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EXPERT REVIEWS

Recombinant B domain deleted porcine factor VIII for the treatment of bleeding episodes in adults with acquired hemophilia A

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Edward Gomperts

Division of Hematology-Oncology, Children's Hospital of Los Angeles, 4650 Sunset Boulevard, Los Angeles, CA 90027, USA
jade818@charter.net

Hemophilia A is an inherited deficiency of clotting factor VIII (FVIII) often complicated by inhibitor development (CHAWI) in which neutralizing antibodies block the therapeutic benefit of replacement therapy. Inhibitors to FVIII can also be seen in an auto-immune disease known as acquired hemophilia A (AHA). 'Bypassing' therapies have been shown to provide hemostasis but dosing must be done empirically because current assays cannot measure objective markers of treatment efficacy and safety. A recombinant porcine sequence factor VIII (r-pFVIII) has been developed for the management of AHA. Preclinical, Phase I and Phase II clinical research studies in CHAWI subjects showed therapeutic potential and safety of this agent. A Phase II/III study in AHA with serious bleeding episodes shows a positive response in all subjects after administration. Based on current preclinical and clinical trial data, r-pFVIII should become the first line of treatment in the management of hemorrhage in patients with AHA.

KEYWORDS: acquired hemophilia A • factor VIII • hemophilia A • inhibitor • OBIZUR • recombinant porcine FVIII

The development of inhibitory antibodies to clotting factor VIII (FVIII) is invariably associated with hemorrhagic manifestations that are a challenge to control. These inhibitory antibodies are seen complicating the management of congenital hemophilia A (CHAWI) and are also associated with a rare acquired autoimmune disorder, acquired hemophilia A (AHA).

Hemophilia A is a sex-linked inherited hemorrhagic disorder associated with mutations to the FVIII gene. Severe hemophilia A is associated with virtually no detectable clotting factor activity in the patient's plasma. These patients sustain frequent bleeds into the major joints, muscles around these joints and even experience life-threatening bleeds [1]. The most effective approach for the treatment of acute bleeding episodes in patients with hemophilia A is FVIII replacement therapy that can be sourced from human plasma pools or from a recombinant biotechnological manufacturing process utilizing well-characterized cell lines. Since the FVIII plasma level correlates with efficacy, these levels can be monitored during treatment [1]. Between 20 and 30% of children with hemophilia A develop an inhibitory alloantibody to the therapeutic protein that blocks function of the clotting factor activity (CHAWI), resulting in inadequate or loss of therapeutic effectiveness. Control of bleeding thus becomes a major challenge [1,2].

Unlike CHAWI, individuals who develop acquired auto-antibodies to FVIII (AHA) have a history of normal hemostasis, but present with a severe bleeding diathesis associated with autoimmunity. These auto-antibodies neutralize endogenous human FVIII creating an acquired functional deficiency of procoagulant activity [3,4].

AHA is a rare disorder with an incidence of about 1.4 per million patients per year and primarily affects elderly individuals [3,5,6]. The clinical presentation is often severe hemorrhages that are anatomically diverse and result

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in a mortality rate from hemorrhage between 3 and 20% [3,5,6]. These hemorrhages are often complicated by the elderly patients' co-morbidities. Bleeding is often spontaneous or in response to minimal trauma. The objectives of treatment in AHA are to stop the acute bleeding and to eradicate the autoimmune antibodies [3].

The development of bleeds due to these allo- or autoantibodies in subjects with inherited or AHA, respectively, prevents treatment with human FVIII, unless the inhibitor titer is low. Alternative hemostatic therapies for patients who have high titer anti-human FVIII antibodies are generally bypassing agents, such as activated recombinant factor VII (rFVIIa) and activated prothrombin complex concentrate. Unlike factor replacement therapy, which replaces the missing clotting factor, bypassing agents go around (bypass) the inhibitor-blocking step of clotting pathway to allow the coagulation process to proceed. Bypassing agents are associated with an increased risk of thrombotic events in the AHA patient population that are already at a higher risk due to age and the presence of comorbidities [6–8]. With bypassing agents, therapeutic dosing cannot be assessed; the plasma FVIII level is not a clinically relevant surrogate marker as for replacement therapy and the dosage does not correlate with clinical outcome. Thus, hemostatic efficacy of bypassing agents is typically determined by clinical assessments alone, which increases the risk of inducing thrombotic events and/or ineffective bleed control [3,5,6]. Further, bypassing agents are associated with a 10–30% failure rate in clinical studies [9–11]; therefore, alternative therapies for the treatment of hemophilia patients with antibodies against FVIII are highly desired.

Plasma-derived porcine FVIII (Hyate:C), fractionated from pig plasma, was used successfully but on a limited basis, for over two decades in CHAWI and AHA [12–14]. Patients with inhibitors to FVIII are likely to have lower initial inhibitor titers against porcine factor VIII (p-FVIII) versus titers against human FVIII [12–14]. Patients with AHA have weaker immune responses against p-FVIII [13,14]. However, adverse events (AEs) were described that include allergic reactions, anaphylaxis, thrombocytopenia and anamnesis [12–14]. These reactions and reductions in platelet count were believed to be caused by porcine non-FVIII proteins present in the product. In fact, FVIII was only around 1% of the total protein content [12]. Specifically, the thrombocytopenia was attributed to porcine von Willebrand Factor, due to the spontaneous agglutination of human platelets by porcine von Willebrand Factor [15,16]. Although the clinical benefit of using Hyate:C was high, the safety at doses above 150 U/kg limited its use to severe bleeding episodes where the benefit-to-risk ratio was highest [13,14].

The use of p-FVIII as a beneficial treatment modality was assessed in several clinical settings. In studies in the USA and Europe [17,18], p-FVIII treatment was assessed in subjects with FVIII antibodies who had limb or life-threatening hemorrhages, required major surgery or who had not responded to other treatments. Of the bleeding episodes treated with p-FVIII, 84% were rated as 'excellent' or 'good' in terms of hemostatic efficacy [17]. There are also reports using data collected via 'registries'. The most focused of these was on data collected from 154 CHAWI patients representing 2472 bleeding episodes [19]. The hemostasis efficacy was reported to be 'excellent' or 'good' in 79.7% of patients [19]. A second report from France reported data in 18 CHAWI subjects and 9 subjects with AHA, where a 'favorable clinical outcome' was seen in 86.2% of the 27 subjects. The AHA subjects showed a low initial inhibitor titer against p-FVIII and a weak immune response post-treatment indicating that p-FVIII should be considered as first-line therapy [14].

The commercial production of Hyate:C was discontinued in 2004 because of problems sourcing porcine plasma uncontaminated with a porcine parvovirus [12]. The successful use of Hyate:C to treat AHA and CHAWI patients and the unmet medical need as a result of its discontinuation provided the basis for the development of recombinant porcine FVIII for the treatment of AHA.

Characterization of recombinant porcine FVIII

Recombinant p-FVIII (r-pFVIII) (OBIZUR [antihemophilic factor, recombinant, porcine sequence]) is a 1448 amino acid heterodimer with a molecular mass of 170 kDa consisting of domains with the sequence A1-A2-B-A3-C1-C2. The B domain is partially deleted, retaining a 24 amino acid linker [20,21]. It is manufactured in baby hamster kidney cell line utilizing protein-free medium. There are two viral inactivation/removal steps of solvent/detergent treatment and nanofiltration incorporated into the manufacturing process [20]. The final product is stabilized without protein and highly purified to exclude most host cell-derived contaminants with a specific activity of approximately 9500 U/mg by the one-stage coagulation assay [21]. While the r-pFVIII product has the same domain sequence and subunit structure as hFVIII, there is a significant amount of divergence in the amino acid sequence in the A2 and C2 domains, which allows r-pFVIII to remain fairly free from inactivation by circulating hFVIII antibodies. This allows functional clotting FVIII, which is not impacted by the patient's inhibitory antibodies and thus unimpeded hemostasis.

Pharmacokinetic studies of r-pFVIII

The manufactured r-pFVIII has similar kinetics of clot formation and lysis to plasma-derived p-FVIII (Hyate:C) and to recombinant human FVIII. The hemostatic activity of this product has been demonstrated in murine and canine models of hemophilia A. Data generated in animal models of hemophilia A and in clinical studies indicate that the B domain deletion and its substitute with a linker has no significant impact on functionality compared with full-length p-FVIII or full-length human FVIII [22,23].

The purity of r-pFVIII is >95% compared with <1% in Hyate:C. Given the increased purity of r-pFVIII, the rate of allergic reactions is expected to be the same or greatly reduced compared with Hyate:C. In contrast to Hyate:C, the recombinant product does not contain p-VWD. In the clinical setting, r-pFVIII activity levels can be measured using general FVIII

activity assays with no additional assays or product-specific reagents. In current clinical trials, both local and central laboratories used the WHO plasma sample for assays.

Clinical efficacy

Phase I study in CHAWI subjects

A Phase I study was carried out in nine subjects (aged 15–57 years) with CHAWI in a non-bleeding state receiving either placebo followed immediately by 100 U/kg r-pFVIII, or 100 U/kg Hyate:C followed immediately by placebo [22]. A total of four subjects received r-pFVIII and five subjects received Hyate:C. In this study, both r-pFVIII and Hyate:C were well tolerated by participants. Two subjects who received Hyate:C experienced chest pain considered infusion-related and both responded to intravenous diphenhydramine. All other AEs were unrelated to r-pFVIII.

Due to the characteristics of Hyate:C, the specified dosage required administration over a relatively prolonged time period. The area under the curve appeared to be greater in subjects who received r-pFVIII compared with Hyate:C and these data support that r-pFVIII has a higher bioavailability [23].

Phase II study in CHAWI subjects

A Phase II study was carried out in nine CHAWI adolescent or adult subjects, who were experiencing a non-life or non-limb threatening bleeding episode [24]. The dosing regimen included a loading dose based on body weight, hematocrit and inhibitor titer in those subjects with measurable anti-r-pFVIII antibody titers. Nine subjects between 14 and 34 years of age received r-pFVIII, receiving up to 8 treatment doses of 50–150 U/kg. A total of 40 OBI-1 injections were administered to 9 subjects to treat 25 bleeding episodes. Twenty of the 25 bleeds (80%) were controlled with 1 treatment dose of OBI-1. The median exposure day was 2 days (range: 1–8). In the nine patients, all 25 bleeding episodes experienced were successfully controlled with r-pFVIII.

Treatment with r-pFVIII was effective in controlling all bleeding episodes despite the presence of high titer r-pFVIII inhibitor levels. Following treatment, 8/9 subjects developed anti-r-pFVIII antibodies. Levels of anti-r-pFVIII antibodies were monitored for 28 days after each injection. The safety and efficacy of r-pFVIII did not appear to be dependent on r-pFVIII inhibitor titer and there was no increase in AEs or bleeding episodes with repeated treatment doses. An independent Data Safety Monitoring Committee recommended stopping the Phase II study after reviewing data on the 25 bleeding episodes, concluding that data on additional subjects would not modify the conclusion that r-pFVIII was effective in establishing hemostasis. The Data Safety Monitoring Committee recommended a fixed initial dose of 200 U/kg for future studies.

Phase II/III study in AHA subjects with serious or life-threatening hemorrhage

This was a prospective, global, multicenter open-label clinical trial of r-pFVIII in the treatment of serious bleeds in adults with AHA and was conducted under International Conference on Harmonisation guidelines and local Institutional Review Board/Ethics Committee oversight [25].

Subjects with AHA may present with severe bleeding episodes that if not controlled, would lead to high morbidity or mortality. The goal of this Phase II/III study of r-pFVIII was to determine the hemostatic efficacy and safety of r-pFVIII in the control of serious bleeding episodes in subjects with AHA [25]. The primary efficacy outcome was the proportion of serious bleeding episodes responsive to r-pFVIII therapy at 24 h after the initiation of treatment. Secondary efficacy outcomes included FVIII activity levels, response rates at 8 and 16 h and ultimate clinical outcomes of r-pFVIII treatment such as proportion of bleeding episodes successfully controlled by r-pFVIII treatment.

There are no published prospective controlled studies in AHA, likely due to the rarity of the disease, the challenges of diagnosis, the variability of the bleeding and the lack of new agents to treat the disease. Given these considerations, a study was designed to treat subjects with AHA at the time of a serious bleeding episode. Additionally, this study was designed to obtain real time FVIII activity data in order to guide treatment and dosing in a rational manner.

Inhibitors in subjects with AHA are expected to be variable across subjects and to change over time. The goal of this study was to obtain both pre-infusion and post-infusion levels at multiple time points to assess the recovery and the rate of decline of blood FVIII levels ('fall-off') for each subject. The additional treatment doses used in subjects were based on each subject's target FVIII levels, anti-r-pFVIII titer and other clinical factors. These data are used to predict the clinical response and to determine subsequent dosing.

Twenty-nine subjects were enrolled and treated with r-pFVIII; however, one subject was found not to have AHA, leaving 28 subjects evaluable for efficacy. All presented with a serious bleed, were hospitalized and treated with an initial dose of r-pFVIII of 200 U/kg, followed by additional doses based on the targeted FVIII activity levels and clinical response. All 28 subjects met the primary endpoint that was a positive response to treatment 24 h after initial r-pFVIII treatment as defined by the study response criteria, with the majority (95%) responding within 8 h of dosing. An effective response was defined as bleeding cessation and ≥50% increase in FVIII. The study defined partial response as bleeding reduction and ≥20% increase in FVIII levels (Table 1). The primary bleed was controlled in 16/17 (94%) subjects who received r-pFVIII as 'first-line' treatment. Overall, 24/28 (87.5%) subjects had control of the primary bleed at the time of final dosing with r-pFVIII. To successfully control a bleeding episode, the median total dose of r-pFVIII infused was 1580 U/kg, the median dose per infusion was 116.5 U/kg and the median total number of infusions per subject was 12.5. The median initial dose was 200 U/kg but subsequent median doses were reduced relative to the initial dose (41.2%). After the first infusion, FVIII activity levels were 20% and 108% by 24 h post-infusion. All subjects with

Table 1. Response to recombinant porcine sequence factor VIII treatment evaluation.

Assessment of efficacy	Control of bleeding	Clinical assessment	Factor VIII levels	Response
Effective	Bleeding stopped	Clinical control	≥50%	Positive
Partially effective	Bleeding reduced	Clinical stabilization or improvement; or alternative reason for bleeding	≥20%	Positive
Poorly effective	Bleeding slightly reduced or unchanged	Not clinically stable	<50%	Negative
Not effective	Bleeding worsening	Clinically deteriorating	<20%	Negative

baseline anti-porcine inhibitors had FVIII activity levels of greater than 100% within the first 24 h.

No related serious AEs (SAEs) occurred during the study. There were no thrombotic events or the development of anti-baby hamster kidney antibodies. Overall, 10/28 subjects had detectable anti-r-pFVIII antibodies prior to treatment (range 0.8–29 BU); in 8/10 subjects, the levels of anti-pFVIII inhibitors returned to non-detectable levels at the final assessment. Two of the subjects continued to exhibit anti-pFVIII inhibitors at the final assessment. Despite the baseline inhibitor status of the subjects within the study, FVIII activity levels ≥20% were achieved at the 24 h time point and all subjects had a positive response to treatment within 24 h of initial infusion of r-pFVIII. The range of baseline r-pFVIII antibodies in patients was between 0.8 and 29 BU, the effect of higher baseline antibody titers on treatment response is unknown.

Five subjects developed inhibitory antibodies while on treatment (range 8–108 BU) and this resulted in the discontinuation of treatment for two of these subjects with reported poor rise in FVIII activity levels immediately post-infusion of r-pFVIII. Both of these *de novo* inhibitor developments were reported as an AE, with these being the only two related non-SAEs in 2/28 subjects (7.1%).

Data from this prospective study demonstrate r-pFVIII as a safe and effective treatment of bleeding episodes in patients with AHA. Compared with bypassing therapies, treatment with r-pFVIII allows for FVIII activity monitoring to determine efficacy and dosing throughout treatment and the healing/recovery phase.

Regulatory affairs

The US FDA approved r-pFVIII for the treatment of bleeding episodes in AHA in October 2014 [26]. The FDA granted r-pFVIII an orphan-drug status based on the fact that AHA is a rare disease and this drug addresses a critical unmet need in this patient population [25].

The prescribing information approved by the FDA includes recommendations for monitoring laboratory tests and dosing guidelines. The approved information states 'Safety and efficacy of OBIZUR has not been established in patients with baseline anti-porcine FVIII inhibitor titer greater than 20 BU. OBIZUR is not indicated for the treatment of CHAWI or von Willebrand disease'.

Conclusion

r-pFVIII has been studied in 28 individuals with AHA who presented with serious or life-threatening bleeds. All 28 of these subjects responded to treatment at 24 h after first dosing, regardless of the presence and titer of baseline anti r-pFVIII antibodies. Dosing was monitored and controlled by FVIII assays, which afforded a reliable index of hemostatic control and more tailored dosing for the treatment of bleeds. There were no related SAEs observed in any subject. The safety and efficacy information in these subjects supported the FDA approval of r-pFVIII for the treatment of bleeding episodes in AHA.

Expert commentary

The recently FDA-approved r-pFVIII is a potentially important therapeutic option with improved safety and efficacy for the management of serious and life-threatening bleeds in persons with AHA. This is a rare but devastating bleeding disorder with high mortality from bleeding. The data generated to date for this indication show a reliable treatment with an outstanding therapeutic index. These data show an efficacy profile that can be more favorable than current inhibitor-bypassing therapies because it is more physiological to use FVIII replacement. Also, the ability to measure FVIII activity with an objective surrogate marker of efficacy and safety affords the ability to tailor dosing without excessive factor consumption. Furthermore, treatment with r-pFVIII provides additional safety from thrombosis due to overdosing with bypassing agents and the inherent increased risk in this patient population. Finally, immunosuppression to ultimately eradicate FVIII neutralizing antibodies is recommended upon diagnosis of these patients. Immunosuppression converts a patient from a bleeding event to a relative hypercoagulable state in a population already at risk for thrombotic events [27]. Treatment with r-pFVIII enables measurement of FVIII levels in order to guide dosing and enhance safety during this transition.

All study subjects currently showed response in serious and in some cases life-threatening hemorrhages within 24 h of first treatment. None of the subjects showed any related SAEs. r-pFVIII should become the treatment of choice in the management of hemorrhage in patients with AHA and should be considered the first line of treatment prior to inhibitor bypassing hemostatic agents.

Five-year view

Potential future applications for the use of r-pFVIII would be treatment of congenital hemophilia patients with inhibitor

development (CHAWI) and prophylactic use in patients with inhibitors. The benefit of using r-pFVIII is the ability to treat inhibitor patients with more physiologic FVIII as opposed to bypassing the coagulation pathway. While the risk of developing anti-pFVIII inhibitory antibodies should be considered and will be seen in some patients during a regimen of long-term prophylaxis, there is no information to date regarding the extent of this risk, either in the number of such impacted patients, nor regarding the level of the inhibitor response in each. However, data collected from CHAWI patients administered plasma-derived pFVIII showed that long-term use could be possible in a sub-population of patients depending on the titer of baseline anti-pFVIII and the post-infusion anamnestic response [28,29]. A major limitation in treating inhibitor patients is the uncertainty of monitoring assays; therefore, there is a need to individualize treatment for patients based on initial response to treatment. At this time, information regarding the application and efficacy of r-pFVIII in the management of bleeds in patients with hemophilia A complicated by a high titer inhibitor is only available in the context of a Phase II clinical trial.

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Key issues

- The efficacy profile of recombinant porcine sequence factor VIII (r-pFVIII) can be more favorable than current bypassing therapies because it is more physiological.
- The use of r-pFVIII allows for more reliable, tailored dosing with unnecessary consumption because of the ability to measure FVIII activity.
- All acquired hemophilia A study subjects showed response in serious and in some cases life-threatening hemorrhages within 24 h of first treatment with r-pFVIII.
- The risk of developing anti-rpFVIII inhibitors during potential future applications of r-pFVIII as a long-term prophylactic treatment option is not known at this time.

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