I think it's important that the physician knows his or her patient well. Not everybody is right for this treatment, though they may think they are. And you know, there are perhaps a lot of reasons why a physician might want to hesitate or put off until later. You know, there's no rush to have this treatment. It could be a year or two years later, and those reasons could be that their personal lives, their psyche, at the moment, is not ripe for gene therapy. So I think that it goes both ways. Physician needs to know the patient and provide information, but it's not a slam dunk that just because a patient wants gene therapy they should have it.

Sarah Ford 22:21
Dr. Chowdary and Dr. Matino, what are some of the things that you'd like your patients to consider before coming in and having the initial shared decision-making process? Dr. Chowdary, we'll begin with you.

Dr. Pratima Chowdary 22:34
Thanks, Sarah. I think one of the things I just want to reiterate is that what has helped us in clinical practice is having a checklist, because one of the challenges is to make sure you have adequately educated the patient and made sure that they have understood that you have given them all the information. And I think for me, the biggest thing that I want patients to be aware is that it's an irreversible treatment. I often actually articulate it as a one-way ticket, so that there is no question of misinterpretation, or what are the consequences. That once it is

done, they do not have the right to then say to me, I'm not going to see you. We insist that that is a prerequisite, that we do see them, at least regularly for the first year. And the second one is being as educated as they can be. But I think we have also made the effort to write the educational materials in a way that we pick up all the FAQs from different patients, and we've written a booklet along with the hemophilia society in the UK, because they gathered the questions from the patients, and we put them in a document so that the information that we are giving to the patients is something that has been agreed by both healthcare professionals and the patient organization, because it's not uncommon for us to have two different booklets. On this one, we felt that is very, very important we have one voice, and if there are any concerns, that we address them in that booklet. From a patient perspective, I think my biggest concern is the young adult who has just transitioned from a pediatric clinic to an adult clinic. They can consent at age 18 or 19, but for them, the concept of risk sometimes is non-existent, so we often ask them to bring in other significant members, so that there is an element of discussion, and they're all open to the idea that there is somebody else helping them to make the decision. So I think the one thing I would say is there's no rush. If it is available, it is available, and I think it's making sure that the treatment aligns with the patient's life circumstances. I mean, we would not agree to give gene therapy if the patient's life was in chaos. So we try and make sure that that is something we do pick up, because what we don't want is this is an additional stress to the patient, and then things then fall apart. So that is the most important thing, that the patient's life circumstances and the treatment intensity align at least for six months.

Sarah Ford 25:03
Okay, thank you very much. Dr. Matino, what would you like your patients to think about as they're coming in for these conversations?

Dr. Davide Matino 25:11
Well, I agree with all the previous speakers. And again, it's a concept that's been mentioned many times, but I think we can repeat it again. Time is important here. It's a decision that needs not to be rushed. You need to think about it. You need to reflect with your family or your significant other, and you need to take your time for this decision. The worst that can happen is to make a decision that is rushed, and then you regret it, or say, oh, I didn't understand that. Oh, I didn't know about this. So everything has to be crystal clear and discussed, reviewed. And I really like what David said before that it's important to ask also to repeat back the information that is being conveyed, so that you make sure that there's no misinterpretation or misunderstanding. It's not to test anybody; it's just to make sure that we're capable of, you know, conveying the proper information and wherever there is uncertainty, because there is with some parts of this therapy, there are some uncertainties. We need to be transparent about the uncertainty and make sure that the uncertainty is discussed and understood, not to scare anybody, just to make sure that there is a clear understanding of what we know for sure, what we think we know and what we don't know. And these three aspects are separate.

Sarah Ford 26:34
Wonderful. Thank you very much. Thank you to all of our guests for the wonderful discussion, and we hope that we've succeeded in clarifying what shared decision-making is in the context of gene therapy for hemophilia B. To learn more about gene therapy, we invite you to tune into the other episodes in the video podcast series entitled Hemophilia Gene Therapy - From Dream to Reality, or visit the shared decision-making resource by the World Federation of hemophilia on wfh.org, and above all, for those eligible for gene therapy, it's important to talk with your healthcare provider or hematologist to better understand if gene therapy is the right option for you. I'd like to say a sincere thanks to all of our guests for joining us today. Your contributions and insights are greatly appreciated by our community.

Signoff 27:21
Thanks for listening to HEMOPHILIA GENE THERAPY - FROM DREAM TO REALITY. This series was funded by CSL Behring via an education and disease awareness grant. CSL Behring has not influenced nor contributed to the content development or dissemination. Another Sound Off Media Company podcast.