A Multicenter Study of Recombinant Factor VIII (Recombinate): Safety, Efficacy, and Inhibitor Risk in Previously Untreated Patients With Hemophilia A


In July 1990, the Recombinate Study Group initiated a prospective, open-labeled investigation of recombinant factor VIII (r-FVIII) to assess its safety and efficacy and to characterize the natural history of inhibitor development in previously untreated patients (PUPs) with hemophilia A. All study subjects have severe FVIII deficiency (baseline FVIII level ≤22% of normal) and no history of blood product exposure before study entry. Following the first r-FVIII infusion, plasma was screened for inhibitors once every 3 months, and plasma recovery of r-FVIII at 30 minutes and 24 hours postinfusion was assayed at least once every 6 months. As of May 1993, 73 of 79 patients originally enrolled in the trial continue to participate. The median number of r-FVIII exposure-days for the 71 subjects who have received at least one r-FVIII infusion is 11. A total of 1,785 infusions have been administered to treat 810 bleeding events. Ninety-two percent of bleeding events responded as anticipated to one or two infusions. Two, nonrecurring, acute adverse reactions occurred coincident with r-FVIII infusion, one of which was unrelated and the other, possibly related to the infusion. Seventeen (23.9%) subjects have developed inhibitors: five with peak titers more than 10 Bethesda units (BU) and 12 with peak titers ≤10 BU (range, 0.5 to 10). Survival analysis showed that the probability of remaining inhibitor-free in this group of patients with severe hemophilia A is 88.4% after 8, 73.6% after 10, and 61.6% after 25 r-FVIII exposure-days. Inhibitors disappeared in five (29.4%) subjects on retesting 2 to 16 months after the last positive inhibitor assay. r-FVIII is safe and effective in the treatment of hemophilia A–related bleeding. To date, the inhibitor risk associated with its use is comparable to that in patients treated with plasma-derived concentrates. The majority of inhibitors identified are low in titer and do not preclude continued on-demand therapy with r-FVIII.

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THE ISOLATION and cloning of the cDNA for human factor VIII (FVIII) paved the way for the biosynthesis of genetically engineered FVIII in cultured mammalian cells. Large-scale application of these methodologies has led to the development of two recombinant DNA–derived factor VIII (r-FVIII) preparations for clinical use. One of these preparations (Recombinate; Baxter Biotech, Hyland Division, Glendale, CA) is derived from the conditioned medium of Chinese hamster ovary (CHO) cell cultures that have been transfected with the cDNAs for FVIII and von Willebrand factor (vWF).

In vitro characterization of r-FVIII has shown that its structure and functional characteristics are identical to those of plasma-derived FVIII. Pharmacokinetic studies of r-FVIII have shown consistent in vivo recovery and biological half-life over time. In crossover studies, r-FVIII recovery and half-life were similar to intermediate and ultrapure plasma-derived FVIII concentrates. In both the treatment and prevention of bleeding, excellent clinical responses to r-FVIII were noted in 55 previously treated, severe hemophilia A subjects. No new factor VIII inhibitors were identified in this cohort during a period of consistent r-FVIII use ≥18 months in duration.

While results of the previously treated patient clinical trial suggest that r-FVIII is not intrinsically more immunogenic than plasma-derived FVIII, two considerations render this group of subjects suboptimal for consideration of inhibitor risk associated with r-FVIII use. Two thirds of the subjects in the previously treated patient cohort were infected with human immunodeficiency virus—type 1 (HIV-1), which could abrogate their ability to mount an appropriate humoral immune response to r-FVIII. More importantly, the vast majority of study subjects were beyond the range of age and cumulative FVIII exposure that is associated with greatest inhibitor risk. To obtain a more relevant assessment of inhibitor incidence from the use of r-FVIII, it is necessary to longitudinally evaluate previously untreated patients from the time of first r-FVIII infusion. The goals of the current study are to assess the long-term safety, efficacy, and immunogenicity of r-FVIII in previously untreated patients (PUPs) with severe hemophilia A.

MATERIALS AND METHODS

This study was approved by the institutional review committees of all participating institutions. Parent(s) of all study subjects gave informed written consent at the time of study entry. Data from this investigation were analyzed every 3 to 6 months by an independent Data Safety and Monitoring Committee composed of hemophilia treatment center directors who did not enroll patients in the study.

Eligibility criteria. All assessable subjects exhibited the following characteristics at study entry: a baseline factor VIII level ≤2% of normal and a negative FVIII inhibitor assay, the latter result

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confirmed in the study’s reference laboratory at the University of North Carolina, Chapel Hill. Additional eligibility criteria included no prior exposure to other sources of FVIII or blood products.

Study design. This is an open-labeled study of r-FVIII (Recombinate). Following enrollment, patients were treated on demand for acute bleeding episodes or for the prevention of bleeding. The location, type of hemorrhage, and the time of onset of symptoms were recorded for each new bleeding event. Each infusion of r-FVIII was monitored for significant changes in vital signs, other adverse signs or symptoms, and clinical response to treatment. The schedule and dose of r-FVIII administration for a given bleeding complication were individually determined at each participating hemophilia treatment center and followed generally accepted guidelines for the treatment or prevention of hemophilia A–related bleeding.

Coincident with the first r-FVIII administration, plasma FVIII levels were drawn preinfusion, and 30 minutes and 24 hours postinfusion and measured in the participating institution’s clinical laboratory. Following the first infusion, 30-minute and 24-hour postinfusion recoveries were assessed at least once every 6 months in the nonbleeding state or in conjunction with the treatment of each new bleeding episode in subjects over 6 months of age. The predicted r-FVIII recovery at 30 minutes postinfusion was calculated based on the ratio of the patient’s baseline r-FVIII activity to the plasma-derived FVIII activity. A ratio of actual to predicted r-FVIII recovery $\geq 0.66$ was considered within normal limits.

 Plasma was obtained for inhibitor screening once every 3 months following the first r-FVIII infusion. All samples drawn for inhibitor screening were assayed in the respective hemophilia treatment center and subsequently in the inhibitor reference laboratory. Any patient who exhibited a 30-minute postinfusion recovery ratio less than 0.66, or in whom an inhibitor was identified on routine screening, was requested to return to the treatment center, where a repeat plasma sample for inhibitor confirmation was obtained and an abbreviated half-life determination was performed. For the latter, plasma FVIII was assayed preinfusion and 30 minutes, 4 hours, and 24 hours postinfusion of r-FVIII (50 IU/kg body weight). At the discretion of the institutional investigator, study subjects who developed inhibitors were allowed to continue treatment with r-FVIII at conventional or increased doses (low responder inhibitors) or initiate immune tolerance induction (ITI).21,22 Patients who elected to undergo ITI were typically, but not invariably, high responders.

Laboratory methods. Citrated plasma and serum were stored at $-70^\circ\text{C}$ and shipped in batches from the participating treatment centers to the reference laboratory. FVIII activity was measured at all participating centers by a one-stage, activated partial thromboplastin time (aPTT)-based assay using substrate plasma deficient in FVIII. Citrated plasma was assayed for the presence of inhibitors using a modification of the Bethesda method.23 Inhibitor titers were quantitated in the reference laboratory using both plasma-derived FVIII and r-FVIII standards. For the latter, r-FVIII was added to plasma congenitally deficient in FVIII to a final concentration of 1 IU/mL.

Statistical analysis. The technique of forward stepwise logistic regression was used to ascertain which risk factor(s) (ie, amount of time on study, number of bleeding events, number of r-FVIII infusions, number of exposure-days, and cumulative number of FVIII units received) correlated best with inhibitor development.24 Inhibitor development (yes/no) was treated as a dependent variable, with the aforementioned risk factors considered as independent variables in the usual regression sense. Once the major predictors of inhibitor development were identified, these were used in a standard survival analysis. “Survival” refers to the absence of an inhibitor and “survival time” is replaced by the magnitude of the risk factor (eg, number of exposure-days). The Kaplan-Meier estimation technique was used to determine the inhibitor-free distribution. From this estimate, both the median amount of each risk factor to inhibitor development and the probability of remaining inhibitor-free after exposure to a given amount of risk factor was determined.

RESULTS

Patient characteristics. As of May 1993, 79 study subjects were enrolled in this trial and 75 received at least one infusion of FVIII. The median age of study subjects at the time of first r-FVIII infusion was 16 months (range, 2 days to 50 months). Subsequent to enrollment, six patients either voluntarily withdrew or were determined to be ineligible. Among the 73 patients who continue to participate, 71 (97.3%) have received at least one r-FVIII infusion, 42 (57.5%) have family members with hemophilia, and at least six (14.3%) have affected relatives with a history of inhibitors. Only four (5.5%) of the 73 assessable patients have baseline FVIII levels of 2%: 69 (94.5%) subjects have levels less than 2% and 55 (75.3%) have baseline levels less than 1%. Subsequent to their first r-FVIII infusion, three (4.2%) study subjects received washed, packed red blood cells on at least one occasion, and two (2.8%) inadvertently received small quantities of plasma-derived FVIII; all five subjects continue to participate in the study. One of the 71 treated patients had a pretreatment inhibitor titer of 0.6 BU detected in the reference laboratory when his plasma sample was assayed against the plasma-derived FVIII standard only. This patient continues to receive r-FVIII on an intent-to-treat basis and is included in the analysis of inhibitor risk.

r-FVIII utilization and clinical efficacy. A total of 1,785 infusions have been administered to treat 810 bleeding events in 75 study subjects. The median number of r-FVIII exposure-days for the 71 assessable subjects is 11. Ninety-two percent of bleeding episodes responded as expected to one or two r-FVIII infusions.

To date, 10 invasive procedures involving seven patients have been performed under cover of r-FVIII, exclusively. These include lumbar puncture (three patients), bilateral myringotomy and pressure equalization tube placement (one patient), bilateral inguinal herniorrhaphy and insertion of a subcutaneous port-a-cath (one patient) and evacuation of a subdural hematoma and central venous catheter placement (two patients), and elective circumcision either with (one patient) or without (two patients) port-a-cath insertion. In all but one of these procedures, the quality of hemostasis achieved with r-FVIII was excellent. In one of the patients who underwent elective circumcision, excessive bleeding occurred postoperatively despite the use of r-FVIII before and subsequent to the procedure. An inhibitor was detected 16 days postcircumcision in this patient. He subsequently underwent removal of a central venous catheter under cover of r-FVIII without experiencing excessive bleeding.

One patient with a high responder inhibitor (see below) received r-FVIII, as well as an activated factor IX complex concentrate (FEIBA; Immuno, Vienna, Austria) for the placement of a central venous catheter before initiating an ITI regimen. The procedure was not complicated by excessive hemorrhage.

Product safety. Nonrecurring erythematous rashes were associated with two (0.1%) of 1,785 r-FVIII infusions. In one case, the eruption was believed to be a viral exanthem and not a consequence of r-FVIII infusion, and in the other,
the rash was present before the infusion and worsened during the infusion, but disappeared within 6 hours after the infusion.

**r-FVIII recovery.** A total of 224, 30-minute postinfusion r-FVIII levels have been measured in 65 patients. Of these, 129 were performed coincident with the treatment of an acute bleeding event. The mean ± SD ratio of actual to predicted recovery for this group is 1.0 ± 0.4. Forty-two recoveries were performed coincident with a follow-up infusion that was given as continuing therapy for a preexisting hemorrhage. Corrected for the preinfusion plasma FVIII level, the mean ± SD recovery ratio for this group is 1.0 ± 0.2. The mean ± SD recovery ratio for 53 recoveries, performed when patients were in the nonbleeding state, was 1.0 ± 0.3.

The ratio of actual to predicted r-FVIII recovery at 30 minutes postinfusion was less than 0.66 on 27 occasions in 13 patients. Twenty-three (85%) of the abnormally low recoveries occurred coincident with the initial or follow-up treatment of an acute bleeding event. None of the patients had an inhibitor detected in plasma samples drawn around the time of the suboptimal recovery. Nine (69.2%) subjects exhibited a suboptimal recovery on a single occasion. Ten (37%) abnormally low recoveries occurred in one subject over a 14-month period during which his clinical response to r-FVIII was consistently good to excellent. Two of these recoveries were performed when the patient was in the steady, nonbleeding state, and when a low level inhibitor (0.7 to 0.9 BU) was identified in the participating institution’s clinical laboratory. When the identical plasma samples were assayed in the study’s reference laboratory, no inhibitory activity was detected. This patient’s two most recent recovery ratios, measured in December 1992 and July 1993, were normal and he continues to be inhibitor-free.

**Inhibitors.** To date, 17 (23.9%) r-FVIII–treated patients have developed inhibitors. These include 11 of 51 white (21.6%), five of 10 black (50%), and one of eight Hispanic (12.5%) study subjects. Of the six study subjects whose affected relative(s) have a history of inhibitors, two (33%) have also developed inhibitors (one high responder, one low responder). Inhibitor titers measured in the reference laboratory using plasma-derived FVIII versus r-FVIII standards correlated well both at inhibitor onset and in follow-up assays. The median number of r-FVIII exposure-days for the subset of patients who have developed inhibitors is 9 (range, 3 to 45), and for the group of subjects who do not have inhibitors, 10 (range, 1 to 129). Thirteen (76%) inhibitors were identified within the first 10 r-FVIII exposure-days (Table 1). Details pertaining to the development of inhibitors in study subjects are listed in Table 2. Regression analysis of potential risk factors for inhibitor formation showed that small numbers of bleeding events (P = .05), exposure-days (P = .05), and cumulative r-FVIII units administered (P = .06) were significant positive predictors of inhibitor development. The probability of remaining inhibitor-free after 8, 10, and 25 exposure-days was 88.4%, 73.5%, and 61.6%, respectively (Fig 1). Inhibitor-free survival for the other predictive risk factors analyzed was similar (data not shown).

Five subjects exhibited peak inhibitor titers more than 10 BU, with two of these showing peak titers more than 30 BU. Three study subjects with peak inhibitor titers more than 10

| Table 1. Frequency Distribution of r-FVIII Exposure-Days for the PUP Cohort |
|---------------------------|-----------------|-----------------|
| r-FVIII Exposure-Days | No. of Patients (%) With Inhibitor Development* | No. of Patients (%) Without Inhibitor |
|<10 | 13 (76.5) | 29 (53.7) |
|11-25 | 3 (17.6) | 12 (22.2) |
|26-50 | 1 (5.9) | 10 (18.5) |
|51-100 | 0 (0) | 2 (3.7) |
|>100 | 0 (0) | 1 (1.8) |
|Total | 17 (100) | 54 (100) |

*Signifies the number (%) of patients within each category of r-FVIII exposure-days at the time of initial inhibitor detection.

| Table 2. Characteristics of Inhibitor Patients in r-FVIII PUP Cohort |
|---------------------------|-----------------|-----------------|-----------------|
| Patient No. | r-FVIII Exposure-Days at the Time of Inhibitor Detection | Maximal Inhibitor Titer (BU)* | Most Recent Inhibitor Titer (BU)* | Current Therapy |
| 1 | 9 | 0.8† | 0.8 | Continues to receive r-FVIII |
| 2 | 6 | 10† | 10 | Continues to receive r-FVIII |
| 3 | 23 | 0.5 | 0 | Continues to receive r-FVIII |
| 4 | 5 | 83† | 83 | Began ITI in 7/93 |
| 5 | 5 | 637 | 138 | Began ITI in 9/92 |
| 6 | 8 | 1 | 0 | Continues to receive r-FVIII |
| 7 | 10 | 16† | 16 | Began ITI in 6/93 |
| 8 | 16 | 21 | 2 | Continues to receive r-FVIII |
| 9 | 9 | 3 | 0 | Continues to receive r-FVIII |
| 10 | 3 | 6† | 6 | Continues to receive r-FVIII |
| 11 | 45 | 3 | 2 | Continues to receive r-FVIII |
| 12 | 26 | 13 | 2 | Continues to receive r-FVIII |
| 13 | 8 | 10 | 2 | Continues to receive r-FVIII |
| 14† | 8 | 191 | 19 | Continues to respond to r-FVIII at increased dose |
| 15 | 10 | 2 | 0 | Continues to receive r-FVIII |
| 16 | 9 | 3† | 3 | Continues to receive r-FVIII |
| 17 | 10 | 0.7 | 0 | Continues to receive r-FVIII |

*Inhibitor titers listed are those measured using the r-FVIII standard.
† Most recent and maximal inhibitor titers are one and the same for these study subjects.
‡ Patient with low-level inhibitor detected in pre-treatment plasma sample.
§ Undergoing ITI regimen consisting of 50 to 100 IU/kg r-FVIII one or two times per week.
BU (patients no. 4, 5, and 12, Table 2) have required occasional doses of activated factor IX complex concentrates for the control of bleeding. Patients no. 4, 5, and 7 have recently begun ITI with daily r-FVIII. Interestingly, patient no. 14, who developed an inhibitor (19 BU) after 8 r-FVIII exposure-days, is the patient whose pretreatment plasma sample at 3 days of age had a low-level inhibitor. He continues to exhibit fair clinical responses to r-FVIII administered at increased dose.

The remaining 12 children have peak titers in the low responder range (0.5 to 10 BU). Subsequent to the detection of their inhibitors, all have received r-FVIII exclusively for the treatment or prevention of bleeding. In most cases, the clinical response has been consistently good to excellent at conventional or increased doses. Details pertaining to the treatment of bleeding events and inhibitor surveillance in these 12 subjects after the identification of their inhibitors are listed Table 3. Patients no. 7 and 11 (Table 3) are being treated with a modified ITI regimen consisting of 50 to 100 IU/kg r-FVIII administered one or two times weekly.24 Patient no. 7 began this regimen in May 1992; his inhibitor screen has been negative on six consecutive occasions between September 1992 and February 1993. Patient no. 11, who has been on this regimen since January 1992, has had negative inhibitor screens on six consecutive occasions between March 1992 and March 1993. In total, five subjects (patients no. 3, 4, 5, 7, and 11, Table 3) no longer have detectable inhibitor in plasma samples obtained 2 to 16 months following the last positive inhibitor assay. In patients no. 5 and 11, 30-minute, postinfusion r-FVIII recoveries have become normal coincident with the disappearance of the inhibitor (Fig 2).

DISCUSSION

The principal benefit of r-FVIII for subjects with hemophilia A is access to a source of clotting factor that is not dependent on the availability of human plasma. This has important implications for the availability of FVIII in general, as well as the risk of transmission of human blood-borne viruses.25 The latter consideration continues to be relevant, because while current virucidal methods (eg, pasteurization and solvent-detergent treatment) are extremely effective at inactivating lipid-encapsulated viruses (eg, hepatitis B virus, HIV-1, hepatitis C virus) from plasma-derived FVIII concentrates,26-28 non-lipid-enveloped viruses (eg, parvovirus B-19 and hepatitis A virus) are at least partially impervious to these viral inactivation strategies.29-33

Experience with r-FVIII in this patient cohort has shown that it is well tolerated and not associated with significant short-term adverse effects. Its clinical efficacy is as good as that noted with intermediate and ultrapure, plasma-derived FVIII in both the treatment of acute hemorrhage and for surgical prophylaxis. In general, actual and predicted r-FVIII recovery have correlated well in the 65 patients who have had at least one recovery determination, indicating consistent potency of the product from lot to lot.34 Among those recovery ratios that were less than 0.66, a significant percentage occurred in a single subject over a prolonged period. Two low recoveries were measured when this patient was in the nonbleeding state and when a low level inhibitor was detected in the treatment center clinical laboratory only. While we cannot rule out the possibility of a low responder inhibitor, the intermittent anemia noted in this subject may have contributed to some of the abnormally low recoveries. Alternatively, it is possible that the peak plasma FVIII level was reached at a time later than 30 minutes postinfusion. Both volume of distribution and the timing of the peak plasma level are variables that have a significant impact on in vivo recovery.34

Prevalence estimates for inhibitor formation among hemophilia A patients reported before 1985 vary from 6% to 15%.35-38 These are based on data collected retrospectively, from hemophilia patient populations with all levels of sever-

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Probability of remaining inhibitor-free as a function of the number of r-FVIII exposure-days for 72 assessable study subjects. The period who voluntarily withdrew after 4 exposure-days is included in the survival analysis, but is censored from consideration after 4 exposure-days. At the time of his withdrawal from the study, he did not have an inhibitor. Inhibitor-free survival after 8, 10, and 25 exposure-days is 84%, 72%, and 61%, respectively. Kaplan-Meier plots of inhibitor risk as a function of the cumulative number of bleeding episodes and r-FVIII units received are similar in appearance.

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<th>Table 3. Clinical Course for 12 Low Responder Inhibitor Patients After Initial Inhibitor Detection</th>
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* Duration of follow-up is from the time of inhibitor diagnosis through April 1993.
† Corresponds to patient no. 6, Table 2, and patient A, Fig 2.
‡ Corresponds to patient no. 15, Table 2, and patient D, Fig 2.
§ Most recent inhibitor titers are 0.
Fig 2. Clinical course for four of five study subjects who developed inhibitors that ceased to be detectable on retesting 2 to 16 months after the last positive Bethesda assay. Solid squares and left-sid ed Y-axis denote cumulative r-FVIII exposure as a function of time; open squares and right-sid ed Y-axis indicate inhibitor titers (r-FVIII standard) at various time points. Patients A and D correspond to patients no. 6 and 15 in Table 2, and have normal r-FVIII recovery at 30 minutes postinfusion in the nonbleeding state documented on at least one occasion following disappearance of the inhibitor. Patient B had a recovery ratio slightly less than 0.66 when determined in the steady-state, and patient C has not yet had a recovery measured since the disappearance of his inhibitor.

Estimates of inhibitor risk as measured by cumulative incidence are biased by the fact that at any given time, the study population in question has varying degrees of exposure to potential risk factors for inhibitor development such as the number of bleeding events treated, cumulative r-FVIII exposure, and the number of exposure-days. The probability of developing an inhibitor can be estimated more precisely from a survival (ie, Kaplan-Meier) analysis of risk factors that are predictive of inhibitor formation as determined by a multiple regression model. Data analyzed from our study using this approach indicate that inhibitor risk is greatest during the earliest stages of r-FVIII replacement therapy, an
observation that has been noted in other PUP cohorts exposed to plasma-derived FVIII and r-FVIII. An as yet unanswered question is whether a given amount of r-FVIII exposure over varying time intervals is associated with similar or different probabilities of inhibitor formation.

An important outcome of our study is a greater appreciation of the frequency of low-titer inhibitors, many of which are evanescent. To date, 29.4% of inhibitors identified in our study are no longer detectable on routine retesting. The transient nature of some inhibitors has been appreciated by other investigators, and was reported in 22.6% of patients with newly identified inhibitors in the US Collaborative Inhibitor Study. We cannot rule out the possibility that low-level inhibitors persist in the five patients in whom they are no longer detectable by the Bethesda assay method. This is especially the case for two of these subjects (patients B and D, Fig 2) who receive r-FVIII one or two times weekly in addition to on-demand therapy for bleeding events. Regularly administered doses of FVIII can neutralize low-titer inhibitors, rendering them undetectable in a Bethesda assay. Radioimmunoprecipitation assays for the detection and characterization of inhibitor antibodies appear to be more sensitive than the Bethesda method in identifying persistent low-level anti-FVIII antibodies in these subjects.

Indeed, such assays have measured residual, low-level antibodies in some patients whose inhibitor is no longer detectable in a Bethesda assay. After 33 months of clinical experience in this cohort of PUPs, r-FVIII has shown a level of efficacy that is comparable to any plasma-derived FVIII or r-FVIII concentrate available. Its safety profile may be superior to that of other plasma-derived FVIII concentrates in view of the low-level, residual risk of blood-borne virus infection associated with the latter. The immunogenicity of r-FVIII is similar to that of plasma-derived concentrates, as well as another r-FVIII preparation currently under study. These results lend further support to the hypothesis that r-FVIII and plasma-derived FVIII are biologically identical.

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APPENDIX

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