

Expert Answers to Common Questions for the Management of Hemophilia A

Eric H. Kraut, MD: Hello and welcome to this educational activity entitled, *Expert Answers to Common Questions for the Management of Hemophilia A*. I am Eric H. Kraut, MD, Professor of Medicine and Director of Benign Hematology at the Ohio State University in Columbus, Ohio. This activity will provide my expert perspective on participant questions from a recent AXIS Grand Round Series on hemophilia A.

This activity will provide answers to questions asked during a recent grand round series on hemophilia A. Treatment-related questions comprised the majority and included general treatment, factor VIII, inhibitors, emicizumab, and extended half-life molecules.

This activity will focus on (1) factor VIII, (2) emicizumab, and (3) other newer therapies in hemophilia A, including extended half-life products, gene therapy and cell therapy, porcine factor VIII, and inhibitors.

First let's discuss factor VIII. Factor VIII functions as a cofactor by binding to factor IX and factor X. This binding enhances the catalytic action of factor IXa and the interaction between IXa and X and generates thrombin. Factor VIII amplifies the effect of factor IX by 1,000 times.

Here is the classic schema for the coagulation pathway. On the right is the generation of tissue factor after injury combining with factor VII and generating thrombin by the common pathway. There is then a feedback with activation of factor VIII to VIIIa combining with IX and then activating X and generating more thrombin.

Emicizumab has made a major difference; it is similar to factor VIII. It's a mimetic antibody that was developed to replace factor VIII. In the upper part of the figure, you see what classically happens with factor VIII. Factor VIII binds to factor IXa and factor X and brings it together as a complex to activate thrombin generation. This bimodal bispecific antibody, emicizumab, binds to a different site in IXa and X, but again brings it together to generate thrombin activation.

In the first trial of emicizumab in 16 patients with both factor VIII deficiency with and without inhibitors, it was demonstrated that achieving a level of emicizumab in the blood of 40 to 60 mcg/mL dramatically shortened the partial thromboplastin time (PTT) and developed a significant increase in reported factor VIII activity sustained over time. This

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is shown in this figure with chromogenic factor VIII activity up to 30% as the emicizumab concentration increases.

In the HAVEN 1 trial, which was a trial of patients with factor VIII deficiency with inhibitors, it was demonstrated that in patients given emicizumab as treatment compared to patients who had no emicizumab, there was an 87% reduction in the average bleeding rate, which is a dramatic finding. In addition, in a group of patients with emicizumab given to patients who were on prophylaxis 3 times a week, there was a similar reduction in the bleeding rate. So this drug made a dramatic impact in patients with inhibitors.

This is also shown dramatically on this next figure in which 63% of patients given emicizumab as prophylaxis had no bleeding episodes. A similar reduction was seen in patients who were on regular prophylaxis with factor VIII, with 70% of patients having no bleeding episodes. So again, this made a dramatic impact in patients with inhibitors.

Now, in this activity and drug treatment, there were some serious side effects, although they were infrequent. The major thing observed was thrombotic microangiopathy, but it was only seen when patients were treated with FEIBA (factor VIII inhibitor bypassing activity, or anti-inhibitor coagulant complex) activated protein complex. And these were seen in 3 of 391 patients. One episode of cerebral vein thrombosis was seen after patients were given activated protein complex—this led to the Black Box warning not to use activated protein complex in patients with inhibitors who are receiving emicizumab and to only use factor VIIa for bleeding events.

Obviously, the success of emicizumab in patients with inhibitors led to the HAVEN 3 trial of patients without inhibitors. Again, as in the patients with inhibitors, there was a dramatic improvement when patients were given emicizumab as treatment. There were 2 cohorts: patients, after getting a loading dose of 3 mg/kg weekly times four, were given either no prophylaxis with emicizumab or 1.5 mg/kg SQ weekly or 3 mg/kg every other week. In both cohorts, there was over a 90% reduction in the average bleeding rate; a dramatic success.

So as a result, at Ohio State and throughout the country, patients are now approved to get treatment with emicizumab whether they have inhibitors or not. We have put

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together guidelines at Ohio State's Thrombosis and Hemophilia Center. Patients with severe hemophilia A with documented inhibitors and a significant number of bleeds are placed on emicizumab. Patients with severe hemophilia A without inhibitors on prophylaxis are also considered for emicizumab. Patients with severe hemophilia A with poor venous access and greater than 4 bleeds a year are placed on emicizumab. And finally, patients with severe hemophilia A with history of recent spontaneous CNS bleeds or life-threatening bleeds are considered for emicizumab.

Now one difficulty for practitioners using this drug is that emicizumab can affect the ability to measure factor VIII activity. However, if you use a specific assessment of chromogenic factor VIII coagulant activity, you can demonstrate adequate thrombogenic activity with this drug, as shown on this figure, and this is related to the emicizumab plasma concentration.

In addition, if you use a specific chromogenic Bethesda Assay, which is used to measure factor VIII inhibitors—and we'll be talking about this later—you can demonstrate, again, factor VIII assay and inhibitor titers using the specific chromogenic assay.

So in summary, emicizumab's mechanism of action is a bispecific factor IXa- and factor X-directed antibody. It's used for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in both adult and pediatric patients from newborns and older with or without inhibitors. And this was demonstrated in the HAVEN 1 and HAVEN 2 trials, in 2017 with inhibitors, and 2018 with or without inhibitors in the HAVEN 3 or HAVEN 4 trials.

Dosage and administration include a loading dose of 3 mg/kg once weekly for the first 4 weeks followed by maintenance of 1.5 mg/kg once every week, 3 mg/kg once every 2 weeks, 6 mg/kg once every 4 weeks. The most common adverse reactions in approximately 10% or more were injection site reactions, headache, and arthralgias. And there's a boxed warning for thrombotic microangiopathy and thromboembolism in patients who were treated with activated protein complex and emicizumab. It has not been seen in patients who don't have inhibitors and who have not received activated protein complex.

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One issue that always comes up in discussing new drugs is the cost of therapy. As noted by the Ohio State Pharmacy and the Institute for Clinical and Economic Review, the average dosing for a 70-kg patient of 105 mg emicizumab weekly is approximately \$12,000 or \$480,000 in the first year. However, standard factor VIII products, as everyone knows, are quite expensive also. Recombinant synthetic factor VIII is \$10,000 a week for prophylaxis. Eloctate extended half-life product is \$18,000 a week in prophylaxis. And Feiba factor VIII inhibitor bypass activity is almost \$29,000 a week. So, it appears that in many patients, emicizumab can also be economically sound.

So, the success of emicizumab is a major advance; however, there are other newer therapies in hemophilia A.

The challenge in hemophilia A treatment is that generally factor VIII products only last approximately 12 hours. As shown in this figure, if you're using the drug for prophylaxis, you want to maintain the drug levels above a certain trough, approximately 3% to 4%. So in the upper part of this graph, you see that there are periods during the week that the curve shows inadequate factor VIII activity and possible bleeding risk. The lower graph shows a proposed factor VIII extended-life product given once a week; you have to reach a higher peak. And the time that the patient may not be adequately covered may actually be longer when given only once a week. So obviously, one has to craft different kinds of schedules.

However, the promise of longer-acting hemophilia treatment is a significant one. As we mentioned, the half-life with standard therapies results in frequent injections. You have to give factor VIII three times a week or every other day. The benefits of replacing this with the longer half-life would include a reduced burden of prophylaxis because of reduced frequency of administration and improved adherence, ability to achieve higher trough levels in certain clinical situations, improved joint health, improved outcomes with immune tolerance therapy, and potential for subcutaneous administration in the future.

Now, extended-action factor VIII and factor IX products have received FDA approval, and several additional agents are currently in development. We're not going to discuss them here, but hopefully they have made some impact on patient management.

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Some of the strategies that are currently being used to develop these new products include to reduce interaction with clearance receptors through PEGylation of the drug, and rescue endocytosed proteins from intercellular degradation pathways through interaction with the neonatal Fc receptor. Others that have been tried include enhancing interaction with von Willebrand factor via single-chain factor VIII variants or eliminating non-human glycans by expressing factor VIII in human cell lines.

Thus, even though emicizumab has had a dramatic impact in the hemophilia community and has allowed for effective prophylaxis in patients, extended half-life products can still be used in patients and probably are better suited for children where prophylaxis is much more common.

A question was raised about the development of gene and cell therapy, a therapy that's being used to cure genetic disorders. As shown in this figure, gene therapy is being tried in factor VIII. And you can see that in gene therapy, the therapeutic gene is inserted into a viral vector infused into the patient, goes to the liver where the factor is then produced. Or, one can take stem cells out of the patient, insert the gene into the stem cell, again insert the stem cell into the patient, and again develop a factor product factor development in the patient.

So, the factor VIII gene trials, which are in development right now, unfortunately, have not resulted in a sustained increase in factor levels, as opposed to the success of factor IX. Initial treatment in patients given these therapies may have failed initially due to immune reactions in liver, and people are using immune suppression to try to prevent that. In addition, upfront cost is significant and can be \$1 to \$2 million, and long-term responses are not yet known.

Another product that has come into the hemophilia treatment community is porcine factor VIII. Porcine factor VIII has a long history. In the 1970s, cross-reactivity of human factor VIII antibodies with porcine factor VIII was noted to only be 30%. Thus, if a patient had an inhibitor to human factor VIII, porcine factor VIII might be effective. In a product, Hyate:C, plasma derived was initially used and seemed to work.

Unfortunately, it was taken off the market due to the development of thrombocytopenia and porcine parvovirus. Then recently, a synthetic recombinant factor VIII—now termed

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Obizur—was tested in patients with acquired hemophilia A and is approved for this use only. Studies in congenital hemophilia A are being done and it's preliminary and its use in that situation is off-label.

To demonstrate its effectiveness, a study of 28 patients with acquired hemophilia A were given a dose of porcine factor VIII and a much higher dose than is usually used in classic hemophilia treatment, 200 units/kg, with a maintenance dose depending on the achieved factor level. The reason this is a different dosing schedule is because patients may have cross-reacting antibodies to porcine factor VIII; and as a result, not have the presumed elevation in factor VIII activity that one would get with standard dosing.

In addition, the half-life of porcine factor VIII may differ due to this cross-reactivity. And thus, using this drug will require, importantly, measurement of factor VIII levels at specific times and continued adjustment in dose depending on the level achieved. One, obviously, does not want to get too high a level because of thrombotic risk, and one doesn't want too low a level because this won't stop any bleeding.

Finally, let's talk about inhibitors. So, inhibitors are the major problem that we see in hemophilia. These are alloantibodies that are directed against factors VIII and IX. They're usually IgG type with type 1 kinetics, and they totally neutralize factor. In fact, before the development of other treatments, you would give all the factor VIII in a pharmacy and not be able to overcome inhibitors. These inhibitors can develop after one single dose of factor VIII but usually occur in the first 25 to 50 treatments.

They are seen in 10% to 50% of people with factor VIII and in 1% to 4% of people with factor IX. But half of these are low titer and/or transient so do not present a problem. Risk factors that cause the development of factor inhibitors include race (blacks more commonly develop these inhibitors), severity (seen more often in patients with severe factor VIII less than 1%), and the type of mutation leading to hemophilia.

Now one will recognize the development of inhibitors by the poor response to therapy and/or increased bleeding events. We mentioned the Bethesda assay, and we'll talk about how it's done. And that's used to measure the inhibitor activity level. Although not usual, they can occur in adults. The current recommendation in all patients receiving factor VIII treatment is to measure inhibitors at least once per year and to measure them

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prior to undergoing major invasive procedures because this will affect the ability to treat with factor VIII.

The Bethesda assay is a measurement of inhibitor activity. One takes the patient's plasma and mixes it with 100% factor VIII plasma. A Bethesda unit is the dilution of the amount of plasma needed to neutralize 50% measured by the standard clotting time. So for example, a low titer (less than 5 units) is 1 to 5 dilution; high titer is greater than 5 units.

The treatment for patients with inhibitors—we mentioned porcine factor VIII can be used. If you have a low titer inhibitor, high concentrations of factor VIII, we mentioned FEIBA or anti-inhibitor coagulant complex, NovoSeven or factor VIIa, emicizumab, or immune suppression.

The key take-away for the education program in hemophilia A is that there is a revolution in the management of hemophilia with new therapies transforming the natural history of the disease. Thus, patients need to be thoroughly evaluated for these therapies taking into account the severity of the disease. For patients with or without inhibitors, emicizumab has decreased spontaneous bleeding and the need for factor replacement. Porcine factor VIII is a viable option when factor is needed. Gene therapy is in the early stages; referral to a hemostasis thrombosis center is important for consideration of all therapy options.

Thank you for participating in this activity.

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