ORIGINAL ARTICLE

Anti-Inhibitor Coagulant Complex Prophylaxis in Hemophilia with Inhibitors

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ABSTRACT

BACKGROUND

Patients with severe hemophilia A and factor VIII inhibitors are at increased risk for serious bleeding complications and progression to end-stage joint disease. Effective strategies to prevent bleeding in such patients have not yet been established.

METHODS

We enrolled patients with hemophilia A who were older than 2 years of age, had high-titer inhibitors, and used concentrates known as bypassing agents for bleeding in a prospective, randomized, crossover study comparing 6 months of anti-inhibitor coagulant complex (AICC), infused prophylactically at a target dose of 85 U per kilogram of body weight (±15%) on 3 nonconsecutive days per week, with 6 months of on-demand therapy (AICC at a target dose of 85 U per kilogram [±15%] used for bleeding episodes). The two treatment periods were separated by a 3-month washout period, during which patients received on-demand therapy for bleeding. The primary outcome was the number of bleeding episodes during each 6-month treatment period.

RESULTS

Thirty-four patients underwent randomization; 26 patients completed both treatment periods and could be evaluated per protocol for the efficacy analysis. As compared with on-demand therapy, prophylaxis was associated with a 62% reduction in all bleeding episodes ($P<0.001$), a 61% reduction in hemarthroses ($P<0.001$), and a 72% reduction in target-joint bleeding (≥3 hemarthroses in a single joint during a 6-month treatment period) ($P<0.001$). Thirty-three randomly assigned patients received at least one infusion of the study drug and were evaluated for safety. One patient had an allergic reaction to the study drug.

CONCLUSIONS

AICC prophylaxis at the dosage evaluated significantly and safely decreased the frequency of joint and other bleeding events in patients with severe hemophilia A and factor VIII inhibitors. (Funded by Baxter BioScience; Pro-FEIBA ClinicalTrials.gov number, NCT00221195.)

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After exposure to factor VIII, alloantibodies (inhibitors) that neutralize factor VIII clotting function develop in approximately 30% of patients with severe hemophilia A.[1] The development of high-titer factor VIII inhibitors (>5 Bethesda units [BU]) complicates treatment because bleeding no longer responds to standard factor VIII replacement.[2,3] Alternative forms of clotting-factor concentrates, known as bypassing agents, are used to treat bleeding in these patients.[3]

Two bypassing agents are currently available: anti-inhibitor coagulant complex (AICC) and recombinant activated factor VII (rFVIIa). Both agents control approximately 80% of bleeding episodes in patients with hemophilia and inhibitors.[4] Nonetheless, their hemostatic efficacy is difficult to predict and does not result in the success rates obtained with factor VIII replacement in patients who have hemophilia without inhibitors.[5] Consequently, patients with inhibitors are at increased risk for bleeding that is difficult to control.[6] Poorly controlled hemarthroses result in the early onset of chronic joint disease and physical disability, which can substantially impair the quality of life.[7]

Prophylaxis, the routine scheduled replacement of factor VIII, is standard care for patients who have severe hemophilia A without inhibitors, because of its ability to prevent bleeding.[8-12] However, for patients with inhibitors who have refractory bleeding with serious consequences and who could derive an even greater benefit from prevention of bleeding, factor VIII prophylaxis is ineffective.

Although anecdotal reports[13-16] have suggested that regular administration of AICC may prevent bleeding in patients with hemophilia A and factor VIII inhibitors, the efficacy of this therapeutic regimen has been unproved. The Prophylaxis with Factor Eight Inhibitor Bypassing Activity (Pro-FEIBA) study was designed to compare the efficacy and safety of AICC prophylaxis with on-demand therapy in this patient population.

METHODS

STUDY DESIGN AND OVERSIGHT

We conducted an investigator-initiated, prospective, randomized, crossover study at 16 hemophilia treatment centers in Europe and the United States. For ethical and practical reasons, patients were aware of the study assignments. We randomly assigned patients to either 6 months of on-demand therapy with AICC (Feiba, Baxter) or 6 months of AICC prophylaxis (Fig. 1). After the initial 6-month treatment period and a 3-month washout period, patients crossed over to the alternative treatment period. During the on-demand period, bleeding was treated with AICC at a target dose of 85 U per kilogram of body weight (±15%) (range, 72 to 98). For bleeding episodes that did not respond to the specified therapy, alternative treatment, including additional doses of AICC, rFVIIa, or factor VIII, was allowed at the discretion of the treating physician. During the prophylaxis period, AICC was administered at a target dose of 85 U per kilogram (±15%) (range, 72 to 98) on 3 nonconsecutive days weekly. Bleeding episodes during the prophylaxis period and the washout period were managed with the use of the on-demand treatment protocol. Throughout the 15-month study, bleeding events were self-reported and documented by each patient in a study log describing the time of onset and site of bleeding and treatment.

Safety issues were reviewed by an independent safety monitor. The study was funded by a grant from Baxter BioScience, which also donated the AICC. The investigators designed and conducted the trial, analyzed the data, and made the decision to submit the manuscript for publication. The study protocol, which is available with the full text of this article at NEJM.org, and the informed-consent form were approved by the institutional review board of each participating institution. Written informed consent was obtained from each patient. The principal investigators, who had unrestricted access to the data, prepared the manuscript with the assistance of a medical writer who was paid from the funds provided to the principal investigators by Baxter BioScience for the performance of the study. The manuscript was subsequently revised by all the authors, who vouch for the accuracy and completeness of the reported data and for the fidelity of the report to the study protocol.

STUDY PARTICIPANTS

Patients were eligible for inclusion in the study if they had severe hemophilia A and a history of a factor VIII inhibitor titer exceeding 5 BU, were older than 2 years of age, were being treated with bypassing therapy, and had six or more episodes

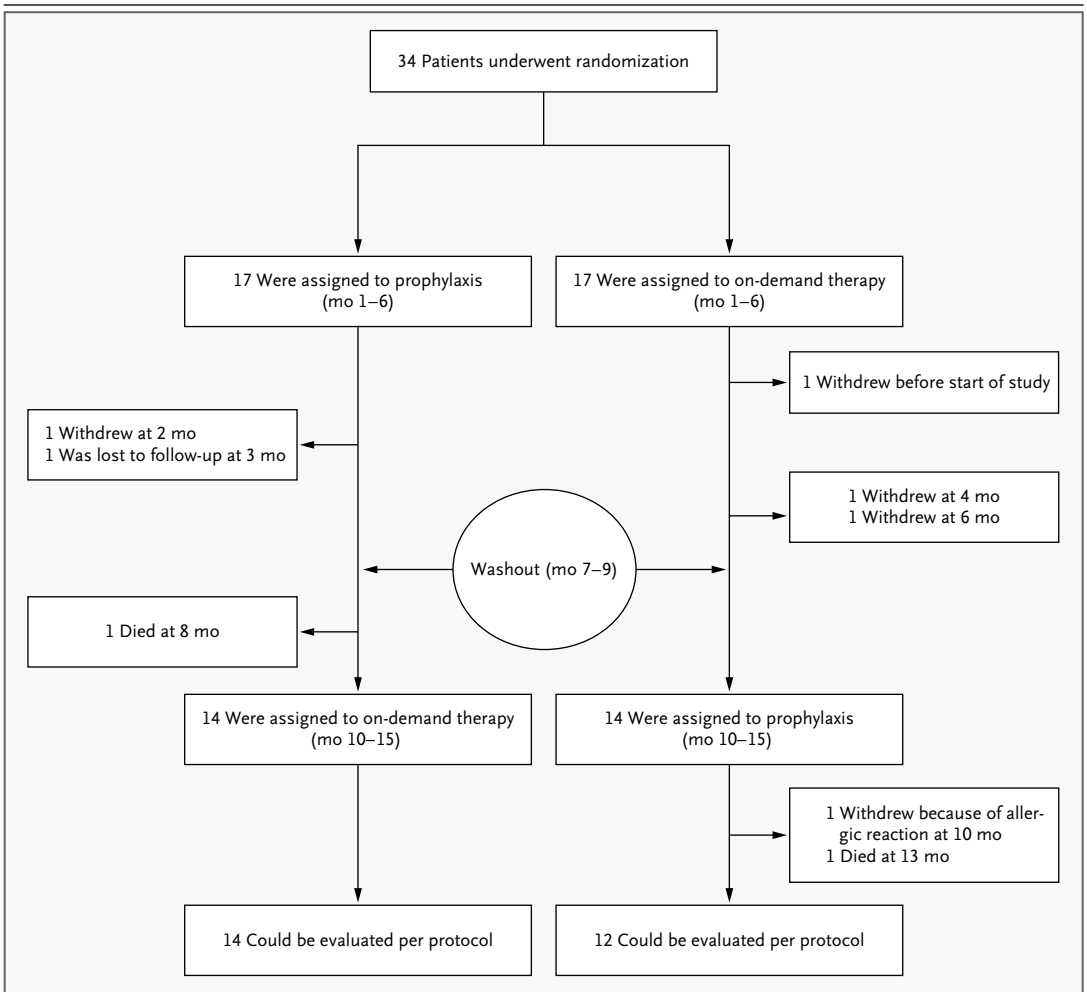

Figure 1. Randomization and Follow-up of the Study Participants.

of bleeding requiring bypassing treatment in the 6-month period before study enrollment.

Patients were excluded from the study if they were receiving immune tolerance therapy or regular prophylaxis with any hemostatic agent, had symptomatic liver disease, had a platelet count of less than 100,000 per cubic millimeter, planned to undergo elective surgery within 12 months, used an investigational product within 1 month before study enrollment, or planned to begin treatment with interferon or a protease inhibitor.

OUTCOME MEASURES

The primary efficacy measure was a significant reduction in bleeding events during the prophylaxis period as compared with the on-demand period in patients who completed both treatment periods (the per-protocol group). Secondary outcome measures in the per-protocol group were reductions in episodes of joint bleeding and target-joint bleeding (defined as ≥3 hemarthroses in a single joint during a 6-month treatment period). To ensure that the per-protocol group did not reflect a favorable selection bias, monthly hemorrhage rates were determined for all patients who received at least one dose of study drug (the intention-to-treat group), and the prophylaxis and on-demand periods were compared. Safety was assessed in all patients who received at least one dose of the study drug.

STATISTICAL ANALYSIS

The Wilcoxon signed-rank test was used to compare the frequency of bleeding events between the prophylaxis and on-demand treatment periods. The Mann–Whitney U test was used to determine

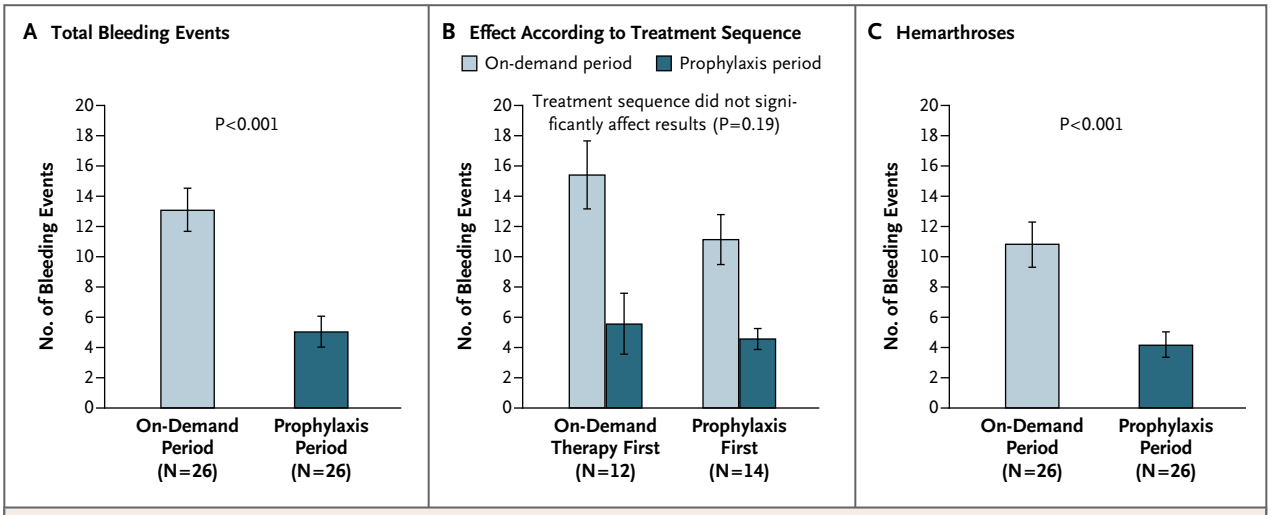

Figure 2. Bleeding Episodes during the Two Treatment Periods.

Panel A shows the mean number of total patient-reported bleeding events, according to the treatment period. A mean of 13.1 bleeding events were reported during the 6-month on-demand period, and 5.0 bleeding events were reported during the 6-month prophylaxis period. Episodes of joint bleeding accounted for approximately 80% of total bleeding episodes. Bleeding was also noted at other sites, including the muscles, other soft tissues, and body cavity. Intracranial and surgical bleeding also occurred. As shown in Panel B, no difference was noted in the treatment (prophylactic) effect on the basis of the order in which patients were randomly assigned to treatment. Panel C shows the mean number of hemarthroses according to the treatment period. A mean of 10.8 joint-bleeding episodes were reported during the on-demand period, and 4.2 joint-bleeding episodes were reported during the prophylaxis period. I bars indicate standard errors.

the effect of treatment sequence (prophylaxis first vs. on-demand therapy first) on the frequency of bleeding episodes. A carryover effect was defined as a statistically significant difference in the prophylactic effect between the two treatment-sequence cohorts. In cases in which the sample size was insufficient for the statistical test, an exact test from the Mann–Whitney U test was used. A two-sided alpha level (type I error rate) of less than 0.05 was considered to indicate statistical significance.

RESULTS

PATIENTS

Study enrollment began in November 2003 and closed in September 2008. Thirty-four patients underwent randomization (median age, 28.7 years; range, 2.8 to 67.9). One patient withdrew consent before receiving study medication. The intention-to-treat group comprised 33 patients, of whom 7 did not complete the study: 1 withdrew because of an allergic reaction, 2 died, 1 was lost to follow-up after Hurricane Katrina, and 3 withdrew consent (2 during the on-demand period and 1 during the prophylaxis period) (Fig. 1). The median time from the development of factor VIII inhibitors to study enrollment was 11.2 years (range, 0.2 to 31.7).

Twenty-six patients completed both study periods and were evaluated per protocol for the primary efficacy analysis. In this group, the median age was 28.7 years (range, 2.8 to 62.8). Six patients were younger than 12 years, 4 were between 12 and 21 years, and 16 were older than 21 years. There were 24 white patients and 2 black patients. Of the 26 patients who could be evaluated per protocol, 14 were randomly assigned to the prophylaxis period first, and 12 were randomly assigned to the on-demand period first.

EFFICACY OUTCOMES

Primary Outcome

During the prophylaxis period, the mean (±SD) number of bleeding events was 5.0±5.0, as compared with 13.1±7.1 bleeding events during the on-demand period (P<0.001), representing a 62% reduction in total bleeding events (Fig. 2A). No significant difference was observed in the primary outcome on the basis of treatment sequence (P=0.19). Thus, no carryover effect was detected when the prophylaxis period preceded the on-demand period (Fig. 2B).

Sixteen of 26 patients (62%) had a reduction of 50% or more in overall bleeding events during the prophylaxis period; this reduction was the target

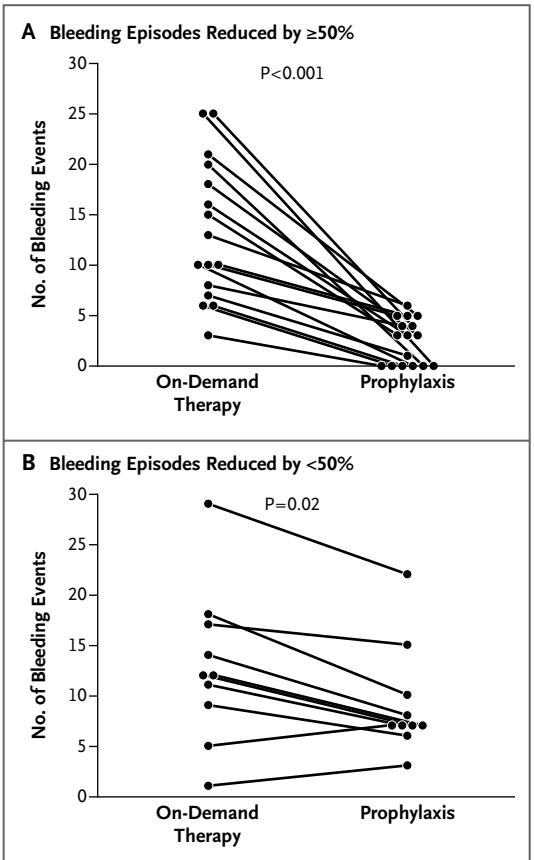

Figure 3. Bleeding Profiles for Individual Patients.

Panel A shows the data on bleeding for the 16 patients in whom bleeding episodes were reduced by 50% or more during prophylaxis. A mean of 13.3 bleeding events were reported during the on-demand period, and 2.1 bleeding events were reported during the prophylaxis period. Panel B shows the data on bleeding for the 10 patients in whom bleeding episodes were reduced by less than 50% during prophylaxis. A mean of 12.8 bleeding events were reported during the on-demand period, and 9.2 bleeding events were reported during the prophylaxis period.

for success as defined in the protocol (Fig. 3A). In this group of patients with a good response, the overall reduction in the bleeding rate was 84%, and 6 of the 16 patients who had a good response (38%) had no bleeding events during the prophylaxis period. Ten of 26 patients (38%) had less than a 50% reduction in bleeding events during the prophylaxis period (Fig. 3B). Even in this group, bleeding was reduced by 28% (P<0.02). Only 2 patients had an increase in bleeding in the prophylaxis period. Both had very few bleeding events overall and received prophylaxis before crossing over to the on-demand period. Among patients with frequent bleeding events (>18 events over the 6-month on-demand treatment period), the mean number of events decreased from 22.8 to 6.6.

Secondary Outcomes

The mean number of hemarthroses was 4.2±4.3 during the prophylaxis period versus 10.8±7.6 during the on-demand treatment period (P<0.001); this difference constituted a 61% reduction in joint bleeding (Fig. 2C). Target-joint bleeding events were reduced by 72% during the prophylaxis period as compared with the on-demand period (P<0.001), and the number of patients with bleeding in target joints decreased from 18 to 11 (Table 1).

In the intention-to-treat group, the mean number of monthly bleeding events was 2.0±1.2 among the 30 patients with data from the on-demand period, as compared with 0.9±0.8 events among the 31 patients with data from the prophylaxis period, representing a reduction of 55% (P<0.001). Similarly, the mean rates of joint hemorrhages per month were reduced by 56%, from 1.6±1.3 events during the on-demand period to 0.7±0.7 events during the prophylaxis period (P<0.001). Target-joint bleeding could not be fully assessed because some patients did not complete the 6-month treatment periods. These results are similar to the results of the per-protocol analysis, suggesting that selection bias was unlikely in the per-protocol group.

SAFETY OUTCOMES

There was one episode of an allergic reaction to the study drug (Table 2). Three patients (9%) had multiple events related to devices for central venous access, including infection, bleeding, and line placement and removal. No thromboembolic events occurred.

Two patients had intracranial hemorrhages during the study (one patient had a subdural hemorrhage and recovered, and the other patient had a cerebral hemorrhage and died). Both events occurred during the washout period. A third patient had a history of hepatitis C and diabetes mellitus, was found unconscious, and was hospitalized with ketoacidosis and coma. He died on the second hospital day from gastrointestinal hemorrhage. The death occurred during the prophylaxis period, although it could not be determined when the patient had received the last dose of AICC.

DISCUSSION

Our study showed that all bleeding events, hemarthroses, and target-joint bleeding events were sig-

nificantly reduced during AICC prophylaxis. With the thrice-weekly dosing regimen, 62% of patients met or exceeded a predefined, clinically significant threshold for a good response to prophylaxis (≥50% reduction in bleeding events with prophylaxis vs. on-demand treatment), and in this group, 38% of patients had no bleeding episodes during the prophylaxis period.

A major challenge in the prospective trial design was achieving statistically meaningful results in a relatively small patient population. The crossover design produced statistically and clinically valid results with fewer patients than would have been required for a parallel study design.[17] The number of patients who completed both treatment periods and thus could be evaluated provided sufficient power (80%) to reach statistical significance (P<0.05). The use of a crossover design in a small study population also helps to prevent overestimation of the benefit of the therapy being tested,[18] making it likely that our results reflect a conservative assessment of the benefits of AICC prophylaxis. The 3-month washout period between study periods appears to have been sufficient to prevent a carryover effect resulting from the crossover design.

One previous prospective trial evaluated the prophylactic use of rFVIIa in patients with hemophilia and factor VIII inhibitors who had frequent bleeding.[19] Konkle et al. enrolled patients in a 3-month lead-in period, during which time each patient had to have 12 or more bleeding episodes to be eligible for randomization to one of two doses of rFVIIa administered daily.[19] The 22 patients who met the criteria for bleeding and who received prophylaxis had an average of 5.5 bleeding events per month during the lead-in period. Prophylactic rFVIIa at a dose of 90 μg per kilogram reduced the frequency of overall bleeding by 45% (to 3.0 episodes per month), and at a dose of 270 μg per kilogram, the frequency of overall bleeding was reduced by 59% (to 2.2 episodes per month) (P<0.001).

In two previous studies of on-demand therapy in patients with hemophilia and inhibitors, the mean number of annual bleeding events was 7.2 (among patients older than 14 years of age)[6] and 13.9 (in a study population in which most of the patients were younger than 14 years of age).[20] Our study was designed to include patients who bled less often than those selected for the rFVIIa study and thus were more reflective of the general population of patients with hemophilia and inhibitors.

Table 1. Prevention of Target-Joint Bleeding.*

Period	All Patients	Patients with Target Joints	Bleeding in Target Joints	P Value†
	no.	*no. (%)*	*no. of episodes*	
On-demand therapy	26	18 (69)	226	
Prophylaxis	26	11 (42)	64	<0.001

* Target-joint bleeding was defined as three or more hemarthroses in a single joint during the 6-month study period.
† The P value, for the comparison between on-demand therapy and prophylaxis, is based on Fisher's exact test.

Entry criteria required that patients had six or more bleeding episodes in the previous 6 months, even though we recognized the potential difficulty of achieving a statistically meaningful reduction in bleeding episodes among patients who on average had as few bleeding episodes as one per month. In the cohort that completed both study periods, the number of bleeding episodes declined from 2.2 per month during the on-demand period to 0.8 per month during prophylaxis (P<0.001). Among the seven patients with the most frequent bleeding (defined as >3 bleeding episodes per month), the mean monthly number of bleeding episodes decreased from 3.8 to 1.1. Five of these patients had more than a 50% reduction in bleeding episodes, and two of the seven had no bleeding whatsoever during the prophylaxis period. Although these data are from a small number of patients, they suggest that patients with frequent bleeding episodes had at least as good a response to AICC prophylaxis as those with less-frequent bleeding. Moreover, the thrice-weekly dosing schedule of AICC prophylaxis may facilitate adherence.[21]

Our outcome data are encouraging because the study was designed for secondary prophylaxis, defined as prophylaxis instituted after the onset of joint bleeding — a situation that makes suppression of bleeding more difficult. In our study, nearly 70% of the patients had target-joint bleeding, which is a strong predictor of existing joint damage. Nonetheless, most patients in the study had an excellent response to prophylaxis, confirming anecdotal reports of a reduction in bleeding associated with long-term AICC prophylaxis.[13-15,22] This demonstrated efficacy raises the possibility that primary AICC prophylaxis in children with inhibitors, when started at a young age and before the development of repeated joint bleeding, could provide benefits similar to those in children with severe hemophilia A who are receiving

Table 2. Serious Adverse Events and Most Common Adverse Events, According to Study Period.

Event	On-Demand Therapy (N=31)	Washout (N=29)	Prophylaxis (N=31)	Total (N=34)
	number of patients (percent)			
Serious adverse events	3 (10)	4 (14)	4 (13)	9 (26)
Chest pain	0	0	1 (3)	1 (3)
Pain	1 (3)	0	0	1 (3)
Drug hypersensitivity	0	0	1 (3)*	1 (3)
Phlebitis	0	0	1 (3)	1 (3)
Hospitalization	1 (3)	0	0	1 (3)
Surgical procedure	1 (3)	0	0	1 (3)
Catheter-site hemorrhage	1 (3)†	0	1 (3)†	2 (6)
Catheter-site infection	1 (3)	0	2 (6)†	3 (9)
Staphylococcal infection	1 (3)†	0	0	1 (3)
Cerebral hemorrhage	0	1 (3)‡	0	1 (3)
Subdural hematoma	0	1 (3)	0	1 (3)
Gastrointestinal hemorrhage	0	0	1 (3)‡	1 (3)
Joint swelling	0	0	1 (3)	1 (3)
Muscle hemorrhage	0	2 (7)	0	2 (6)
Adverse events§	16 (52)	19 (66)	17 (55)	21 (62)
Anemia	1 (3)	0	0	2 (6)
Headache	1 (3)	1 (3)	1 (3)	3 (9)
Pain	3 (10)	0	2 (6)	4 (12)
Pyrexia	2 (6)	1 (3)	6 (19)	6 (18)
Drug hypersensitivity	0	0	1 (3)*	1 (3)
Hypersensitivity	2 (6)	0	0	3 (9)
Ecchymosis	2 (6)	1 (3)	3 (10)	4 (12)
Cough	0	2 (7)	3 (10)	5 (15)
Influenza	1 (3)	4 (14)	1 (3)	5 (15)
Nasopharyngitis	1 (3)	2 (7)	2 (6)	3 (9)
Pharyngitis	1 (3)	0	2 (6)	2 (6)
Upper abdominal pain	0	1 (3)	1 (3)	2 (6)
Vomiting	1 (3)	1 (3)	2 (6)	4 (12)
Poor venous access	0	0	1 (3)†	1 (3)
Catheter-site hemorrhage	1 (3)†	0	2 (6)†	2 (6)
Catheter-site infection	1 (3)	0	2 (6)†	3 (9)
Staphylococcal infection	1 (3)†	0	0	1 (3)
Tongue hemorrhage	1 (3)	1 (3)	0	2 (6)

* This allergic reaction was noted while the drug was being infused, and the infusion was discontinued prematurely.
† This event was deemed to be related to study participation.
‡ This event resulted in death.
§ Adverse events are listed when more than one patient had an event or when one patient had an event deemed to be related to study participation.

primary factor VIII prophylaxis.[12] Ettingshausen and Kreuz recently reported a case series of six patients who started AICC prophylaxis during childhood (median age, 7.6 years).[23] After a median follow-up of 6.7 years, the annual incidence of hemarthrosis was 1.5 episodes, and no patient had major joint damage while receiving prophylactic AICC infusions. These results strongly argue for additional prospective studies of early AICC prophylaxis in children with hemophilia and persistent inhibitors in an effort to prevent repeated joint bleeding and joint damage.

No major safety issues were raised during our study, and no thromboembolic events were detected. Among the 34 enrolled patients, 2 adults died from bleeding, underscoring the substantial health risks associated with persistent factor VIII inhibitors. Two patients had intracranial hemorrhages. Several reports have suggested an increased incidence of clinically significant intracranial hemorrhage and worse outcomes for patients with hemophilia and inhibitors.[24-29] Our study was not powered to detect the benefit of prophylaxis for low-incidence, high-morbidity bleeding events such as intracranial hemorrhage. However, it is reasonable to assume that patients who have a good response to prophylaxis are also likely to have a reduced risk of life-threatening bleeding.

The cost of prophylaxis for patients who have hemophilia without inhibitors is 2.4 to 3.1 times as high as the cost of on-demand therapy.[30] Similarly, the cost of AICC prophylaxis in our study was 2.4 times as high as that of on-demand therapy ($493,633 vs. $205,549, per patient, based on an average cost of $1.56 per unit of AICC for patients in the United States and $1.13 for patients in the European Union). The cost of AICC was $15,691 per bleeding episode during the on-demand period. After deducting the costs for bleeding episodes avoided and bleeding episodes treated during the prophylaxis period, the remaining cost for prophylaxis was $288,081. The cost of bypassing therapy per bleeding episode avoided was $35,565 (or $585 per kilogram of body weight for our somewhat older patient population with a mean body weight of 60.8 kg). These costs do not reflect the potential benefits of avoiding hospitalizations and days lost from work or school and preventing long-term complications, such as worsening joint disease and disability.

One limitation of this study was its relatively short duration. Although joint and other bleed-

ing episodes were reduced during the 6-month prophylaxis period, a longer trial is necessary to determine whether regular AICC infusions can prevent the onset of joint disease or halt the progression of arthropathy in patients with minimal joint damage. In addition, because of the small number of children and adolescents enrolled in our study, it is not possible to draw conclusions regarding relationships between age and the benefits of prophylaxis. Finally, although a crossover design has the advantage of economy and allows comparisons of treatments in small patient populations, the parallel design has the benefit of a more straightforward analysis over a shorter period with lower dropout rates.[17]

In conclusion, bleeding in patients with hemophilia A and factor VIII inhibitors can be difficult to control, and uncontrolled bleeding has serious clinical consequences. AICC prophylaxis at a dose of 85 U per kilogram (±15%), administered on 3 nonconsecutive days weekly, significantly decreased overall bleeding, hemarthroses, and target-joint bleeding and was associated with few adverse effects.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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