UNMET NEEDS

Hemophilia: Epidemiology

Guy Young, MD: First, a brief overview of hemophilia. Hemophilia A is due to factor VIII deficiency and is present in 1 in 5,000 live male births; and hemophilia B is factor IX deficiency and is less common, with 1 in 30,000 live male births. Hemophilia is classified into 3 different severity categories based entirely on the factor levels. Severe hemophilia is less than 1% factor activity, moderate is 1% to 5%, and mild is 6% to 40%. The key difference is that, in severe hemophilia, the bleeding tendency is frequent bleeds into joints and muscles, often spontaneous, and that ultimately hemophilic arthropathy will occur unless interventions, such as prophylaxis, are utilized. Mild hemophilia typically doesn't result in functional limitations, although it can, in some patients. And moderate hemophilia falls in between, with some patients behaving more like severe and others behaving more like mild.

Hemophilia: Complications

The main complication of hemophilia is bleeding in the joints, which accounts for 80% of the spontaneous bleeding events. These events can result in permanent joint damage, which we call hemophilic arthropathy. Muscle bleeding can occur as well, and rare—but very serious—would be cerebral bleeding, so intracerebral bleeding or intracranial hemorrhage and retroperitoneal hemorrhage. Typically, the joint bleeding occurs in the knees, elbows, and ankles, and the typical symptoms are swelling, pain, and decreased range of motion in those joints when they are bleeding. Treatment of bleeds with factor replacement will resolve those bleeds in some period of time, depending on the severity and the location of the bleed.

Hemophilia: A balancing act

As far as management of hemophilia, and as far as choosing treatments for hemophilia, a number of factors need to be taken into consideration, and these all result in a bit of a balancing act. Adherence is really critical, because if patients don't take their medications, of course, they're not going to work. And with the understanding that factor therapy is given intravenously, classically it was 3 times a week, although with newer products, it can be twice a week or even once a week. But still, that's a minimum of 52 intravenous injections a year for hemophilia A. With hemophilia B, it's similar, although there are some options to give it less frequently.

When to administer prophylaxis? With factor, we want the doses given in the morning, which creates additional challenges when people are getting ready for school or work or parents are getting ready for school or work if they have to provide the medication to their children. And then, obviously, the other 2 key points are efficacy and safety. Efficacy is typically measured by the annualized bleeding rate (ABR). Long-term efficacy really involves assessment of joint damage and the prevention of joint health problems, so joint damage and mobility issues, and, of course, quality of life. But in the short term, we measure efficacy by the ABR. And then, of course, safety with respect to factor products, we want to make sure that we have products that at least limit the likelihood of developing an inhibitor because developing inhibitors to factor products is a really key negative issue that can result for patients. And then other things, such as thrombosis, infection, hepatotoxicity, and infusion injection site reactions, are all part of the safety equation that's taken into account. So, when we're choosing a product, we really want to maximize efficacy, maximize safety and maximize adherence.

CLOTTING FACTOR CONCENTRATES

Clotting factor concentrates

Craig M. Kessler, MD: Over the years, we've seen advancement in the therapeutic armamentarium for both hemophilia A and B and we've moved very rapidly from the days where we could only rely on fresh-frozen plasma or cryoprecipitate for hemophilia A and B into an era where we rely primarily on genetically engineered clotting factor concentrates.

There is now a panoply of commercial options for these products, particularly in the hemophilia A realm. And I think the bottom line here is rather than going through each one of the products is to understand that the majority of these genetically engineered recombinant factor VIII concentrates are limited in their circulating half-lives according to the way that they interact with von Willebrand factor protein in the circulation. So, despite the contrived types of molecules that are now available commercially, whether they be Fc-fusion proteins or whether they're pegylated specifically or nonspecifically on the factor VIII molecule, for all intents and purposes their circulating half-life is dependent on the half-life of von Willebrand factor which chaperones these molecules through the circulation. Therefore, the majority of these products will have a half-life which is only approximately 1½-times what factor VIII concentrate that is not fused or contrived, essentially native genetically engineered factor VIII, has in the circulation. Now, the caveat here is the following: even though, in clinical trials, data are provided that give you a number for the half-life timing of these molecules, this is typically a mean value of a large number of individuals who have received these concentrates. There is a large variability in the half-lives from individual to individual. It's critically important that individual pharmacokinetics be performed on your patient at some point early in their treatment switch from a native genetically engineered factor VIII half-life product to the extended half-life products that we have available now.

Similarly, when we talk about the extended half-life products for hemophilia B or factor IX deficiency, the same caveat exists. Now, in this category, there are fewer options that we have available, but these genetically engineered extended half-life products also have their own individual profiles. And all of these extended half-life products, they're not used necessarily only for severe hemophilia. For instance, we can use these products to make extended half-life postoperative care of patients much more convenient. Instead of having to infuse factor VIII on a daily basis, we might be able to infuse factor VIII replacement every 3 to 4 days postoperatively. We can use these in patients with mild and moderate severe hemophilia, both hemophilia A and B, which makes their care much more convenient and cost-effective overall.

IMPROVED RECOMBINANT FACTOR

Efanesoctocog alfa: Pharmacology

Craig M. Kessler, MD: Now, let's look specifically at what I consider to be one of the major game-changers in extended factor VIII use in severe hemophilia. The product that I'm going to be highlighting is efanesoctocog alfa (Altuviiio). This is a genetically engineered recombinant Fc-fusion factor VIII protein. This has a molecule which is attached to certain areas of the factor VIII molecule itself, which will extend its circulating half-life. Efanesoctocog alfa also has certain peptides that are blocking the typical von Willebrand factor protein binding sites which essentially confuses the body to think that this molecule is already attached to von Willebrand factor. Consequently, it will remain in circulation for an extended period of time, instead of being limited by the half-life of the natural, native von Willebrand factor protein which is in the plasma of each one of our patients and binds very rapidly to the infused native factor VIII molecule. Efanesoctocog alfa is contrived in such a way that the body does not clear the factor VIII molecule because the body perceives this molecule as being perpetually bound by von Willebrand factor protein. So, this is an ingenious protein which has had rigorous clinical trialing and has been shown to be extremely safe and effective.

XTEND-1 trial: Design

The seminal trial XTEND-1 was a randomized, phase 3, open-label, multicenter, international trial which studied individuals over the age of 12 years and who had severe hemophilia without prior history of an alloantibody inhibitor. These patients all had been exposed to at least 150 days of genetically engineered recombinant or plasma-derived factor VIII concentrate or cryoprecipitate. The patients were divided into 2 groups. One group received prophylaxis treatment using efanesoctocog alfa at a dose of 50 IU/kg weekly for 52 weeks. The second group was on on-demand therapy for 26 weeks and then were converted over to a prophylaxis regimen for the rest of the 26 weeks so that the on-demand use of clotting factor replacement therapy could be compared to a prophylaxis regimen.

XTEND-1 trial: Efficacy

Now, one of the interesting results from this study is the examination of the mean annualized bleeding rate in individuals who were tracked for annualized bleeding rates prior to their entry into the clinical trial and then following their use with efanesoctocog alfa. And there was a definite increased, almost I would say, superiority in the reduction of annualized bleeding rates in those individuals who had been on efanesoctocog alfa vs their prior prophylaxis regimen products. This really gives us the confidence that we have a product that doesn't need to be infused more than weekly, for most cases, whereas the use of the other extended half-life products usually has the requirement for patients to treat themselves every 3 to5 days. We now have a product that has an even greater extended half-life capacity than we had with others within the extended half-life recombinant factor VIII armamentarium. This is really a game-changer in my mind.

And, of course, whenever we see contrived molecules like we see here for the factor VIII molecule, we always worry about whether we're going to stimulate the immune system to produce alloantibodies. And fortunately, in this clinical trial, there has not been observed any development of alloantibody inhibitors to the contrived factor VIII molecule Efanesoctocog alfa and this is also extremely reassuring.

XTEND-1 trial: Safety

In the XTEND-1 safety study, over 75% of the patients did experience at least 1 adverse event. However, when you begin to take a look at the profiling of these types of events, there were none serious, except for a couple of patients in the study and I think that that's very important to appreciate that this product was extremely well tolerated.

Clotting factor concentrates: Key points

Now, I think, again, that the caveat here is that we have a menu of clotting factor concentrates. These extended half-life products may have an individualized profile. It's important for each individual to have his own profile established prior to the ongoing use of these extended half-life products. They are well tolerated. The measurement in the laboratory may be somewhat difficult, both for the factor IX extended half-life products and the factor VIII extended half-life products, so it's important that you, as a hemophilia expert, understand the activating products that are used in your 1-stage factor VIII or factor IX assay. It's critical to understand how to use your chromogenic assays for both factor VIII and factor IX. This will become much more apparent further on in our discussion. And it's also reassuring that these extended half-life products can be used in numerous types of clinical scenarios, but certainly for prophylaxis, they are extremely useful, and improve patient compliance, overall joint health, and also overall need for the hemophilia team to be contacted with every bleed that the patient might be experiencing.

Recommendations for prophylaxis

Guy Young, MD: So, let's move on and discuss recommendations for prophylaxis. On the left side are the Medical and Scientific Advisory Council (MASAC) and (World Federation of Hemophilia (WFH) statements. I'm not going to read them in great detail. Suffice it to say that prophylaxis should be initiated at an early age, ideally before age 3 years and before the second joint bleed. Also, prophylaxis needs to be individualized by dose and/or frequency adjustment. And it needs to be sufficient to prevent all bleeds at all times. The options for prophylaxis include all the various factor products, plasma-derived, standard half-life, extended half-life, as well as the new product that Dr. Kessler just discussed and nonfactor replacements.

More recently, the International Society on Thrombosis and Haemostasis (ISTH) put out its own guidelines, and [they] essentially also agree that prophylaxis is recommended over episodic treatment for both hemophilia A and hemophilia B. For patients without inhibitors, you can use emicizumab or factor VIII concentrate. For those with inhibitors, emicizumab is recommended over bypassing agents. And for hemophilia B, any of the factor IX concentrates could be used for prophylaxis.

Personalizing clotting factor concentrates

As far as treatment personalization, considering clotting factor concentrates, standard half-life and extended half-life, for infants and

young children in particular, the need for regular intravenous infusions is challenging. That needs to be balanced with the need to prevent joint damage and other morbidities, as well as thinking about the potential quality of life, mental health implications, the potential cost, and these issues with frequent venous access and potential complications from venous access, including the placement of central venous catheters. For older children, adolescents, or adults, really prophylaxis with factor therapy should be given according to the prescribing information for all the various products that are available. Obviously, there's different choices, some with less frequent infusions, some with more frequent infusions. There are strengths and weaknesses to both approaches. By and large, I do agree with Dr. Kessler about efanesoctocog alfa, which is really a game-changer, and it does allow for patients to dose weekly and have truly the best outcomes with respect to factor VIII levels, bleed prevention, and the convenience of weekly infusions. So, these are all the things that need to be taken into consideration when you're thinking about personalization with factor products.

Inhibitor formation

As far as inhibitor formation is concerned, inhibitors are neutralizing alloantibodies to exogenous factor VIII or factor IX proteins. These will result in ineffective treatment with factor therapy and they can occur in both hemophilia A and hemophilia B. It's more common in patients with hemophilia A, with an incidence of 25% to 30% more or less, regardless of factor product, although there is some data that plasma-derived factor VIII may result in lower rates of inhibitors based on some previous studies that are published. In hemophilia B, the incidence is lower, about 3% to 5%, and it doesn't seem to matter which factor product is used in that case. And so inhibitors are a key safety issue when it comes to factor therapy and the development of inhibitor really does change the way that hemophilia needs to be managed for both hemophilia A and hemophilia B.

FACTOR VIII MIMETICS: EMICIZUMAB

Emicizumab: Pharmacology

Craig M. Kessler, MD: In our discussion thus far, we've concentrated on the use of specific clotting factor concentrates to replace the deficiencies that are the cause of bleeding in individuals with hemophilia A with factor VIII deficiency and hemophilia B with factor IX deficiency. So, I'd like to proceed now with what we have as a very important, novel alternative to the use of specific clotting factor concentrates and that is the use of factor VIII mimetics in individuals who have severe and moderately severe hemophilia A, as well as individuals who have severe hemophilia A or other types of severity of hemophilia A complicated by the development of alloantibody inhibitors. And that is with the use of the first factor VIII mimetic emicizumab.

Now, this is an extremely ingenious molecule because it takes into account the basic physiology of coagulation that occurs most efficiently on a phospholipid template. We know that the role of factor VIII is to bridge the distance between factor IXa and factor X on the surface of a phospholipid template. And when these 2 proteins come into juxtaposition, factor IXa activates factor X in order to generate and stimulate the Xa's complex which then eventually leads to thrombin generation. With emicizumab, we now have a tool that we can use for individuals with factor VIII alloantibody inhibitors, those inhibitors that neutralize the factor VIII that you would infuse into these individuals to treat their acute bleeds. Therefore, we no longer have to rely on some of the prothrombin complex concentrates or the activated prothrombin concentrates to affect coagulation.

And, in the comparison with factor VIII and emicizumab, there are certain features that I think are quite important in the physiology of thrombin generation and coagulation and hemostasis. One is that this monoclonal antibody, emicizumab, has a low binding affinity to factor IXa. Now, this is important because the scientists were very aware that if you have too strong an affinity, you might not be able to turn off thrombin generation and you may transform a bleeding patient with severe hemophilia A into one who was hypercoagulable to develop venous and arterial thrombotic complications. So, having a lower affinity to the substrate is an advantage to emicizumab and, thus far, to my knowledge, there have been very few cases, if any, of severe hemophilia A patients who have developed thrombotic complications when emicizumab is used in the absence of activated prothrombin complex concentrates (aPCC). So, it appears that this product is relatively safe. In nonsevere hemophilia A, there have been some thrombotic complications and, of course, we have to be very careful about looking for what we call thrombogenic consequences with microangiopathic anemias. They can occur with this disease.

The real game-changer characteristic of emicizumab vs the factor VIII concentrates is that you can use emicizumab as a subcutaneous injectable drug rather than always relying on the intravenous route of administration, which is the bane of the existence of these factor VIII products, even the novel ones, that all require intravenous access. The other issue is the half-life of emicizumab vs factor VIII. So, emicizumab is a bispecific monoclonal antibody, it's a humanized IgG molecule and, therefore, it circulates in plasma for weeks to months, whereas the factor VIII products, as we've shown outside of efanesoctocog alfa, have a half-life of somewhere between 12 to 18 hours, maybe a little more in certain individuals. Efanesoctocog alfa has a half-life which is longer, but the issue is that it's in days vs emicizumab whose half-life and hemostatic efficacy lasts for weeks to over a month.

Emicizumab: Dosing

Emicizumab has been extensively studied in many clinical trials in many age groups, in many different kinds of scenarios, both in patients with and without inhibitors. And it appears that a dosing regimen which is user-friendly has been established for patients with and without inhibitors. It requires, however, a loading dose regimen for emicizumab as you initiate the treatment. We usually start off with a loading dose of 3 mg/kg subcutaneously weekly for 4 weeks. Once that loading dose regimen has been accomplished, you can determine from patient preference whether you want to use weekly, every 2 weeks or every 4-week regimens. And, of course, the dosing of emicizumab is going to be higher in the longer-interval dosing vs the shorter-interval dosing. Most of my patients are on every 2-week intervals at 3 mg/kg. I might add that in adults who are on the high basal metabolic index range, that there may be more than 1 subcutaneous injection required. That is also to be taken into

consideration if you're going to use the every 4-week dosing instead of every 2 weeks.

The drug is well tolerated. Patients do sometimes complain about burning at the injection site, but this is overall well tolerated, particularly compared to having to give yourself intravenous infusions of clotting factor concentrate.

Emicizumab: Clinical monitoring

Now, again, when we talk about these bypassing mimetics, we have other issues that we need to consider. We've talked about the thrombotic microangiopathic changes that can occur in some individuals, as well as thrombotic events, particularly when activated prothrombin complex concentrates are also used as part of therapy. So, the recommendation these days is to try to avoid the concurrent use of both of these classes of products when you're dealing with inhibitor-related bleeding complications or if you are going to be using the aPCCs, then you should be using them at reduced dosing regimens. This is all delineated in the package insert and in many articles that have been published in the literature.

The other issue about emicizumab is that you can develop anti-idiotypic antibodies against this particular monoclonal antibody. Fortunately, this is a relatively rare phenomenon, but when you do develop these antibodies against emicizumab, there is a dramatic reversal of the hemostatic effects of emicizumab. We'll be talking in a few minutes about how you can detect the development of these antibodies, but they can occur. If the individual develops sudden, increased bruising or bleeding after being well controlled on emicizumab, you should be prepared to look for the development of an antibody against the emicizumab molecule.

Otherwise, the drug is easy to use and is really a major game-changer as well for patients with inhibitors. Emicizumab can also be used in individuals with moderately severe and severe hemophilia, without inhibitors. And again, in those individuals, there's established safety and efficacy.

Emicizumab: Laboratory monitoring

Let's talk a little bit about laboratory monitoring of emicizumab. It's not unusual for Dr. Young and me to get a call from the emergency department when one of our emicizumab patients comes in with a bleed or a breakthrough bleed and the emergency medicine clinician says, "Dr. Kessler, I'm going to discharge this patient because his factor VIII level is 500% and his partial thromboplastin time (PTT) is 14 seconds. So, obviously, the bleed that he has is not related to his hemophilia." Well, in actuality, that tells us how ineffective and inaccurate our 1-stage clotting factor activities are in patients who are using the factor VIII mimetics. You cannot use a routine PTT or a routine factor VIII activity assay to monitor patients who are on emicizumab. What you have to resort to is a bovine substrate-based, chromogenic factor VIII activity assay for these patients. Unfortunately, not every medical center has these bovine substrate clotting factor activity assays readily available. What I typically do, however, is, realizing that when you give emicizumab, you're not necessarily monitoring the factor VIII activity. You're looking at the effects on hemostasis of the thrombin that's been generated by the use of emicizumab. There is no good laboratory assay, even if you measured emicizumab in the plasma, which gives you an exact factor VIII activity value. So, what has been contrived by Genentech is a thrombin equivalency to what would be expected to be achieved hemostatically by factor VIII, so that the amount of thrombin-generated efficacy is typically about 20% factor VIII activity. Now, that means then that these individuals on emicizumab may have difficulty with breakthrough bleeding, particularly related to trauma.

If a patient comes in with a traumatic bleed, then I do not dismiss the contribution of their underlying hemophilia despite what the clotting factor or laboratory assays might tell you otherwise These patients can be treated with a bolus of factor VIII concentrate in order to reverse their bleeding episode. So again, just because they're on emicizumab and just because their clotting factor activities may appear to be providing adequate hemostasis, these patients still need to be treated with some form of clotting factor replacement. If they have an inhibitor, of course, you may need to use recombinant factor VIIa or aPCC to achieve adequate hemostasis.

FACTOR VIII MIMETICS: MIM8

Mim8: Pharmacology

Guy Young, MD: I'd like to discuss another bispecific antibody. This is called Mim8; it is investigational. The generic name you can see is denecimig. So, that is a fully humanized, bispecific IgG4 antibody which mimics the function of factor VIIIa by bridging factor IXa and X. So, essentially functioning very similar, really in exactly the same way, as emicizumab. It is designed a bit differently in order to improve some of its properties.

FRONTIER1 trial: Design

FRONTIER1 is the phase 2 trial that involved multiple ascending doses. This was essentially a dose-finding trial. The eligibility for the trial was males between the ages of 12 and 64 years with hemophilia A, with or without inhibitors. They all had to have severe hemophilia A. I won't get into all the detail of the trial design. Suffice it to say that the whole idea here was to find what would be the ideal dose for different dosing schedules, including a weekly and an every 4-week dosing schedule. And the key primary endpoint was adverse events, but the key secondary endpoints were injection site reactions, anti-Mim8 antibodies, and change in safety biomarkers. But essentially the other main point here was to find the right dose.

FRONTIER1 trial: Safety

If we look at adverse events, really nothing too noteworthy. In particular, the ones that were potentially related to Mim8 were generally speaking injection site reactions, which is something that is seen with most of these products that are subcutaneous injections. There were no thrombotic events. I think that's a key point. And there were no severe adverse events that were attributed to Mim8.

FRONTIER1 trial: Summary

Now again, this was a phase 2 trial. It's really not designed to look in detail about efficacy, but, of course, we do want to see a little bit about the impact of the different doses. Here we have cohorts 1 through 5 with the dosing increasing, going from cohort 1 to cohort 5. And this figure is showing bleeds per participant per cohort. The

number of bleeds during the time period that they were receiving Mim8 and dividing it into traumatic bleeds in the dark blue and spontaneous bleeds into the light blue. In cohort 1, we see a lot of bleeds, but then cohorts 2, 3, and 4, we see very, very few bleeds. Cohort 5, there was 1 patient who reported a lot of spontaneous bleeds, but the other 2 reported a fairly minimal number of bleeds. From this, that's where the dosing for the phase 3 study was drawn from. The conclusion here was that the pharmacokinetic properties of Mim8 were consistent with dose proportionality and supported weekly and monthly dosing approaches. The terminal half-life of Mim8 was about a month and the maximum plasma concentration was reached after 10 days. There is a dose-dependent increase in thrombin generation observed as well, which is not surprising. To make a correlation to emicizumab, the concentration of Mim8 required to reach the same thrombin peak height as emicizumab was 15-fold lower. Remember I mentioned that Mim8 was designed to have some enhanced properties, one of those properties is that it takes far less Mim8 in terms of a concentration to achieve the same effect as emicizumab. How that translates clinically remains to be seen. I think one way it obviously translates clinically is that the total dose of Mim8 is actually less on a milligram for milligram basis and that has to do with its increased potency. But whether that translates clinically into better efficacy is something that remains to be seen. There were no antiMim8 antibodies reported in FRONTIER1.

FRONTIER2 trial: Design

More recently, we have the results of the FRONTIER2 study. It was just presented a couple of months ago at the ISTH meeting. FRONTIER2 was an international, open label, randomized, phase 3 trial. Doses of Mim8 were once weekly and once monthly. Again, Mim8 is subcutaneous like emicizumab. Mim8 was compared to either no prophylaxis or to patients who were on prior coagulation factor prophylaxis. In other words, there was an on-demand arm and a previous prophylaxis arm.

FRONTIER2 trial: Results

As far as the no prophylaxis treatment or the no prior prophylaxis [were concerned], Mim8 had a 97% and 99% reduction in bleeding. Now, that's not surprising when you're comparing things to no prophylaxis, but essentially proves that Mim8 does work to prevent bleeding. And most of the patients who were treated with once-weekly Mim8 had zero treated bleeds with 86% with the weekly and 95% with monthly dosing. None of the patients on no prophylaxis had zero treated bleeds.

Compared to prior factor prophylaxis, we do see a reduction in bleeding as well of 48% and 43% in treated bleeds vs prior coagulation factor prophylaxis, the 48% and 43% refer to the dosing, again weekly 48% and monthly a 43% reduction. So, Mim8 was superior to factor prophylaxis. A key point here is that this was standard half-life or extended half-life factors and did not include efanesoctocog alpha, as was discussed earlier, since that product is a newer product. And this reduction is fairly similar to what was seen in the emicizumab clinical trial, specifically the HAVEN 3 clinical trial. And, as far as patients experiencing zero bleeds, it's around two-thirds of patients, regardless of which dose of Mim8 they were on. There were no deaths and no thromboembolic events reported in the trial. So that's a brief nutshell of the FRONTIER2, phase 3 clinical trial of Mim8.

REBALANCING AGENTS: CONCIZUMAB

Concizumab

Craig M. Kessler, MD: I'd like now to begin discussion on a different group of hemostatic agents which are classified as rebalancing agents. These are agents which are nonclotting factor-related proteins that actually stimulate coagulation with thrombin generation, but by rebalancing the natural physiologic mechanisms which are intact in normal individuals to prevent the overproduction of thrombin to produce a hypercoagulable state. Concizumab is an investigational molecule which inhibits tissue factor pathway inhibitor (TFPI). Now, tissue factor pathway inhibitor is a naturally occurring inhibitor of coagulation which all of us have.

It is TFPI which inhibits the extrinsic pathway generation of thrombin. If you were to take a look at individuals with severe hemophilia A or B, you realize that their extrinsic pathway of coagulation is normal. They have normal prothrombin times, but why do they bleed? And the reason they bleed is because TFPI prevents thrombin generation through the extrinsic pathway. All thrombin is generated through the intrinsic pathway as factor VIIa, tissue factor, and TIM-AR stimulating the activation of factor IXa or XI in the intrinsic pathway.

Concizumab Explorer7 trial: Design

Here we have a molecule that disrupts this naturally occurring inhibitor of extrinsic pathway generation of thrombin. Essentially, by blocking TFPI, you make an individual who is a bleeder with factor VIII or factor IX deficiency, either naturally or by having developed an alloantibody inhibitor, into an individual who is potentially hypercoagulable. In the Explorer7 clinical trial using the TFPI inhibitor concizumab, patients who had either hemophilia A or hemophilia B with alloantibody inhibitors over the age of 12 years and who had been on bypassing agent prior to going into the clinical trial were randomized into 2 groups. One group was on an on-demand therapy where they continued to use their prothrombin complex concentrate or recombinant factor VIIa for at least 24 weeks and the second group received prophylaxis treatment with concizumab. Concizumab was subcutaneously injected over 32 weeks.

Now, the primary endpoint was spontaneous and traumatic bleeding. There were also substudies that were also evaluated for prophylaxis, but I think that I'm going to concentrate on these other 2 major groups 1 and 2.

Explorer7 trial: Efficacy

The ABR in individuals who were not on prophylaxis vs those who were on concizumab prophylaxis was a very statistically significant reduction in the ABR. In fact, their ABR went from 11.8 down to 1.7. Certainly, that is a remarkable improvement and gives us confidence that we can use this drug in patients with inhibitors and make a major difference in their ABR. And this was seen whether you were talking about joint bleeds, target bleeds, or any spontaneous bleeding episode.

As we discussed earlier with emicizumab and with contrived molecules, we're always concerned about the development of

antibodies to these contrived molecules by our immune system and, indeed, one of the problems with concizumab in the Explorer7 clinical trial is that over 25% of individuals developed antibodies that were directed against concizumab. Fortunately, these antibodies did not interfere with the hemostatic efficacy of concizumab, but I think that this is something that we need to be aware of. Up to now then, no evidence of neutralizing antibodies, but certainly evidence of alloantibodies against the contrived molecule.

Explorer7 trial: Safety

As far as safety is concerned, again as I alluded to before, the interference of our naturally occurring anticoagulant, TFPI, inhibiting that naturally-occurring anticoagulant pathway may lead toward a hypercoagulable state. Up to now, there have been very few cases of thromboembolism in patients. There was 1 serious thromboembolic complication. This was a renal infarction that occurred in the concizumab arm in the Explorer7 safety profile. As this molecule becomes more widely used, I think it's going to be extremely important to monitor for hypercoagulability.

REBALANCING AGENTS: MARSTACIMAB

Marstacimab BASIS trial: Design

Guy Young, MD: Now we're going to discuss marstacimab, which is an investigational monoclonal antibody to TFPI, similar to concizumab. Marstacimab is delivered subcutaneously and the dosing is weekly. I'm going to show you the results of the BASIS trial. This was an international, open-label, phase 3 trial. This included only patients without inhibitors, so hemophilia A, severe, hemophilia B, severe or moderately severe meaning less than or equal to 2% factor IX, but for patients without inhibitors. There was a comparison again to an on-demand group as many of these trials do and there was a 6-month observational phase where data was collected on bleed outcomes.

Then, the patients went into the active treatment phase. We're going to have the comparisons to on-demand and the comparisons to prior factor prophylaxis. The dosing started with a loading dose of 300 mg and then the dosing proceeds with 150 mg subcutaneously once weekly. One thing to note here, which is a bit of a difference from the other products, is that this drug is on fixed dosing for patients older than 12 years. It doesn't matter what your weight is, everybody gets the same dose. The main endpoints, of course, were ABR, as usual, and safety as well.

BASIS trial: Efficacy

Let's take a look first at the left panel. The left panel is the previously on-demand patients. In the observational phase, which is what the OP is in that bluish bar, the ABR was a 38. In the active treatment phase, so this is the treatment with concizumab, that's in that orange color, the ABR was substantially lower at 3.2, so that's about a 92% reduction in bleeding. Some of those patients then continued into a long-term extension, which is what LTE is, for up to 16 months and they maintained the low bleeding rate of an ABR of 3.9.

On the right panel, is the group that previously was on routine factor prophylaxis and the same color conventions and abbreviations apply. So, the observational phase here had an ABR of about 8 and that's a little bit unusual. Most patients on routine prophylaxis would have ABRs far lower than that and furthermore, in the other clinical trials that had been done for other products, those ABRs in the routine prophylaxis observational phase are typically about 2, 3, or maybe 4. So, there's something a little bit unusual about this group. It's not entirely clear why they had a higher ABR. They were receiving full factor prophylaxis, not low-dose prophylaxis, in case you were wondering about that.

If we look at the active treatment phase, the ABR is 5.1. This represents a 35% reduction with marstacimab over factor prophylaxis, but that is a rather high ABR, 5.1. We don't see that with most of the new products. Now, those patients that did continue into the long-term extension, you'll notice it's a proportion of the patients, their ABR was a lot lower at 2.3 and certainly that would be acceptable by most accounts and comparing it to other products, at least much more in line with the other products. I think the conclusion here is that marstacimab does show efficacy in terms of reducing bleeds, however, I think there's still some questions about just how efficacious marstacimab is, given this data. But we just need more data to really confirm the ABR outcome in more of the long-term extension having more patients moving into that arm, particularly those from the routine prophylaxis group.

BASIS trial: Safety

When we look at safety, I think 1 main advantage here is that there were no thrombotic events. This is different from fitusiran, which we'll talk about shortly, and different from concizumab and even some of the other products that have been in development where there is the occasional thrombotic event. There were no thrombotic events with marstacimab, so that's a strength of the safety data. Other adverse events were fairly minimal. Injection site reactions were reported, but in a relatively small percent of patients.

Anti TFPI therapy: Summary

What about anti-TFPI therapy and future considerations? So, this is another category of drugs that can be delivered subcutaneously, so that is an advantage. As we talked early, subcutaneous therapy is going to improve adherence. Anti-TFPI therapy has shown reduced bleeding rates, both of these products have shown reduced bleeding rates compared to factor prophylaxis. And these can be used in patients with inhibitors as we've seen already from the trials with concizumab, but we don't yet have that data on marstacimab. Mild or moderate injection site reactions do occur. I think these are fairly minimal. The risk of thromboembolic events is low, including with concizumab, it is low but not absent and with marstacimab, we have yet to see any thrombotic events.

REBALANCING AGENTS: FITUSIRAN

Fitusiran: Overview

Guy Young, MD: Now we're going to talk about the investigational medication fitusiran. This is a small interfering RNA molecule with a mechanism of action that targets hepatic antithrombin. The idea here is if we can lower the antithrombin level, that we'll have less

interference with the thrombin generation that hemophilia patients can make. Hemophilia patients can generate some thrombin, it's a limited amount, but if we don't block that thrombin with antithrombin, then we can get into the feedback loop and generate sufficient thrombin generation.

Fitusiran has been extensively studied, including ATLAS-INH, which was the study for only patients with inhibitors. ATLAS-AB was for patients without inhibitors. Essentially, these trials showed that fitusiran can significantly reduce bleeding rates with a mean ABR of 1.7 in the ATLAS-INH trial, so the patients with inhibitors, and a median of 0 with 66% of the patients on fitusiran having no bleeds compared to 5% on bypassing agent therapy. There were some thrombotic events in 5% of the patients in the fitusiran group. With the ATLAS-AB trial, there were no thrombotic events. The other results are fairly similar with substantial reductions in the ABR compared to factor prophylaxis with a fitusiran mean ABR of 3.1 and a median of 0 in 51% of the patients having no bleeds at all.

Fitusiran: Early safety

Initially, the dose of fitusiran was 80 mg subcutaneously once a month, which was shown to be a really effective approach. However, there were some safety considerations. There were aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations in all the different studies, including one I didn't discuss, ATLAS-PPX, which was for patients on prior prophylaxis. There were also some hepatobiliary disorders of around 20%, with cholecystitis and cholelithiasis. And then there were some thrombotic events, as I mentioned, a total of 4 in all of these trials, which represents about 2% of the total population. The liver enzyme elevations and other safety issues led to a change in the dosing regimen. Instead of 80 mg once per month, patients now start on 50 mg every other month. The new trial that's going on now, as well as all the patients on the extension trials of these other studies that I've mentioned, start at 50 mg every other month with the goal of an antithrombin level between 15% and 35%. If the level is below 15%, the dose can be lowered. If the antithrombin level's above 35%, then the dose can be intensified, either to monthly or even to the original dose of 80 mg once per month.

Fitusiran: Updated safety

The question is, did this new dosing regimen aimed at reducing thrombotic events, aimed at reducing hepatobiliary events, and ALT/AST elevations, actually work? And, in fact, it did. Thrombotic events were substantially lower and compared to another small study that was done, the thrombotic events now look like they're the same rate as hemophilia baseline populations. In other words, no real increase in the incidence of thrombotic events compared to hemophilia patients who are not on fitusiran. We also had a reduction in the ALT/AST which was substantial from about 18 per hundred patient-years down to 2 per hundred patient-years, so much lower rate of ALT/AST elevation. There also was a reduced rate of cholelithiasis and cholecystitis. This new dosing regimen of fitusiran is clearly safer in terms of fewer ALT/AST elevations, fewer hepatobiliary events, and fewer thrombotic events. Unfortunately, though, there is an increase in bleeding events. So, once we've raised the antithrombin level from what was around 10%, 11% on the original dose regimen to 15% to 35%, averaging around 25%, on this newer dosing regimen, while we have definitely improved safety, as I mentioned, we have compromised a bit on bleeding. So now, the median ABRs which, remember, were 0 across the board are now 3.7. While more than half the patients had 0 bleeds, we're now down to about a third of the patients had 0 bleeds. Now, this is still a clinically meaningful bleed protection. Median ABRs of around 3 are certainly potentially considered reasonable and a third of the patients having 0 bleeds is also reasonable. In fact, half the patients had 0 or 1 bleed per year. A reasonable outcome, but I think it's clear with fitusiran that if you're going to increase the antithrombin levels, in other words have less of the fitusiran effect for safety, you are going to have an increased bleeding event rate. And the final slide I'll share with you is one that looks at the ABR compared to the antithrombin level where you see a clear reduction in ABR compared to what the antithrombin level is. And once fitusiran is available clinically, I think decisions will be made on a case-by-case basis about where to aim the antithrombin level. It is easily measurable in a regular lab to determine how you might dose fitusiran in your patient to maximize the efficacy while maintaining safety.

GENE THERAPIES

Gene therapies: Overview

Craig M. Kessler, MD: Now we can begin to discuss the ultimate therapy for individuals who have hemophilia A or B and that is the next step toward the cure of the bleeding disorder. Now, it's remarkable that we've made such great strides in the treatment of the bleeding disorder, the phenotypic bleeding disorder, with all of the novel therapies that we've discussed up to now. And now we're beginning to see emerge the possibility of actually changing the genotype in addition to changing the phenotype of bleeding in individuals who have hemophilia.

Gene therapies: Approved products

In that regard now, we have 3 products that have been FDA-licensed for gene therapy in hemophilia A and B, 1 product, valoctocogene roxaparvovec (Roctavian), for the gene therapy of hemophilia A, and 2 products for gene therapy for the treatment of hemophilia B, etranacogene dezaparvovec (Hemgenix) and fidanacogene elaparvovec (Beqvez). Now, are these gene therapies that are now commercially available actual cures for hemophilia A and hemophilia B? Well, we're not really sure that we can say that they're cures. We know that gene therapy has been very effective in modifying the phenotypic characteristics of bleeding in those who have undergone gene therapy. And even if these gene therapies have not universally been able to produce what we would say would be recoveries in factor VIII or factor IX levels that would be within the normal range, most of these patients still see a phenotypic improvement in their bleeding rate, in their annualized bleeding rate, even if they don't achieve what I would consider to be an adequate level of clotting factor activity. Now, in the factor VIII and IX gene therapy realm, it's important to understand that all of these gene therapies are currently what we call episome gene therapies. That means that, when we introduce the factor VIII or factor IX gene into the individual's nucleus, and all of these are hepatic-based therapies, that these are not integrated into the DNA of the patient. Instead, these interact in such a way that the messenger RNAs will produce the clotting factor for which the gene is dedicated to produce. The liver certainly knows how

to make factor IX because it's a vitamin K-dependent clotting factor which is made in the liver and we see, in individuals who have received gene therapy for factor IX, that the fidanacogene elaparvovec and etranacogene dezaparvovec gene therapies produce durable factor IX activities, much more so than the limited durability that we see for factor VIII gene therapy valoctocogene roxaparvovec. Valoctocogene roxaparvovec is a hepatocyte-related synthesis of factor VIII in a cell that isn't used to making factor VIII normally. Factor VIII is made, as you know, in the blood vessel endothelial cells of the liver, but not in the hepatocyte itself. That may actually explain why the durability of gene therapy in hemophilia A is less robust than it is in factor IX gene therapy.