Haemophilia (2009), **15**, 718–726 DOI: 10.1111/j.1365-2516.2008.01960.x

ORIGINAL ARTICLE *Inhibitors*

Experience with a third generation recombinant factor VIII concentrate (Advate®) for immune tolerance induction in patients with haemophilia A

L. A. VALENTINO,* M. RECHT,† J. DIPAOLA,‡ A. D. SHAPIRO,§ S. W. PIPE,¶ N. EWING,** J. URGO,* T. BULLOCK,‡ M. SIMMONS§ and C. DEGUZMAN**

**Departments of Pediatrics and Internal Medicine, Rush University Medical Center, Chicago, IL, USA; †Hemophilia Center, Phoenix Children's Hospital, Phoenix, AZ, USA; ‡Department of Pediatrics, University of Iowa Children's Hospital, Iowa City, IA, USA; §Indiana Hemophilia and Thrombosis Center, Indianapolis, IN, USA; ¶Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI, USA; and **Division of Pediatrics, City of Hope National Medical Center, Duarte, CA, USA*

Summary. The development of an inhibitor represents one of the most challenging complications in patients with haemophilia A. Optimal management is immune tolerance induction (ITI), typically through the administration of high doses of factor VIII (FVIII) concentrate. Among 12 patients who underwent ITI using Advate, a third-generation recombinant FVIII product that is free of animal and human protein additives, tolerance was achieved in nine (75%), including seven of 10 patients (70%) with high-titre inhibitors. ITI is ongoing in two patients and not yet successful; immune tolerance failed in the third patient. The median time to success was 4.0 months for group as a whole and for patients with high-titre inhibitors. Treatment was well tolerated, and no adverse events were observed. Advate was found to be equivalent to other FVIII products with regard to both ITI success rates and the incidence of adverse effects when used in these immune tolerance regimens.

Keywords: Advate, haemophilia A, immune tolerance induction, inhibitor, third-generation recombinant factor VIII

Introduction

The development of inhibitors, immune globulin G antibodies that neutralize the function of factor VIII (FVIII) [1] remains the most serious treatment complication in patients with haemophilia A. Inhibitors occur in approximately 30% of individuals with severe haemophilia [2] and in 3–13% of those with mild or moderate haemophilia [3] following exposure to FVIII replacement therapy. The development of inhibitors is linked to a variety of genetic factors [4–8] and may also be influenced by certain environmental factors [9–13]. The presence of an inhibitor makes the treatment of bleeding episodes more difficult and increases the risk of uncontrollable bleeding and disability, particularly arthropathy [14–16].

Bleeding episodes in patients with low-titre inhibitors are often effectively managed with high-doses of FVIII. Bypassing agents are typically needed to control haemorrhage in patients with high-titre inhibitors [15], defined as a historical peak titre exceeding 5 Bethesda units (BU mL^{-1}) [17]). The haemostatic efficacy of bypassing products is difficult to predict, however, it does not reach the overall success rates obtained with FVIII replacement in patients without inhibitors [18–21]. Consequently, immune tolerance induction (ITI) is often undertaken in patients with high-responding inhibitors in an effort to achieve antigen tolerance, and restore normal or near-normal FVIII replacement kinetics [22]. Historically, approximately 50% to nearly 80% of patients are successfully tolerized, according to date from the International [23], North American [24], and German [25] ITI registries.

Correspondence: Leonard A. Valentino, MD, Associate Professor of Pediatrics and Internal Medicine; Director, Hemophilia and Thrombophilia Center; Rush University Medical Center and Rush Children's Hospital, 1653 West Congress Parkway, Chicago, IL 60612-3833, USA.
Tel.: +1 312 942 8114; fax: +1 312 563 2317;
e-mail: lvalentino@rush.edu

Accepted after revision 17 October 2008

Aim

This study describes 12 children who underwent ITI using a third-generation recombinant FVIII (rFVIII) concentrate (Advate rAHF-PAFM; Baxter Healthcare Corp., Westlake Village, CA, USA) that is formulated using a plasma/albumin-free method to eliminate the risk of blood-borne pathogen transmission [26].

Patients and methods

The records of 12 children with severe haemophilia A, who developed inhibitors and used Advate for immune tolerance over a period of 30 months following the approval of Advate by the US Food and Drug Administration in July 2003 were reviewed for data abstraction and analysis. ITI regimens were prescribed by the treating physician. Information for all patients was retrospectively provided via anonymous data collection forms.

The pharmacokinetic parameters used to define ITI success are those established by consensus at the Second International Conference on Immune Tolerance held in Bonn, Germany in 1997. These parameters include an undetectable inhibitor level (<0.6 BU mL^{-1}), FVIII plasma recovery ≥66% of predicted, FVIII half-life of ≥6 h after a 72-h FVIII washout period and the absence of anamnesis upon further FVIII exposure [27]. The definitions of *good risk* and *poor risk* used in this study are the same ones that are being using in the International ITI (I-ITI) Study [28]:

- Good risk: age <8 years, inhibitor present <12 months, peak inhibitor titre ≤200 BU mL^{-1} and inhibitor titre at the start of ITI <10 BU mL^{-1}.
- Poor risk: age >8 years, inhibitor present >12 months, peak inhibitor titre>200 BU mL^{-1} and inhibitor titre at the start of ITI >10 BU mL^{-1}.

Results

Patient 1

Patient 1 was diagnosed with severe haemophilia A at the age of 7 days. At the age of 23 months and following 24 exposure days to rFVIII, including both Recombinate (Baxter Healthcare Corp., Westlake Village, CA, USA.) and Advate (total cumulative dosage: 1139 IU kg^{-1}), an inhibitor measuring 1.8 BU mL^{-1} was detected during routine surveillance. ITI was initiated using rFVIII, including Advate, at a dose of 100 IU kg^{-1} day^{-1}. The inhibitor peaked at 5.6 BU mL^{-1} upon initiation of ITI but was undetectable after 3 months. Thirty-six months after the patient was successfully tolerized, his inhibitor titre was measured at <0.8 BU mL^{-1}.

Patient 2

Patient 2 was diagnosed with severe haemophilia A within hours of birth because of excessive bruising following vaginal delivery. An inhibitor measuring 5 BU mL^{-1} was detected during routine surveillance when the child was 10 months old and had had a total of 10 exposure days to Recombinate (total cumulative dose: 583 IU kg^{-1}). ITI was initiated immediately using Advate at a dose of 100 IU kg^{-1} day^{-1}. During ITI, the peak inhibitor titre was 19 BU mL^{-1}. Two serious soft tissue haemorrhages were treated with a total of three doses of activated recombinant factor VII (rFVIIa; Novo Nordisk, Bagsvaerd, Denmark). ITI was deemed successful after 5 months, at which time the inhibitor titre measured <0.8 BU mL^{-1}. Thirty-six months after the completion of ITI, the child's inhibitor titre was measured at <0.8 BU mL^{-1}.

Patient 3

Patient 3 was diagnosed with severe haemophilia A at the age of 5 months. An inhibitor measuring 89.6 BU mL^{-1} was detected 2 months later when a soft tissue haematoma was refractory to standard doses of rFVIII. Prior to this bleeding event, the child had had four exposure days to Recombinate and Advate (total cumulative dose: 143 IU kg^{-1}). Once the inhibitor was detected, subsequent bleeding episodes were treated with rFVIIa at a dose of 90–120 mcg kg^{-1} administered every 2–3 h until bleeding resolved (2–10 doses). After 2.5 years, the child's inhibitor titre had decreased to 12.4 BU mL^{-1} and ITI was started using rFVIII, including Advate, at a dose of 100 IU kg^{-1} administered twice daily. Despite 52 months of high-dose ITI, the inhibitor has persisted; the patient's most recent inhibitor titre was 23 BU mL^{-1}. Immune tolerance is ongoing with a plasma-derived FVIII that has a high concentration of von Willebrand factor.

Patient 4

Patient 4 was born to a known carrier of severe haemophilia A and was diagnosed with severe haemophilia A at birth. His maternal uncle is also affected with severe haemophilia A and developed a low-titre inhibitor that was successfully eradicated using a plasma-derived FVIII concentrate. A central

venous access device (CVAD) was placed and primary prophylaxis with Advate was started at the age of 10 months. Three months later, after 46 exposure days to rFVIII (total cumulative dose: 4820 IU kg^{-1}), an inhibitor measuring 4.2 BU mL^{-1} was detected. ITI was initiated with Advate at a dose of 100 IU kg^{-1} day^{-1}. Tolerance was achieved after 9 months, and the child's most recent inhibitor titre, measured 28 months after the completion of ITI, was <0.6 BU mL^{-1}.

Patient 5

Patient 5 was also born to a known carrier of haemophilia A and was diagnosed with severe disease at birth. His maternal uncle had a high-titre inhibitor that was successfully eradicated using a combination of plasma-derived and rFVIII. When this patient was 15 months old, a CVAD was placed to allow administration of primary prophylaxis. One month later, after 13 exposure days to Advate (total cumulative dose: 353 IU kg^{-1}), he developed significant bruising, and an inhibitor measuring 32 BU mL^{-1} was diagnosed. Over the next 6 months, rFVIIa was used to treat bleeding episodes, and his antibody titre decreased to 2 BU mL^{-1}. ITI was started using Advate 100 IU kg^{-1} daily. Immune tolerance was achieved after 6 months of treatment; the child's most recent inhibitor titre, measured 22 months after the completion of ITI, was <0.6 BU mL^{-1}.

Patient 6

Patient 6 was diagnosed with severe haemophilia A at 1 year of age. His family history includes a third cousin with haemophilia and an inhibitor. At the age of 15 months and following 14 exposure days to Advate (total cumulative dose: 1135 IU kg^{-1}), the patient was diagnosed with an inhibitor measuring 150 BU mL^{-1}. ITI was initiated immediately using Advate at a dose of 100 IU kg^{-1} twice daily. The child was successfully tolerized after 4 months; his most recent inhibitor titre, measured 19 months after completing ITI, was <0.6 BU mL^{-1}.

Patient 7

Patient 7 was diagnosed with severe haemophilia A at the age of 7 months because of excessive bruising. During the ensuing months, he had trauma-related bleeding, particularly in the gluteal area, but had no evidence of joint bleeding. At the age of 19 months, following 14 exposure days to Recombinate and Advate (total cumulative dosage: 540 IU kg^{-1}), he was diagnosed with an inhibitor when his mother observed that increasingly larger doses of factor were needed to treat bleeding episodes. His inhibitor titre at diagnosis measured 1.3 BU mL^{-1}. A CVAD was placed under rFVIIa coverage, and ITI was initiated with Advate at a daily dose of 100 IU kg^{-1}. His pre-ITI titre was 11 BU mL^{-1}. After 3 months, his antibody titre had decreased to <0.5 BU mL^{-1}. Daily ITI was continued for a total of 11 months. The patient currently receives Advate at a dose of 80 IU kg^{-1} three times weekly, and his inhibitor titre has remained <0.5 BU mL^{-1}.

Patient 8

Patient 8 was diagnosed with severe haemophilia A 2 days after birth because of excessive bleeding following circumcision. When the child was 22 months old and had more than 25 exposure days to rFVIII (Helixate FS; ZLB Behring, Kankakee, IL, USA) (total cumulative dose: 1745 IU kg^{-1}), an inhibitor measuring 1.4 BU mL^{-1} was detected on routine surveillance. One month later, his antibody titre was <0.5 BU mL^{-1}, and the patient's family decided to change infusion products to Advate. After 23 exposure days to Advate, his inhibitor level had increased to 2.5 BU mL^{-1}; 2 weeks later, it measured 3.8 BU mL^{-1}. ITI was initiated using Advate at a dose of 100 IU kg^{-1} day^{-1} and was successful after 21 days. Daily ITI was continued for approximately 12 months, at which time the dose was reduced to 75 IU kg^{-1} daily for an additional 2 months. At month 11, the dosing frequency was decreased to six times weekly for an additional 6 months. The patient currently receives Advate prophylaxis 70 IU kg^{-1} three times weekly and his inhibitor titre has remained <0.5 BU mL^{-1}.

Patient 9

Patient 9 has a strong family history of haemophilia that includes a maternal uncle with an inhibitor. The child was diagnosed with severe haemophilia A in utero and developed an inhibitor measuring 32 BU mL^{-1} at 14 months of age following 12 exposure days to Advate (total cumulative dose: 927 IU kg^{-1}). ITI was started immediately using Advate at a dose of 100 IU kg^{-1} twice daily. Within 1 month, his inhibitor titre measured <0.6 BU mL^{-1}. Nine months later, he continued to have a negative titre. A modified prophylactic regimen of 74 IU kg^{-1} every other day is ongoing.

Patient 10

Patient 10 was diagnosed with severe haemophilia A at birth. His family history includes an older brother with severe haemophilia without an inhibitor. The patient exhibited infrequent bleeding episodes (approximately 4–6 haemorrhages annually) and was managed with on-demand infusions. At the age of 6 years, following 20 exposure days to Recombinate (total cumulative dose: 300 IU kg^{-1}), the patient exhibited increased bleeding frequency and a decreased response to FVIII and was placed on a twice-weekly prophylactic regimen. An inhibitor measuring 7.9 BU mL^{-1} was subsequently diagnosed. Eight months after diagnosis, the patient was enrolled in the I-ITI and was randomized to the low-dose regimen of 50 IU kg^{-1} three times weekly (the high-dose regimen used in the I-ITI is 200 IU kg^{-1} daily) [28]. Advate was used for ITI. The patient was initially non-adherent to the ITI regimen and was withdrawn from the I-ITI. Adherence was reestablished several months after ITI initiation (new dose: Advate 100 IU kg^{-1} bid), but the clinical course was complicated by major trauma, including an upper extremity compartment syndrome that required fasciotomy and multiple CVAD infections. ITI has continued for a total of 27 months. The most recent inhibitor titre was 13.8 BU mL^{-1}.

Patient 11

Patient 11 was diagnosed with severe haemophilia A 11 days after birth when he presented with postcircumcision bleeding. He was treated with fresh frozen plasma in the newborn nursery; at the age of 15 days, he first received rFVIII (Kogenate FS; Bayer HealthCare LLC, Tarrytown, NY, USA). At the age of 13 months, following 11 exposure days to Kogenate FS (total cumulative dose: 400 IU kg^{-1}), an inhibitor measuring 14 BU mL^{-1} was diagnosed when a bleeding event failed to respond to standard therapy. Subsequently, bleeding episodes were managed with rFVIIa at standard doses. Immune tolerance was postponed because the child's mother wished to avoid the need for port placement. A low-dose ITI regimen was initiated 4 years after inhibitor diagnosis using Advate 115 IU kg^{-1} three times weekly. After 18 months, his inhibitor titre was measured at <0.6 BU mL^{-1}. A pharmacokinetic study performed after 21 months of therapy showed a FVIII recovery of 76% and a half-life of 6–8 h. The patient's most recent inhibitor titre, measured 2 years after the completion of ITI, remains <1.0 BU mL^{-1}.

Patient 12

Patient 12 was diagnosed with severe haemophilia A at 11 months of age because of extensive bruising. His family history includes a maternal uncle with haemophilia complicated by an inhibitor. At the age of 13 months, following four exposure days to Recombinate, an inhibitor measuring 24.4 BU mL^{-1} was diagnosed. ITI was started 11 months later when his titre was 7.1 BU mL^{-1} using Recombinate and Kogenate at a dose of 200 IU kg^{-1} once daily. The patient was subsequently changed to Advate at the parent's request. During ITI, the inhibitor titre peaked at 989.7 BU mL^{-1}. ITI was discontinued after 44 months, at which time the inhibitor titre measured 18 BU mL^{-1}.

Tables 1 and 2 and Figs 1–3 show the data for these 12 patients.

Discussion

Among the 12 patients with severe haemophilia A described in this report, five (patients 1, 2, 4, 7 and 8) had inhibitor titres ≤5 BU mL^{-1} and seven (patients 3, 5, 6, 9, 10, 11 and 12) had titres >5 BU mL^{-1} at initial detection of the inhibitor (Table 1). The inhibitors developed approximately 1 year after the diagnosis of haemophilia and after an average of 15.5 exposure days (median, 13.0 days; range, 4–46 days) to FVIII replacement concentrate (Figure 1). ITI, the only treatment for eradicating inhibitors [2], was performed, with Advate used at some time during each patient's ITI regimen (between 0–907 days after inhibitor diagnosis). Overall, tolerance was achieved in nine patients (75%) after a median of 4.0 months (average, 5.5 months) (Figure 2), which corresponds to success rates of 50–80% reported by the International, North American and German ITI registries [23–25] and to historical success rates of 75–82% observed by investigators in the United States [29] and Sweden [30], respectively. Eight of the patients described (1, 2, 4, 5, 7, 8, 10 and 12) fulfilled the criteria for *good risk* used in the ongoing I-ITI Study (Table 2, Figure 3) [28]. ITI was successful in six of these patients (75%), is ongoing in one patient (10) and failed in one patient (12). Immune tolerance was also successful in three of four patients (6, 9, 11; 75%) who met the I-ITI criteria for *poor risk*. ITI is ongoing in patient 3.

Low-titre inhibitors

Cases 4 and 8 are representative of low-titre inhibitors that remit with ITI (Table 2). It is possible that

Table 1. Summary of patient data.

Subject	Age at diagnosis of haemophilia	Age at diagnosis of inhibitor	No.of Exposure Days	Titre at inhibitor diagnosis (BU mL^{-1})	Peak titre before ITI (BU mL^{-1})	Titre at start of ITI (BU mL^{-1})	Time between inhibitor diagnosis and start of ITI	ITI dose	Maximum titre during ITI	Most recent titre (BU mL^{-1})	Duration of ITI to achieve tolerance (months)
1	7 days	23 months	24	1.8	1.8	1.8	0 days	100 qd	5.6	<0.8	3
2	1 day	10 months	10	5	19	3.6	0 days	100 qd	19	<0.8	5
3	5 months	7 months	4	89.6	1823	12.4	2.5 years	200 qd	96.5	23	(52)
4	1 day	13 months	46	4.2	4.2	4.2	0 days	100 qd	4.2	<0.6	9
5	1 day	16 months	13	24	38.4	2	6 months	100 qd	2	<0.6	6
6	12 months	15 months	13	150	150	150	0 days	200 qd	150	<0.6	4
7	7 months	19 months	14	1.3	11	1.3	3 months	100 qd	11	<0.5	3
8	2 days	22 months	15	2.5	3.8	2.5	1 month	100 qd	3.8	<0.5	0.7
9	1 day	14 months	12	32	37	32	0 days	200 qd	37	<0.6	1
10	1 day	6 years	20	7.9	49.8	4.6	8 months	100 tiw	49.8	13.8	(27)
11	12 days	13 months	11	14	43	0	4 years	100 tiw	8.8	<1.0	18
12	11 months	13 months	4	24.4	989.7	7.1	11 months	200 qd	989.7	19	(44)*
Median		14.5 months	13.0	10.95	37.7	3.9					4.0
Low				1.3	1.8						
High				150	1823						
Average		19.8 months	15.5	29.7		18.5					5.5

these patients had transient inhibitors, defined as low-titre antibodies that gradually disappear over time [31,32]. Transient inhibitors accounted for 20–55% of the anti-FVIII antibodies reported in three rFVIII studies of previously untreated patients [33–35], and their development suggests that natural tolerance to exogenous clotting factor can occur. However, as both patients reported here experienced bleeding episodes, it can be argued that their inhibitors were clinically significant, and that ITI was appropriate. ITI was initiated in patient 4 because of serious bleeding episodes coupled with family history

Table 2. Patient characteristics based on titre and prognostic classifications and outcome.

Patient number	Titre classification [17]		Prognostic classification [23]		Outcome	Time to Immune tolerance (months)
	High	Low	Poor	Good		
1	X			X	Successful	3
2	X			X	Successful	5
3	X		X		Ongoing	52
4		X		X	Successful	9
5	X			X	Successful	6
6	X		X		Successful	4
7	X			X	Successful	3
8		X		X	Successful	0.7
9	X		X		Successful	1
10	X			X	Ongoing	27
11	X		X		Successful	18
12	X			X	Failure	44

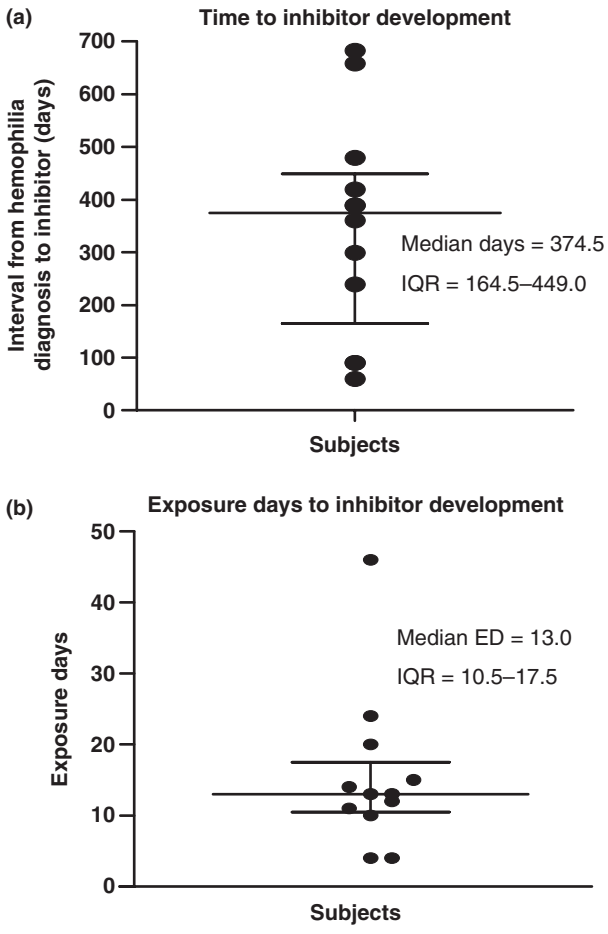

Fig. 1. Time and exposure days to inhibitor development.

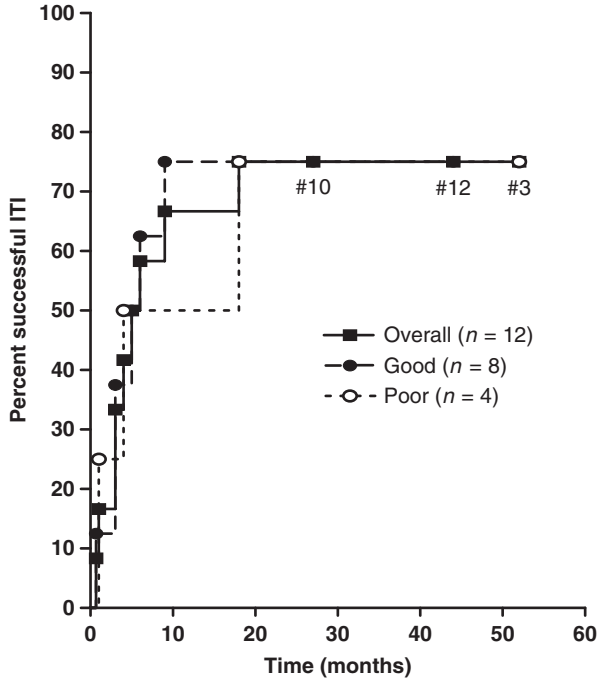

Fig. 2. Response of patients to ITI therapy.

of an inhibitor. In patient 8, ITI was started when the inhibitor persisted for 1 month. ITI at a daily dose of 100 IU kg^{-1} was successful in both patients with low-titre inhibitors.

High-titre inhibitors

Cases 1, 2, 5, 6, 7, 9 and 11 are examples of high-titre, high-responding inhibitors that were successfully eliminated with ITI (Table 2). High-titre inhibitors are characterized by brisk anamnesis (peak historical titre >5 BU mL^{-1} [17]) and the resultant inability to treat bleeding episodes with specific factor replacement [15]. Historically, high-responding antibodies were thought to account for approximately 80% of all inhibitors [36]. However, data from studies of previously untreated patients exposed to rFVIII indicate that the true incidence of high-titre inhibitors ranges from 41% to 53% [33–35]. Four of our patients (1, 2, 6 and 9) started ITI immediately upon detection of the high-titre inhibitor, and two (6 and 9) were treated with a high-dose regimen (Advate 200 IU kg^{-1} day^{-1}) (Table 1). Three patients (5, 7 and 11) did not begin ITI until 6 months, 3 months and 4 years, respectively, after inhibitor detection. During the interval between inhibitor diagnosis and the start of ITI, bleeding events in patient 5 and 7 were managed with rFVIIa to avoid the theoretical possibility of an anamnestic response to trace amounts of FVIII present in activated prothrombin complex concentrate (FEIBA; Baxter, Deerfield, IL, USA). Patient 11 was treated with both rFVIIa and FEIBA to control bleeding.

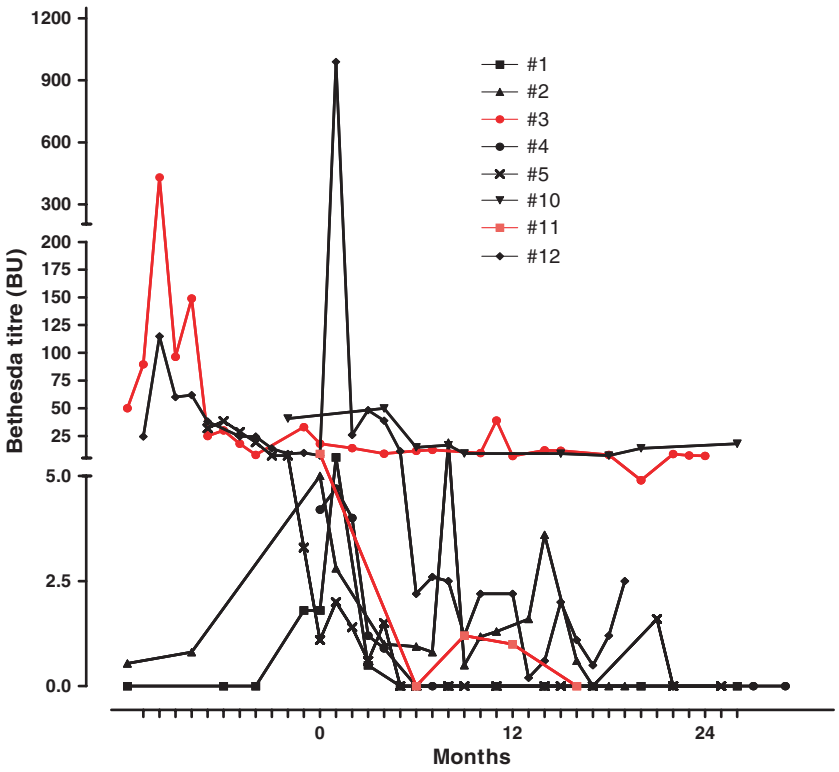

Fig. 3. Response to ITI based on prognostic factors. Interval inhibitor titres were available for eight patients prior to and during ITI therapy. Black symbols represent patients with favourable prognostic features, as defined by the I-ITI study; symbols in red denote patients with unfavourable prognostic factors.

Despite intensive ITI for 52, 27 and 44 months, respectively, patients 3, 10 and 12 represent high-titre, high-responding inhibitors that persist despite ITI (Table 2). These children developed inhibitors after 4, 20 and 4 exposure days, respectively (Table 1). Because patients 3 and 12 had inhibitor titres that exceeded 10 BU mL^{-1} at diagnosis (89.6 BU mL^{-1} and 24.4 BU mL^{-1}, respectively), ITI was delayed for 2.5 years and 11 months, respectively. Patients 3 and 12 received an aggressive ITI regimen of Advate 200 IU kg^{-1} daily, and patient 10 received Advate 100 IU kg^{-1} three times weekly. Ultimately, 20–50% of patients undergoing ITI fail to become tolerized [23,24,27]. One possibility is that the immune systems of these patients are dysfunctional and the inhibitors are entrenched. ITI failure may also be attributable, at least in part, to uncertainties about the optimal dosing regimen and the ideal time to initiate ITI. The I-ITI Study, launched in 2002, is evaluating the efficacy, morbidity and cost-effectiveness of low- vs. high-dose ITI in inhibitor patients with a good prognosis (i.e. age <8 years, inhibitor present <12 months, maximum inhibitor titre ≤200 BU mL^{-1}, inhibitor titre <10 BU mL^{-1} at the start of ITI), but the results will not be known for several years [37].

It is noteworthy that immune tolerance can be beneficial even when the inhibitor is not eradicated. When ITI reduces the titre to ≤5 BU mL^{-1}, FVIII can be used to control bleeding in an emergency situation until anamnesis occurs, typically after 6–7 days [21].

The choice of factor concentrate for use in ITI is controversial and is being investigated as part of the I-ITI study. Recently, Kurth *et al.* described the impact of a FVIII concentrate containing von Willebrand factor (FVIII/VWF) on ITI outcome in 25 patients considered to have a poor prognosis for successful tolerization because of clinical and laboratory characteristics or because of a poor response to initial ITI with a monoclonal antibody-purified or recombinant FVIII concentrate [38]. Among 11 patients who started ITI with a FVIII/VWF concentrate, all attained partial tolerance after an average of 15 months (range: 1–62 months), and three patients achieved complete tolerance after an average of 38 months of ITI. Among 14 patients who initially started ITI with a monoclonal or recombinant FVIII product and subsequently switched to a FVIII/VWF concentrate, five attained complete tolerance within 3–14 months following the product change. While these data are tantalizing, it remains unclear whether the type of FVIII concentrate contributes to ITI success. Nonetheless, patients who fail to respond to ITI with monoclonal or recombinant concentrates may benefit from a change to products containing VWF.

Safety

ITI with Advate was associated with anamnesis during ITI in three patients (1, 2, and 7). This phenomenon is expected during immune tolerance with any FVIII-containing product and, therefore, does not represent a safety issue specific to Advate. No other adverse events, including viral transmission, occurred.

Conclusion

Advate is a third-generation rFVIII product that can be used to effectively and safely induce immune tolerance in patients with severe haemophilia A and inhibitors, including those with high titre inhibitors. The overall success rate of 75% at a median of 4.0 months observed in our patients corresponds to that reported to the ITI registries, and the 70% success rate among the 10 patients with high-titre inhibitors is similar to that reported to the ITI registries and observed by other investigators.

Disclosures

M. Recht has received research funding from Baxter Pharmaceuticals. No Baxter funded research funding was involved in the gathering of data for this paper. S. W. Pipe has received honoraria for speaking at Baxter BioScience-sponsored symposia and as a paid consultant. N. Ewing has acted as a paid consultant to Baxter, and has received funding for speaking and for research, as well as reimbursement for attending symposia. T. Bullock has received payment for speaking from Baxter. The other authors stated that they had no interests which might be perceived as posing a conflict or bias.

References

1 Kasper CK. Diagnosis and management of inhibitors to factors VIII and IX. An introductory discussion for physicians. Treatment of Hemophilia. World Federation of Hemophilia: September 2004: no. 34.
2 Brackmann HH, Wallny T. Immune tolerance: high-dose regimen In: Rodriguez-Merchan EC, Lee CA eds. *''Inhibitors in Patients with Hemophilia''*. Oxford, England: Blackwell Science, Ltd, 2002: 45–8.
3 Hay CR. Factor VIII inhibitors in mild and moderate-severity haemophilia A. *Haemophilia* 1998; **4**: 558–63.

4 Schwaab R, Brackmann HH, Meyer C *et al.* Haemophilia A: mutation type determines risk of inhibitor formation. *Thromb Haemost* 1995; **74**: 1402–6.
5 Astermark J, Oldenburg J, Carlson J *et al.* Polymorphisms in the TNFA gene and the risk of inhibitor development in patients with hemophilia A. *Blood* 2006; **108**: 3739–45.
6 Astermark J, Oldenburg J, Pavlova A, Berntorp E, Lefvert AK. Polymorphisms in the IL10 but not in the IL1beta and IL4 genes are associated with inhibitor development in patients with hemophilia A. *Blood* 2006; **107**: 3167–72.
7 Astermark J, Wang X, Oldenburg J, Berntorp E, Lefvert AK. Polymorphisms in the CTLA-4 gene and inhibitor development in patients with severe hemophilia A. *J Thromb Haemost* 2007; **5**: 263–5.
8 Astermark J, Berntorp E, White GC, Kroner BL. The Malmo International Brother Study (MIBS): further support for genetic predisposition to inhibitor development in hemophilia patients. *Haemophilia* 2001; **7**: 267–72.
9 Gouw SC, van der Bom JG, Marijke van den Berg H. Treatment-related risk factors of inhibitor development in previously untreated patients with hemophilia A: the CANAL cohort study. *Blood* 2007; **109**: 4648–54.
10 Koestenberger M, Raith W, Muntean W. High titre inhibitor after continuous factor VIII administration for surgery in a young infant. *Haemophilia* 2000; **6**: 120.
11 Goudemand J, Rothschild C, Demiguel V *et al.* Influence of the type of factor VIII concentrate on the incidence of factor VIII inhibitors in previously untreated patients with severe hemophilia A. *Blood* 2006; **107**: 46–51.
12 Sharathkumar A, Lillicrap D, Blanchette VS *et al.* Intensive exposure to factor VIII is a risk factor for inhibitor development in mild hemophilia A. *J Thromb Haemost* 2003; **1**: 1228–36.
13 Santagostino E, Mancuso ME, Rocino A *et al.* Environmental risk factors for inhibitor development in children with haemophilia A: a case-control study. *Br J Haematol* 2005; **130**: 422–7.
14 Ingerslev J, Freidman D, Gastineau D *et al.* Major surgery in haemophilic patients with inhibitors using recombinant factor VIIa. *Haemostasis* 1996; **26**(Suppl 1): 118–23.
15 Leissinger CA. Prevention of bleeds in hemophilia patients with inhibitors: emerging data and clinical direction. *Am J Hematol* 2004; **77**: 187–93.
16 Lusher JM. Inhibitor antibodies to factor VIII and factor IX: management. *Semin Thromb Hemost* 2000; **26**: 179–88.
17 White GC, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost* 2001; **85**: 560.
18 Key NS, Aledort LM, Beardsley D *et al.* Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (Novoseven) in haemophiliacs with inhibitors. *Thromb Haemost* 1998; **80**: 912–8.
19 Hilgartner M, Aledort L, Andes A, Gill J. Efficacy and safety of vapor-heated anti-inhibitor coagulant complex in hemophilia patients. FEIBA Study Group. *Transfusion* 1990; **30**: 626–30.
20 Arkin S, Blei F, Fetten J *et al.* Human coagulation factor FVIIa (recombinant) in the management of limb-threatening bleeds unresponsive to alternative therapies: results from the NovoSeven emergency-use programme in patients with severe haemophilia or with acquired inhibitors. *Blood Coagul Fibrinolysis* 2000; **11**: 255–9.
21 Negrier C, Goudemand J, Sultan Y, Bertrand M, Rothschild C, Lauroua P. Multicenter retrospective study on the utilization of FEIBA in France in patients with factor VIII and factor IX inhibitors. French FEIBA Study Group. Factor Eight Bypassing Activity. *Thromb Haemost* 1997; **77**: 1113–9.
22 Ho AY, Height SE, Smith MP. Immune tolerance therapy for haemophilia. *Drugs* 2000; **60**: 547–54.
23 Mariani G, Kroner B. International immune tolerance registry, 1997 update. *Vox Sang* 1999; **77**(Suppl 1): 25–7.
24 DiMichele DM, Kroner BL. The North American Immune Tolerance Registry: practices, outcomes, outcome predictors. *Thromb Haemost* 2002; **87**: 52–7.
25 Lenk H. The German Registry of immune tolerance treatment in hemophilia–1999 update. *Haematologica* 2000; **85**: 45–7.
26 Baxter Healthcare Corporation. *ADVATE: [package insert]*. Westlake Village, CA: Baxter Healthcare Corporation, 2006.
27 Astermark J, Morado M, Rocino A *et al.* Current European practice in immune tolerance induction therapy in patients with haemophilia and inhibitors. *Haemophilia* 2006; **12**: 363–71.
28 DiMichele DM, Hay CR. The international immune tolerance study: a multicenter prospective randomized trial in progress. *J Thromb Haemost* 2006; **4**: 2271–3.
29 Ewing NP, Sanders NL, Dietrich SL, Kasper CK. Induction of immune tolerance to factor VIII in hemophiliacs with inhibitors. *JAMA* 1988; **259**: 65–8.
30 Nilsson IM, Berntorp E, Zettervall O. Induction of immune tolerance in patients with hemophilia and antibodies to factor VIII by combined treatment with intravenous IgG, cyclophosphamide, and factor VIII. *N Engl J Med* 1988; **318**: 947–50.
31 DiMichele D. Inhibitors: resolving diagnostic and therapeutic dilemmas. *Haemophilia* 2002; **8**: 280–7.
32 Rothschild C, Gill J, Scharrer I, Bray G. Transient inhibitors in the Recombinate PUP study. *Thromb Haemost* 2000; **84**: 145–6.
33 Schwartz RS, Abildgaard CF, Aledort LM *et al.* Human recombinant DNA-derived antihemophilic

factor (factor VIII) in the treatment of hemophilia A. recombinant Factor VIII Study Group. *N Engl J Med* 1990; **323**: 1800–5.
34 Bray GL, Gomperts ED, Courter S *et al.* A multicenter study of recombinant factor VIII (Recombinate): safety, efficacy, and inhibitor risk in previously untreated patients with hemophilia A. The Recombinate Study Group. *Blood* 1994; **83**: 2428–35.
35 Lusher JM, Spira J, Rodriguez D. A four-year update of safety and efficacy of an albumin-free formulated B-domain deleted factor VIIII (BBD rFVIII, rVIIISQ) in previously untreated severe hemophilia A patients. *Thromb Haemost* 1999; **82**: 1493.
36 Ehrenforth S, Kreuz W, Scharrer I *et al.* Incidence of development of factor VIII and factor IX inhibitors in haemophiliacs. *Lancet* 1992; **339**: 594–8.
37 IITI. *International, Randomised, Controlled Trial of Immune-Tolerance Induction*. Available at: http://www.itistudy.com (accessed 12 January 2007).
38 Kurth MAH, DiMichele D, Sexauer C *et al.* Immune tolerance therapy utilizing factor VIII/von Willebrand factor concentrate in haemophilia A patients with high titre factor VIII inhibitors. *Haemophilia* 2008; **14**: 50–5.