DN : Welcome to the World Haemophilia Day and the discussion on the future of Haemophilia Care and Haemophilia products. Thank you, Flora & Brian for joining us today. We have the EHC Novel products review coming out next week so we were looking at the information coming from EAHAD and I had some questions for both of you. We'll talk about replacement therapies first and the non-replacement therapies, some on gene therapies, bleeding disorders and on Von Willebrand.

REPLACEMENT THERAPIES

With EHL's at EAHAD there were a lot of (abstract) submissions for EHL with trough levels of 3-5 %. Flora, in your experience do you see general trends in countries with good access to EHL's an increase to improve patients' trough levels?

FP: Actually, we did some analyses recently and we sent some abstracts to ISTH and now we are going to see what is going to happen but our experience was very positive. At the beginning, we were switching our FIX patients to extended half-life products but for FVIII we were waiting to see the results, the switch was slower than for FIX. But the results are good and the patients are doing well and the number of infusions is lower, the trough level is higher, so I guess people are getting more and more confident to switch most of the patients and if you are not seeing any side effects for the patients – because it is not very clever to switch of course all of them when a new product is coming to the market, you never know how is the safety, but if the safety is as good as it seems to be, I think now is the time to switch nearly most of our patients to EHL and I have the feeling that lots of countries are doing that.

DN : Thank you. For the countries that have less access to factor concentrates, first Flora - how should they be thinking about using EHL concentrates and then Brian - how do patient organisations help in improving access?

FP: That is a difficult question, Declan, because I think that the most important point for those countries who do not have access is to have access to more product that could be available for the patients. Now, in my mind, after a few years with EHL, as I said, and the safety of the product, so if the company could produce the EHL product and this product was safe and the price is not jumping, I would prefer for all countries around the world to use the EHL product. But we have to see whether that is possible in terms of production and cost. If I am in a country with access to products, standard (SHL) products, and some of the products are EHL products, I have to make a stratification of my patients and to choose which patients should go for this or that. But if I have the possibility to use the EHL product even in those countries where the amount of the products is less, I would go for the EHL. So my main message - in the future - to understand is there any sense yet to go with a recombinant standard product when the efficacy of the EHL product is higher and the safety is similar. We have to see the results of the PUPs (previously untreated patients) study. If we do not see any problem in terms of side effects, I do not really understand why we are not switching…we do not have to switch all the production from standard to the EHL, if there is no difficulty in terms of production.

BOM : Well, you know these are not quite new and have been on the market for 5 or 6 years. As you know Declan, here in Ireland for example, we took a very systematic and national approach to this. We looked at this a couple of years ago and we switched the entire

population to EHL factors. You asked about preparing patients organisations or helping to prepare patients. I think we did a lot of workshops, we did a lot of educational meetings and events and the people with haemophilia understood that these products could be either used with less frequency of infusion or in fact giving higher trough levels and more protection from bleeding or in the case of EHL FIX you could achieve both aims. I agree with Flora, I think we should be seeing more of a switch to EHL factors, I think they have definite advantages we've certainly seen that. They are very much welcomed and work with the EDQM recommendations for the increased trough levels. I think a trough level of 1% is a 40-year old idea which we should e moving beyond and certainly 3-5% is more what we should be looking for. We are now seeing in Ireland trough levels of at least 8% for everybody with severe FIX deficiency and about 3% for FVIII. And I think this is a very nice improvement in the quality of life.

FP: I fully agree with Brian.

DN: Yes, I am always struck by the parent who was talking about treating his child less often and having more protection and feeling very good about it.

BOM: That point was made 7 years ago at the first EHC novel products meeting by a parent when he talked about his child at the time who was on clinical trial for EHL FVIII and he saw a distinct advantage to that.

DN: At last year's EAHAD Congress there were some really interesting topics such as access to the EHL and some really interesting data coming out on low dose prophylaxis for small children. Brian, I will pick you back on that point when you said about 1% being a 40-year old idea. The Den Uijl data is one we see all the time, it is everywhere for the last few years and that indicates that once you drop below (a constant factor level) of 12% , then you're talking about small amounts of joint damage that we are seeing in patients with prophylaxis for last few years. We start hearing about "stiff ankle" syndrome , with no real visible damage but they are sore. Is that something that we should be trying to avoid with EHL's and if so, is it the same for FVIII and FIX or is there anything coming out in the future that may be easier in terms of products or clinical trials for patients with EHL's?

FP: Actually you know Declan I was thinking to this subject very frequently for the last few years because what is happening now at this stage is that clinicians are thinking is "if I am using gene therapy, I have to target this, using the non-replacement therapy I have to use that". I think we need to come up with some conclusion and say which target I need in irrelevant of different instruments I am going to use and which of the tools I have available is bringing me close to that target level. I think now with the improvement that we did have, you know with all the different strategies, there is no way to stay with the recommendations as Brian was mentioning about 1% or 3% - that's too old, we have to forget about that.

And now I think definitely we need to target about 10-15%, which I couldn't even think about 3 years ago, that I would be telling you something like that? But I think this is the point, the technology moves so fast but we have to be cautious about bringing that kind of target, how is the cost of that, not only about the economy but also about the safety issue. So if I am going to have 10-15 % of target level if I am using EHL product how many times do I have to inject

myself and what are the pro's and con's of that? If I am using non-replacement therapy what are again, what are the positive and negative points of that and if I am using gene therapy which amount of vector do I have to inject and what I know about the safety at that point and finally, I have to know how much each of these strategies will cost me. Once I have that cleared up I can decide what I am spending and what I am getting, this is the thought I have in my mind. But there is no doubt that we are now using in our clinical activity ultrasound for all our patients to see better if there is any minimal amount of bleeding that we are not able to see and we are trying to understand more and more. There is no doubt that we can really point out with a higher trough level and what you were using is not enough and what is exactly the target level that we have to aim for – I think this still need more time.

We still need to understand for example is it really convenient in terms of what we know to go over 15%? If I go, what am I going to get in terms of safety and efficacy, using every instrument that we have mentioned up to now, I think this what the scientists and clinicians must think about.

BOM: I think there is a growing body of compelling evidence that clinical optimization would require a trough level of 12-15% and I totally agree with Flora, I think that this is what we should be aiming. However, we have to marry clinical optimization with economic reality. The only reason why the trough was 1% for so many years is the fact that, it was expensive. If it was only €0.01/IU we wouldn't have this problem. So you could legitimately say now that we accept the Den Uijl graph for example and other evidence and say that, yes, we should be aiming at the trough of 15% now, the problem is that it is not economically viable in many countries, including Western Europe at this point in time. So I think that the 3-5% is a step in the right direction and we expect that in the coming EDQM meetings over the coming years to change upwards, to change maybe to 5-7%; 10%, 12%, 15%. Now I think that this is very difficult to achieve, trough levels of 15% with current factors of even with EHL factors. You could probably do with EHL FIX, not with FVIII. But now with alternatives, with Emicizumab, with perhaps improved EHL products like BIV001 and certainly with gene therapy we can see a pathway to get to troughs of 12-15%.

FP: I perfectly agree with Brian.

NON-REPLACEMENT THERAPIES

DN: Moving on to some discussions around non-replacement therapies. There's been a lot of uptake in terms of non-replacement therapies that are currently on the market, like Emicizumab, and one question that I wanted to ask both of you is when it comes to discussions between the clinicians and the patients, how is that conversation going? What should patients be asking themselves in thinking about that decision to switch or not to switch?

FP: You know Declan, that depends on switching or is it the first treatment. For example, for those people who were used to other types of treatment like standard or EHL products, there is a history and knowing about what they have to measure, what they have to see, how they have to evaluate the clinical efficacy and there is a lot of thought around that. For those patients who didn't have the chance to use all these different types of product the conversation is completely different. So let's go to those in the first group- people who have

had the chance to go with the standard and EHL products. And of course, this product - Emicizumab) gives the easiest way for administration, there is no doubt, and is more manageable, especially for the younger people. It also gives you a higher protection, however you do need to have a long observation time. The results we have achieved up to now, as you said, is very satisfactory – no doubt about the efficacy of this drug-but we have to understand a little bit more on the mucosal type of bleeding and the minor bleeding. This kind of more detailed information is required for that type of efficacy and in terms of safety, to understand whether we have the similar type of safety as with other products. That needs to be established. Now you need to understand what level of protection is needed for that specific type of patients. If you have an elder patient, sitting on a sofa, doing well and is doing well with one or two administrations of FVIII and is happy with that you might not really need to change and you do not need to push for that I think. But if you have patients who were not doing prophylaxis because it was difficult, I think, this group, really needs to switch to Emicizumab. Or those patients who were not happy. I think you could make a stratification of the groups piece by piece but at the end of this story, if this product is going to work, as it is, I think there will be always a bigger proportion of patients that are going for non-replacement therapy.

BOM: Obviously, for the first time you are seeing a number of different choices out there and I think in terms of non-replacement therapies, products like Emicizumab, some of the considerations people with haemophilia will look at is the convenience factor, sub-cutaneous versus intravenous, certainly a big deal for people who have poor venous access, some others who would need a higher trough and better protection from bleeding and a steady level of protection, as opposed to the up and down that you get from factor. This will lead to less problems with joints, with less subclinical bleeding and then with less chronic pain and maybe a greater ability to do normal activities. I think that some of the reluctance would be around potential side-effects, report of thrombosis and the fact that some people are not early adopters, they'll take a "wait and see" attitude. And I think that certainly when we look at educating large groups of patients and parents about this, you'll see this, with all these new technologies, you'll see those we're very keen to embrace the newer stream of treatment immediately, you'll see some who are late adopters, who have a "wait and see" attitude, I'll wait a year or two and see any side effects that become apparent after licensing and then, a lot of people the middle. They may not switch immediately but they are keen to learn very quickly and then keep an eye for perhaps a year before switching.

DN : I think there is a number of discussions that you hear back that people are trying to balance what are their strengths and if you are extremely active and you need a very high level of protection, people are considering a switch for themselves in a very different way than someone, as you said, who is not that active. And also in terms of the information on intracranial hemorrhages (ICH), you are still not fully protected against those sorts of things. It is a consideration.

BOM: Yes, we have a significant number of people , especially parents, who would say "my child is doing really well on their current therapy, he's on EHL factor, he's very active, he plays these sports a couple of times a week, so I think you also have to educate the population and the parents to understand the needs of peaks as well as troughs on some occasions.

DN: I really think that this is a discussion that really needs to be facilitated between the clinician and the patient. Brian, you mentioned thrombosis – we cannot not talk about that, so this is a consideration that has come up a lot with the bi-specific antibodies and there is a number now in development with MiM-8, with other ones coming out as well in the near future. At EAHAD this year there was a presentation on the report of thrombotic events and the cardiovascular risk factors that were associated with some of them. I think one question is on the safety issue if we increase trough levels. Is there a potential class effect, so is it the type of drug that may be an issue in term of thrombosis or is it because we are potentially raising trough levels in general and we might be unmasking some of those people with haemophilia who have cardiovascular risk factors?

BOM: Well, surely with people with haemophilia for the first time with all those new therapies perhaps we are changing, for the first time, in the normal population, risk for thrombotic events. We've always had some level of cardio-protective effect from having low factor levels and maybe some of this is just the impact of that being normalized to higher trough levels. There are certainly two different thrombotic issues you have to take into consideration with Emicizumab, with Fitusiran, with the anti-TFPI, they all seem to have a different impact here and they are actually being discussed in some detail at the moment as well in terms of the potential impact of COVID-19 on a person with haemophilia. So maybe some of this have been normalized. I would be very interested in Flora's view on that.

FP: I think this is a very important point and we need to be very careful about how we are looking at that data. To be very honest we do need to have better data regarding all previously used products which we don't have. So we started with Emicizumab since it was a new chapter and a new molecule in the treatment of haemophilia to look on the data more closely, which was absolutely a must, but we have a big issue and the big issue we are missing is the denominator. And without a clear denominator, it is really not clear data and we only have some reports, you know, reports from the company or a few reports for example from EAHAD, but this data is reporting the side effects but we don't know exactly how many patients have been treated. And mainly, we don't know, compared to previous by-passing agent or regular (SHL) FVIII or extended FVIII, what was the incidence of thrombosis in different age ranges, because without that information it is just really not good data. Once I became the president of the EAHAD, this was my first action – I wrote to EMA and I told them "we need a round table, we have to sit and look at the post-registration surveillance data of all previous products and Emicizumab and every new product that is coming on the market". I am waiting for the response from the EMA. But that's the most important action that EHC, EAHAD and all the other organisations have to think about – having good data.
And regarding the thrombogenicity, I think definitely there is no doubt – this new molecule is stronger to what we were used but we have to learn how to use it alone or in association. If you look on the data on thrombosis, most of these new molecules did have a trouble when there was association with other molecules, when there is acute bleeding, surgery or something like that. So I think we need also to understand the potency of these molecules particularly in association with other components and in different situations associated with the risk factor, like people with a chronic disorder, cardio-vascular hypertension, COVID-19 or any other condition that could increase the hypercoagulability of the patient.

DN: this is a very interesting discussion and it is really good to see that EUHASS have now put thrombotic events on their adverse events open page and we see that it is now reported in non-replacement therapies, so this is a background issue.

FP: Yes, again, that was EAHAD action for understanding and I think EHC was contacted too, so doing something at the European level, and even for COVID and understanding what is happening.

DN: At the WFH Global Forum last year and also at the EAHAD this year there was a discussion on the closure of one clinical trial for anti-TFPI's and then we had a later issue with pausing another one. We still have a couple more in the pipeline. Just wondering – with the anti-TFPI's, with the Fitusiran with those types of rebalancing agents, what additional information, if these come to the market, do we need to consider for patients? So from a patients organization side, or from the patient choosing side, what additional supports do we need for these types of therapies where we are really not sure?
Fitusiran, last year, came out with the treatment level for using FVIII and FIX and by-passing agents in a very good poster. So this was a very good example of 'this is how you treat'. From a clinical perspective, Flora, what should be patients thinking about these products and Brian, from a patients organization side, how do we put those in place, hopefully you 'd talk about the identity character of sever bleeding disorder card, that type of things.

FP: We are just at the beginning of the use of novel molecules and we do not know them very well. If I was a patient and some side effect was going to be out, I'd want to know exactly what was the situation and how that happened. Now we have two components of anti-TFPI, the first one was associated in the high dose with arterial thrombosis. And the second component has been used for such a long time and now again, we are hearing that this component had 3, if I am not wrong, thrombotic events. But still, there are really not enough information. I think that what we have to ask from the company is to come up as soon as possible with transparent data about what is happening and how is the thrombosis, what type of thrombosis and giving the possibility to the scientists to understand whether there is any difference, a big difference between any component, like anti-TFPI, miRNA for anti-thrombin, like Fitusiran you were mentioning, or any other product that could come up with the non-replacement therapy or is just drug-related, to a specific type of drug. So that is something that the haemostasis community must understand and for that, we need the data, we need to understand very well.
For example, I have no clue about this second clinical trial, whether the thrombotic event, what type of thrombosis was that or it was associated with other type of drugs, like FVIII, was it normal FVIII or an EHL product, so if I were a patient, I'd need to understand more for that one. For example, Fitusiran, at this point of time, when COVID-19 is frequent all over the world I want to know what is level of D-Dimer for patients when they get enrolled. As you know, COVID-19 is associated with increased level of D-dimers but that might not help very much because these patients could have a high level of D-dimers but this could also be a good bio-marker because if I know as a patient that using Fitusiran and my level of D-dimer is just a little bit higher, what is the level? And if I get infected with COVID-19 what is going to happen, and how my physician should understand my condition. So really at this point from patient point of view and from physician point of view, we need to be more transparent and bringing more data to the society in order to better understand the new components.

DN: Brian, in terms of patients community and making sure that when these products come to the market, what sort of things should the organisations be thinking about?

BOM: I think that what's really important for people with haemophilia on these new therapies is to be told, to have a clear explanation on what is the protocol to treating a break-through bleed and how and when should you contact your CCC. I think this also increases the importance of the statement by EAHAD and EHC that these should be monitored by CCC's with expertise. I think this is still important, and remains important. You won't have an average person with haemophilia wanting to or being able to understand all of the complexities of this. What they need to be told, very clearly, is what happens when you get a bleed, how do you treat that bleed, at what point you contact your CCC and you should perhaps have with you, in your wallet in all times, a special card which explains to non-comprehensive hospital doctor that I am under this therapy and you should phone this number if I am coming to you for treatment.

GENE THERAPY

DN: Time to move on to gene therapy. First gene therapies for FVIII will possibly be licensed this year, hopefully COVID-19 won't slow any of that down, and the FIX maybe in the next year, or slightly beyond. With them finally being this close, they are no longer 5 years away the questions that patients need to be thinking about when they are considering this type of therapy.

BOM: You are being faced with licenced gene therapy, I think that will include the following – what would my likely factor expression be under this gene therapy and how predictable is this? So I'd want to know probably what kind of factor expression I should expect to get and also within what sort of range should, it would have to be within a relatively narrow range. What is my likely duration of expression and likely the minimum duration. How many years will it last and the potential impact on your loss of expression and maybe concern about would I get transaminitis or the risk of that or how close would I be monitored for that. And in terms of long-term I think the big concern would be insertion and mutagenesis from gene therapy. You have to think about what is the possibility of future retreatment if you tell me that my duration of expression might be 5-10 years, what happens after 5-10 years? Can I confidently expect that at that point you would have solved the retreatment conundrum, whereas at the moment you cannot be retreated. These are the questions somebody would think for themselves. Will I go now and take this gene therapy or wait a couple of years for the next generation, so I think this all to play for.

DN: Flora, with the treatment being possibly "one and done", how we think about, you know, one injection and sustain a level for a very long period of time. Brian mentioned transaminitis – that's the raising of the liver enzymes in patients. There are some discussions on steroids and prophylactic steroids. If I maximize my one chance, can you go through some of the ideas or concerns that you may have in terms of taking steroids or avoiding steroids to try and maximize that opportunity. And I think you told in the past about models of care where treating centres are really key and expert, and then you go to that centre (for the gene therapy) and then you go back home and be treated in your home centre.

FP: Yes, I still believe that this is an ongoing discussion with our colleagues from the US and I think that in Europe we have to point up with the model of hub and spoke. We need at least in the beginning for the first 3 years or 5 years when we get more and more experience in the treatment of patients using gene therapy we have to start with the big centres where there is a facility to understand where, for example, any type of side effect would happen or any increase in ALT or AST, as you mentioned, so how much corticosteroids I have to use for how long do I have to use them and whether I have to inject the patient before the treatment or I have to wait and see what is going to happen.
That's a very good question actually and I think, still scientifically talking, I haven't seen enough data that could convince me using or not using it, which is more beneficial for the patient, because my experience, for example, for the patients that I had, they didn't have any side effects and they are doing well and I am thinking why do I have to treat them with corticosteroids if they are doing well, in particularly in a time that we are living in, with the COVID-19 in Milan. I would wait and see and immediately when the level of ALT and AST is jumping, I would start the treatment, but for how long would I have to treat them? The first clinical trial with Amit (Natwani) and Ted (Tuddenham), they started to treat the patient for almost a month or so and there were some discussion but yet, no clear report that some of the patients for other types of clinical trial showed that if you stop after a month of corticosteroid treatment, an event of increase of ALT and AST might happen again. And that would be an indication to treat the patient for one month but for a longer period of time in order to avoid the reoccurrence of liver damage. So I think that, all in all, again, we need to have data and for having the data, I think Biomarin was the company with the highest number of treated patients, we have to pull all the data first, one company with the highest number then making a meta-analysis of the data all together, especially for those vectors that are similar, to understand if there is any common behaviour in terms of the steroid therapy that could be joined together and give us the conduction and guide us on how to treat the patients. So for doing so, I think that even when the product is getting licensed, I cannot even imagine that every doctor could prescribe the drug and making injections to the haemophiliac patient -that would be ridiculous. I cannot really imagine that and I think we need, at east in Europe, to work on it and to make things clearer and more established for the safety and better efficacy for our patients in the future.

DN : I think that initiatives such as a WFH global gene therapy registry will be excellent pulling this forward. But there is a lot to think about. Brian, we have talked about it before, when you almost want somebody to talk you out of it and then still make a decision. In the original trials they had a bioethicist, that's a really interesting point I think. What sort of things do we need to put in place so people don't have "buyer's regret that we sometimes we sometimes hear about?

BOM: It's a good question, Declan, because it's the first irreversible therapy, you cannot change your mind the day after. So once you get treated with the gene therapy vector, that's it – you had the vector, you can't change your mind. That's never been the case before. So I think we need very clear educational material for people with haemophilia, we need booklets, we need publications, we need videos, we need online content and we also need to organise groups, meetings for groups of people with haemophilia where we give them enough of a baseline and enough information about the therapy in front of a group setting. Where we actually prepare them to the point where they are then ready to go and to meet a Flora

Peyvandi or a Michael Makris or somebody else and talk about it, having an informed discussion about this. It is very difficult for a person who knows nothing about gene therapy to go to their clinician and sit down and expect that, that clinician will explain all of this to them to the point so that they can then make an informed decision. This is not one consultation, this is a process of learning, of videos, of written material, of meetings. Certainly what we did here before anybody participated in a clinical trial, before they had a meeting with the clinicians – we had group meetings, groups of people with haemophilia, together with clinicians and the gene therapy company to discuss all of this, to have a presentation. What we found is that somebody in the room would ask a question, which really somebody else hadn't thought of to give them more information. So this is a process of continuing education. And I don't think this is a rapid decision to take, I think patients need to be very well informed, you don't want "buyers" regret and at the same time I think that this is something we have been waiting for many years, it is a very exciting threshold in terms of the science of haemophilia or we must really work out to make sure that people are as well educated about this as possible, before making decisions to take gene therapy.

FP: Declan, maybe something I have to mention. As you know the ISTH is doing a huge plan to release a big programme of 5 years for the education and I think that patients organisations like WFH or EHC have to collaborate with the ISTH. Because you know the people doing this job are always the same people and we don't want to make a duplication and I think that these 2 organisations have different types of duties. So the scientists should think about what is the state of the art of science and where we are going. The patients organisations have to think about how to make the communication to the patients, as Brian was saying. The language that is used is very important and the language of the scientists and the clinicians, as we know, is not the language of the patient. Patients need to understand and need to be sure that their real question is going to be solved. And for the latter – there is the need of a patient organization and I think we have to work together all of us for that.

DN: That's very true about the importance of the lexicons that we hear about. These are very important to translate the science. The science we talked about it, when you work for a patients organisation you aim to have a science level up here and to translate that to patients who sometimes find it difficult; but the science for gene therapy is way higher and the jump is very significant.

BOM: It is literally a different language! You also need to translate that lexicon in the language that will work, back into (simple) English for people.

FP: One thing I think we really need to think about, and probably not as a patient organization, but has some effect, and I was thinking again these days, so the level of expression by different assays has a very important role for the mind of the patient. For example, when you start a gene therapy, you start to have some expression which is getting to 10% (on one assay) and another assay is showing 20%. I have a patient sitting in front of me and saying "OK, so what IS the level?". That is very important to know that. Maybe the physician will say "what is the problem, it is about 10% to 20%". No! I want to know exactly. That is important we need to focus a little bit more on that as a scientist and also on understanding these doubts in the patient and that is missing, in my feeling.

DN: That is a very fair point but I will make one comment. I was in a shopping centre recently and I do think that some gene therapy language is coming into the general population as a woman referred to her children as “vectors”.

vW & PLATELET DISORDERS

DN: I am moving on to vWD. So we are seeing a few changes in the vWD space. ISTH have the related guidelines out as of last week for review, EHC is developing a VWD platform, there is a WFH initiative, we have the first recombinant vWF (von Willebrands Factor) on the market now. What changes do you think are going to happen for people with vWD? For me, when I was looking at the women with bleeding disorders data, the concept of prophylaxis seems very fluid. You have to balance the FVIII with the vWF that’s in the product as some patients have lower FVIII levels. Where are we going with vWD and better treatment?

FP: This is different from haemophilia and we are a little bit behind from what we have for haemophilia. So for years and years we were having only few combined FVIII and vWF plasma-derived products, which had more or less similar amount of FVIII and vWF, we had only one single product that had 2 or 2.5 the amount of vWF compared to FVIII, so there was not really much choice and people were used to treat the patients with these products and for prophylaxis again, we are really far away from what we have for haemophilia. And that is the reason why I am seeing the people, the patients at my age, at my centre, who have arthropathies and that is ridiculous when you think about it because there are not doing the prophylaxis. If you compare the level and the number of people who are on prophylaxis with severe vWD compared to severe haemophilia there is a big difference because we were not doing the prophylaxis in these patients and we started only a few years ago.
So that’s the first step – we need to improve the prophylaxis and we have to treat the patients, those with severe type, there are about 10%; they are not all of them and we have to make a good decision – type 3, some of the type 2, we have to understand what are the severe cases.

The second point is – now we have a pure product; one plasma-derived pure product and a recombinant vWF. These products are completely different compared to what we had. Why are they different? Because you have to learn how to use them. You cannot use these products alone, during acute bleeding or during acute surgery if you are not using FVIII in combination with them. When the level of FVIII in your patient with vWD is very low, it needs to be raised at these times. But, if you have a surgery which is planned before or you want to use prophylaxis, you don’t need to use any FVIII, because this product, by itself alone, in a few hours, can raise the level of FVIII because they are binding to FVIII and you don’t need to add other factors. So this is education. Not all the physicians do understand exactly this point. So that means we are bringing a new chapter in the treatment and we are bringing a recombinant product, which is the first recombinant product coming to the market.
We also have to understand the safety and efficacy of this product and in terms of thrombogenicity, so there are a lot of things. And how are you going to measure it? Do we use the RICOF assay, do we use collagen-binding assay, so there many different things. And I think we are happy to finally have the first recombinant product, we have the plasma-derived pure vWF but we also have to start to move forward and that’s the reason why, I think, the guideline of the ISTH, WFH and ASH (American Society of Hematology) tried to put the data together.

BOM: I certainly think from talking recently to quite a large number of people with vWD as part of our strategic planning process, there is certainly a pending demand for more home-treatment and more prophylaxis in that group. A lot of them are not on prophylaxis. Some of them really should be. I think we need more research in the implications of having low vWF levels. I think for many of our organisations, we have for many years put vWD in the same basket as women with bleeding disorders and therefore we have neglected men with vWD and they have problems also. I think vWD have been neglected within our community. And even if you have a new diagnosis of vWD and you Google it, do you even now that heamophilia societies provide services or support for people with vWD? So I think we all need to think about changing the tag lines of our organisations to make it clear and inclusive of vWD and rare bleeding disorders.
Another point by the way which I think is important, why do we call it von Willebrands Disease? A lot of people don't like that. Why can't we call that von Willebrands Disorder? Flora, could you comment on that?

FP: I agree with you, I think we can call it von Willebrands Disorder and also because there are few cases of vWD, especially type 1, that still is not justified by mutation on vWD gene that we are used to look for and that condition is still under investigation and I agree that it should be called "disorder".

DN: That's a very good point. We do see things changing quite rapidly, we hopefully would see a lot more access and better treatment. We have the 10 principles of haemophilia care, the 10 principles of management of inhibitors and maybe we could get to a couple of principles on the overall care of patients with vWD.

At the EAHAD this year, Flora, there was a very exciting poster presentation on Glanzmann gene therapy, so the GT GT, sound like a really fancy fast car. Could give us just a very quick overview for the patients with Glanzmann?

FP: You know Glanzmann or Bernard-Soulier and all other platelet disorders – even these guys they are neglected. In some of the patients we have the trouble that they are not responding to the treatment, so I know when we will be able with the gene therapy to cure the platelet disorders. Definitely in the future, when we have good models for gene therapy, with good safety and things like that we might want to consider that. The group that was working on it is a Spanish group, unfortunately at this point, with the COVID-19, they have a slowed the progress a little in their activity because they are busy in some other field now, but I think that yes, that was one of the projects that have been selected for the EAHAD. In terms of Glanzmann, you know, some of these patients they really do not have so much treatment and some of them are terribly bleeding and they are not responding, not responding to the platelet infusion, to FVIIa and some of them even went through the bone-marrow transplantation. So really, I think that some of the rare disorders and some of the platelet disorders need more attention since now we are doing a better job with haemophilia and we can move on and work on these patients.

RESPONSE TO COVID-19 AND CHALLENGES

DN: I will move on to my last question – we obviously can't leave COVID-19 aside, it's devastated the entire globe in terms of healthcare, and politically, economically - it is a

massive change scenario but I want to take a second and talk about some of the changes that have been forced on us. We have responded relatively quickly in terms of telemedicine, which possibly should have happened years ago but we just didn't have time or the space. We have seen some patients getting blood tests collected at home to keep them away from the hospital. These are things we are doing now for COVID-19. What are the positive things that we can learn from what has been implemented for the treatment of patients with haemophilia? When we think about gene therapy, we think about the concept of that hub and spoke model, where you need that very good link. How do we monitor patients better and make it easier for them to take part in clinical trials, follow-up or whatever it may be?

FP: I think COVID-19 taught us a lot, as you said. For example, in my centre, which is a big centre, we have 300 severe cases and more than a thousand patients with all types of disorders, we have people available 24/7, physicians available for the patients. What we don't have is a good telemedicine and I thought that this is ridiculous. My centre is doing COVID-19 and I have a full telemedicine activity for COVID-19 but for the haemophilia centre, we are doing by phone but we are not doing telemedicine. So I thought it would be nice that we are making a monitoring all the course for haemophilia patients and understand how many people you need to see and how many of them you could provide a consultation by phone. For example, you know especially mom's who think that maybe their children could have a bleeding but they are not sure to treat it or not to treat, we have to improve the telemedicine to help them. I was also working with the informatics group if our centre to understand whether we could have an ultrasound system managing the minor bleeding in a way the patient could just use a mobile phone and put it on their knees and that would come to our centre and we would see if there is a bleeding or not. How can we do that by monitoring hundreds and hundreds of bleeding and trying to come up with some kind of algorithm which could help us understand whether there is a bleeding or not. So this project was ongoing when COVID-19 happened. So now, I think after this mess of COVID-19, that would be my priority to work on telemedicine and helping really to improve the quality of care of patients and making it easier for them.

BOM: Yes, I think COVID-19 has accelerated trends which were starting to happen. These were happening sometimes, reluctantly and slowly from hospitals, telemedicine, phone-clinics, video-clinics. As you know Declan, we here in Ireland have been planning for the last year or two about rolling out a patients portal for patients – that's now have been accelerated. We now have video consultations, we have phone consultations, we had started doing phone clinics of people with mild haemophilia and vWD and now that's' been extended to severe patients. And I can tell you the centre directors said to me they're not sure a lot of severe patients will want to come to routine clinics anymore because we have designed the phone clinics. The other thing that changed is the way that we all interact. Here we are doing a meeting by Zoom this morning so I think healthcare professionals, multi-disciplinary teams, meetings are happening by Zoom, or Microsoft teams and Skype and I think this is not going to go away. I think we 're missing less international meetings, these certainly will not replace face-to-face interactions but I think the number might be smaller. We will see much more efficient work like this This is time-efficient. You have people who can actually connect very quickly, you can have a peer consultation and you are not spending half of your time travelling to and from the meeting. I remember a similar situation in 2001, after 9/11 attacks in the USA, where some meetings were cancelled and people did the meetings virtually. The

difference is, at the time technology was expensive, it was slow so it didn't really take off. But this time it is taking off and I don't see it going back to the way the things were. I think you'll see much more virtual working, you'll see more flexibility in terms of working from home, you'll see more interaction between clinicians and patients and between clinicians and their colleagues by remote means. I think the world's changed permanently because of this.

DN: I do entirely agree and it is great to see patients organisations do lunch meetings. You literally have to go nowhere and you can still interact with people, get the information and keep it short, timely and still have time for the other things in your life. I've had my first physiotherapy telemedicine appointment recently and it is a bit strange at first but I agree that it really changed the way how we work, how we interact and it is also really nice to see friends on video over long distances.
So thank you both for your time, I had a really interesting discussion I hope everybody at home enjoyed that.