Practical Hematologist

Selecting Optimal Therapy for Patients with Hemophilia

Meera B. Chitlur, MD
Professor of Pediatrics
Central Michigan University College of Medicine
and Wayne State University School of Medicine
Detroit, Michigan

What is the current role of prophylaxis, and how is it evolving?

In the past, the focus was on managing bleeding episodes after they occurred. However, with the availability of more effective treatment options, the focus has shifted to preventing bleeds altogether, particularly major bleeds such as intracranial hemorrhage and joint bleeds.

Prophylaxis has been shown to be effective in reducing joint bleeding rates by over 90% and preventing joint degenerative disease when started early in life. This leads to improved quality of life, increased participation in school and recreational activities, and better professional engagement. It is recommended that patients with severe hemophilia be on prophylaxis at all times and that prophylaxis be started before age 3.[1]

One challenge in initiating prophylaxis has been the need for frequent venous access, especially in children. However, the development of extended half-life concentrates and non-factor therapies such as emicizumab has made prophylaxis more feasible, as they require less frequent dosing and the non-factor options can be given subcutaneously rather than intravenously. These therapies have also been shown to have a low rate of breakthrough bleeding, with the non-factor treatment option, emicizumab resulting in almost no bleeding events even in patients with inhibitors.

How does extended half-life factor prophylaxis compare to standard clotting factor concentrate (CFC) replacement therapy? Does this translate into better patient outcomes?

The extended half-life factor concentrates were shown to have a significantly longer half-life for the Factor IX (FIX) extended half-life factor concentrates, meaning patients can be dosed less frequently. This leads to improved compliance, and allows for higher levels to be maintained for longer periods of time, thereby decreasing breakthrough bleeds and improving compliance. With the FIX concentrates, the dosing could be once weekly or in older patients, once every 10 days, or even monthly. Unfortunately, the same could not be said for the Factor VIII (FVIII) extended half-life factor concentrates, as the half-life extension was only minimal (about 24 hours).[2] Even with this, we were able to decrease the number of pokes to 2/week instead of 3/week which was still considered an improvement for these patients. With better compliance, we can expect to see decreased numbers of bleeding episodes, and thereby better joint health and ultimately outcomes.

How do the new therapies change practice?

The introduction of new therapies has changed the expectations of patients with hemophilia. The focus is no longer just on preventing bleeds, but also on normalizing their lifestyles and allowing them to participate in activities such as sports to the same extent as non-hemophilia patients. With the newer therapies, the goals of prophylaxis have shifted to allow patients to engage in more vigorous sports and activities than before. This has been a significant change in the management of patients with hemophilia due to the availability of these newer therapies which facilitate compliance and maintenance of higher steady state factor activity levels.

What challenges remain in the use of longer-acting therapies?

One significant challenge is the need for venous access which is still the only way to administer factor concentrates, which can be difficult, especially for younger patients. Non-factor therapies do not require venous access, as they can be administered subcutaneously. Another aspect is the concept of peaks and troughs. It has been shown that peak levels of factor at times of maximum activity are effective in preventing joint bleeds and major hemorrhages.[3] However, non-factor agents do not have "peaks", which presents a challenge. The question remains as to whether it is safe for patients on emicizumab, which is given in weekly or monthly doses, to participate in sports and other high-activity events. It is known that infusing before participating in high-activity events, such as basketball or baseball practice, provides protection. However, it is unclear if taking emicizumab provides the same level of protection as infusing before the event. This is a question that requires further research.

Another challenge we sometimes encounter is the lack of experience with bleeding episodes in patients who have been started on the longer-acting or non-factor therapies. Occasionally, this means there is a delay in seeking care for bad bleeds, as they often have never experienced bleeds and are not prepared for them. In addition, these patients and parents are not trained to administer factor, and therefore cannot administer factor for treatment of bleeds. This delay can be detrimental.

What are the challenges in understanding the long-term joint and bone health of patients when trying to determine the best treatment option?

This is currently poorly understood, particularly for non-factor therapies such as emicizumab. It was previously thought that factor VIII and IX played a more significant role in bone health, but it is now believed that thrombin generation may be more important.[4] As long as adequate thrombin is generated, it is hoped that bone health will be maintained. We will need to observe patients on non-factor therapies over the long term to determine if factor VIII and IX themselves play a role in bone health. In terms of joint health, it is believed that non-factor therapies will not have a negative impact as long as they are effective in preventing bleeding during high-risk activities. However, the effects on bone health are still uncertain and require further study.

What factors are taken into consideration when individualizing prophylaxis and how are they applied?

The availability of new therapies may reduce or eliminate the need for individualization of prophylaxis. If these therapies are available to all individuals with hemophilia, there would be no need to restrict prophylaxis to only those with severe hemophilia. In this case, prophylaxis could be offered to all patients with hemophilia, regardless of the severity of their condition. It would not seem fair to restrict certain activities, such as playing baseball/soccer, to those with severe hemophilia who are able to receive prophylaxis, while denying the same opportunities to those with mild hemophilia. I believe prophylaxis should be offered to all individuals with bleeding disorders, regardless of the severity of their condition, in order to provide equal opportunities and experiences.

So the question of individualizing prophylaxis and tailoring treatment based on joint status may not be relevant in the era of non-factor therapies. Therefore, prophylaxis should be offered regardless of the severity of their condition or their current joint status. The goal of prophylaxis is to prevent major bleeds and deterioration of joint health, and with the availability of extended half-life concentrates and non-factor therapies provided early in the course of the disease, individualization may be less of an issue.

Individual pharmacokinetics may still play a role in the individualization of therapy for extended half-life factor concentrates, and certainly for standard half-life factor concentrates. However, it is currently unclear if pharmacokinetics will have a significant influence on non-factor therapies, such as emicizumab. Some data suggests that some patients may require dose escalation to prevent bleeding with emicizumab; in pooled data from phase 3 studies in patients with hemophilia A, dose-uptitration to 3 mg/kg weekly improved bleed control in most participants with inadequately controlled bleeding, with an annualized bleed rate reduction exceeding 70%.[5] However, further research is needed to fully understand the role of pharmacokinetics in these treatments.

By contrast, the role of patient self-assessment and preference in prophylaxis will remain an important factor to consider. Lifestyle is also a key element to consider when prescribing prophylaxis: the more active a patient's lifestyle, the more likely they may need to use factor concentrates along with non-factor therapies, based on current knowledge. However, as more data is gathered, this may change. The availability of non-factor therapies and their effectiveness in preventing bleeds and normalizing lifestyle may determine if all patients can use these therapies or if a subset will still require extended or standard half-life therapies.

Can you give brief examples of how treatment can be individualized using available therapies?

Individualization of therapy is important to consider across all age groups. For a 4-year-old on prophylaxis with standard half-life concentrates, it may be necessary to administer the treatment at least 3 times a week in order to prevent bleeding episodes. However, using extended half-life concentrates for the same age group can reduce the frequency of dosing to twice a week, providing a significant advantage by decreasing the number of treatments per week while still

effectively preventing bleeds. With emicizumab in this age group, there is no need as of now to individualize frequency of therapy, as emicizumab dosing is generally based on the vial size and the weight of the patient. Patients can be dosed weekly, bi-monthly or monthly at this point in time, and that is consistent across different age groups.

For children in older age groups who are using standard half-life factor concentrates, their treatment frequency is often based on their level of physical activity. Children with higher-risk activities may need to be treated more frequently, such as twice a week or three times a week. However, they may also require additional infusions on the day of a high-risk activity or before a particular activity. For extended half-life factor concentrates, treatment can be either a standard prophylaxis schedule or personalized based on their level of activity. For example, if a child plays basketball on the weekend and has practice on Tuesday and Wednesday, their prophylaxis could be scheduled for Friday or Saturday morning to cover the weekend and then again on Tuesday. This way, they are still receiving twice-weekly prophylaxis, but it is tailored to their specific activity schedule. By contrast, with standard half-life factor concentrates, they may require an additional dose on that Thursday, for example.

For adults who are less active and do not engage in high-risk activities, prophylaxis may be more tailored to maintain a trough >1% with SHL or EHL factor concentrates. However, many young adults with hemophilia who have received prophylaxis throughout their lives and have maintained an active lifestyle may choose to continue with the same prophylaxis regimen. In these cases, prophylaxis may be given once or twice during the week, with an additional dose on the weekend for recreational activities. And in older patients with hemophilia, dosing schedules are often determined by the severity of joint damage and current level of physical activity. This is due to a lack of access to proper care in the past, leading to poor joint health in this population.

Adherence has been a major challenge in achieving the prophylactic benefit of CFC therapy. Do the newer therapies change this equation?

We have seen in studies that patients receiving standard half-life concentrates often have poor adherence, and as a result, reduced quality of life due to the large number of missed and delayed doses.[6] Extended half-life concentrates have shown improvements in adherence. One of the key issues is intravenous administration, which can be difficult for patients with hemophilia, leading to challenges with adherence to prophylaxis. Non-factor therapies, such as emicizumab, are given subcutaneously and have significantly improved adherence due to the weekly dosing schedule, which is manageable for most patients, including young children. When it comes to adolescent and young adult populations, I'm still seeing quite a few challenges with adherence despite subcutaneous administration of extended half-life concentrates. The less frequent the dosing becomes, the less it is on their minds, and they may forget to take their doses. It may have improved somewhat with the ability to use smartphones apps and set alarms that can remind them, but it still remains a challenge.

How has gene therapy changed your thinking regarding the role of prophylaxis in hemophilia?

Gene therapy is currently only available to adult patients, and even then, I believe it is only an option for those who understand the many unknowns surrounding it. These unknowns include the duration of its benefit, and the long-term effects of introducing a gene into a person. While the trials so far have shown gene therapy to be safe, the limited amount of data available means that we do not know what the effects of the therapy will be in the long term for patients who receive it at a young age and live into their 80s and 90s.

In conclusion, I think gene therapy can be thought of as prophylaxis of sorts, and one would hope, a potential cure for hemophilia. The ultimate goal of gene therapy is to normalize factor levels and potentially cure the disease entirely. As we continue to improve our understanding and use of gene therapies, this ideal outcome is something that we hope to see in the future.

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Provided by MediCom Worldwide, Inc.
This activity is supported by an educational grant from CSL Behring, LLC.