Recombinant factor XIII: a safe and novel treatment for congenital factor XIII deficiency

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Congenital factor XIII (FXIII) deficiency is a rare, autosomal-recessive disorder, with most patients having an A-subunit (FXIII-A) deficiency. Patients experience life-threatening bleeds, impaired wound healing, and spontaneous abortions. In many countries, only plasma or cryoprecipitate treatments are available, but these carry a risk for allergic reactions and infection with blood-borne pathogens. The present study was a multinational, open-label, single-arm, phase 3 prophylaxis trial evaluating the efficacy and safety of a novel recombinant FXIII (rFXIII) in congenital FXIII-A subunit deficiency. Forty-one patients ≥ 6 years of age (mean, 26.4; range, 7-60) with congenital FXIII-A subunit deficiency were enrolled. Throughout the rFXIII prophylaxis, only 5 bleeding episodes (all trauma induced) in 4 patients were treated with FXIII-containing products. The crude mean bleeding rate was significantly lower than the historic bleeding rate (0.138 vs 2.91 bleeds/patient/year, respectively) for on-demand treatment. Transient, non-neutralizing, low-titer anti-rFXIII Abs developed in 4 patients, none of whom experienced allergic reactions, any bleeds requiring treatment, or changes in FXIII pharmacokinetics during the trial or follow-up. These non-neutralizing Abs declined below detection limits in all 4 patients despite further exposure to rFXIII or other FXIII-containing products. We conclude that rFXIII is safe and effective in preventing bleeding episodes in patients with congenital FXIII-A subunit deficiency. This study is registered at http://www.clinicaltrials.gov as number NCT00713648. (Blood. 2012;119(22):5111-5117)

Methods

Study design

The study was approved by the ethical committees at each participating hospital. Informed consent was obtained from each patient in accordance with the Declaration of Helsinki.

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In total, 41 patients were enrolled from 23 centers in 11 countries (Austria, Canada, Finland, France, Germany, Israel, Italy, Spain, Switzerland, the United Kingdom, and the United States). After a screening visit, eligible patients entered a 4-week run-in period, followed by a 52-week treatment period (visits 2-15) of monthly (28 ± 2 days) IV doses of 35 IU/kg of rFXIII. Patients receiving prophylaxis with a FXIII-containing product before the trial received their last prophylactic dose just before screening. Only patients with a confirmed FXIII-A subunit deficiency were given rFXIII at visit 2 (week 4). At each visit, the dose was adjusted according to the patient’s body weight.

Nonemergency use of FXIII-containing products other than rFXIII was not allowed during the trial. In cases of acute bleeds, the investigator judged whether to treat with an additional FXIII-containing product in accordance with local standard practice. Additional rFXIII doses could not be used to treat any breakthrough bleeds.

For safety-monitoring purposes, an additional interim visit (visit 3) was conducted 2 weeks after the first dose of trial product. The follow-up period of 4 weeks after the last administration of trial product ensured that the majority of rFXIII would have cleared when patients ended their participation in the trial.

Patients ≥ 6 years of age weighing ≥ 20 kg with diagnosed congenital FXIII-A subunit deficiency (confirmed by genotype analysis) were enrolled. Patients who had received regular replacement therapy before entering the trial had to have initiated this treatment at ≥ 6 months before screening and either a documented history of ≥ 1 treatment-requiring bleed before starting regular replacement therapy or a documented family history of congenital FXIII deficiency. Patients who had only received on-demand treatment before entering the trial had to have had a documented history of ≥ 2 treatment-requiring bleeds within 12 months before screening.

The rarity of congenital FXIII deficiency and the low bleeding frequency of patients currently on regular replacement therapy did not allow for a sample size large enough for sufficient statistical power to compare clinical outcome between rFXIII and any other type of regular replacement. Furthermore, a placebo-controlled trial in congenital FXIII deficiency would have been unethical because of the risk of serious bleeding complications. Therefore, the current trial was designed as a superiority trial: the primary efficacy parameter was the annualized frequency of bleeds requiring treatment with FXIII-containing products during the rFXIII prophylaxis treatment period versus the historical bleeding rate in patients with congenital FXIII deficiency treated on demand.

To define the historical control, Novo Nordisk conducted a comprehensive global survey of physicians asking how many bleeds per year patients had experienced based on 92 patients with congenital deficiency. Of these, 23 patients were only treated on-demand to manage acute bleeds. Bleeding frequency data were not available for 4 patients receiving on-demand treatment and, in 3 patients, the diagnosis was made less than 1 year before the survey. As a result, the statistical analysis was based on the remaining 16 patients, including 13 male and 3 female patients. Four of the 16 patients (25%) had no bleeds requiring on-demand treatment, and 12 patients (75%) experienced bleeds requiring treatment. The number of bleeds requiring on-demand treatment ranged from 0-12 per year (mean, 2.91). Based on a normal distribution approximation to the bleeding rate, a 95% confidence interval (95% CI) for the bleeding rate was calculated to be 0.95-4.86.

Of the 92 patients in the survey, 69 had a history of regular FXIII-replacement therapy. For 5 patients on prophylaxis, complete information regarding breakthrough bleeds was not available, so data from these patients were not included in the calculations. Seventeen of the 64 patients (26.6%) were reported to have experienced breakthrough bleeds while receiving regular replacement therapy. There were 20 breakthrough bleeds in total, ranging from 0-7 per year (data from 13 patients). The number of bleeds per year was not available for 4 patients. The annual bleeding rate estimated from 60 patients receiving prophylaxis was 0.33 bleeds per year (95% CI, 0.08-0.59). Basic demographic data for patients receiving on-demand and prophylaxis treatment are summarized in Table 1. The mean age in the 2 populations was 31.7 and 28.6 years, respectively, which is comparable to the mean age of the current trial population.

### Patient genotype

FXIII-A subunit deficiency was confirmed for all patients by genotyping. One patient also had a heterozygous missense mutation in the F13B gene, the effect of which is unknown. However, ELISA results for FXIII-B subunits showed that this patient had quantitatively normal B-subunits that were functionally capable of binding to A-subunits (as reflected by reduced levels of B-subunits and increased FXIII-A2:B1 levels after rFXIII injection).

### Patient assessments

At each participating center, the local investigator collected a medical history and performed a physical examination of each patient at baseline and at each subsequent study visit. Adverse events were recorded at every visit. Basic laboratory hematology, biochemistry, urinalysis, and coagulation-related parameters (prothrombin time reported as international normalized ratio, activated partial thromboplastin time, thrombin time, and fibrinogen) were assessed at baseline and at every subsequent visit. In addition, the following tests were performed at baseline and at every study visit at a central laboratory.

### FXIII activity assay

A modified Berichrom FXIII assay kit (Siemens Healthcare Diagnostics) was used to determine FXIII activity. The modifications refer to the use of rFXIII calibrators and the buffer used for sample dilution. Overall assay precision (percent coefficient of variation) was 5%-10% and accuracy (as the percent relative error) was 4.3%-10%. Recovery of FXIII activity was determined from the FXIII activity levels 1 hour after dosing and is expressed as the percentage increase from the predosing levels per unit of rFXIII administered per kilogram body weight.

### Clot-solubility assay

The clot-solubility assay is a qualitative assay used to assess clot strength. Plasma was allowed to clot after the addition of calcium and then a 1% chloroacetic acid was added to the clot. The clot will dissolve within 24 hours if < 1% FXIII is present. A normal result is greater than 24 hours without clot lysis. This assay is traditionally used as a primary screening test for the detection of FXIII deficiency; however, this assay only detects severe deficiencies, is poorly standardized, and varies in its degree of sensitivity.6,8-10 The usefulness of this assay was also not confirmed in the present study.

### FXIII-A2 determination

FXIII-A2 was detected by ELISA using a polyclonal rabbit anti–FXIII-rhuA2 subunit Ab (Novo Nordisk) to capture the FXIII-A2 subunit. After incubation with plasma, bound FXIII-A2 subunit was detected by incubation with biotin-labeled polyclonal rabbit anti–FXIII-rhuA2 subunit Ab and streptavidin labeled with HRP. An ortho-phenylenediamine hydrochloride substrate solution was used for color development, which was directly proportional to the FXIII-A2 subunit concentration. Data were collected.
were collected as for the FXIII-A2 assay. The assay recognized rhuA2 subunit binding to human endogenous B2 subunit (the rhuA2B2 tetramer). rhu-FXIII was used to prepare the assay calibrators.

**FXIII-A2B2 determination**

FXIII-A2B2 was also detected by ELISA in which a polyclonal rabbit anti–FXIII-B subunit Ab (Novo Nordisk) was used to capture the FXIII-B subunit. After incubation with plasma, bound FXIII-A2B2 was detected by incubation with biotin-labeled polyclonal rabbit anti–FXIII-A subunit Ab (Novo Nordisk) and subsequent incubation with streptavidin-HRP. Color development with an ortho-phenylenediamine hydrochloride substrate solution was directly proportional to the FXIII-A2B2 concentration. Data were collected as for the FXIII-A2 assay. The assay recognized rhuA2 subunit complexed to human B2 subunit (rhuA2B2), as well as endogenous human A2B2. Purified rhuA2B2 was used to prepare assay calibrators.

**Detection of anti-rFXIII Abs**

All patients receiving rFXIII were monitored for the development of binding Abs before administration of the trial product at visits 1-16, as well as at any unscheduled visit. For step 1, a direct ELISA was developed and validated to detect, confirm specificity, and quasi-quantify human IgG against rFXIII. The rFXIII (10 μg/mL) was used as the coating agent and residual binding was blocked by 5% skim milk. Samples (EDTA plasma diluted 1:100) were applied and bound Abs were detected using a secondary reagent (HRP-conjugated polyclonal rabbit anti-human IgA, IgG, IgM, and kappa; DAKO). After the addition of tetramethylbenzidine, substrate detection of Abs was performed by reading the absorbance at 450 nm (reference, 630 nm). An assay-plate-specific cut point was established using plasma from 100 healthy subjects which was directly proportional to the FXIII-A2B2 concentration. Purified plasma FXIII-B subunit was used to prepare the calibrators.

**Free FXIII-B determination**

Free FXIII-B subunit was determined by ELISA using a polyclonal donkey anti–mouse IgG Ab (Jackson ImmunoResearch) as a first-capture Ab to optimize binding of a second specific-capture Ab, a monoclonal free B-subunit Ab (Novo Nordisk). After incubation with plasma, free FXIII-B subunit was detected by incubation with a biotinylated polyclonal rabbit anti–FXIII-B subunit Ab (Novo Nordisk) and then incubation with streptavidin-HRP. A tetramethylbenzidine substrate solution was used for color development, which was directly proportional to the free FXIII-B subunit concentration. Purified plasma FXIII-B subunit was used to prepare the calibrators.

**Results**

**Patients**

Forty-one patients were enrolled and dosed (mean age, 26.4 years; range, 7-60 years; 56% male; 68% white; Table 2), with a mean treatment period of 322 days. With the exception of 2 patients, all received regular replacement therapy with FXIII-containing products before study enrollment. Five patients withdrew from the trial and 3 discontinued rFXIII treatment because of non-neutralizing Abs and returned to the previous local standard of treatment; however, they remained in the trial for follow-up and completed other trial-related activity visits. The remaining 33 patients completed the predefined trial treatment period (Table 2).

**Bleeding episodes**

During the rFXIII treatment period, 5 bleeding episodes treated with an FXIII-containing product were observed in 4 patients, resulting in a mean annualized bleed rate of 0.138 bleeds per patient/year. All 5 events were traumatic bleeds (Table 3). No intracranial hemorrhage or severe bleeds into internal organs occurred during rFXIII treatment. Bleeds occurred on days 5, 14, 15, 22, and 27 after treatment with rFXIII. There is no statistical evidence to conclude that treatment-requiring bleeds occurred more frequently in the late postdose phase, when plasma levels of rFXIII are expected to be lower.

In the primary end point analysis, the age-adjusted rate (number/patient-year) of treatment-requiring bleeds during the rFXIII treatment period was 0.048/year (95% CI, 0.0094-0.2501; a model-based estimate corresponding to the mean age of the trial
The influence of age was statistically significant at $P = 0.022$. Compared with retrospectively collected data from patients with congenital FXIII deficiency, the bleeding frequency in the present trial was numerically lower than for patients on regular replacement therapy (on average, approximately 0.33 treatment-requiring bleeds/year). It was also significantly lower than the rate of treatment-requiring bleeds/year in patients receiving on-demand treatment both compared with the historic rate (2.91 bleeds/year) and based on the lower 95% CI limit (0.95 bleeds/year).

Thirty-seven of the 41 patients did not experience any bleeds requiring treatment during the trial. Age-adjusted statistical analysis via a binomial model determined the probability of not having any treatment-requiring bleeds during the trial period to be 0.9581/year (95% CI, 0.7242-0.9950). No patients withdrew because of lack of efficacy of rFXIII treatment. During the rFXIII treatment period, 48 nontreatment-requiring bleeds were observed. The frequency of minor (nontreatment-requiring) bleeds had a similar distribution within all age groups with the exception of an 8-year-old patient who experienced 18 minor bleeds (mostly trauma induced).

**FXIII laboratory parameters**

**FXIII subunits and tetramer analyses.** The shape of the mean profiles for FXIII-A$_2$B$_2$ tetramer and total FXIII-A$_2$ subunit corresponded to the FXIII activity profile. FXIII-A$_2$ subunit and FXIII-A$_2$B$_2$ tetramer concentrations increased after rFXIII administration. Because the FXIII-B subunit functions as a carrier protein for the FXIII-A$_2$ subunit, administration of rFXIII resulted in decreased FXIII-B subunit because of the rapid binding of rFXIII to free FXIII-B subunit.

**FXIII activity.** Mean predose trough levels of FXIII activity (corresponding to 4 weeks after the preceding dose of rFXIII) were 0.19 ± 0.05 IU/mL (Figure 2). As expected, rFXIII elevated the mean FXIII-Berichrom activity significantly at 1 hour after treatment to 0.77 ± 0.20 IU/mL (both trough and 1-hour postdose levels).

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### Table 2. Patient disposition and baseline demographics

<table>
<thead>
<tr>
<th>Patient disposition, n</th>
<th>41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled and dosed</td>
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<tr>
<td>Withdrawals</td>
<td>5</td>
</tr>
<tr>
<td>Inconvenience (parent decision; visit 5)</td>
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</tr>
<tr>
<td>Adverse events of worsening leukopenia and neutropenia (visit 6)</td>
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</tr>
<tr>
<td>Pregnancy (visit 8 and 14)*</td>
<td>2</td>
</tr>
<tr>
<td>Personal reasons (visit 9)</td>
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</tr>
<tr>
<td>Discontinuation of rFXIII treatment due to detection of non-neutralizing Abs</td>
<td>3†</td>
</tr>
</tbody>
</table>

| Completed trial        | 33 |

### Table 3. Baseline demographics, n 41

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Minimum/Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>26.4 (15.9)</td>
<td>23.0</td>
<td>7.0/60.0</td>
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<tr>
<td>Sex, n (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>18 (44)</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>23 (56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race, n (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>28 (68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>5 (12)</td>
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<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>2 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown‡</td>
<td>1 (2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*One pregnancy was identified through pregnancy screening and the other was reported by the investigator.
†Of the 3 patients who discontinued rFXIII treatment due to the detection of non-neutralizing Abs, the decision was made by the Novo Nordisk Safety Committee for 2 patients (following recommendations from contracted external experts who reviewed data from these patients) and by the patient’s parents for 1 patient. All 3 patients remained in the trial for follow-up and completed all trial-related activity visits.
‡Not permitted by local authority.

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**Figure 1. Subunit concentrations.** Mean ± SD concentration of the FXIII-A$_2$ subunit (A), A$_2$B$_2$ tetramer (B), and B-subunit (C) are shown. FXIII-A$_2$ subunit and FXIII-A$_2$B$_2$ tetramer concentrations increased after rFXIII administration. Because the FXIII-B subunit functions as a carrier protein for the FXIII-A$_2$ subunit, administration of rFXIII resulted in decreased FXIII-B subunit because of the rapid binding of rFXIII to free FXIII-B subunit.
statistics are as calculated over the mean activity level per patient). The overall recovery of FXIII activity at 1 hour after dose was similarly estimated to be $1.68 \pm 0.51$ (IU/mL)/(IU/kg). As a posthoc analysis, the half-life of FXIII activity was estimated by a single exponential model for mean FXIII activity levels—calculated over all records—at 3 time points (1 hour, 0.78 IU/mL; 14 days, 0.30 IU/mL; and 28 days, 0.19 IU/mL) to be approximately 11.8 days. This is consistent with the calculated half-life from the phase 1 trial.7

**Clot-solubility test.** The occurrence of a positive clot-lysis assay did not appear to be associated with the onset of treatment-requiring bleeds or temporal trends in the before or after dose FXIII activity for the individual patient. However, positive clot lysis seemed to occur sporadically throughout the trial period and did not show a consistent trend in any of the investigated patients. Therefore, these data are not presented.

**Safety assessment**

In total, 231 adverse events occurring after initiation of rFXIII administration were reported in 32 patients. The most commonly reported events were headache (21 events in 12 patients), incorrect dosing (14 events in 7 patients), nasopharyngitis (11 events in 8 patients), and pyrexia (7 events in 7 patients). The majority of events were otherwise of mild to moderate severity. Eight serious adverse events were observed completely. The remaining 170 events were not serious and had a frequency of less than 3%.

One patient was withdrawn from the trial by the investigator because of worsening of previously existing leukopenia and neutropenia. The patient had mild neutropenia (neutrophil count, 1200/μL; normal range, 2500-7500/μL) before the initial trial drug administration. The neutrophil count decreased to 940/μL at week 12, at which point the patient was withdrawn from the trial. The neutrophil count at the end-of-trial visit (week 16) was low at 1350/μL, but returned to pretreatment value.

Overall, no significant changes were observed over time in hematology and biochemistry parameters or fibrinogen, prothrombin time, activated partial thromboplastin time, D-dimer, and thrombin time. No thromboembolic events or deaths were reported.

Four patients (8, 8, 14, and 16 years of age and including 2 siblings) developed transient, low-titer (2.3-2.6; lowest quantification level was 2.0 in logarithmic scale), non-neutralizing anti-rFXIII Abs after starting rFXIII treatment. No neutralizing activity was identified by functional (inhibitory) assay at any time point. Two siblings (a 14-year-old male and a 16-year-old female patient) developed Abs after the first exposure to rFXIII. Treatment with trial product was discontinued because non-neutralizing Abs had not been described previously and the risk of inhibitor development or changes in the pharmacokinetics were unknown. These patients resumed their local standard treatment, but continued to be monitored throughout the trial. The Ab titer declined below the detection limit at 4 and 8 months after initial rFXIII treatment for the 14-year-old and 16-year-old patient, respectively. The third patient, an 8-year-old male patient, also developed Abs after the trial.

Table 4. Serious adverse events

<table>
<thead>
<tr>
<th>Patient age, y</th>
<th>Preferred term</th>
<th>Days from dosing to onset</th>
<th>Relationship to trial drug*</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Ab test positive</td>
<td>15</td>
<td>Probable</td>
<td>Recovered</td>
</tr>
<tr>
<td>14</td>
<td>Small intestinal obstruction</td>
<td>4</td>
<td>Unlikely</td>
<td>Recovered</td>
</tr>
<tr>
<td>16</td>
<td>Ab test positive</td>
<td>17</td>
<td>Possible</td>
<td>Recovered</td>
</tr>
<tr>
<td>19</td>
<td>Road traffic accident</td>
<td>28</td>
<td>Unlikely</td>
<td>Recovered</td>
</tr>
<tr>
<td>55</td>
<td>Noncardiac chest pain</td>
<td>23</td>
<td>Unlikely</td>
<td>Recovered</td>
</tr>
<tr>
<td>57</td>
<td>Headache</td>
<td>24</td>
<td>Unlikely</td>
<td>Recovered</td>
</tr>
</tbody>
</table>

*Relationship to trial drug assessment definitions: probable, good reasons and sufficient documentation to assume a causal relationship; possible, a causal relationship is conceivable and cannot be dismissed; and unlikely, the event is most likely related to an etiology other than the trial product.

Figure 2. FXIII Berichrom activity. The mean profile of FXIII Berichrom activity (IU/mL) shown with SEM per visit. Dosing with rFXIII resulted in the maintenance of average FXIII activity trough levels above 0.10 IU/mL throughout the rFXIII prophylaxis period.
first exposure to rFXIII. Despite the non-neutralizing Abs decreasing below the level of detection at the time of the second dose, the patient's parents withdrew informed consent and rFXIII was discontinued. The fourth patient was an 8-year-old male patient who developed non-neutralizing Abs after the second exposure to rFXIII. He continued receiving monthly treatment with rFXIII, and the Ab titer declined below the detection limit 4 months later.

No allergic reactions, treatment-requiring bleeds, or changes in pharmacokinetics were observed in any of these patients at any time while the non-neutralizing Abs were present or during follow-up. Furthermore, the Abs declined below the detection limit in all patients despite repeated exposure to any FXIII-containing products, in 2 of the patients while receiving rFXIII and in the remaining 2 patients while receiving other FXIII-containing products with retrospectively collected data from patients with congenital FXIII deficiency, the bleeding frequency in the present trial was significantly lower than the rate of 2.91 treatment-requiring bleeds per year in patients receiving on-demand treatment. Surveyed patients receiving on-demand treatment are likely to have a less severe disease state and perhaps bleed less often compared with prophylaxis patients before starting regular prophylaxis. However, the outcome of our survey was similar to other data sources; for example, in a small study of 7 patients, the mean annual number of spontaneous bleeds was 2.5 events per year before and 0.2 events per year during Fibrogammin P prophylaxis.12 Yoshida et al reported that bleeds markedly decreased from 4.2 ± 1.5/year to 0.2 ± 0.2/year with no life-threatening hemorrhaging, including intracerebral hemorrhaging, in 4 patients given regular replacement therapy with Fibrogammin P every 4 weeks for 10-19 years.13 Finally, a recent prospective study showed that, under prophylaxis with Fibrogammin P, the majority of patients with FXIII deficiency had no hemorrhaging, supporting the effectiveness of prophylactic treatment.14

The most feared complication when introducing new factor concentrates is inhibitor development. In contrast to hemophilia A, in which the cumulative incidence of inhibitor development ranges from 15%-30%,15,16 the incidence of inhibitory Abs in patients with congenital FXIII deficiency is very rare and has been reported in only 5 patients treated with plasma-based products,6,17-19 The development of an inhibitor in hemophilia or congenital FXIII deficiency complicates continued management of the patient substantially; therefore, the present trial closely evaluated and monitored for Ab development to FXIII by testing patients monthly for anti-rFXIII Abs. No inhibitory Abs were found in this trial.

Four of 41 patients developed transient, low-titer, non-neutralizing anti-rFXIII Abs. These Abs did not inhibit FXIII activity and patients continued to be treated with either rFXIII or plasma-derived FXIII. The anti-rFXIII Abs were of the IgM isotype in 3 of the 4 patients, with no increase in Ab levels or isotype switching. Analysis of Ab isotype in the fourth patient was inconclusive due to Ab levels being too low to allow characterization. The presence of these non-neutralizing Abs was not associated with any treatment-requiring bleeds, changes in FXIII pharmacokinetics, or allergic reactions. Furthermore, the Abs declined below the detection limit in all patients despite repeated exposure to rFXIII or other FXIII-containing products. These data indicate that the observed low-titer, specific, non-neutralizing Abs were not clinically significant. The 4 patients who developed these non-inhibitory Abs were all young adolescents (ages 8-16 years) who had received prophylaxis with FXIII concentrates for many years before this trial. It is possible that patients with FXIII deficiency, when exposed to plasma-derived sources of FXIII, might also develop transient non-neutralizing Abs, but this has not been evaluated in previous studies. The development of non-neutralizing Abs is known to occur in patients with hemophilia and in healthy individuals with no underlying bleeding disorders.20,21 In the present study, although the 4 events of non-neutralizing, low-titer Abs all occurred in patients below the age of 18 years, it is not known why Abs have been detected more frequently after the initiation of treatment in children and adolescents. The present study did not suggest a relationship between genetic mutations and a predisposition for Ab development in these patients or any indication of inhibitor development; however, long-term follow-up studies are highly warranted to understand the immunogenic reaction in this rare bleeding disorder.
The small numbers included in this trial may be a limiting factor of this study. However, congenital FXIII deficiency is a rare disease and the trial included 41 patients, accounting for approximately 7% of the diagnosed congenital FXIII deficiency population worldwide. To date, this is the largest completed prospective clinical trial in patients with congenital FXIII deficiency. Apart from the issue of Ab development, there were no other safety issues and rFXIII was well tolerated. No thromboembolic or fatal adverse events were reported. The results of the present study demonstrate that rFXIII as a monthly replacement therapy is efficacious and safe for prophylactic treatment in patients with congenital FXIII-A subunit deficiency.

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References


Authorship

Contribution: A.I. conducted the trial, reviewed the data, and wrote the manuscript; J.O. conceived the study, performed the research, collected and analyzed the data, and reviewed the manuscript; M.C. performed the research, collected and analyzed the data, and wrote the manuscript; A.R. analyzed the data and wrote and reviewed the manuscript; R.T. designed the study, performed the research, collected and analyzed the data, and wrote the manuscript; and D.N. designed the study, performed the research, analyzed the data, and wrote the manuscript.

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