Cross-reacting inhibitors against recombinant porcine factor VIII in acquired hemophilia A: Data from the GTH-AH 01/2010 Study

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Abstract

Background: Recombinant porcine factor VIII (rpFVIII, OBI-1, susoctocog alfa) is used for the treatment of acute bleeds in patients with acquired hemophilia A (AHA). Inhibitors in AHA can sometimes cross-react with rpFVIII.

Objectives: To assess the frequency, strength, and determinants of cross-reactivity.

Patients/methods: Baseline samples from 70 patients of the prospective, observational cohort study GTH-AH 01/2010 were assessed for anti-human FVIII and anti-rpFVIII inhibitors using modified Nijmegen-Bethesda assays, as well as anti-human FVIII domain reactivity using enzyme-linked immunoassay (ELISA).

Results: Anti-human FVIII inhibitors were present in all samples ranging between 0.7 and 3891 Bethesda Units (BU)/mL. Inhibitors from 31 of 70 patients (44%) partially inhibited rpFVIII with anti-rpFVIII titers ranging between 0.5 and 471 BU/mL. Anti-rpFVIII titers were ≤5 BU in most patients. Patients with cross-reacting inhibitors, as compared to patients without, had significantly higher anti-human FVIII titers (27.8 versus 5.4 BU/mL) and lower baseline FVIII activity (<1 versus 2.6 IU/dL). The ratio between anti-rpFVIII to anti-human titers was highest for inhibitors involving the C1 domain. Cross-reactivity was very rare, if inhibitors reacted only with the C2 domain of FVIII (6%). An anti-human FVIII titer of >100 BU/mL predicted cross-reactivity with 97% likelihood, whereas an anti-human FVIII titer of <3.8 BU/mL predicted absent cross-reactivity with 90% likelihood.

Conclusion: Cross-reacting inhibitors should be considered when choosing a treatment for bleeding patients with AHA. Cross-reactivity is frequent in patients with anti-human FVIII titers of >100 BU/mL.
INTRODUCTION

Acquired hemophilia A (AHA) is a bleeding disorder characterized by neutralizing autoantibodies against factor VIII (FVIII). Anti-FVIII antibodies, also called inhibitors, cause a severe deficiency of hemostasis resulting in spontaneous or trauma-induced bleeds in men and women without a recent history of bleeding. Known risk factors for AHA include advanced age, malignancy, autoimmune diseases, and pregnancy or the postpartum period, although about 50% of cases are idiopathic. Susoctocog alfa (OB1-1, Obizur®) is a B-domain deleted, recombinant porcine-sequence factor VIII concentrate (rpFVIII) that is licensed for the treatment of acute bleeds in AHA. The drug is able to restore hemostasis in the presence of inhibitors against human FVIII in cases of low or absent cross-reactivity with rpFVIII. The pivotal clinical trial demonstrated definite bleed control in 24 of 28 patients; 10 of the 28 patients had cross-reacting inhibitors against rpFVIII with no apparent effect on the clinical response to treatment. However, the rpFVIII dose and dosing interval were adjusted to measured FVIII activity (FVIII:C) levels in this trial and patients with cross-reacting anti-rpFVIII inhibitors had lower FVIII:C levels and considerably higher product consumption. Patients with anti-rpFVIII inhibitors >20 Bethesda Units (BU)/mL had been excluded from the trial because efficacy of rpFVIII was considered unlikely. In a published case series of seven AHA patients treated with rpFVIII, one of two patients not responding to treatment had a cross-reacting anti-rpFVIII inhibitor of 4 BU/mL. The drug is considered for treating a patient with AHA.

No information is currently available on the prevalence and magnitude of anti-rpFVIII inhibitors in unselected patients with AHA. A commercial assay for anti-rpFVIII is not available. Susoctocog alfa can be used as substrate in a modified Bethesda assay (BA) instead of human plasma, but this assay may not be readily available in every clinical setting, potentially limiting the rational and cost-effective use of rpFVIII.

GTH-AH 01/2010 was a prospective cohort study of patients with AHA. This study provides a reasonable population for an unbiased assessment of cross-reactivity to rpFVIII. We, therefore, used baseline plasma samples from GTH study patients to assess the prevalence and strength of anti-rpFVIII antibodies. We also attempted to provide predictive markers for cross-reactivity that may be useful for routine clinical use of rpFVIII.

PATIENTS AND METHODS

Study population

The GTH-AH 01/2010 was a multicenter, prospective observational study of patients with AHA who were treated according to the GTH consensus protocol by 29 registered sites in Austria and Germany between 2010 and 2013. The research protocol was approved by the ethics committees of all participating institutions. AHA was defined by the presence of neutralizing (anti-human) FVIII inhibitors >0.6 BU and FVIII:C <50 IU/dL. Patients were eligible if they had AHA and were enrolled ≤7 days after starting immunosuppressive treatment (IST). Outcome data were available in all patients. Backup samples for the current study were available in 70 patients and were stored in the central laboratory (Hannover Medical School) in small aliquots at −80°C.

2.2 Nijmegen-Bethesda and anti-rpFVIII inhibitor assay

The Nijmegen-modified Bethesda assay (NBA) was performed as previously described. Our anti-rpFVIII inhibitor assay was a modified NBA with rpFVIII as substrate. Susoctocog alfa laboratory standard was obtained from Shire (now Takeda) and had a stock concentration of approximately 11 U/mL. It was diluted in FVIII-deficient normal human plasma to a concentration of 1 U/mL. All subsequent steps were identical to the standard NBA. In brief, FVIII:C was determined by a one-stage clotting assay using activated partial thromboplastin time reagent Actin FS and buffered FVIII-depleted normal human plasma containing >40 IU/dL von Willebrand factor activity (both Siemens). The residual activity (RA) was determined in percent of the activity of a control mixture of rpFVIII substrate with FVIII-depleted normal human, inhibitor-free plasma. The RA nearest to 50% was used to calculate the inhibitor concentration as described.

2.3 Domain mapping

Human serum albumin (HSA) fusion proteins with the human A2, C1, and C2 domains were constructed, expressed in HEK293T cells, and purified as previously described. The conformational integrity of HSA-hA2, HSA-hC1, and HSA-hC2 fusion proteins was confirmed by binding to commercially available anti-human FVIII domain-specific antibodies.
Sufficient material for binding studies was available from 66 patients in this study. An amount of 3 pmol fusion proteins or HSA (negative control) were coated on microrotater plates (Microlon 600, Greiner BioOne) at 4°C for 12-14 hours, followed by washing with phosphate buffered saline with 0.05% v/v Tween-20 (PBST). Plates were blocked with 5% w/v skim milk powder (Sigma-Aldrich) in PBST (MPBST) for 2 hours at room temperature. Human plasma samples diluted 1:100 in MPBST (or twofold serially diluted in MPBST starting at 1:100). After thorough washing with PBST, bound human IgG were detected using an horseradish peroxidase-conjugated goat anti-human IgG (H + L) antibody (Invitrogen) diluted 1:5000 in MPBST, and developed with O-phenylenediamine for 6 minutes at room temperature. Absorbance (optical density, OD) was measured immediately with a microplate absorbance reader (Sunrise, Tecan) at 492 and 620 nm (reference; subtracted). IgG binding was considered positive if net OD values at 492 nm were above 0.3.

### 2.4 Statistical analysis

Statistical analysis was performed using GraphPad Prism 6 (GraphPad Software Inc.). After testing all variables for normality, baseline characteristics from patients with and without cross-reactivity were compared. Because normality was not given, Fisher's exact test was performed to compare categorical data, and nonparametric Mann-Whitney test was performed to compare continuous data between these two groups. To assess whether the time required to achieve partial and complete remission in patients without cross-reactivity was significantly different from patients with cross-reactivity, a log-rank test was performed. The capacity of the anti-human FVIII inhibitor titer to predict an anti-rpFVIII titer ≥0.5 BU was expressed as the area under the receiver-operator characteristic (ROC) curve (AUC) with its 95% confidence interval. The likelihood ratio was used to describe clinically useful cut-offs. For all analyses, a P value <.05 was considered statistically significant.

### 3 RESULTS

Baseline demographic, clinical, and laboratory data of the 70 patients are provided in Table 1. Inhibitors from 31 patients (44%) showed cross-reactive inhibition of rpFVIII. The anti-rpFVIII titer in BU/mL ranged from <0.5 to 471 BU/mL, and the ratio of anti-rpFVIII to anti-human inhibitors ranged from 0 to 0.47. Anti-rpFVIII titers were always low (<5 BU/mL) with the exception of one patient, who had a high-titer anti-rpFVIII inhibitor of 471 BU/mL. This patient also had a very high anti-human FVIII inhibitor of 3891 BU/mL.

We compared baseline characteristics and outcomes of patients with and without cross-reactivity to rpFVIII (Table 2). Age, gender and underlying disorders, as well as number of bleed, were not significantly different. Patients with cross-reactivity had higher anti-human FVIII inhibitor titers and lower baseline FVIII:C. Time to partial and complete remission was significantly shorter in patients without cross-reactivity, probably reflecting their lower baseline anti-human FVIII titer.

Figure 1 illustrates the trend towards higher anti-human FVIII titers in patients with detectable anti-rpFVIII reactivity, but the correlation between anti-human and anti-rpFVIII titers was poor. Figure 2 shows a ROC curve for predicting anti-rpFVIII titers ≥0.5 BU/mL from the anti-human FVIII titer. The AUC was 0.76 (95% CI 0.65-0.87, P = .0002). A likelihood ratio of 11.3 was calculated for an anti-human FVIII titer of 100 BU/mL (sensitivity 29%, specificity 97%), indicating that 97% of patients above this threshold had a cross-reacting inhibitor. A sensitivity of >90% for detecting cross-reactivity was observed at an anti-human FVIII titer of 3.8 BU/mL, indicating that below this threshold, a cross-reacting inhibitor can be excluded with reasonable certainty.

Figure 3 shows FVIII activity measured after incubating rpFVIII (1 IU/mL for 2 hours) in AHA plasma of different anti-rpFVIII inhibitor strength (data taken from the first dilution of the Bethesda assay described above). It becomes apparent that even low titers between 1 and 5 BU/mL result in very low activity recovered after 2 hours in vitro incubation. However, FVIII activity was always detectable unless the inhibitor titer exceeded 5 BU/mL.

Next, we were interested to know whether the domain reactivity of autoantibodies in AHA would influence the frequency or strength of rpFVIII inhibition. Immunoassays were performed to detect domain-specific autoantibodies by binding to recombinant

| Characteristic | All AHA patients (n = 70) |
|---------------|--------------------------|
| Clinical data |                          |
| Gender        |                          |
| Female        | 26 (37.1)                |
| Age in years  | 70 (15, 26-94)           |
| Underlying disorders |               |
| Malignancy    | 8 (11.4)                 |
| Autoimmunity  | 12 (17.1)                |
| Pregnancy     | 3 (4.3)                  |
| Local laboratory measurements |       |
| Baseline FVIII:C in IU/dL, median (IQR, range) | 1.4 (<1-3.4, <1-31) |
| Central laboratory measurements |           |
| Patients with anti-human FVIII inhibitor, n (%) | 70 (100) |
| Anti-human FVIII inhibitor BU/mL, median (IQR, range) | 8.5 (3.9-33.3, 0.7-3891) |
| Patients with any anti-rpFVIII inhibitor, n (%) | 31 (44) |
| Anti-rpFVIII inhibitor 0.5-<1 BU/mL, n | 17 |
| Anti-rpFVIII inhibitor 1-<2 BU/mL, n | 8 |
| Anti-rpFVIII inhibitor 2-<5 BU/mL, n | 5 |
| Anti-rpFVIII inhibitor ≥5 BU/mL, n | 1 |
| Anti-rpFVIII inhibitor BU/mL, median (IQR, range) | <0.5 (0.5-0.8, 0.5-471) |
| Ratio anti-rpFVIII to anti-human FVIII inhibitor, median (IQR, range) | 0 (0-0.032, 0-0.467) |

Abbreviations: AHA, acquired hemophilia A; BU, Bethesda units; FVIII:C, coagulation factor VIII activity; IQR, interquartile range; IU, international units; SD, standard deviation.
HSA fusion proteins of the human A2, C1, and C2 domains. Samples from most patients reacted with either C1 or C2 or both, whereas binding to A2 was less frequent (Figure 4A). Anti-rpFVIII inhibitor activity was rarely detected in samples that reacted only with the C2 domain (1 of 16, 6%; Figure 4B). In contrast, anti-rp-FVIII inhibitor activity was more frequent in samples that reacted only with the C1 domain (8 of 19, 42%), with both C1 and C2 (15 of 20, 75%) or with any pattern involving the A2 domain (6 of 11, 55%). The ratio of anti-rpFVIII to anti-human FVIII inhibitors was highest for inhibitors involving the C1 domain (Figure 4B, right panel). The anti-human FVIII inhibitor activity was higher for samples involving both C1 and C2 as compared to inhibitors involving single domains only (Figure 4C). In contrast, the anti-rpFVIII inhibitor activity was not higher in samples involving C1 and C2 together versus single domains (Figure 4C).

### 4 | DISCUSSION

Rapid and effective bleed control is the priority in the management of AHA. Treatment options include bypassing agents, comprising activated prothrombin complex concentrate (APCC, FEIBA®) and recombinant factor VIIa (eptacog alfa activated, NovoSeven®). Susoctocog alfa, a recombinant porcine-sequence FVIII concentrate, became an additional treatment option since it was approved for AHA in 2015. Its use has been reported in several case reports and series. Porcine FVIII had already been used in the past for the treatment of AHA because anti-FVIII autoantibodies often exhibited low or absent cross-reactivity. A porcine plasma-derived concentrate (Hyate:C®) was licensed in the UK in 1984, in the United States 2 years later, and revolutionized the treatment of bleeds in AHA at that time. Hyate:C also contained porcine von Willebrand factor (VWF), which had been implicated as a potential cause for platelet aggregation and thrombocytopenia sometimes observed with this drug. On the other hand, the presence of VWF in Hyate:C may have also contributed to the protection against inhibitors in AHA patients. Sukhu et al. showed that inhibition of a range of human FVIII concentrates by AHA plasma was highly variable, with the lower inhibition seen in concentrates that contained large amounts of VWF. Of note, VWF binds to the FVIII C1 and C2 domains that are frequent targets of inhibitors in AHA. Susoctocog alfa is devoid of VWF, perhaps raising the question whether it is similarly well protected against inhibitors as plasma-derived porcine FVIII.

### TABLE 2 Characteristics of AHA patients with or without anti-porcine FVIII cross-reactivity

| Characteristic                                     | With cross-reactivity (n = 31) | Without cross-reactivity (n = 39) | P   |
|----------------------------------------------------|-------------------------------|----------------------------------|-----|
| Clinical data                                      |                               |                                  |     |
| Female gender, n (%)                               | 13 (41.9)                     | 13 (33.3)                        | n. s.|
| Age in years, mean (SD, range)                     | 71 (14, 29-92)                | 70 (16, 26-94)                   | n. s.|
| Underlying disorders                               |                               |                                  |     |
| Malignancy, n (%)                                  | 2 (6.5)                       | 6 (15.4)                         | n. s.|
| Autoimmunity, n (%)                                | 5 (16.1)                      | 7 (17.9)                         | n. s.|
| Pregnancy, n (%)                                   | 2 (6.5)                       | 1 (2.6)                          | n. s.|
| Number of bleeds, median (IQR, range)              | 3 (2-4.5, 0-9)                | 3 (2-4, 0-8)                     | n. s.|
| Local laboratory measurements                      |                               |                                  |     |
| FVIII:C in IU/dL, median (IQR, range)              | <1 (<1-2, <1-20.4)            | 2.6 (<1-6.1, 0-31)               | .0026|
| Central laboratory measurements                     |                               |                                  |     |
| Anti-human FVIII inhibitor in BU/mL, median (IQR, range) | 27.8 (8.4-120.2, 1.5-3891)   | 5.4 (2.3-14, 0.7-582.4)          | .0002|
| Partial remission                                  |                               |                                  |     |
| Achieved, n (%)                                    | 25 (80.6)                     | 33 (84.6)                        | n. s.|
| Time in days, median (IQR, range)                  | 47 (29-71, 10-202)            | 26 (17-35, 8-68)                 | <.0001|
| Complete remission                                 |                               |                                  |     |
| Achieved, n (%)                                    | 17 (54.8)                     | 25 (64.1)                        | n. s.|
| Time in days, median (IQR, range)                  | 91 (81-132, 40-588)           | 63 (50-73, 26-113)               | .0396|

Abbreviations: AHA, acquired hemophilia A; BU, Bethesda units; FVIII:C, coagulation factor VIII activity; IQR, interquartile range; IU, international units; SD, standard deviation.
In our study, 31 of 70 patients (44%) had inhibitors that cross-reacted with susoctocog alfa to a certain degree. This rate appears higher than previously reported for Hyate:C. It is also somewhat higher than in the susoctocog alfa pivotal study that found anti-rp-FVIII inhibitors in 10 of 29 patients (34%). However, anti-rpFVIII titers >20 BU/mL were an exclusion criterion in that study, which may have contributed to a selection of patients with low or absent cross-reactivity. Our study provides the first estimate for the anti-rpFVIII inhibitor frequency in an unselected cohort of patients with AHA.

The absolute anti-rpFVIII inhibitor titer was low in most of our patients. High-titer inhibitors were seen in just 1 out of 70 patients. This is important information because the current approval status of susoctocog alfa does not require the anti-rpFVIII titer to be known before starting the treatment. The manufacturer rather recommends close monitoring of the FVIII activity during therapy, thereby identifying patients with lack of response. However, the recognition of low-titer anti-rpFVIII inhibitors may not be so easy during the treatment of an individual patient because it can impact the drug’s half-life more than the incremental recovery. Therefore, frequent monitoring of the FVIII activity is required during treatment. Low trough levels may result from cross-reactive inhibitors, but also from individual variation in the drug’s half-life or consumption because of the bleed. In fact, the detection of anti-rpFVIII inhibitors may potentially be improved in the future by using pre-analytical heat treatment and/or enzyme-linked immunoassay (ELISA) technology as it has been demonstrated for anti-human inhibitors in AHA.

Fosbury et al demonstrated in their review of the susoctocog alfa pivotal study that patients with low cross-reacting anti-rpFVIII inhibitors, compared to those without, had much higher dosing requirements (median 1400 and 300 U/kg in the first 24 hours, respectively). This may not only result from inhibition by the low titers of neutralizing antibodies, but also from increased clearance due to non-neutralizing anti-rpFVIII antibodies that may be coincidentally present in those patients but remain undetected in the Bethesda assay. Tarantino et al reported in their case series two out of seven patients who did not clinically respond to rpFVIII. Both had very
high anti-human FVIII titers (205 and 374 BU/mL). In one of these patients, no meaningful increase in FVIII activity could be achieved and a cross-reacting anti-rpFVIII inhibitor of 2 BU/mL was found retrospectively in a day 1 backup sample. This observation is supported by our data demonstrating the low FVIII activity observed after spiking rpFVIII into AHA plasmas with anti-rpFVIII titers of about 2 BU/mL. Taken together, the existing observations shed light on the potential clinical relevance of low-titer anti-rpFVIII inhibitors. Probably,
knowledge of the anti-rpFVIII titer at the commencement of treatment would be useful in most clinical scenarios.

Analysis of our data suggested that cross-reactivity is likely in patients with anti-human FVIII inhibitors >100 BU/mL. On the other hand, cross-reactivity was unlikely in patients with anti-human FVIII inhibitors <3.8 BU/mL. This information may be helpful in clinical settings where the anti-rpFVIII titer is not immediately available.

Our data further suggest that the domain reactivity pattern may influence the cross-reactivity of inhibitors. This analysis was done only on IgG antibodies that exist in >98% of patients with AHA. We were not able to repeat this analysis for IgA and IgM antibodies that exist in 46% and 9% of patients, respectively. Anti-FVIII IgG involving the C1 domain showed the highest degree of cross-reactivity reflecting the higher degree of conservation between the human and porcine C1 domain (92.8% identity and 96.7% similarity) as compared to other domains. In contrast, IgG antibodies exclusively involving the C2 domain rarely inhibited rpFVIII. This finding does not support the notion that a higher frequency of cross-reactivity of anti-human FVIII inhibitors with susoctocog alfa, as compared with Hyate:C, might be due to the lack of VWF.

The ratio of anti-porcine/anti-human inhibitor titer (as a fraction or in percent) has been reported in the susoctocog alfa clinical trial and was also calculated from our data. It is interesting to note that this ratio was highest in samples of inhibitors reacting with the C1 domain only. However, given the inaccuracy of the Bethesda assay as such, these data must be interpreted with caution and do not have implications on current clinical practice.

Some limitations of our study should be considered. First, Bethesda inhibitor titers against human FVIII and rpFVIII cannot be compared directly, because the assay substrates are very different: human FVIII was from normal human plasma, containing VWF, whereas rpFVIII is a recombinant, B-domain deleted molecule, devoid of VWF, but of much higher specific activity. Second, our patients were not treated with susoctocog alfa because it was not approved at the time of enrolment. Therefore, we cannot correlate the finding of cross-reactive inhibitors with clinical efficacy. Third, we used only samples obtained at baseline. Sometimes, patients may develop de novo inhibitors against rpFVIII during treatment. We cannot predict the likelihood of this event from our study.

In conclusion, our study is the first unbiased assessment of the frequency and strength of cross-reacting inhibitors against rpFVIII in patients with newly diagnosed AHA. Anti-rpFVIII inhibitors were found in 44% of patients and were particularly frequent in patients with anti-human FVIII titers >100 BU/mL.

ACKNOWLEDGEMENTS

The authors acknowledge all members of the GTH AH working group, who enrolled patients into the study. The GTH-AH 01/2010 study was supported by grants from GTH e.V., Novo Nordisk, and Shire. This post-hoc analysis of the GTH-AH 01/2010 study was supported by an unrestricted grant from Shire. Shire and Novo Nordisk played no role in the design, conduct, or analysis of the study and were not involved in manuscript preparation.

CONFLICT OF INTEREST

HT has no competing interests to declare. CK has received honoraria or consultation fees from Bayer, Biotest, Chugai/Roche, CSL Behring, Grifols, Novo Nordisk, Pfizer, SOBI/Sanofi Genzyme, Shire/Takeda. AT has received honoraria or consultation fees for participating at educational meetings organized by Alnylam, Bayer, Biogen Idec, Biotest, Boehringer Ingelheim, Chugai, CSL Behring, Daiichi Sankyo, Leo Pharma, Novo Nordisk, Octapharma, Pfizer, Portola, Roche, Shire, and SOBI. PK has received honoraria, speaker and consultancy fees, or travel grants from Biotest, CSL Behring, Novo Nordisk, Roche, Shire/Takeda. HE received fees to act as a speaker, consultant, or to participate in Advisory Board meetings from Bayer, CSL Behring, Novo Nordisk, Shire/Takeda, SOBI, and Roche, and received research grants from Bayer Vital, CSL Behring, and Pfizer. KH has received honoraria, speaker and consultancy fees, or travel grants from Biotest, CSL Behring, Novo Nordisk, Roche/Chugai, Shire/Takeda, Pfizer, SOBI, Bayer and research grants from Bayer, Pfizer, CSL Behring.

AUTHOR CONTRIBUTIONS

AT designed and supervised the study, enrolled patients, analyzed and interpreted data, and participated in manuscript drafting. HT performed the laboratory measurements, analyzed and interpreted data, and participated in manuscript drafting. CK contributed domain mapping analysis. PK, RK, KH, AHK, UG, and HE enrolled patients and critically revised the manuscript. All authors approved the final manuscript version.

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