

Highlights in Hemophilia and von Willebrand Disease From the 2013 American Society of Hematology Meeting

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OBI-1 Found Safe, Effective in Patients With Acquired Hemophilia A

The investigational agent OBI-1 was found to be safe and effective for episodes of bleeding in patients with acquired hemophilia A, according to a phase 2/3 trial. OBI-1 is a bioengineered form of porcine recombinant factor VIII.

In the global, prospective trial, which was presented by Dr Rebecca Kruse-Jarres of Tulane University School of Medicine in New Orleans, Louisiana, 18 adults with severe bleeding episodes caused by acquired hemophilia A received an initial 200 U/kg dose of OBI-1, followed by additional doses as needed based on individual target levels of factor VIII, anti-OBI-1 titers, and clinical factors.

The bleeding complications of all 18 participants responded to treatment at 24 hours after administration; 14 patients had a complete response and 4 had a partial response. The response to treatment was apparent within 8 hours in 14 patients and within 16 hours in 16 patients. The median total dosage of administered OBI-1 was 1782.5 U/kg per patient. Study participants who received additional doses of OBI-1 received between 9180 and 13,561 U per dose. Most of the patients (17) also received immunosuppressive therapies.

More than one-quarter (27.8%) of the patients experienced a nonserious adverse reaction to treatment. Mild tachycardia, hypotension, and constipation occurred in 1 patient; mild peripherally inserted central catheter line occlusion occurred twice in 1 patient; and mild hypofibrinogenemia occurred in 1 patient. All side effects resolved completely, and no serious adverse side effects occurred. One-third of the patients had anti-porcine factor VIII inhibitors prior to infusion of OBI-1, and 3 patients developed anti-porcine factor VIII inhibitors after infusion but these inhibitors did not affect the hemostatic effectiveness of additional doses of OBI-1.

Acquired hemophilia A is a rare bleeding disorder that typically affects young women and older men in a bimodal age distribution. Bypass therapies such as OBI-1 are designed to promote the generation of thrombin and effective hemostasis by “circumventing” the inhibitory effects of autoantibodies that are directed against factor VIII and neutralize its coagulant activity. The development of these autoantibody inhibitory immunoglobulins has been associated with underlying disease states and factors such as autoimmune diseases, cancers, pregnancy, and

medications. One advantage of OBI-1 over other bypass therapies is that patients can have factor VIII monitoring throughout the treatment and healing phases. This allows for more accurate dosing and appears to reduce the frequency of hypercoagulability complications, which occur with other bypassing agents.

Kruse-Jarres R, St Louis J, Greist A, et al. Treatment of serious bleeds with a B-domain deleted recombinant porcine sequence factor VIII (OBI-1) in patients with acquired hemophilia A: a prospective clinical trial [ASH abstract 206]. *Blood*. 2013;122(21).

Inhibition of Tissue Factor Pathway Inhibitor: a Potential Strategy for Hemophilia

New information about tissue factor pathway inhibitor (TFPI) isoforms has the potential to aid in the development of TFPI-blocking agents to treat hemophilia, according to a presentation by Dr Alan E. Mast of the BloodCenter of Wisconsin in Milwaukee, Wisconsin.

The anticoagulant protein TFPI works to regulate the extrinsic clotting pathway by inhibiting thrombin generation mediated by the complex formed by tissue factor, factor Xa, and factor VIIa. One way to enhance the impaired hemostasis in people with bleeding disorders such as hemophilia could involve specific blockade of TFPI; this approach has been shown to be effective in animal models. Agents that block TFPI activity are believed to work by allowing the generation of tissue factor-mediated thrombin through the extrinsic pathway, fully bypassing the intrinsic pathway proteins that are deficient in the hemophilias (factors VIII and IX).

The 2 primary isoforms of TFPI are TFPIa and TFPIb. Endothelial cells and megakaryocytes produce TFPIa, which limits the growth of blood clots after vascular injury. Endothelial cells also produce TFPIb, which inhibits tumor factor-mediated cellular migration. In mouse models of hemophilia, TFPIa had been shown to alter bleeding and TFPIb has been shown to dampen the effects of tumor factor-induced intravascular coagulation.

“This new knowledge of TFPI isoform expression patterns and anticoagulant activities has important implications for the development of TFPI-blocking pharmaceuticals to treat hemophilia,” according to Dr Mast.

Mast AE, Maroney SA. The potential to enhance hemostasis by inhibiting tissue factor pathway inhibitor [ASH abstract SCI-9]. *Blood*. 2013;122(21).

Long-Lasting Factor VIII Replacement Therapies Expected to Transform Treatment of Hemophilia A

The emerging class of long-lasting recombinant factor VIII proteins is poised to transform prophylactic therapy for children with severe hemophilia A, explained Dr Amy D. Shapiro during the American Society of Hematology (ASH) Education Program. The first of these agents is expected to receive US Food and Drug Administration (FDA) approval soon.

Recombinant factor VIII Fc fusion protein (rFVIII-Fc), an agent that employs Fc fusion technology, was submitted for FDA review in early 2013 based on the results of the ALONG (Study to Evaluate the Safety, Pharmacokinetics and Efficacy of Recombinant Factor VIII Fc Fusion Protein in Subjects With Severe Hemophilia A) trial of children aged 12 years and older with at least 150 days of exposure to factor VIII (NCT01181128). In this trial, the agent was injected once or twice a week for the treatment of bleeding episodes.

In addition, Dr Shapiro said that 3 recombinant factor VIII polyethylene glycol (PEG) conjugates were being studied in ongoing phase 2/3 trials: BAY 94-9027, which employs site-specific PEGylation (NCT01184820); BAX 855, which uses PEGylation by controlled chemical means at specific lysine residues (NCT01736475); and N8-GP, which employs single site-specific glycoPEGylation (NCT01480180). She added that the Kids ALONG (Study of Recombinant Coagulation Factor VIII Fc Fusion Protein, BIIB 031, in Pediatric PTP Subjects With Hemophilia A) trial is evaluating the use of rFVIII-Fc for bleeding prophylaxis in approximately 50 patients younger than 12 years with severe hemophilia A and at least 50 documented prior exposures to factor VIII (NCT01458106).

Current treatment of bleeding episodes requires frequent infusions, and prophylactic regimens must be administered 3 times a week or every other day. These newer agents raise the possibility of treating bleeding episodes with fewer injections, and preventing bleeding with 1 or 2 injections per week.

“Long-acting factors have the potential to substantially improve acute management of bleeds, markedly simplify prophylactic regimens, and provide an opportunity for improved individualized treatment for hemophilia A,” Dr Shapiro concluded.

Similar technologies have also been applied for factor IX replacement products and several are awaiting FDA approval.

Dr Shapiro is affiliated with the Indiana Hemophilia and Thrombosis Center in Indianapolis, Indiana, and Michigan State University in East Lansing, Michigan.

Shapiro AD. Long-lasting recombinant factor VIII proteins for hemophilia A. *Hematology Am Soc Hematol Educ Program*. 2013;2013:37-43.



Dr Katherine A. High delivering the E. Donnell Thomas Lecture. Photo courtesy of the American Society of Hematology.

The Development of Gene Therapy for Use in Hematologic Disorders

Tremendous advances have been made in gene therapy over the past 2 decades, according to Dr Katherine A. High of The Children's Hospital of Philadelphia in Philadelphia, Pennsylvania, who gave an overview of the use of gene therapy to treat inherited disorders as the E. Donnell Thomas Lecture. ASH awarded the 2013 E. Donnell Thomas Prize to Dr High for her trailblazing work in hemophilia.

A 4-year-old girl with adenosine deaminase deficiency became the first gene therapy patient in 1990, said Dr High. Alipogene tiparvovec (Glybera, UniQure) became the first approved gene therapy drug in the Western world after it received approval from the European Medicines Agency in 2012 to treat lipoprotein lipase deficiency.

Gene therapy is also being studied for use in hematologic disorders, including hemophilia B, porphyria, hemophilia A, and Gaucher disease. Like alipogene tiparvovec, these treatments employ gene transfer with adeno-associated virus (AAV) vectors. AAV vectors are excellent vehicles for gene delivery because they lack pathogenicity, are replication-defective, are predominantly nonintegrating, and can establish long-term transgene expression. In addition, different serologic subtypes work in different cell types.

Discussing her own work in AAV therapy for hemophilia, Dr High said that her team has identified a dose that can be administered safely and that leads to long-term expression at therapeutic levels in humans. Her studies used transaminase elevation as a marker of cellular immune response, and included provisions for administration of high-dose corticosteroids in case such an immune response—which would endanger the transduced hepatocytes—should occur.

Potential complications of gene therapy include gene silencing, genotoxicity, phototoxicity, immunotoxicity, and horizontal and vertical transmission.

High KA. Sailing to Ithaca: Gene therapy's odyssey from investigational agent to therapeutic product. The E. Donnell Thomas Lecture.

New Light Shed on Molecular and Clinical Biology of von Willebrand Disease

Sequence variations and levels of von Willebrand factor (VWF) less than 40 IU/dL are common among people with type 1 von Willebrand disease (VWD), according to a recent analysis of patients with the disease. The analysis was based on a cohort of nearly 500 patients from the NIH-supported Zimmerman Program for the Molecular and Clinical Biology of VWD.

Dr Robert R. Montgomery of the BloodCenter of Wisconsin and colleagues identified 499 patients with type 1 VWD from a group of 651 people with various forms of the disease. All patients had extensive laboratory testing that included testing for VWF antigen (VWF:Ag), VWF ristocetin cofactor activity (VWF:RCo), factor VIII activity, VWF propeptide (VWFpp), and VWF collagen binding (VWF:CB); analysis of VWF multimers and linkage; and blood typing. A quantitative bleeding score was obtained, and full-length VWF sequencing was conducted.

The researchers found that VWF levels were below 40 IU/dL in 232 patients, between 40 IU/dL and the lower end of the normal range in 93 patients, historically below normal but normal by study testing in 119 patients, and historically normal and normal by study testing in 55 patients. Sequence variations were identified in 53% of the 444 patients in the first 3 groups, and in 74% of the 232 people with VWF levels below 40 IU/dL.

Abnormal bleeding scores, defined as a score of 5 or greater using the International Society on Thrombosis and Haemostasis Bleeding Assessment Tool, occurred in 63% of participants with VWF:Ag of 2 to 10 IU/dL, 66% of those with VWF:Ag of 11 to 20 IU/dL, 64% of those with VWF:Ag of 21 to 30 IU/dL, 48% of those with VWF:Ag of 31 to 40 IU/dL, and 58% of those with VWF:Ag of greater than 40 IU/dL.

The researchers concluded that VWF levels less than 40 IU/dL could be a useful cutoff for the definition of VWD, and that detection of abnormal bleeding scores did not add further diagnostic information. They wrote that “further analysis of the cohort should shed further understanding on the molecular and clinical biology of VWD.”

Montgomery RR, Christopherson P, Bellissimo DB, et al. The complete type 1 VWD cohort of the Zimmerman Program for the Molecular and Clinical Biology of VWD - phenotypic assignment, mutation frequency, and bleeding assessment [ASH abstract 332]. *Blood*. 2013;122(21).

Commentary

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I have chosen to highlight these 5 presentations on hemophilia and VWD because they are provocative and interesting, and potentially will improve the care of patients with bleeding disorders.

In the first presentation, OBI-1 was found to be safe and effective in patients with acquired hemophilia A. OBI-1 is the genetically engineered porcine version of the factor VIII molecule that is missing in acquired hemophilia A. The 2 agents that are currently available to treat or prevent the bleeding complications caused by acquired hemophilia A are factor eight inhibitor bypass activity (FEIBA) and activated recombinant factor VII (rFVIIa) concentrates. The limitations of these products include the fact that their hemostatic capacity cannot be measured in the laboratory with the commonly used global tests of coagulation and the fact that these replacement products are associated with the development of hypercoagulability complications, which may be life- and limb-threatening. In contrast, recombinant porcine factor VIII, similar to the porcine factor VIII concentrate that was formerly available that was purified from the pooled plasmas from pigs (this was removed from the marketplace owing to contamination by porcine parvovirus), has now been shown to restore the coagulation deficiency in humans with acquired hemophilia A (factor VIII deficiency). The coagulation deficiency in these individuals is due to the direct neutralization of their normally synthesized factor VIII protein by their pathologic immunoglobulin G autoantibody. Porcine factor VIII is not usually as susceptible to neutralization by these anti-human factor VIII-directed autoantibodies but can interact with factor IX and phospholipid in

vivo to form the tenase complex necessary for thrombin generation. As a result, one can gauge how much OBI-1 patients will need to reverse or prevent bleeding since the factor VIII activity can be measured in the laboratory. We still have a lot to learn about the clinical usefulness of OBI-1, about the potential problems regarding immunogenicity of this molecule in humans, and about the vagaries of laboratory testing techniques. Despite this, the development of porcine recombinant factor VIII presents hematologists with a different and promising approach to the treatment of acquired hemophilia A bleeding complications, which are often refractory to the currently available bypassing agents.

The second presentation I chose described the theoretical usefulness of inhibiting the inhibitory effects of the TFPI protein. Positioned at a critical location in the common pathway of the coagulation cascade, TFPI is responsible for the need to generate most of the thrombin generation for normal hemostasis through the intrinsic pathway. Overcoming the TFPI blockade of the extrinsic pathway provides a potential strategy for generating effective thrombin levels without the need to depend on the intrinsic pathway. Thus, this treatment approach may be able to treat bleeding complications produced by deficiencies of coagulation factors in the intrinsic pathway, such as hemophilia A and B (factor VIII and factor IX, respectively). Several modulators of coagulation exist in the coagulation cascade. TFPIs block or modulate the extrinsic pathway of coagulation. We now have an experimental blocking antibody that will inhibit TFPI activity, thereby enhancing coagulation through the extrinsic pathway. This approach is the prototype of a means of manipulating the coagulation pathway in such a way that you can bypass the area of deficiency without infusions of the specific deficient clotting factor protein. This new approach provides a rationale for the development of TFPIs for clotting and for the development of other techniques to affect the activity of other modulators in the coagulation pathway (eg, interfering with antithrombin activity to create a “hypercoagulable” tendency in a coagulopathic patient).

The third presentation, on long-lasting replacement therapy for hemophilia A, addressed the development of new products for replacement of either factor VIII or factor IX. By manipulating the factor VIII or factor IX protein via recombinant technology or by altering the genetically engineered factor VIII or factor IX protein in a postsynthetic fashion, one can delay the naturally occurring proteolysis of these proteins in the circulation and thus extend their usual pharmacokinetics. These extended half-life replacement products have the potential to improve the quality of life and the preservation of joint health in individuals with hemophilia. Infusing clotting factor concentrates that “last longer” in the body will allow patients with severe

hemophilia who are on prophylaxis regimens to reduce the frequency of their infusions with clotting factor replacement concentrates. For those with severe hemophilia A (factor VIII deficiency), 3 infusions every week may be reduced to once or twice weekly. This evolution would make treatment more convenient, and would likely lead to an improvement in quality of life and a decrease in joint damage caused by microbleeds in the joints or other tissues by being able to maintain a “trough level” of circulating clotting factor adequate to prevent even subclinical bleeding. Extended factor VIII and factor IX products await approval by the FDA, and several other products will be submitted to the FDA this year. I would expect to see such replacement products for factor VIII and factor IX deficiencies on the US marketplace within the next 6 to 9 months.

The presentation on gene therapy for hematologic disorders was very enlightening and encouraging after so many years of disappointing clinical trials and complications associated with the technology in hemophilia and other diseases. Dr Katherine High, a pioneer in hemophilia gene therapy, provided an excellent overview of gene therapy, including its safety and feasibility. Hemophilia B in particular has been the most advanced target of gene therapy owing to the smaller factor IX gene compared with the factor VIII gene. Vector delivery into the host genome is thus easier to achieve. The goal is to treat and virtually cure not only deficiencies in factor VIII and factor IX, but also deficiencies in other clotting factors and other hematologic diseases. If we could transform an individual with severe hemophilia (factor VIII or factor IX activities <1%) into one with mild or moderately severe hemophilia (factor VIII or factor IX activity 3%-5%) through gene modification, we could expect to see a reduction in morbidity, improved convenience, and an enhanced quality of life. Several other new approaches to gene therapy for hemophilia A and B were presented at the ASH meeting, indicating that the area of gene therapy is alive and well, very promising, and safer than ever before.

Also at the ASH meeting, gene therapy was shown to be potentially useful in cancer patients. For example, upregulating the immune system with gene therapy after chemotherapy might increase the duration of remission in diseases such as leukemia and lymphoma.

The final presentation was the first report on the Zimmerman program, which is looking at the various genes and mutations that are associated with VWD, the most common inherited bleeding disorder. This study represents one of the biggest efforts in the world to increase our understanding of the molecular basis of this bleeding disease, and has added dramatically to our knowledge of how VWD occurs. Learning more about the genotype of VWD is likely to lead to better approaches to treating patients, and undoubtedly will lead to development of innovative therapies.