An Open-label, Single-Dose, Pharmacokinetic Study of Factor VIII Activity After Administration of Moroctocog Alfa (AF-CC) in Male Chinese Patients With Hemophilia A

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ABSTRACT

Purpose: Hemophilia A represents up to 80% of all hemophilia cases in China. In patients with this condition, bleeding can be prevented and controlled by administering clotting factor VIII (FVIII). Since their initial availability, recombinant FVIII products have undergone several iterations to enhance their safety. Moroctocog alfa albumin-free cell culture (AF-CC) is among the third generation of recombinant FVIII products and received regulatory approval in China in August 2012. The present study characterizes the single-dose pharmacokinetic parameters of FVIII activity (FVIII:C) after administration of moroctocog alfa (AF-CC) in male Chinese patients with hemophilia A.

Methods: This multicenter, open-label, single-dose study enrolled 13 male Chinese patients diagnosed with severe hemophilia A (FVIII:C <1%) and a history of at least 150 exposure-days to any FVIII-containing product. Eligible patients received a single dose of moroctocog alfa (AF-CC) 50 IU/kg IV within 10 minutes. Blood samples were collected within 2 hours before administration and through 72 hours after dosing.

Findings: Pharmacokinetic parameters were assessed based on FVIII:C and were analyzed by age groups: ages 6 to <12 years (n = 3) and ≥12 years (n = 10). The mean plasma concentration-time profile for FVIII:C activity was consistently lower in patients aged 6 to <12 years compared with those aged ≥12 years. Geometric $AUC_{0-\infty}$ and C_{max} were approximately 57% and 28% lower in the younger patients relative to the older patients, respectively. A total of 4 adverse events occurred in 4 patients. Low-titer, transient FVIII inhibitors were observed in 2 patients and were considered serious adverse events. Neither case resulted in clinical manifestations nor required treatment.

Implications: This is the first report of the pharmacokinetic parameters of FVIII:C after moroctocog alfa (AF-CC) in an all-Chinese population of males with hemophilia A. The pharmacokinetic profile in older patients was similar to that previously reported with recombinant FVIII products in studies with a predominantly white population; younger patients had reduced exposure to FVIII:C. The single doses of moroctocog alfa (AF-CC) were well tolerated; 2 cases of transient, low-titer FVIII inhibitor development were observed. ClinicalTrials.gov identifier: NCT02461992. (*Clin Ther.* 2017;▮:▮▮▮–▮▮▮)

Key words: age groups, China, factor VIII, pediatrics, pharmacokinetics, recombinant.

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INTRODUCTION

Hemophilia A is an X-linked congenital bleeding disorder caused by a partial or total deficiency of coagulant factor VIII (FVIII).[1] Hemophilia affects residents of mainland China at a rate of approximately 3.6 per 100,000 people, increasing to approximately 5.5 per 100,000 males. The predominant form of the disease is hemophilia A; in China, hemophilia A represents 70% to 80% of the total hemophilia burden, followed by hemophilia B at 10% to 20%, with hemophilia C and von Willebrand disease accounting for the remainder.[2]

The primary strategy for managing bleeding events in patients with hemophilia is to administer the deficient clotting factor. In patients with hemophilia A, bleeding events may be prevented and controlled by administering FVIII clotting factor concentrates.[1] Moroctocog alfa is a recombinant FVIII replacement product for treatment of patients with hemophilia A that has undergone several iterations since the US approval of the original product (antihemophilic factor*) in 2000. A B-domain–deleted recombinant FVIII compound, this agent contained human albumin in the formulation. Efforts to enhance the safety profile drove the development of an albumin-free cell culture (AF-CC) manufacturing process that used a synthetic peptide affinity ligand in the affinity chromatography step, plus nanofiltration during purification, resulting in a product free of human- or animal-derived proteins.[3] Moroctocog alfa (AF-CC),† available in the United States, Canada, and other regions as Xyntha and in the European Union and other regions as ReFacto AF,[3–5] increases plasma levels of FVIII activity (FVIII:C) and temporarily corrects the coagulation deficiency in patients with hemophilia A.[4,5]

The pharmacokinetic properties of FVIII replacement products are assessed by evaluating FVIII:C in plasma after administration of the clotting factor rather than measuring concentrations of the replacement. The pharmacokinetic properties of FVIII:C after the administration of the original moroctocog alfa, before reformulation, was described in patients with hemophilia A after single doses and was determined to be bioequivalent to purified plasma-derived FVIII.[6–9]

Since the initial approval in 2000, considerable experience has been documented concerning the tolerability and efficacy of recombinant FVIII for the treatment and prevention of bleeding events in patients with hemophilia A. Moroctocog alfa (AF-CC) received regulatory approval in China in August 2012 with an indication for the control and prevention of bleeding episodes and for surgical prophylaxis in patients with hemophilia A.[10] A recent study summarized the clinical efficacy and tolerability of moroctocog alfa (AF-CC) in Chinese patients with hemophilia A.[11] The primary objective of the present study was to characterize the single-dose pharmacokinetic profile of FVIII:C of moroctocog alfa (AF-CC) in male Chinese patients with hemophilia A. Tolerability was assessed as a secondary end point.

PATIENTS AND METHODS

Eligible patients were Chinese males aged ≥6 years (weight >20 kg) with a diagnosis of severe hemophilia A (FVIII:C <1%) and previously treated with a documented history of >150 exposure-days to any FVIII-containing products. Patients had to be in a nonbleeding state before study treatment administration on day 1. Key exclusion criteria included infusion of any FVIII product within 3 days before receiving study treatment; current FVIII inhibitor or history of FVIII inhibitor use (defined as above the upper limit of normal of the local reporting laboratory); any other bleeding disorder in addition to hemophilia A; treatment with immunomodulatory therapy within 30 days or 5 half-lives (whichever was longer) before study entry or planned use for the duration of study participation; known hypersensitivity to the active substance or to any of the excipients of moroctocog alfa (AF-CC) or Chinese hamster ovary cell proteins; history of sensitivity to heparin or heparin-induced thrombocytopenia; and evidence or history of clinically significant conditions or findings at screening that may have compromised the patient's participation in the study.

Study Design and Setting

This multicenter, open-label, single-dose study was conducted at 2 centers in China. The study protocol was approved by the ethics committee at each center,

*Trademark: ReFacto (Wyeth Pharmaceuticals, Inc [Pfizer], Philadelphia, Pennsylvania).

†Trademark: Xyntha (Wyeth Pharmaceuticals, Inc [Pfizer], Philadelphia, Pennsylvania).

and the study was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice Guidelines. All participants or, for pediatric patients, their legal guardians provided written informed consent before study participation.

After a 28-day screening period, all patients received a single dose of moroctocog alfa (AF-CC) 50 IU/kg,[‡] which was calculated based on the patient's actual weight and administered by intravenous infusion within 10 minutes in the morning on day 1 (at approximately 0800 hours [±2 hours]). Treatment administration was initiated under the supervision of a physician experienced in the treatment of hemophilia A and in accordance with the instructions detailed in the package insert.[10]

Blood samples (2.7 mL) were collected within 2 hours before administration and at 0.25, 0.5, 1, 3, 6, 9, 24, 28, 32, 48, and 72 hours after dosing. Patients were admitted to the Clinical Research Unit at least 12 hours before dosing (day 0) and were required to remain in the Clinical Research Unit at least through completion of the 24-hour pharmacokinetic sample collection; afterward, patients could remain at the Clinical Research Unit or provide the remaining samples on an outpatient basis, at the discretion of the investigator.

Bioanalytical Method

Blood samples (2.7 mL to yield a minimum of 1 mL of plasma) for FVIII:C and for FVIII inhibitor analysis were collected in tubes that contained sodium citrate anticoagulant. The plasma was separated and stored at −60°C to −80°C until analysis. Plasma samples were analyzed for FVIII:C and FVIII inhibitors at Covance Laboratories Inc (Chantilly, Virginia) using validated, sensitive, and specific analytical 1-stage coagulation assays. FVIII:C calibration standard responses were linear over the range of 0.0078 to 0.5000 IU/mL for both FVIII:C and FVIII inhibitor assays. The lower limit of quantitation (LLOQ) for FVIII:C was <0.0100 IU/mL. Inhibitor samples with results <0.6000 BU/mL were reported as negative. The intra-assay precision of the quality control samples was within the targeted acceptance criteria of <20%. The intra-assay accuracy at all nonzero levels except LLOQ and low were within the targeted acceptance criteria of relative error, ±20%. The inter-assay precision of the quality controls was within the targeted acceptance criteria of <20% or <25% at LLOQ. The interassay accuracy at all nonzero levels, except LLOQ and low, was within the targeted acceptance criteria of relative error ±20% and total error <30%.

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Pharmacokinetic Analyses

Pharmacokinetic measures included the FVIII:C C_{max}, T_{max}, $AUC_{0–last}$, $AUC_{0–\infty}$, steady-state V_d, k_{el}, $t_{½}$, mean residence time, clearance (CL), and incremental recovery (the increase in circulating FVIII:C for every international unit of moroctocog alfa [AF-CC] administered per kilogram of body weight). Pharma parameters were calculated using noncompartmental analysis methods and an internally validated software system (eNCA, version 2.2.4; Pfizer, Groton, Connecticut). Samples below the LLOQ were set to 0 for analysis.

Tolerability

Tolerability was assessed during the study by monitoring adverse events (AEs) and serious adverse events (SAEs). All patients who received at least 1 dose of study drug were included in the tolerability analyses. Events considered medically important were inhibitor development and thrombogenicity. If these events occurred after the administration of the study medication, they were reported as SAEs. As noted previously, inhibitor development was defined as activity of neutralizing antibodies (>0.6 BU/mL) detected in patients receiving FVIII-containing products. Any result deemed positive after the administration of the study medication required reporting of relevant data concerning the temporal relationship to the administration of test article and changes in frequency of bleeding episodes or increased bruising. Laboratory, physical examination, and ECG measures were also recorded.

Statistical Analysis

The anticipated enrollment was 12 patients aged ≥6 years with severe hemophilia A (FVIII:C <1%), 3 to 4 of whom would be 6 to 12 years of age. The planned sample size of 12 male Chinese patients was based on China Food and Drug Administration requirement for a pharmacokinetic study in Chinese patients and to support the continued registration of moroctocog alfa (AF-CC) in China.

The pharmacokinetic concentration analysis population was defined as all patients enrolled and treated who had at least 1 reported FVIII:C measure, and the pharmacokinetic parameter analysis population was defined as all patients enrolled and treated who had at least 1 of the pharmacokinetic parameters of primary interest reported. Pharmacokinetic parameters were summarized descriptively by age group (6 to <12 years and ≥12 years of age) using an internally validated software system (eNCA, version 2.2.4).

The FVIII:C results were summarized by sampling time, using an internally validated software system (eNCA, version 2.2.4). Mean (SD) profiles of the FVIII:C-time data by age group were plotted. For mean plots the nominal sampling times were used.

RESULTS

Patients

Of the 14 patients screened, 13 met the eligibility criteria and were enrolled in the study. Three patients were aged 6 to <12 years and 10 patients were aged ≥12 years (Table I). All 13 patients completed the study and were included in the pharmacokinetic and tolerability analyses.

Table I. Patient demographics and characteristics.

Characteristic	Patients (N = 13)
Age, y	
6–11	3
12–17	5
18–44	2
45–60	3
Mean (SD)	24.4 (19.6)
Range	6–60
Weight, kg	
Mean (SD)	54.1 (19.2)
Range	23.5–84.0
Body mass index, kg/m^2	
Mean (SD)	20.5 (4.6)
Range	15.0–26.5
Height, cm	
Mean (SD)	159.7 (19.6)
Range	125–178

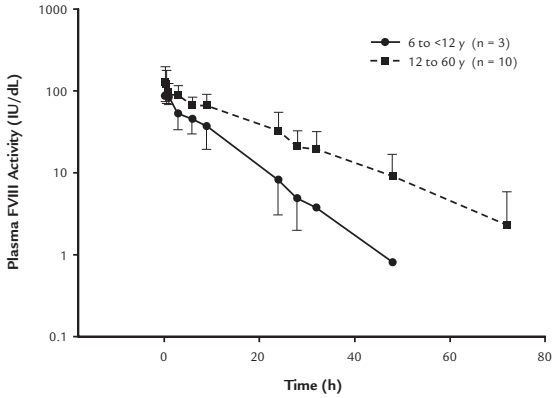

Figure 1. Mean (SEM) plasma factor VII (FVIII:C) activity concentration–time profiles by age group after administration of 50 IU/kg moroctocog alfa.

Pharmacokinetic Parameters

As shown in Figure 1, the mean plasma concentration–time profile for FVIII:C after a single dose of moroctocog alfa (AF-CC) 50 IU/kg was consistently lower in patients aged 6 to <12 years compared with those aged ≥12 years. A comprehensive summary of pharmacokinetic parameters is provided in Table II. Geometric mean $AUC_{0-\infty}$ and C_{max} were approximately 57% and 28% lower in the younger patients relative to the older patients, respectively. Moreover, CL was higher and $t_{½}$ was shorter in younger patients than in older patients, whereas V_{dss} was higher in younger patients compared with older patients. A plot of CL versus age is shown in Figure 2. Incremental recovery was lower in younger patients than older patients, with geometric mean values of 1.7 (IU/dL)/(IU/kg) and 2.5 (IU/dL)/(IU/kg) in patients aged 6 to <12 years and ≥12 years, respectively.

Tolerability

Overall, 4 patients experienced a total of 4 AEs, all of which were considered by the investigator to be treatment related (FVIII inhibition, n = 2; abdominal pain, n = 1; and headache, n = 1). No clinically significant abnormalities were observed in laboratory values, vital signs, ECG readings, or physical examination observations.

The 2 incidents of transient, low-titer FVIII inhibition were considered medically significant and were defined as SAEs, per the study protocol. The first

Table II. Descriptive summary of plasma factor VIII activity pharmacokinetic parameter values by age group.

Parameter	Moroctocog Alfa (AF-CC) 50 IU/kg*	
	6 to <12 years (n = 3)	≥12 years (n = 10)
$AUC_{0-\infty}$, IU · h/mL	7.931 (50)	18.48 (41)
AUC_{0-last}, IU · h/mL	7.702 (51)	17.51 (40)
C_{max}, IU/dL	89.52 (18)	12.35 (47)
T_{max}, h	0.25 (0.25–0.50)	0.50 (0.25–3.0)
k_{el}, 1/h	0.09844 (24)	0.05215 (28)
$t_{½}$, h	7.2 ± 1.8	13.8 ± 3.8
MRT, h	10.09 (27)	18.92 (26)
CL, mL/h/kg	6.653 (30)	2.669 (38)
V_{dss}, mL/kg	67.18 (10)	50.53 (30)
Incremental recovery, IU/dL/IU/kg	1.695 (5)	2.498 (47)

AF-CC = albumin-free cell culture; CL = clearance; CV, coefficient of variation; MRT = mean residence time.
*Data are presented as geometric mean (%CV) for all, except for T_{max}, which is median (range), and $t_{½}$, which is arithmetic mean (SD).

incident occurred in a 6-year-old boy without significant medical history, aside from severe hemophilia A, who had been treated with secondary prophylaxis with human FVIII replacement product for a total of approximately 400 exposure-days approximately 5 years before enrolling in the study. During the screening visit, negative FVIII inhibitor (defined as <0.6 BU/mL) was detected. During the study, the patient received a single infusion of moroctocog alfa (AF-CC) 1000 IU (42.55 IU/kg), and 4 days after dosing, a positive low-titer inhibitor result was observed (0.9840 BU/mL). During a routine follow-up approximately 2 months later, the patient had returned to negative FVIII inhibitor status. The second patient was aged 15 years without significant medical history aside from severe hemophilia A. He had been treated with secondary prophylaxis with human FVIII replacement product for a total of approximately 300 exposure-days about 14 years before enrollment in the study. During screening and on the day before dosing, negative FVIII inhibitor was observed. The patient received a single infusion of moroctocog alfa (AF-CC) 2500 IU (52.08 IU/kg), and on study day 4, a low-titer inhibitor result was observed (0.7044 BU/mL). During a routine follow-up approximately 2 months later, the patient had returned to negative FVIII inhibitor status. In both patients, no clinical manifestations of FVIII inhibitor were observed, and the patients did not require or receive treatment for the events. In the opinion of both the investigator and the sponsor, there was a reasonable possibility that both events were related to the study treatment but unrelated to clinical trial procedures.

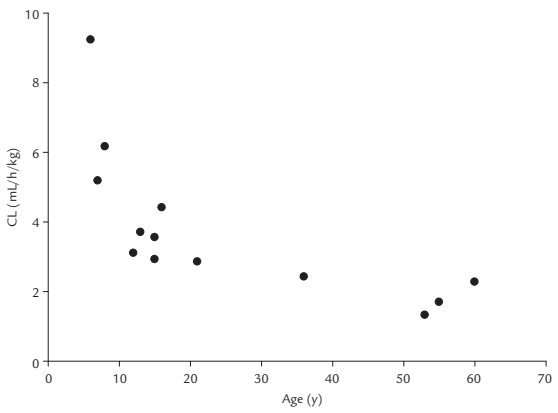

Figure 2. Relationship between age and weight-normalized clearance (CL) in study patients.

DISCUSSION

This study assessed the pharmacokinetic parameters of FVIII:C after administration of moroctocog alfa (AF-CC) in Chinese male patients with severe

hemophilia A aged from 6 to 60 years. To our knowledge, the present study was the first to evaluate the pharmacokinetic parameters of a recombinant FVIII product in an exclusively Chinese population. Results indicate that children aged 6 to <12 years have lower exposure ($AUC_{0-\infty}$, AUC_{0-last}, and C_{max}), larger V_{dss}, lower recovery, higher CL, and shorter $t_{½}$ for the activity of moroctocog alfa (AF-CC) compared with older children and adults. The results of this study were limited by the small sample size, including the unbalanced number of patients in each age strata; however, this is an expected challenge when studying young patients and patients with rare diseases. The study was too small to support formal statistical comparisons between the age groups or the development of a population pharmacokinetic model to more formally test for important covariates that influence the parameters of the model. However, Figure 2 shows the association between age and weight-normalized CL observed in the patients studied.

The pharmacokinetic properties of moroctocog alfa (AF-CC) in the older children and adult Chinese patients in our study are similar to those previously reported for recombinant FVIII products in studies of primarily white patients aged at least 18 years with moderate or severe hemophilia A. Kessler et al[6] reported a mean (SD) recovery of 2.43 (0.38) IU/dL/IU/kg and a $t_{½}$ of 14.8 (5.6) hours in 18 men aged 18 to 44 years. Di Paola et al[9] reported mean (SD) recovery of 2.23 (0.33) IU/dL/IU/kg, CL of 3.85 (1.36) mL/h/kg, and a $t_{½}$ of 13.0 (3.1) hours in 17 men aged 19 to 72 years. The results of our study are also consistent with the analysis performed by Bjorkman et al,[12] which assessed pharmacokinetic data for recombinant FVIII products in patients aged 1 to 6 years compared with patients aged 10 to 65 years. The analysis found lower median recovery (1.84 IU/dL/IU/kg), higher CL (4.34 mL/h/kg), and shorter $t_{½}$ (9.4 hours) in younger children compared with adults (2.42 IU/dL/IU/kg, 3.26 mL/h/kg, and 11.2 hours, respectively), although robust comparisons were made difficult by differences in sample collection methods between the 2 populations.[12] In addition, several other reports of the pharmacokinetic parameters of FVIII:C in children with hemophilia A (with a mean age of 10 months to 13 years) reported pharmacokinetic observations supportive of those observed in the younger patients in this study. Courter and Bedrosian[13] reported a mean recovery of 1.9 IU/dL/IU/kg (n = 46) and a $t_{½}$ of 7.5 hours (n = 39) in children with a mean age of 10 months. Barnes et al[14] reported a mean recovery of 1.87 IU/dL/IU/kg and a $t_{½}$ of 10.7 hours in 20 children aged 4.4 to 18.1 years. Blanchette et al[15] reported mean recovery of 1.88 IU/dL/IU/kg and a $t_{½}$ of 9.71 hours in 52 children with a mean (SD) age of 3.1 (1.5) years.

Weight-based dosing is widely used in the treatment of hemophilia. The differences in pharmacokinetic parameters in young children compared with adolescents and adults indicate that young children may require higher doses per kilogram to achieve the desired FVIII activity if treating an acute bleeding episode and more frequent dosing to maintain target trough concentrations through prophylaxis. The possibility of differences in posology has been added to the European Medicines Agency's guideline on core Summary of Product Characteristics for human plasma derived and recombinant coagulation FVIII products.[16]

A single dose of moroctocog alfa (AF-CC) 50 IU/kg administered by IV infusion in this study was well tolerated. Low-titer, transient, positive FVIII inhibitors were reported in 2 patients and were considered SAEs by protocol definition; however, no associational clinical signs or symptoms were observed in either patient.

CONCLUSION

The pharmacokinetic parameters of moroctocog alfa (AF-CC) found in this study of male Chinese patients with hemophilia A were generally consistent with those of previous reports. Younger children were found to have lower exposure, a larger V_{dss}, higher CL, lower recovery, and shorter $t_{½}$ compared with adolescents and adults, as has been reported for other FVIII replacement products.

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CONFLICTS OF INTEREST

Drs. Liu, Hu, and Wu served as investigators for Pfizer Inc for this study. Mr. Huard and Drs. Xu, Sun, Liang, Nepal, Qu, and Korth-Bradley are employees of Pfizer Inc and own stock in that company. Pfizer employees were involved in the study design, the collection, analysis, and interpretation of data, the review of the manuscript, and the decision to submit for publication. No author received an honorarium related to the development of the manuscript.

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