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REVIEW ARTICLE

Recombinant porcine factor VIII: Lessons from the past and place in the management of hemophilia A with inhibitors in 2021

Yesim Dargaud MD, PhD[1,2] | Carmen Escuriola-Ettingshausen MD[3]

[1]Unite d'Hemostase Clinique, Centre National de Reference de l'Hemophilie, Hôpital Louis Pradel, Lyon, France

[2]UR 4609 Hemostase and Thrombose, Universite Claude Bernard Lyon 1, Lyon, France

[3]HZRM Hemophilia Center Rhine-Main Frankfurt-Mörfelden, Mörfelden-Walldorf, Germany

Correspondence
Yesim Dargaud, Unite d'Hemostase Clinique, Hopital Cardiologique Louis Pradel, 28, Av Doyen Jean Lepine, 69500 Bron, France.
Email: ydargaud@univ-lyon1.fr

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Abstract

The most serious complication of factor VIII (FVIII) replacement therapy is the occurrence of anti-FVIII alloantibodies that can strongly reduce or abolish the effect of human FVIII products. Bypassing agents to control bleeding episodes are recommended for these patients, but their efficacy is difficult to predict and monitor. FVIII products derived from porcine plasma had an important role in the treatment of hemophilia A for 50 years, from 1954 to 2004. Indeed, porcine FVIII could achieve hemostasis in patients in whom human FVIII products were ineffective. A recombinant porcine FVIII product is now available. This highly purified protein has the same biochemical and hemostatic properties, but much lower risks of infection and toxicity compared with plasma-derived porcine FVIII. The product is licensed in the United States and Europe for the treatment of acquired hemophilia A. However, this recombinant molecule could also be of clinical interest for people with inherited hemophilia A and inhibitors, particularly for the management of bleeding episodes in people receiving emicizumab as prophylactic treatment in the absence of anti-porcine FVIII antibodies.

KEYWORDS
anti-factor VIII antibodies, acquired Hemophilia A, porcine factor VIII hereditary

Essentials

- Porcine factor VIII (FVIII) was successfully used in people with inherited hemophilia A and inhibitors.
- Recombinant porcine FVIII (r-pFVIII) is now available and licensed for acquired hemophilia A.
- r-pFVIII can be easily monitored with routine FVIII assays.
- The safety and efficacy of r-pFVIII need to be studied in inherited hemophilia A with inhibitors.

1 | INTRODUCTION

Hemophilia A is one of the most common inherited bleeding disorders and is caused by the complete (severe hemophilia) or partial (moderate or minor hemophilia) absence of coagulation factor VIII (FVIII). The treatment of severe forms is classically based on FVIII replacement by plasma-derived or recombinant FVIII concentrates. These products can be administered on demand to treat acute

bleeding episodes or prophylactically to prevent bleeding episodes and their complications, such as arthropathy from recurrent hemarthrosis, and life-threatening hemorrhages.[1] However, FVIII is an immunogenic molecule, and its administration can lead to the development of neutralizing alloantibodies (inhibitors), the major and most dreaded complication of hemophilia A treatment.[2] The development of FVIII inhibitors has been observed in ≈30% of people with severe hemophilia A and less frequently (3% to 13%) in people with moderate or mild hemophilia A.[3] Thise polyclonal IgG recognizes FVIII molecules, thus rendering it ineffective or strongly reducing the benefit of FVIII replacement therapy due to the rapid FVIII clearance from the circulation. In addition to the anti-FVIII alloantibodies detected in people with inherited hemophilia A, autoantibodies against endogenous FVIII cause acquired hemophilia A,[4] a rare bleeding disorder occurring in women after giving birth and particularly in older patients with comorbidities. Acquired hemophilia A has been associated with the postpartum period, other autoimmune diseases, cancers, lymphoproliferative syndromes, and multiple blood transfusions.[5] Its incidence is estimated to be one case per million individuals/year,[6] but due to the lack of adequate diagnosis, the real incidence might be higher, up to six cases per million individuals/year.[7]

In patients with inherited or acquired hemophilia A with anti-FVIII antibodies (allo- or autoantibodies), the choice of treatment depends on the bleeding type and the inhibitor titer (low or high responder status):

- If the inhibitor titer is <5 Bethesda Units (BU)/mL (low responder), high-dose FVIII may be effective.[8] Treatment becomes ineffective in case of anamnestic response (rapid rise in the inhibitor titer due to new antigenic stimulation).
- If the inhibitor titer is >5 BU/mL (high responder), FVIII is ineffective, and treatment with a bypassing agent, such as recombinant activated factor VII (rFVIIa) or activated prothrombin complex concentrates (aPCCs), inhibitor removal strategies, such as immune tolerance induction (ITI), or porcine FVIII (pFVIII) concentrates to treat bleeds can be considered.[9]

In this review article, we describe the biochemical features of pFVIII concentrates, and the improvements to pFVIII molecules in terms of safety (toxicity, infection, and side effects). We then provide an overview of the published clinical studies on pFVIII use in people with hemophilia A and inhibitors. We also discuss its potential benefits compared with bypassing agents, including in people receiving emicizumab, a bispecific antibody that mimics FVIII function in the presence and absence of FVIII inhibitors and that is licensed for prophylaxis in people with hemophilia A.

2 | PLASMA-DERIVED PORCINE FVIII

Replacement therapy for people with hemophilia A has reached high levels of safety and efficacy. Currently, the main complication is the development of inhibitors that increase the bleeding risk and reduce or abolish the effect of the administered clotting factor concentrate. ITI, in which high doses of FVIII are administered daily or every other day, can eliminate the inhibitory activity of these antibodies in 60% to 70% of people with hemophilia A.[10,11] Bleeding management is a major problem in people who develop FVIII inhibitors. In people with high-titer inhibitors (>5 BU/mL), bypassing agents may be used to control bleeding.[12] In high responders (in whom inhibitor titer rises when exposed to factor VIII), but with inhibitor titers in the lower range, a pFVIII concentrate could be useful[13] because the anti-FVIII antibodies should not display major cross-reactivity toward it. Indeed, FVIII inhibitors most frequently bind to the A2 and C2 domains of human FVIII (hFVIII). The A2 and C2 domains in pFVIII show 84% and 76% of sequence homology with the A2 and C2 domains of hFVIII, respectively, thus explaining the lower reactivity of anti-hFVIII alloantibodies toward pFVIII (≈ 15%), compared with hFVIII.[14]

In the early 1980s, a plasma-derived pFVIII (pd-pFVIII) concentrate (Hyate:C, Speywood Pharmaceuticals, Wrexham, UK)[15] was developed. This pd-pFVIII concentrate was the only product to give circulating levels of FVIII procoagulant activity (FVIII:C) in people with high-titer inhibitors. Pharmacokinetic studies showed a long half-life (8-24 hours) and high recovery of pd-pFVIII compared with hFVIII.[16] Moreover, in selected individuals with inherited hemophilia A and inhibitor titers <20 BU/mL, pd-pFVIII treatment gave a good response in 90% of acute bleeding episodes.[17] In addition, in people with low inhibitor titers, regular home treatment with pd-pFVIII at low doses did not lead to antibody titer increase.[18,19] It is noteworthy that people with acquired hemophilia A treated with pd-pFVIII displayed lower, almost absent, anti-pFVIII cross-reactivity and responded well to this treatment.[14]

This molecule had several advantages compared with the bypassing agents available in 1980s. Clinically effective plasma levels of FVIII could be obtained in patients with inhibitors, and FVIII level could be measured and monitored using one-stage clotting assays. This was particularly interesting for patients undergoing surgery because no routine hemostasis assay was available to evaluate the efficacy of aPCCs and the potential risk of thrombosis associated with their use.[20,21] Moreover, some clinical efficacy of pd-pFVIII was reported also when circulating FVIII could not be detected,[22] unlike with hFVIII. The mechanism of the procoagulant action associated with pd-pFVIII–based therapy in the absence of measurable plasmatic levels of FVIII remained unclear for several years. It was suggested that the observed clinical efficacy could be related to complex interaction kinetics between pd-pFVIII and anti-hFVIII antibodies. According to this hypothesis, pd-pFVIII inhibitor complexes continue to have FVIII functional activity, or they might dissociate and release free pd-pFVIII.[23] Moreover, Lollar et al[24] showed that pd-pFVIII had greater procoagulant activity than hFVIII, and was more stable after activation.[24] Later, Chang et al[25] described the crucial role of platelets in the clinical efficacy of undetectable circulating pd-pFVIII levels. Specifically, they demonstrated that in vitro, resting platelets are activated upon exposure to pd-pFVIII, leading to a hypercoagulable state. Freedman et al[26] confirmed that as observed in vitro, platelets were significantly activated by pd-pFVIII also in vivo

after pd-pFVIII infusion in nine people with inherited hemophilia A with inhibitors. They demonstrated that pd-pFVIII–induced platelet activation enhanced hemostasis and that this effect was due to the presence of residual porcine von Willebrand factor (VWF) in pd-pFVIII concentrates. Other studies showed that platelet microparticles, generated by pd-pFVIII-activated platelets, also contributed to the observed hemostatic effect.[27] However, the presence of a significant amount of VWF in pd-pFVIII preparations was also associated with disadvantages, such as thrombocytopenia occurring 30 to 60 minutes after pd-pFVIII administration (54% of cases) due to the reversible agglutination of platelets induced by porcine VWF.[28] Allergic reactions, such as chills, fevers, rashes, muscle or abdominal cramps, and wheezing, were another side effect of pd-pFVIII,[29] especially after administration of large doses of pd-pFVIII. Rare severe anaphylactoid reactions were reported by Gringeri et al,[30] particularly in one individual who received an abnormally high dose of pd-pFVIII (>600 IU/kg).

Therefore, a second-generation pd-pFVIII concentrate (Hyate:C; Ipsen Ltd, Maidenhead, UK) was developed to improve its purity. This preparation contained polyelectrolyte fractionated pd-pFVIII, was depleted of porcine VWF (FVIII:C/VWF ratio of 30/1), and displayed high specific activity (>100 U/mg).[31] In 2004, the absence of viral attenuation or depletion led to the market withdrawal of this product, despite the absence of reports on viral transmission, including porcine parvovirus, in patients treated with this high-purity pd-pFVIII concentrate.[9]

3 | PLASMA-DERIVED PORCINE FVIII IN PEOPLE WITH CONGENITAL HEMOPHILIA A AND INHIBITORS

Before its market withdrawal, pd-pFVIII was used safely and effectively in people with inherited hemophilia A and inhibitors for almost 20 years. For instance, an international retrospective study on the clinical outcome in 157 patients treated for 2472 bleeding episodes with a mean pretreatment cross-reactivity of 24% found an overall response rate of 90%.[32] Specifically, the clinical response (graded on a 4-point scale) was considered excellent only in 8.7% of people with inherited hemophilia A, good in 71%, and fair in 13.4%. As expected, efficacy was correlated with the inhibitor titer and the achieved circulating FVIII levels. However, as discussed above, good and fair responses were reported also in the absence of detectable FVIII:C. Continuous infusion of pd-pFVIII was safe and effective and resulted in fewer side effects, such as allergic reactions and lower platelet reduction than bolus injection.[33,34] Moreover, continuous infusion avoided low FVIII trough levels during which people with inherited hemophilia Aare at risk of bleeding, and reduced FVIII consumption by 30% to 35%.[35] Therefore, continuous infusion was proposed as the preferred mode of administration when intensive replacement therapy with pd-pFVIII was needed in individuals with inhibitors. In addition, pd-pFVIII was effectively and safely used in home therapy settings in people with inherited hemophilia A and inhibitors at doses from 20 to 60 IU/kg for several years.[32,36] Interestingly, all these people lost the alloantibodies against hFVIII over time.[18]

Besides its excellent clinical efficacy in people with congenital hemophilia and inhibitors, a lower risk of anamnestic response was reported with pd-pFVIII than with hFVIII (increase in anti-FVIII antibodies between 25% and 35%).[15,29] The use of pd-pFVIII has been associated with the risk of appearance of specific anti-pFVIII antibodies.[17] In one-third of people with anti-pFVIII inhibitors, regular treatment with pd-pFVIII was compromised, but most did not become fully resistant to pd-pFVIII.[17,18]

4 | PLASMA-DERIVED PORCINE FVIII IN PEOPLE WITH ACQUIRED HEMOPHILIA A

Similar positive results with pd-pFVIII were observed in people with acquired hemophilia A. The risk of anamnestic response was very low in this group (4%).[14] Morrison et al[37] analyzed data on 74 bleeding episodes in 65 individuals with acquired hemophilia A and treated with pd-pFVIII from 47 centers in Europe and North America. At presentation, the anti–pd-pFVIII antibody levels were lower (0–15 BU/mL) than the anti-hFVIII antibody titers (1.2–1024 BU/mL). Clinical responses were rated as excellent or good in 78% of patients. Unlike people with congenital hemophilia A, the plasma FVIII level and the human or porcine inhibitor titer at presentation did not predict the response to treatment. The mean initial dose of pd-pFVIII was 84 IU/kg, and it increased the plasma FVIII activity by 85 IU/dL. Side effects were uncommon. Treatment resulted in the development of anti-pd-pFVIII antibodies in two-thirds of patients. Among them, about half continued to respond to treatment despite the presence of high titers of anti-pd-pFVIII inhibitors, but not the other patients.

4.1 | From plasma-derived pFVIII to recombinant pFVIII

The lessons learned from pd-pFVIII, its shortcomings/safety concerns, and also its advantages (good clinical efficacy and the possibility to objectively monitor FVIII activity), compared with bypassing agents, were crucial for the development of recombinant pFVIII (r-pFVIII), a safer and possibly more effective molecule.

Different recombinant hybrid h/pFVIII molecules were studied. Lollar et al[38] evaluated seven recombinant hybrid B domainless h/pFVIII molecules in which porcine sequences replaced part of the A2, ap-A3, and/or C2 domains of hFVIII. They found that the cross-reactivity of high-titer inhibitory antibodies with hFVIII and the hybrid molecules was inversely related to the degree of porcine substitution. Using plasma samples with high inhibitor concentrations, the authors concluded that the porcine sequences within the A2, A3, C2, and ap regions of hFVIII were necessary and sufficient to decrease hFVIII antigenicity to levels similar to what observed with pFVIII.

These studies on hybrid h/pFVIII molecules improved our understanding of the key amino acid sequences required to avoid the inactivation of these hybrids by most inhibitory hFVIII antibodies. They also helped to develop susoctocog alfa, a high-purity recombinant pFVIII product that shows low cross-reactivity with human anti-FVIII inhibitors.

4.2 | Recombinant porcine FVIII

Susoctocog alfa (OBI-1; r-pFVIII, Obizur; Takeda, Tokyo, Japan) is a 1448 amino acid B domain-deleted recombinant pFVIII (r-pFVIII) molecule. The B domain is replaced by 12 N-terminal and 12 C-terminal amino acids of the native porcine B domain.[39] The molecule is produced in baby hamster kidney cells cultured in serum-free and VWF-free medium. Following purification by two-step chromatography, the protein undergoes two steps of viral inactivation (solvent detergent treatment and 15 nm nanofiltration). In blood, r-pFVIII circulates as a heterodimer, and it is activated by thrombin. In vitro studies showed that the stoichiometry of the binding between susoctocog alfa and VWF is ≈1:1 mole equivalent. Moreover, susoctocog alfa improves, in a dose-dependent manner, thrombin generation and clot formation in plasma samples from people with inherited hemophilia A and inhibitors.[40]

Comparison of r-pFVIII (susoctocog alfa) and pd-pFVIII pharmacokinetics in a double-blind randomized study in people with hemophilia A[41] showed that bioavailability of r-pFVIII was higher than that of pd-pFVIII after a single dose, without detectable antiporcine inhibitors. As reported for pd-pFVIII, FVIII activity in samples containing r-pFVIII was 15% to 45% higher when measured with the one-stage clotting assay than with the chromogenic assay.

A FVIII knockout mice model presensitized to hFVIII was used to compare the immunogenicity of r-pFVIII (susoctocog alfa) and pd-pFVIII (Hyate:C).[42] After four intravenous injections of r-pFVIII or pd-pFVIII (three different doses) at weekly intervals, the mean anti-FVIII response was statistically higher in pd-pFVIII–treated than in r-pFVIII–treated mice. This suggests that r-pFVIII might be less immunogenic than pd-pFVIII. The high purity of r-pFVIII (>95% compared with <1% for pd-pFVIII) and the absence of porcine VWF might explain the very low rate of allergic reactions and the absence of thrombocytopenia.[43] On the other hand, it should be important to determine whether and to what extent the "impurities" in pd-pFVIII contributed to the rather low anamnestic response,[15,17,18,29] particularly in people with congenital hemophilia A and inhibitors. Therefore, the impact of r-pFVIII high purity on its clinical efficacy needs to be investigated in clinical studies in people with congenital hemophilia A and inhibitors.

5 | CLINICAL EFFICACY OF R-PFVIII IN PEOPLE WITH ACQUIRED HEMOPHILIA A

A prospective, multicenter, open-label, phase 2/3 study evaluated the hemostatic efficacy and safety of susoctocog alfa (r-pFVIII) for the treatment of bleeding episodes in 28 adults with acquired hemophilia A.[44] People with a severe bleeding episode and anti–r-pFVIII antibody titer <20 BU/mL received an initial dose of 200 U r-pFVIII/kg. This was followed by adjusted doses to maintain the target FVIII activity levels and clinical efficacy. All 28 individuals had a positive response to r-pFVIII (ie, bleeding control and at least 50% increase in plasma FVIII levels) 24 hours after the initial dose, and the majority responded within the first 8 hours. In patients with baseline anti-pFVIII inhibitors (<20 BU/mL), FVIII levels rose to 20% after the first infusion, and increased to 108% at 24 hours after infusion. No allergic reaction, thrombocytopenia, or thrombotic event was reported. The results of this clinical trial showed that susoctocog alfa is a valuable first-line treatment option for acute bleeding episodes in people with acquired hemophilia A.

This molecule has been licensed for the treatment of acute bleeding episodes in people with acquired hemophilia A in Europe, Canada, and the United States (approved dose of 200 U/kg, followed by additional doses to maintain FVIII trough levels >50%). It is well tolerated, and the most frequent adverse event is the development of antibodies against r-pFVIII. Two recent independent studies reported that cross-reacting inhibitors were more frequent in people with anti-hFVIII inhibitor titers >100 BU/mL.[45,46] Following drug approval, some case reports and studies on cohorts of people with acquired hemophilia A treated with r-pFVIII have been published, all confirming susoctocog alfa good efficacy and safety for the management of severe bleeding episodes.[47-49] A retrospective case series (n = 4 individuals with acquired hemophilia A) showed that this molecule is effective and safe. However, after a mean of 12.4 exposure days, pFVIII inhibitors were detected, resulting in a decreased efficacy and duration of the effect. Furthermore, in three individuals, the anti-hFVIII inhibitor titer also increased.[50] Another group reported a rather high incidence (44% of 70 individuals) of anti-r-pFVIII inhibitors, although titers were low in most people.[46] More studies are needed to precisely determine the incidence of neutralizing antibodies against r-pFVIII and their impact on anti-hFVIII antibodies.

Recently, Ellsworth et al[51] described an algorithm-based approach for the use of r-pFVIII in people with acquired hemophilia A at a starting dose (100 U/kg) that is lower than what is recommended. In this approach, baseline human and porcine FVIII inhibitors are quantified at diagnosis/presentation, and FVIII plasma levels are monitored using a one-stage clotting assay before and after the first r-pFVIII dose of 100 U/kg. This approach showed hemostatic efficacy at doses that were substantially lower than what is recommended in a cohort of 18 patients with acquired hemophilia A. The use of such algorithm might help physicians to quickly determine the efficacy or lack of response to r-pFVIII.

International recommendations for the treatment of acquired hemophilia A were recently published,[52] and they suggest the use of r-pFVIII, rFVIIa or aPCC for the treatment of clinically relevant bleeding events.

6 | CLINICAL EFFICACY OF R-PFVIII IN PEOPLE WITH INHERITED HEMOPHILIA A AND INHIBITORS

The clinical development of susoctocog alfa (r-pFVIII) started with a randomized, double-blind, phase 1 clinical trial that compared the pharmacokinetic profiles of r-pFVIII and pd-pFVIII in nine inedividuals with congenital hemophilia A and inhibitors.[41] This study found higher bioavailability, good tolerance, and absence of anti-pFVIII antibodies with susoctocog alfa. Then, an open-label, nonrandomized, uncontrolled, multicenter phase 2 study evaluated the efficacy and safety of susoctocog alfa for bleeding control in people with congenital hemophilia A and inhibitors (n = 9 individuals with 25 non–life- or non–limb-threatening bleeding episodes). People with pFVIII inhibitors >0.8 BU/mL received a loading dose followed by 50 to 150 U/kg every 6 hours until bleeding cessation. People with negative pFVIII inhibitors received 50 U/kg. All bleeding episodes were controlled with one injection (median dose). All individuals had anti-pFVIII inhibitor titers <20 BU/mL.[53] As acute bleeds require immediate treatment and pFVIII inhibitor testing takes time, the data safety monitoring committee of the study recommended a fixed initial dose of 200 U/kg for future studies based on the fact that 80% of bleeds were controlled with a median dose of 200.8 U/kg r-pFVIII. Alternatively, anti-pFVIII inhibitor assays could be routinely performed in people with inhibitors.

Overall, these phase 1 and 2 studies suggest that replacement therapy with r-pFVIII can be an alternative to bypassing agents for the treatment of bleeding episodes in people with inherited hemophilia A complicated by alloantibodies and pFVIII antibody titers <20 BU/mL. However, no phase 3 study was carried out in people with congenital hemophilia A and inhibitors, and r-pFVIII has not been approved in Europe and North America for the treatment of acute bleeding episodes in people with congenital hemophilia A. Single case reports described the use of r-pFVIII in people with inadequate response to bypassing agents (rFVIIa and aPCC). A child with severe hemophilia A and high-titer inhibitors (10–11 BU/mL) presented with severe hematuria despite vigorous hydration, bed rest, and bypassing therapy.[54] Plasma FVIII levels increased to 61% at 1 hour after the infusion of r-pFVIII 100 U/kg, and decreased to 20% at 4 hours after infusion. A second dose of 150 U/kg was given 8 hours after the first infusion and was associated with a peak of FVIII activity at 210%. Additional doses and intervals were determined on the basis of target FVIII activity levels of 40% to 50%. Hematuria was successfully resolved, and the child was discharged from the hospital at day 7 after starting treatment with r-pFVIII. Abou-Ismail et al[50] reported the use of r-pFVIII in another individual with congenital hemophilia A and inhibitors. Although clinical efficacy was initially achieved, upon r-pFVIII readministration, FVIII levels decreased, and the activated partial thromboplastin time increased as well as the anti-pFVIII antibody titer. Moreover, among the nine individuals with congenital hemophilia A and inhibitors in whom r-pFVIII was administered to control non–life- or non–limb-threatening bleeds,[53] three developed de novo inhibitors against r-pFVIII, and the five with pFVIII inhibitors at baseline had higher anti-pFVIII titers at the study end. Although neither safety nor efficacy was affected in these individuals, this observation raises the question of whether r-pFVIII has only a limited effect, and consequently should be reserved for emergency situations (eg, people who do not respond to bypassing agents).

More studies are needed to better evaluate r-pFVIII hemostatic efficacy, safety, and immunogenicity in people with congenital hemophilia A and inhibitors. Moreover, no data is available on r-pFVIII use for prophylaxis and home treatment of inherited hemophilia A.

7 | USE OF R-PFVIII IN PEOLE WITH INHERITED HEMOPHILIA A AND INHIBITORS TREATED WITH EMICIZUMAB

Emicizumab (Hemlibra, Roche, Basel, Switzerland) is a new nonfactor therapeutic agent for hemophilia A with inhibitors. This bispecific antibody mimics FVIII coagulation function, and it is licensed for prophylaxis in people with inherited hemophilia A, with and without inhibitors. In case of breakthrough bleeding while receiving emicizumab, people, particularly those with inhibitor titers >5 BU/mL, still require treatment with bypassing agents. Emicizumab is also recommended to prevent bleeds in people with inhibitors undergoing surgery. However, coadministration of emicizumab and aPCC (repeated high doses) has been associated with the development of thrombotic microangiopathy and thrombotic events. This was not the case when people on emicizumab were cotreated with rFVIIa.[55,56] Therefore, rFVIIa has become the first choice for the treatment of acute bleeding episodes and during surgery in people with hFVIII inhibitors >5 BU/mL receiving emicizumab. If the inhibitor titer decreases to <5 BU/mL during long-term emicizumab prophylaxis, which occurs in a large percentage of people with hFVIII inhibitors, the administration of hFVIII concentrates can be considered and monitored using bovine chromogenic assays.

Adjunctive therapies with bypassing agents can be monitored, and doses can be adjusted and tailored using global hemostasis assays.[57,58] This can help to predict the individual response and also to ensure safety, for instance, when using aPCC. However, in practice, only few centers use global hemostasis assays to guide the treatment of individuals with inhibitors. Therefore, in people receiving prophylaxis with emicizumab, r-pFVIII might be an alternative to bypassing agents in case of severe breakthrough bleeding episodes or in the absence of adequate response to rFVIIa and aPCC. Moreover, an in vitro study based on a modified one-stage FVIII assay showed increased FVIII activities in plasma spiked with 10 or 50 μg/mL of emicizumab and r-pFVIII compared with emicizumab alone. This indicates that the modified one-stage FVIII assay is specific not only for emicizumab.[59] Therefore, the combined use of r-pFVIII and emicizumab might present the additional advantage of easier and precise monitoring using FVIII assays. In addition, it has been shown that FVIII measurement with one-stage coagulation assays and chromogenic assays show smaller difference with r-pFVIII compared with pd-pFVIII.[41]

Emicizumab use in acquired hemophilia A has been assessed in few case reports and small retrospective series of individuals that reported good results.[60,61] One ongoing international, multicenter, open-label, single-arm, prospective clinical trial (NCT04188639) is evaluating the prophylactic efficacy of emicizumab administered on a scheduled basis to prevent bleeding events in people with acquired hemophilia A. A stroke was reported in an individual who received repeated rFVIIa doses because of surgical procedures while on emicizumab.[7] We hypothesize that in frail individuals with acquired hemophilia A and cardiovascular risk factors, r-pFVIII might be a good alternative to bypassing agents when concomitant treatment with emicizumab is needed. Moreover, as r-pFVIII can be monitored using one-stage clotting factors or chromogenic assays, treatment decision making can be easily guided to make the concomitant treatment with emicizumab effective and safe. However, the increase of anti-hFVIII inhibitor titers observed in a small case series (three of four individuals with acquired hemophilia A treated with r-pFVIII) and the potential impact on therapy outcome have to be better investigated.[50]

In the presence of hFVIII inhibitors, acute bleeding and surgery can be managed with bypassing agents or with r-pFVIII. Indirect evidence suggests an overall similar efficacy of bypassing agents and r-pFVIII. The choice of treatment in clinical practice must take into account the person's individual response to each agent, the presence of anti-pFVIII antibodies, the therapeutic molecule availability, the monitoring requirements, the underlying treatment (eg, emicizumab prophylaxis), the costs, and the physician's experience. As emicizumab prophylaxis is widely used in people with hemophilia A and inhibitors, the availability of r-pFVIII, a therapeutic agent that can replace FVIII hemostatic activity and where dosing can be guided and monitored using standard assays, might improve the treatment efficacy and safety in individuals with inhibitors.

R-pFVIII has been available in Europe and North America for acquired hemophilia A for >5 years, and its safety and effectiveness in these individuals has been confirmed. On the other hand, phase 3 studies to demonstrate its safety and efficacy in people with inherited hemophilia A and inhibitors are lacking. This seems to be a clear barrier to its clinical use in these individuals. Particularly, the impact of r-pFVIII high purity on its clinical efficacy needs to be thoroughly assessed in clinical studies in people with congenital hemophilia A and inhibitors. Moreover, a method for the detection of anti-pFVIII antibodies in people receiving emicizumab prophylaxis should be developed and validated. These issues must be addressed before proposing r-pFVIII for the treatment of acute bleeding episodes in people with congenital hemophilia A and inhibitors.

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AUTHOR CONTRIBUTIONS

YD and CEE wrote the manuscript and approved the final version of the manuscript.

ORCID

Yesim Dargaud https://orcid.org/0000-0002-4888-1463

TWITTER

Yesim Dargaud @DargaudYesim

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