The Treatment of von Willebrand Disease: Does the Type Matter?

A HEMOSTASIS CONNECT podcast

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Dr Jonathan Roberts
Hello and welcome to this podcast on the treatment of von Willebrand disease. I'm Dr Jonathan Roberts. I am a haematologist at a haemophilia treatment centre in central Illinois in the United States. And I'm here with my colleague Ana.

Prof. Ana Boban
Hello, everybody. Hello, Jonathan. And thank you for the introduction. I am Professor Ana Boban. I'm an adult haematologist working in Zagreb, in Croatia. And I'm dealing mostly with patients with coagulation disorders. So, we are here today because we want to talk to you about von Willebrand disease. The guidelines tell us that von Willebrand disease requires individualised treatment. But on the other hand, the high certainty evidence to guide decision making is quite limited. So ,we are going to share some of our clinical experience with you to help you to manage von Willebrand disease.

Dr Jonathan Roberts
So, we'll focus on the impact of the different types of von Willebrand disease on treatment decisions that we make on a daily basis. And then we'll talk about some other treatment options and some clinical scenarios for how we manage von Willebrand disease.
So first, let's talk about the different types of von Willebrand disease. So there's types 1, 2 and 3. Briefly, type 1 von Willebrand disease is the most common form. It's about 80% of cases of von Willebrand disease. And quite simply, it's just a lack of the von Willebrand factor protein. I describe to patients that von Willebrand factor is a protein that's kind of like Velcro for your platelets. It helps to stick those platelets to the site of injury, binds to platelets, binds to collagen. And when there's an injury to a blood vessel, it really helps to

start the coagulation process, so the bleeding will stop. Patients with type 1 von Willebrand disease simply have a lack of protein, and it can quite vary in degree of severity to how much of that protein they're missing. Type 2 von Willebrand Disease, there's many different subtypes: type 2A, B, M and N, and they can all vary in the quality or the functionality of the von Willebrand factor protein, how it does its job. So sometimes the von Willebrand factor levels not quite as low, but it's a dysfunctional protein. In particular, there's type 2B von Willebrand disease that also can be associated with patients having low platelets. And this can come into play when we talk about the different treatment options we have for von Willebrand disease that we'll talk about further on in this discussion. Type 3 von Willebrand disease is the most severe form, where patients essentially make no von Willebrand factor at all. And these patients can have the most severe types of bleeding, bleeding into muscles and joints, very similar to patients with severe haemophilia.

So before we dive into it, Ana, do you want to briefly recap on the key elements of treatment of von Willebrand disease?

Prof. Ana Boban
Yes, of course, Jonathan. So as you mentioned von Willebrand disease has kinds of different presentation, quite different bleeding, so we don't have the same treatment options for all of the patients. So first we have these haemostatic drugs, which are drugs that control the bleeding. We use a couple of different approaches in von Willebrand disease. One of the most commonly used is antifibrinolytics or tranexamic acid, which decreases fibrinolysis and in that way stops bleeding, especially mucosal bleeding, so bleeding into the skin and the mucous membranes. And it's quite easy to use. It can be used orally, as a tablet, or intravenously. It doesn't have lots of side effects, so patients can really take it for a long time without any problems.
If you have major bleeding then you have to think about raising levels of von Willebrand factor which can be done in two ways. We can do it by desmopressin, or DDAVP. It's one specific drug that increases the endogenous levels of von Willebrand factor by releasing it from its physiological stores, which is called Weibel-Palade bodies in the endothelial cells. In this way, this von Willebrand factor is moved from the endothelial cells to the blood system and the level is increased. But if you need treatment of some big trauma, heavy bleeding, surgery, or type 3 patients, then we need to use von Willebrand factor concentrates. So there are also various types of concentrates. Some of them consist only of Willebrand factor, some of them, von Willebrand factor plus factor VIII, and they can be given intravenously. And the levels of factor VIII and Willebrand factors should be monitored in these patients.
But besides these measures, we use some other drugs. For example, we use oral hormonal treatment for reducing the heavy menstrual bleeding during the menstruation. And we use iron supplements for treating iron deficiency anaemia, because iron deficiency and iron deficiency anaemia are very common in patients with von Willebrand disease and even maybe the first symptom or first sign that would bring the patient to see a haematologist.
So then if we move further and go to the key question of this podcast: Jonathan, what role does the type of disease play in your clinical decision making? So are there any treatments you tend to avoid in certain types of the disease?

Dr Jonathan Roberts
Thanks. That's a very good question. So, as you mentioned, there are quite a few treatment options for von Willebrand disease, and it really does vary on what really the bleeding phenotype is or when we say that we mean how the patient bleeds and on the actual type of the von Willebrand disease. So, for example, of the treatment options you mentioned desmopressin or DDAVP that can be given as a nose spray or subcutaneous or intravenous, works by helping to raise the natural levels of von Willebrand factor and factor VIII release from the endothelial cells in the lining of your blood vessels. So because of that, in certain subtypes of von Willebrand disease it's not recommended to treat with DDAVP because it doesn't work or it's not safe. So for example, in type 3 von Willebrand disease, because there is really no production of von Willebrand factor at all, if you would give the DDAVP, essentially it would not work. There would be no release of von Willebrand factor because the patient cannot make von Willebrand factor at all. It still would make some factor VIII. It's important to know that factor VIII and von Willebrand factor work together in the circulation. von Willebrand factor is the chaperone protein. But in the absence of von Willebrand factor, essentially there's no factor VIII. So you may make factor VIII levels rise, but they're immediately going to go back down and it won't help you stop bleeding.
The other is type 2B von Willebrand disease, as I mentioned earlier, that can be associated with low platelets. And so if you would give the DDAVP in that situation, you actually could activate more platelets and make the platelet count lower and make the patient more at risk for bleeding. So, you know, the decision of what to use is really something between the clinician, the physician or nurse practitioner, physician assistant, and the patient. So as Ana mentioned, antifibrinolytics that help to stabilise the clot, they are oral and that can be very useful for minor bleeding. So ,if the patient has minor bleeding, for example as a first-line treatment for heavy menstrual bleeding, commonly we will use tranexamic acid to help prevent the breakdown of the clot. So, if I describe it to patients as a clot stabilising medicine. And then if the bleeding is more significant, you know, we use DDAVP, if it's possible, or the von Willebrand factor concentrates as she mentioned, that would directly replace any missing von Willebrand factor. I think using the von Willebrand factor concentrates can be most important in situations where you really need to make sure haemostasis is occurring, like with surgeries or other major bleeding, a woman delivering a baby, things like that.
So why don't we go through and now discuss a few clinical situations to kind of give everyone an example of how we as clinicians would make a treatment decision if someone with von Willebrand disease came in with a spontaneous bleed.

Prof. Ana Boban
Well, thank you, Jonathan. So spontaneous bleeds are the most common presentation of von Willebrand disease. And surely it will be the most common cause why the patient wants to see you. And then, of course, you have to evaluate: what kind of bleeding is that? Because spontaneous bleeding can be quite mild, like mild bruising. But on the other hand, it could be really major bleeding, life-threatening bleeding that really requires immediate action. So, when you are assessing a patient, so beside having diagnosed which type of disease or which subtype of type 2, you have to look the levels of factor VIII, levels of von

Willebrand factor, but also personal history of the disease. Some patients have really mild clinical presentation, even some patients with type 3 disease. On the other hand, some patients with type 1 have really heavy phenotype of the bleeding, so that also have should take into account when tailoring treatment. So, when you're seeing a patient, then you have to think, does this patient need immediate treatment or to which drug? Is it enough to give some antifibrinolytics or you should a DDAVP test or even make immediate infusion of factor concentrate or to start prophylaxis. So, prophylaxis is possible, we have huge experience of prophylaxis in haemophilia but not so much in von Willebrand disease. And I would say just a part of patients with von Willebrand disease really require prophylaxis. The majority of them are type 3 patients, but nevertheless some type 2 patients or severe type 1 patients need prophylaxis. And the prophylaxis in Willebrand disease means really rather high treatment burden for our patients. So, we want to make sure which patients will take the most from the prophylactic treatment.

Dr Jonathan Roberts
Yeah, I completely agree. I mean, I think that prophylaxis does add a layer of a treatment burden to patients. And certainly that is something that, as you mentioned, we're used to doing in haemophilia, but we haven't done it as much, certainly in the US compared to Europe. And I think that it's really now, especially with the newer guidelines coming out, the 2021 international guidelines for the diagnosis and management of von Willebrand disease, there's more a unified global perspective on the need for prophylaxis, if it's warranted for an individual patient. So I think, just as you mentioned, having an open conversation with your patient and deciding, you know, what kind of bleeding symptoms you're having, how is it affecting your day-to-day life? Here are the treatment options that are available going all the way up to learning to infuse medications at home if they're having recurrent bleeding, things like gastrointestinal bleeding or joint bleeding, definitely those patients should be on prophylaxis. And so, teaching them those infusion skills and really sometimes initiating that later in life, right? Because in haemophilia, a lot of patients with severe disease are in childhood. So the families learn early on. Sometimes we're diagnosing people well into adulthood and the thought of them going their whole life with no real medical expertise and then we're asking them to infuse themselves by sticking a vein with a needle and giving intravenous medicine at home can be daunting. So I think it's definitely an individualised patient specific conversation to do prophylaxis, but it's needed and sometimes, not just like I mentioned, the joint disease, but if someone has like nosebleeds during certain parts of the year, maybe they need to do some preventative treatment just during the wintertime. Or maybe, if it's a woman with heavy menstrual bleeding, she just needs to do treatment, once a month or so. So, it can definitely be individualised to your patient.

Prof. Ana Boban
Yeah, absolutely. Doesn't have to be constant prophylaxis just in the cases one period before once monthly before menstrual period or as you said, many times during the winter because of nosebleeds. But I think the problem with von Willebrand disease is it's hard to predict bleeding. So it's much easier in haemophilia, because the problem is quite simple. You have just one factor missing. And von Willebrand factor, has so many functions, so it's much more difficult to anticipate which patients will bleed in which situation. But what do

you think about surgery? How do you approach it if you have a patient with Willebrand disease that needs surgery?

Dr Jonathan Roberts
Yeah, I think, again, it's specific on what the surgery is. If it's something very minor, say like… Well, I just had it in clinic the other day, a patient with mild type 1 von Willebrand disease that needed just dental fillings. So, they're going to get some injection of some lidocaine, probably to numb them up. Pretty minimal risk. Their levels aren't too low. Maybe they're okay just with some antifibrinolytic therapy and then if they have further bleeding, they could use the DDAVP that they have at home for a minor procedure like that. I think when we think about major surgery, like open heart surgery or even a woman delivering a child, we want levels higher. And personally I like to have better, more predictable control of that. So those would be instances where I would be more inclined to use von Willebrand factor concentrate because I can give them a dose, I can follow their level in the hospital, and I can target whatever von Willebrand brand factor level is needed to be sure they get through surgery safely. So again, for the updated guidelines, usually for more minor things, having a level above 50 is usually okay. But a lot of times with our patients having more complex surgeries, I want the level over 100 so that I can ensure that if they have any bleeding, it's not because I didn't raise the von Willebrand factor level high enough. But again, it's a very open conversation with the patient and the multidisciplinary team because the surgeons sometimes I'm sure you've encountered this as well, they don't want to even consider a patient for surgery because they're so terrified that the patient's going to bleed. And I try to reassure them and say: No, we can make their von Willebrand disease go away with our treatment, but we just have to be mindful of monitoring. So what about you? How do you approach it?

Prof. Ana Boban
Yeah, I completely agree with you. I think it's more assuring for anaesthesiologists and for the surgeons to make a plan. So clear plan what to do and which time of the day, which hour, when to administer factor, how to measure factor and when to measure von Willebrand factor, when to measure factor VIII. And then additionally, so that might be a problem in a number of hospitals to call the laboratory and say, okay, we might need during the night or during the weekend the measurements of von Willebrand factor and factor VIII so they know in advance. So we do not have to wait too long for the factor. And then to leave the phone number where the haematologists would answer if they have any questions. In that way, that they're feel much more secure and sure that operation will end well.

Dr Jonathan Roberts
Yeah, absolutely. And then I guess kind of a final scenario to discuss would be, we've mentioned a little bit already, but women with von Willebrand disease having heavy menstrual bleeding. So on Ana do you see that more often in certain disease types? And what do you consider for kind of your first line treatment and beyond.

Prof. Ana Boban
Yeah, thank you for that question I think it's really important because lots of women with Willebrand disease have heavy menstrual bleeding. And on the other hand, a lot of patients have been diagnosed because of the heavy menstrual bleeding. And I think the close collaboration with the gynaecologists is crucial because they're the ones that should start with the first line treatment. So either oral hormone treatment or intrauterine device, I think that's the way to go and the way to start. And then, if that doesn't work, then I would include antifibrinolytics. Usually it's working quite well and I believe just one smaller part of the patients needs either DDAVP or a factor concentrate before menstrual bleeding. So I have a couple of patients that are on prophylactic treatment, but just once or twice monthly, so one or two infusions a month because of the heavy menstrual bleeding. And then I always check for the iron levels. So to check if the patients… Even checking iron levels before developing anaemia because then we know the iron stores really are missing. So regarding the disease type, I would say the type 3 because there are no Willebrand factor and really low factor VIII would be most commonly presenting with really heavy menstrual bleeding. But nevertheless the other disease types can also be presented. What is additionally needed to be discussed with the patient and with the gynaecologist is pregnancy and planning on pregnancy, when to stop oral treatment. What to do when you stop oral hormonal treatment. How to follow patients through the pregnancy and then delivery. What is your experience?

Dr Jonathan Roberts
Yeah, I mean, you raise some really great points. Very similar to what you describe, I think I can't emphasise enough the importance of the iron deficiency anaemia treatment or even early iron deficiency, and it sounds like we both do that as well. We see many patients with, you know, sometimes being referred to me for iron deficiency anaemia and then it turns out they really have undermanaged heavy menstrual bleeding and then it turns out then we'll diagnose that they have von Willebrand disease. So I think that that's something that I think worldwide is not recognised enough really is iron deficiency and to treat it before it gets to be severe iron deficiency anaemia, because it really can help with fatigue and cognitive functioning in school or work or parenting, you know. So I think that that's a very important point.
Similarly, I have usually my more severe patients are the ones that we have considered for von Willebrand factor concentrate at the time of their periods. I guess in my experience we've tried DDAVP for a few and it sounds like maybe you have some patients where that's helped. I've been less fortunate in my patients. It hasn't helped with menstrual bleeding as much. But I think I do have a few patients with severe von Willebrand disease, but I also have a few patients that have mild type 1 von Willebrand disease that really have refractory menstrual bleeding. And some of these patients, maybe they don't want to use hormonal options for personal reasons. I have had one patient recently, they were afraid to use hormones to treat their heavy menstrual bleeding because they had a family history of gynaecologic cancer. And so they didn't want to have additional hormones in that regard. And so because of that, and they also had von Willebrand disease, we didn't use any hormonal therapy but use the antifibrinolytics and von Willebrand concentrate. And that really helped stop their excessive bleeding cycle as well. So I think it is something, again, you

know, the patient has to be on board because it's a little bit more of a treatment burden with the at home infusions, but it definitely can be helpful. So I would agree more commonly in the more severe types type 2s and 3s, severe type 1s. But it can happen with any patient.

So I think as we're getting closer here to the end, you know thanks Ana really good discussion today. It provides me reassurance that though we're on other ends of the world or we're doing things very similarly and actually I guess gives me some more confidence that I think we as a global community are doing better. We have still work to do, but I think we're doing better in our management of patients with von Willebrand disease. So I'll just give a few key takeaways and then I'd love to hear from you. We've talked today about different types of von Willebrand disease, that even though maybe VWD is a certain diagnosis, there's many subtypes and the bleeding can vary quite a bit from patient to patient. We reviewed different treatment options that patients can use and talked about some complex scenarios that patients may encounter and how we as clinicians may manage that. Again, I think Ana's point of iron deficiency is very important. And really I think that having that kind of shared decision making with an individual patient on, you know, here all the treatment options that are available, here's what we can do to treat your bleeding and continue to have an ongoing dialogue so that we're helping our patients, not just seeing them once a year or how often they come for a regular check-up, but encouraging them to contact their treatment centre and help us really to tailor therapy so that they're really optimising their treatment and minimising the disease burden on themselves. What are your thoughts?

Prof. Ana Boban
Yeah, I think you summed up perfectly. I would like just to end with one sentence that although we see von Willebrand disease as quite difficult to recognise, difficult to diagnose, the treatments are…treating is possible. So we have a couple of very good treatments. Patients do not have to bleed just if we raise awareness about the disease, I think it can be really managed in a very good way. So thank you, Jonathan. Thank you all for listening. It was great discussion and goodbye.

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