Questions for Consideration

What is the risk of thrombosis with use of non-factor products in the setting of acute bleed treatment?

The adverse event that clinicians are most concerned about when using these agents while trying to achieve hemostatic balance, is the risk of thrombosis. Emicizumab is the bispecific antibody that is currently available in many parts of the world for prophylaxis with hemophilia A, both with and without inhibitors. The considerations here are quite different for those with and without inhibitors. Speaking about the treatment of acute bleeds in patients with hemophilia A with inhibitors, it should be acknowledged that emicizumab is used for prophylaxis not for the treatment of acute bleeding. We rely on the use of bypassing agents such as recombinant factor VIIa (FVIIa) or activated prothrombin complex concentrate (aPCC).

In the early HAVEN trial, there were patients enrolled who experienced thrombotic events and thrombotic microangiopathy when treated with higher doses of aPCC. This led to cessation of the use of aPCC for these patients, and instead the use of recombinant FVIIa. Since then, there have been no episodes of thrombosis that have been reported with concomitant FVII use as well as emicizumab, and it is recommended that when patients do experience an acute bleed, in those who have inhibitors, that recombinant FVIIa is the agent of choice for those who are treated with emicizumab.

For patients without inhibitors, there have NOT been reported cases of thrombosis when they are concomitantly treated with FVIII replacement. This is because we believe FVIII has a much higher binding affinity for FIX and FX than emicizumab. It “bumps” it off and there does not appear to be any synergistic hemostatic activity, unlike the cases of concomitant aPCC and emicizumab where there was clear evidence of increased thrombin generation. With inhibitors that does not appear to be the case and therefore it is recommended that patients be treated with FVIII in the same way they would have been treated without emicizumab.

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What monitoring challenges exist with use of non-factor products and what is their impact on safety?

Emicizumab is a bispecific antibody that identifies factor IXa (FIXa) and FX, and pulls them together in a similar way that FVIII (FVIII) does, so it is therefore a FVIII mimetic. This is a humanized bispecific antibody meaning that it sees human clotting factors and pulls them together. This is important because when a patient has a blood test to evaluate for something such as residual factor activity in emicizumab, this is going to lead to an overestimation of FVIII activity and an overestimation of other clotting factors as well because it leads to enhanced thrombin generation and fiber clot formation.

When you have a patient who is on emicizumab, and you want to run a FVIII activity assay, you should not be using clot based factor activity assays, because those reagents will be seen by the emicizumab and that is what leads to the overestimation of FVIII activity. To get around this you need to use reagents that will not be “seen” by emicizumab. Meaning you can use a chromogenic assay which is a different way to measure residual FVIII activity. FVIII activity in this case is estimated by the amount of conversion of FX to FXa. To remove the effect, or ignore the effect of emicizumab in the sample, you have to have a reagent that emicizumab will not see. That reagent is a bovine reagent that comes from cattle. Emicizumab is a humanized antibody that sees human clotting factors, so it doesn’t see the cows clotting factor. It is blind to it, and therefore the emicizumab doesn’t interfere with the test.

You need to have access to this very specialized test with these specialized reagents and use it to evaluate for residual FVIII activity, which is particularly relevant for patients with inhibitors who are undergoing any tolerance induction therapy or patients with hemophilia A who have underlying inhibitors. If you need to know their FVIII activity, for example, when they are presenting with an acute bleed or need acute surgery and they are still on emicizumab, they should remain on emicizumab. If you are treating with FVIII and you’d like to know how much FVIII is in circulation, a similar principle applies for measuring inhibitor titers. Again, you need to use reagents that emicizumab will not see so that you can get an accurate result. Otherwise the emicizumab will interfere with the assay.

Questions for Consideration

Will previously untreated patients, also known as PUPs, treated with nonfactor products have lower risk of inhibitors?

Within pediatrics this is an important question as inhibitors are the biggest complication that we see with hemophilia and what makes treatment very difficult. We know that prior to non-factor products, between 20% and 40% of patients were affected by inhibitors within the first fifty days of exposure to factor VIII, and about 70% of those typically would resolve with the use of ITI. There are questions about PUPs that are started out with treatment on emicizumab and what their rate of inhibitors will be. There was a poster at ASH in 2020 where six either untreated patients or minimally treated patients were followed after being started on emicizumab. There were two cases of high titer inhibitors in that six, which does fall within the range of what we've seen prior to nonfactor treatments.

There are also questions about patients who have previously had inhibitors and whether they will have recurrence of inhibitors with the use of emicizumab, especially if they are not continually exposed to factor VIII products. There was a consensus document put out in the UK stating that if patients with prior inhibitors were to use emicizumab, they should use concomitant low dose factor VIII at less than 30 units per kilo once a week to try to prevent recurrence of their inhibitors.

There have been some small retrospective studies looking at tolerized patients and what happens to their inhibitor levels after starting emicizumab. There is an ongoing study, the *Prevent Study* where they're looking at time to inhibitor development with the use of emicizumab compared to a factor product. Then, if patients develop inhibitors, looking at what is the best way to treat them from that point on whether it's emicizumab with ITI or ITI alone. There remain many of these big questions and luckily some studies are being done to hopefully provide us some answers.

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What effect do non-factor products have on joint health compared to factor replacement?

This is an important question for patients and physicians, specifically about how ultimately people's bone and joint health compare using non-factor products compared to those that have historically used factor VIII products. We know that in the trial and especially with emicizumab, that it does reduce joint bleeds which is obviously good for joint health. There were some exploratory analyses done within HAVEN 3, looking at the Hemophilia Joint Health Score (HJHS).

71 patients that had at least 1 target joint, were looked at and had a mean improvement in both the joint specific domain of the HJHS, as well as the total score. They also did some analyses of 117 patients looking at some bone and joint health biomarker data. There was not a significant change during an eighteen month period of prophylaxis with emicizumab. This remains a question and there are a number of physicians and patients who are concerned about whether factor VIII may play some role outside of just preventing bleeding, and whether that may ultimately result in changes in overall bone and joint health in patients who are not treated with factor VIII.

There are many ongoing trials looking at this, including HAVEN 6, HAVEN 7, and a BEYOND ABR study. Additionally, there are other trials such as MSK and MMHUS, as well as the *APP* and *Transcend* study that are all trying to look at some of these other outcomes as we gather more data over a longer period of time.

Questions for Consideration

Will we see increased physical activity and fitness as patients are less hesitant and possibly feel more protected?

Many of these patients have been on prophylaxis since they were babies and have had their lives revolve around their hemophilia and treatment. They were infusing multiple times a week and now may just require a subcutaneous injection once a month. Some of these patients report that they feel as if they don't have hemophilia anymore, and they definitely seem to be participating in activities that their physicians prefer they didn't participate in.

This is a concern. On the positive side, if patients are more physically active and can be more fit, that is good for their cardiovascular health and their overall health. We additionally have had patients who've struggled with weight management because they have been hesitant to be physically active due to their risk of bleeding. But physical therapists worry that these patients may forget they have hemophilia and may engage in activities that really put them at risk for serious complications because they feel so much more protected or can forget that they have the underlying condition because it's not such a huge part of their lives anymore.

Questions for Consideration

Can non-factor products be used to treat spontaneous or breakthrough bleeds?

It is important for both physicians and patients to understand that non-factor products are meant to be used for prophylaxis and not for treatment. This is particularly important in a disease like hemophilia where patients have been treating themselves at home for many years. Often by the time they switch or get started on a nonfactor product, they are very used to having one product at home that they use for both prophylaxis and for treatment of bleeds. This is going to be a bit of a paradigm shift for those patients using one non-factor treatment at home for regular prophylaxis, and then needing another treatment, such as factor or a bypassing agent for patients with inhibitors, ready if they do have a bleed.

This is also important to think about, as these are patients who have been doing intravenous infusion at home for long periods of time but are now switching to nonfactor products that are not intravenously administered. Some of these patients may lose the ability to do intravenous access at home or may not feel as comfortable. It is important that families are both aware that their subcutaneous non-factor product is not going to be helpful in acute bleed situations and that they are going to need to have a good plan for using an intravenous treatment, such as a bypassing agent or a factor product in those acute scenarios. This is a challenge going forward and explains why there is a need to make sure that everyone is educated and prepared with their plan for those times.

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If factor VIII replacement is administered on top of a non-factor product, are the effects additive?

If you provide factor VIII (FVIII) to somebody who is already on emicizumab, because FVIII has a higher binding affinity to FIX and FX, it's going to bump emicizumab away and the FVIII is really what is going to be the main haemostatic player at that time. So no, the effects are not additive. However, we often maintain emicizumab prophylaxis when someone is being treated for an acute bleed, or for a surgical procedure. Therefore, it does allow for a more smooth transition to the prophylactic phase after the acute bleed or acute surgical procedure treatment phase has been completed.

How much factor should patients keep at home in case of a breakthrough bleed on a non-factor product?

The answer to this depends on the patient's bleeding phenotype and how good emicizumab is at controlling the patient's risk of bleeding. We know that emicizumab currently has incredible effectiveness and decreases the risk of bleeding in patients with severe hemophilia substantially, both with and without inhibitors. We do believe that patients should still keep factor VIII (FVIII) at home. It is suggested that patients maintain about 20%-30% of the typical inventory that they had at home when emicizumab was not a treatment that they were on. This is something that continually needs to be revisited of course with an eye on not wasting any product.