Practical Hematologist

Prophylaxis as a New Strategy for the Management of Patients with VWD

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Introduction

Von Willebrand disease (VWD) has been poorly recognized by clinicians since 1926, despite a much higher prevalence than other bleeding disorders.[1] In fact, clinicians are more familiar with the rare diseases of hemophilia A and B.[2] However, hematologists and first-line clinicians can learn from the more aggressive treatment of Hemophilia A and B. Prophylaxis can ameliorate the life-altering and -threatening consequences of moderate-to-severe bleeding disorders.[3,4]

Due to its underrecognized status, clinicians have often taken a reactive stance to VWD and its' sequalae. Yet, the development of safe plasma-derived von Willebrand Factor (pdVWF) and recombinant von Willebrand Factor (rVWF) have allowed clinicians to individualize therapy—tailoring replacement therapy for patients, regardless of VWD phenotype.[5]

Mary McGorray, MD, contributing author, had the privilege of interviewing hematologist Miguel Escobar, MD, Professor at the McGovern School of Medicine at the University of Texas in Houston, regarding the role of prophylaxis in the management of people living with VWD.

Dr. Escobar, is giving prophylactic von Willebrand Factor (VWF) now standard of care? Are we going to be able to get this done?

Yes, I think it's possible to get it done. There are new guidelines published in 2021, endorsed by the American Society of Hematology (ASH) and the International Society on Thrombosis and Haemostasis (ISTH), talking about the role of prophylaxis in VWD. In terms of products that have been approved for prophylaxis, we have a rVWF, that has been recently approved. We have been doing prophylaxis for quite a while, using different products. Data coming from Europe, using plasma-derived products (pdVWF), shows it is beneficial. Patients do benefit from the use of prophylaxis. If you have a patient with a severe phenotype, with heavy menstrual bleeding, or frequent bleeds, the guidelines suggest that long-term prophylaxis should be used in these patients. It depends on the type of bleeding—every patient might be a little bit different. You must individualize management, but they can benefit from long-term prophylaxis.

Would prophylaxis only apply to severe type 3 and type 1 VWD, and some of the type 2 phenotypes, or could it apply to an average woman living with VWD who is having significant menorrhagia with anemia?

The patients need to have a diagnosis of VWD. Prophylaxis in the US has been approved for adult patients with type 3 VWD. For women that don't have VWD, but do have heavy menstrual bleeding (HMB), tranexamic acid (TA) has been approved for that population, without the diagnosis of VWD. For all different types of VWD that have severe phenotypes, we've been using prophylaxis with different VWF products.

What are the real risks of administering pdVWF? Have you seen hepatitis B, C, and HIV-related disease?

These products are extremely safe. In the US, I don't think there has been a transmission of any pathogen, since the early 1980s. There is always a theoretical risk, but there have been no reports.

Dr. Escobar, should we be very careful about pdVWF in terms of potentially creating prothrombosis?

Yes, there are reports in the literature of patients receiving pdVWF that have developed deep vein thrombosis or pulmonary embolism. It's important to monitor a patient, especially if they are receiving frequent doses of replacement factor, either rVWF or pdVWF. The recommendation is to not exceed over 200% of VWF activity, or

more than 250% of factor VIII (FVIII) activity over a period of time. If you give doses infrequently, it is not an issue, but if your patient has other comorbidities, like cardiovascular disease, and you maintain those high levels for a period, they could certainly be prothrombotic.

When you have patients on routine prophylactic therapy, what lab tests would you do to monitor them monthly and/or weekly?

I don't think we need to do weekly, maybe only when patients are in the hospital, or they come in for surgery or an acute bleed – then, we will monitor the levels maybe once a day or every couple of days. Once they are in the outpatient setting, we might do pharmacokinetic studies to get an idea where the patient is in terms of their levels (i.e., peak and/or trough). If they only get prophylaxis 2 or 3 times a month, I don't think there is a necessity to do monitoring. I suggest monitoring hemoglobin and iron levels, to ensure they are not becoming anemic. It's important to individualize management.

Let's say you have a patient who is a mild to moderate bleeder, and you have them on prophylactic therapy, in the first month, do you monitor them, or the second month, and after that once a year?

Yes, if this patient takes a dose two or three times a week, these are going to be the severe phenotypes. These patients may be monitored initially, once, and then, when treatment is started, I might do a follow-up in about a month, once things are more stable. Then, I might do it every three months. If things are going well, I might see her/him every six months in terms of monitoring.

Do you measure von Willebrand factor antigen or VWF Ristocetin Cofactor (vWF-RCo) Assay?

Initially we might monitor all of them, especially if they are on a continuous prophylaxis regimen. When patients get admitted for surgery or delivery, we do monitor levels in the hospital more frequently.

So, you've made a diagnosis of VWD in a patient, and you've determined that they need prophylactic therapy: either pdVWF or rVWF. What labs would you order initially, and then, in six months?

I will usually do a CBC to make sure they are not getting anemic. I might not necessarily check any factor levels if things are stable. If you have the patient on 2 to 3 times a week treatment, and her bleeding is well controlled, then I probably won't check anything else.

If I have a patient that has other risk factors, cardiovascular disease, or a history of stroke, for that patient I might consider checking trough or peak levels of factor VIII or von Willebrand activity to make sure that he or she is maintaining high levels of these proteins. Those patients, many of them young individuals, we usually do not do a lot of monitoring, if they are stable. We will dose them based on the label and the results of the clinical trials.

Dr. Escobar, when thinking about prophylaxis in a patient you know has VWD: If they are going for surgery—what makes you decide to choose pdVWF versus rVWF in that patient?

A lot depends on their baseline levels. If a patient is going for major surgery, and their baseline FVIII level is low, you could choose a plasma-derived product, or you can choose a recombinant VWF. If you choose a recombinant VWF, most likely you will need to administer FVIII with the initial dose, to be able to get the factor VIII level high enough for the surgery. Or you could even start your recombinant product the day before surgery, and you'll have time to increase that factor VIII, but, knowing that you should monitor FVIII levels on the morning or day of surgery to make sure it is adequate. You could use either one. Again, it all depends on what is available in your hospital, how easy, or how difficult it is to measure levels in your hospital – both products could definitely be used.

Is there any time when you would give both recombinant VWF and rFVIII? Wouldn't that be incredibly expensive?

If you want to use rVWF the day of surgery, and the factor VIII is low, then you might consider using both products. But in a prophylactic setting, there's really no need to give both. Most patients will have an elevation of their factor VIII once you start giving the recombinant VWF. Now, if you're using a pdVWF, you don't need to do that. Certainly, you need to monitor your levels.

Now that prophylaxis is routinely recommended, why are we still seeing evidence of people bleeding even when they are easily given prophylaxis? For example, women who are prone to postpartum hemorrhage (PPH), 25% of women still bleed, regardless of having gotten prophylaxis.

I think PPH needs a multidisciplinary approach. There are so many things that could certainly be putting this patient at risk, not necessarily only VWD. The use of products is going to help, certainly, but I think that there are so many factors that can influence the bleeding in PPH.

Dr. Escobar, aside from the obstetric concerns, what is your experience in how prophylaxis benefits patients with VWD in terms of mucocutaneous bleeds, GI bleeds, and non-OB/GYN-type bleeding? Is it working?

Absolutely. We do have patients with severe VWD, where GI bleeding is not infrequent. We have been using prophylaxis for many years on these patients—and it definitely decreases the amount of bleeding. Some type 3 VWD patients bleed in the joints, like hemophiliacs. The use of prophylaxis has really decreased the number of joint bleeds in these patients, too.

Is it too soon to say, Dr. Escobar, about whether prophylaxis reduces morbidity and mortality in VWD patients?

I don't think we can talk about mortality—there's probably not enough data. But definitely, I think morbidity in those individuals has decreased. With the use of prophylaxis, many of these patients do not get admitted. We avoid procedures and many other complications that can happen with acute bleeds, especially GI bleeds.

Now, we're preventing joint bleeds long term in many patients. It's very beneficial to those patients because they are not going to develop arthropathy compared to the ones that are not getting prophylaxis. When you look at the recent phase III trial, where they compared on-demand vs prophylaxis with rVWF, the number of bleeds decreased substantially. It definitely was very beneficial.

Would doses be different for various VWD phenotypes?

Yes, they could be. Again, it all depends on the type of VWD and type of bleeding and the frequency— clinicians might have to tailor their management.

For example, if you have a patient with severe VWD that has GI bleeding—those patients can be quite complicated and most likely require prophylaxis with frequent infusions a few times a week. On the other hand, if you have a patient with episodic gum bleeding or nose bleeds, you may need to treat them on-demand, once or a few times a month depending on the frequency of the bleeds.

Summary

Multiple trials are underway or have been completed regarding on-demand, combination therapy, and long-term prophylaxis with rVWF, in patients living with VWD. Investigations include the use of rVWF either singly or in combination with rFVIII to assess safety, efficacy, and benefits in the more severe forms of VWD and hemophilia A, where VWF is an important escort molecule in the coagulation cascade.[3,6–12]

Clinician-researchers are now looking forward to 2025 results in a phase III study assessing long-term prophylaxis with VWD in both children and adults for reduction in ABRs as its endpoint.[11]

We thank Dr. Miguel Escobar for explaining how prophylactic therapy for people living with VWD can improve their clinical outcomes and quality of life. We are especially grateful to him for sharing his 25 years of real-world experience caring for people living with bleeding disorders.

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