Untreated bleeds: Unveiling the subtleties and challenges of bleeding event counts and patient experience in clinical trials for bleeding disorders

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Emicizumab, the bispecific human antibody that mimics factor VIII by bringing together activated factor IX and factor X, has significantly improved care for persons with hemophilia A (HA), by providing a subcutaneous means of prophylaxis that is given less frequently than intravenous factor infusions. The HAVEN studies, 1-4 which have demonstrated the efficacy and safety of emicizumab, differed from most previous hemophilia studies not only in prophylaxis mechanism; they presented bleeding event data for both treated and untreated bleeds. In this issue of RPTH, Callaghan et al. 5 present all available details of the untreated bleeds in HAVEN studies 1-3, including adults with HA and inhibitors (HAVEN 1), children with HA and inhibitors (HAVEN 2), and adults with HA without inhibitors (HAVEN 3).

In the HAVEN studies, as in all bleeding disorder studies, bleeding was based on participant/caregiver report of bleeding events. Bleeding and medication administration were recorded separately, and whether a bleed was treated or untreated was determined by investigator linking of treatment episodes to bleeding episodes.

Although a count of bleeding events seems at first to be a straightforward proposition, in practicality it can be quite challenging. As an illustration, consider epistaxis, which should be easy to count because blood can be seen coming from the nose. Imaginary hemophilia study participant Q has a gushing nosebleed. Q holds pressure for 20 min, stopping the nosebleed temporarily, but an hour later it starts bleeding again. At that point, she takes an oral antifibrinolytic (which she does not want to do because it tastes terrible) and continues to hold pressure. The nosebleed stops, and Q goes to sleep. She wakes up a few hours later with blood covering her pillow. She really does not want to get out of bed and infuse factor because needles hurt and she might not get the vein on the first try, and factor is expensive, and this is her last factor dose. She wonders what will happen if it takes the insurance company a month to approve the next factor refill. What will she do if she has a joint bleed that keeps her from working next week and she cannot get factor? Should she save this last factor dose for an even worse bleed? After much internal debate and many hours of short recurrent nosebleeds, she decides to treat with factor. How should that nosebleed be counted as a bleeding event? Should each short period of bleeding count as one bleed, or should the whole episode be counted as one bleed? If counted as just one bleed, it does not fully capture this patient’s miserable experience in comparison to another participant whose nosebleed stops completely with briefly holding pressure. On the other hand, counting this epistaxis episode as multiple bleeds would inflate the bleed count.

Now consider a similar situation with joint bleeding. Fortunately, joint bleeding has a published definition, which was used in the HAVEN studies. 5 The 2014 ISTH guidelines define joint bleeding as a joint “aura” in combination with swelling/warmth, pain, and loss of range of motion of the joint, and note that improvement of symptoms with administration of clotting factor and rest can help distinguish arthropathy pain from bleeding. 6 A new musculoskeletal bleed is defined as bleeding occurring more than 72h after an
initial moderate to excellent response to treatment, meaning at least moderate pain improvement prior to worsening pain. In the present study, the joint aura could not be applied to younger participants, and the 72-h rule could not be applied for untreated bleeds.

When a person with hemophilia experiences joint pain, the differential diagnosis includes joint bleeding, arthritis related to previous joint damage, or other musculoskeletal pain (eg, patellofemoral syndrome or Achilles tendonitis). Determining whether or not pain is bleeding gets layered over decisions about factor treatment that were outlined with participant Q’s epistaxis. In addition, concluding that a pain episode is consistent with bleeding may take days, requiring monitoring how the pain changes with rest and activity, how it responds to factor treatment, and often professional clinical evaluation. Although ultrasound can help with determination of bleeding, waiting on ultrasound could delay treatment, especially for participants living farther from a study site. If a participant decides after entering a bleed in the study diary that it was not actually bleeding, that cannot easily be changed in the study diary. Although this could be solved by making study diaries more flexible, that would increase the potential for accidental data alterations. Finally, musculoskeletal bleeds can last days to weeks. A 2-week long bleed and a 2-h long bleed count similarly in annualized bleeding rates, but reflect very different participant experiences.

The HAVEN studies’ analytic inclusion of untreated bleeds was extremely important, and the work by Callaghan et al. in this issue of RPTH is crucial to understanding what types of bleeds may go untreated. It also illustrates how much remains unknown about untreated bleeds.

Bleeding event identification is likely to get even more challenging as prophylaxis continues to improve and bleeding rates continue to decrease (Figure 1). Children started on prophylaxis before they experience a joint bleed may be less likely to recognize an aura associated with joint bleeding, and they may be more likely to do activities that could cause nonbleeding musculoskeletal pain. Furthermore, barriers to intravenous infusion are likely to increase, as intravenous infusions become less of a habit for patients and families. The number of untreated bleeds in future studies may increase. It will be critical for future studies to include outcomes beyond bleeding events, including physical exam, magnetic resonance imaging (MRI), and quality-of-life scores. Previous studies have shown that, although joint bleeding rates, physical exam, and MRI scores generally correlate, it is possible to have a low annualized bleeding rate with higher levels of joint damage on MRI and vice versa, further emphasizing the importance of long-term outcomes. Fortunately, the HAVEN-7 study, which follows infants started on emicizumab prior to age 12 months, does include those evaluations (clinicaltrials.gov, NCT04431726).

In addition to longer-term joint outcomes and quality-of-life measures, future trials may need participants to identify episodes of pain that could be bleeding and to estimate the likelihood that a pain episode is a bleed. This would add further burden to statistical analyses of studies, and it would need to be balanced with the inconvenience of additional logging for participants. The number of days without bleeding or pain may be an alternative patient-centric outcome, but variation in pain experiences would further complicate analysis and randomization.

The HAVEN studies are likely the first of many to note untreated bleeding events. Future studies will need to delve even deeper to understand how new prophylaxis treatments influence not only bleeding events but also the true patient experience.

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