American Journal of Hematology 82:145–149 (2007)

Successful Self-Infusion of Activated Prothrombin Complex Concentrate for Prophylaxis in a Child With a Factor VIII Inhibitor

Shouichi Ohga,* Akihiko Nomura, Hidetoshi Takada, Naohiro Suga, and Toshiro Hara

Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Regular self-infusion of an activated prothrombin complex concentrate (APCC) has been successfully introduced to a 14-year-old boy with hemophilia A. The child was diagnosed as a neonate, and at age 7 years, developed a high titer (127 BU/mL) factor VIII inhibitor coincident with a protracted ankle joint bleeding. From age 7–10 years, he received on-demand therapy using a prothrombin complex concentrate (PCC), PROPLEX-ST. From age 10–14 years, he received prophylaxis with PROPLEX-ST, initiated after an intracranial hemorrhage and coincident anamnestic inhibitor response. Throughout 7-year period of PCC treatment, he experienced recurrent bleeding episodes. Self-prophylaxis with APCC, FEIBA VH [Anti-inhibitor Coagulant Complex] (50 U/kg/dose three times per week) using infusion pump was initiated at 14 years of age and has continued for 2 years. There were no bleeding, thrombotic events or other adverse events after initiation of this prophylaxis, and inhibitor levels decreased to 1 BU/mL. His quality of life was improved, particularly with respect to school. Our long observation proposes a well-disciplined home-based FEIBA prophylaxis in inhibitor-positive hemophiliacs. Am. J. Hematol. 82:145–149, 2007. © 2006 Wiley-Liss, Inc.

Key words: FEIBA; PROPLEX; rFVIIa; prophylaxis; inhibitor

INTRODUCTION

Prothrombin complex concentrates (PCC) and activated PCC (APCC) are used to treat bleeding episodes in patients with hemophilia who develop an inhibitor to factor VIII (FVIII) or FIX [1]. FVIII inhibitor bypassing activity (FEIBA VH [anti-inhibitor coagulant complex]) has been one of the most widely used APCC for the management of congenital or acquired hemophilia with high-titer inhibitors [2–5]. FEIBA also has been used for prophylaxis during immune tolerance induction [6]. Regular prophylactic replacement with PCC or APCC, however, has not been used routinely in inhibitor-positive patients in the United States, as controlled trials of prophylaxis have not been conducted and there is no consensus on standard dosing [7]. There are several reports on the efficacy for prevention of bleeding by PCC or APCC in patients with inhibitors [6,8–12]. To determine the safety and efficacy of PCC and APCC for prophylaxis, long-term observations are needed for sufficient number of patients. Negrier et al. [4] suggested that the hemostatic efficacy of FEIBA was not compromised by the occurrence of anamnestic responses. This report documents successful home-based prophylaxis of FEIBA in a 14-year-old Japanese boy with severe hemophilia A and a high-titer inhibitor.

CASE REPORT

A 14-year-old Japanese boy with severe hemophilia A and a high-titer FVIII inhibitor had been diagnosed with hemophilia A on the basis of intra-

Contract grant sponsors: Ministry of Education, Science, Sports and Culture of Japan and the Mother and Child Health Foundation.

*Correspondence to: Shouichi Ohga, MD, PhD, Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi Higashi-ku, Fukuoka 812-8582, Japan.
E-mail: ohgas@pediatr.med.kyushu-u.ac.jp

Received for publication 7 April 2006; Accepted 30 June 2006

Published online 5 September 2006 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ajh.20751

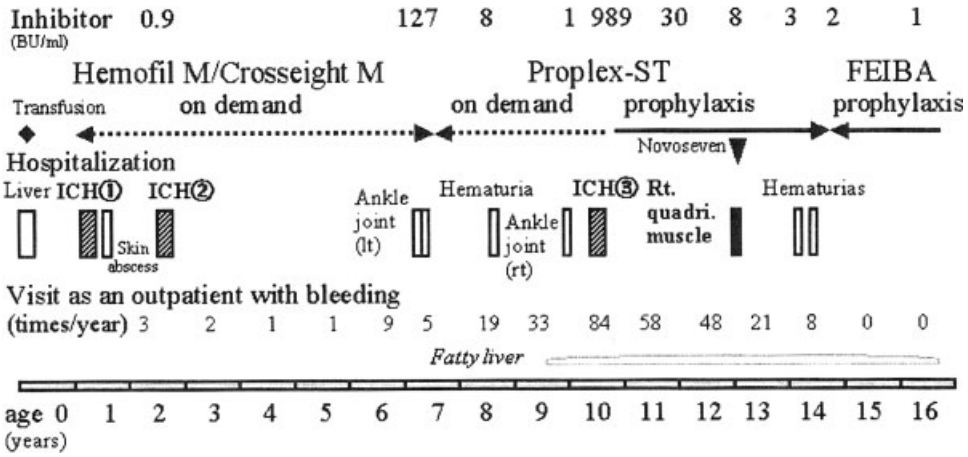

Fig. 1. Treatment history and current prophylaxis. Major bleeding: Bars indicate the period of hospitalization due to major bleeding episodes including three episodes of intracranial hemorrhage (ICH) (hatched bars), and muscle bleeding on this presentation at age 12 years (closed bar) or associated infectious complication (skin abscess at age 1 year). Minor bleeding: The number of hospital visit (times/year) represents the minor bleeding episodes including superficial, oral, and joint bleedings. The hospital visits for prophylactic infusion or nonhemorrhagic problems were excluded. There has been no bleeding episode in this patient for 24 months of current FEIBA prophylaxis.

hepatic bleeding 1 day after birth. A schematic of the patient's treatment history is shown in Fig. 1. Briefly, replacement therapy with monoclonal antibody-purified plasma-derived FVIII concentrates (Hemofil-M® and Crosseight-M®) was initiated on-demand at the time of diagnosis and continued for 7 years in our hospital. The patient experienced subarachnoid hemorrhages that were treated with high-dose FVIII concentrates and no surgical intervention at age 1 year and 2 years. At age 7, the patient suffered a protracted left ankle joint bleed, and testing revealed the presence of a high-titer (127 BU/mL) FVIII inhibitor. Treatment with on-demand infusions of PROPLEX-ST was initiated and continued over the next 3 years, but he frequently bled into the ankle joints, oral cavity, and urinary tract. The FVIII inhibitor level decreased to 1 BU/mL at age 9.5 years. At 10 years of age, he had a third intracranial hemorrhage concomitant with an anamnestic inhibitor response (989 BU/mL). Prophylaxis with PROPLEX-ST (50 U/kg/dose, three times per week) was initiated at that time and continued for 4 years. However, joint and mucosal bleedings repeated frequently during the 4-years' observation period.

At age 12 years, the patient presented with a swollen right leg resulting from a fall the previous night. On the admission, the pale boy was afebrile, alert, but listless with abnormal vital signs (pulse, 90/min; respiration, 24/min; and blood pressure, 158/80 mmHg). Weight and height were 61 kg and 152 cm, respectively. Conjunctivae were anemic, but not icteric. Chest auscultation revealed normal respiratory and cardiac sounds. Neither hepatosplenomegaly nor lymphdenopathy was found. The right thigh was tender and swollen, with ecchymosis, and had a circumference of 55.0 cm; by comparison, the left thigh circumference was 50.5 cm. Computed tomography scanning of the legs revealed a right quadriceps muscle hematoma and right knee joint bleeding (Fig. 2). There was no joint disease assessed by physical function. Neurological findings were normal. Peripheral blood counts showed WBC of 15.07×10^9/L, with 85% segmented neutrophils, 7% lymphocytes, and 8% monocytes. RBC was $2{,}860 \times 10^9$/L, hemoglobin was 8.6 g/dL, hematocrit was 26.1%, and a platelet count was 414×10^9/L, indicative of massive bleeding. Blood chemistries were unremarkable. Serological studies revealed no evidence of infection. C-reactive protein level was 4.54 mg/dL. Coagulation studies were as follows: prothrombin time (PT) 11.2 sec (control: 11.1 sec), activated partial thromboplastin time (APTT) 79.1 sec (control: 28.5 sec), fibrinogen 577 mg/dL (reference range: 150–400 mg/dL), fibrinogen/fibrin degradation product (FDP) 7.8 μg/mL (ref. range: 0–5.0 μg/mL), and D-dimer 5.7 μg/mL (ref. range: 0–0.5 μg/mL). Coagulation factor assays revealed the FVIII level of <1%, FVIII inhibitor of 8 BU/mL, von Willebrand factor (vWF) antigen 254%, and vWF activity 267%.

Initial treatment comprised three doses (6 mg/dose) of recombinant activated factor VII (rFVIIa) (Novoseven®), followed by 30–50 U/kg/day of PROPLEX-ST. However, anemia gradually progressed 10 days after admission, and then the daily

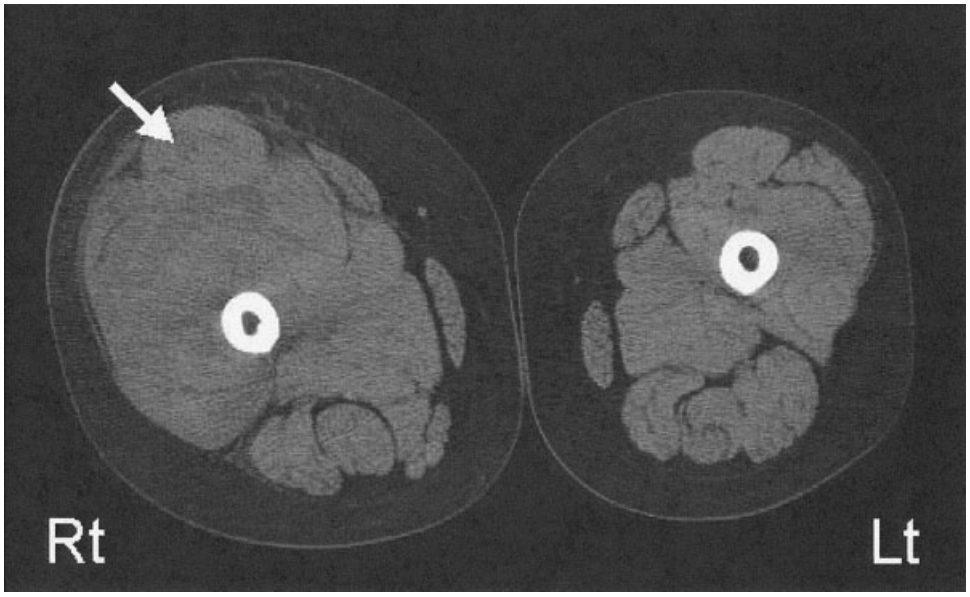

Fig. 2. Computed tomography scanning of bilateral thighs on admission. Right (Rt) and left (Lt) quadriceps muscles are indicated. Arrow indicates the presence of hematoma. Circumferences of the right and left thighs were 55.0 and 50.5 cm, respectively.

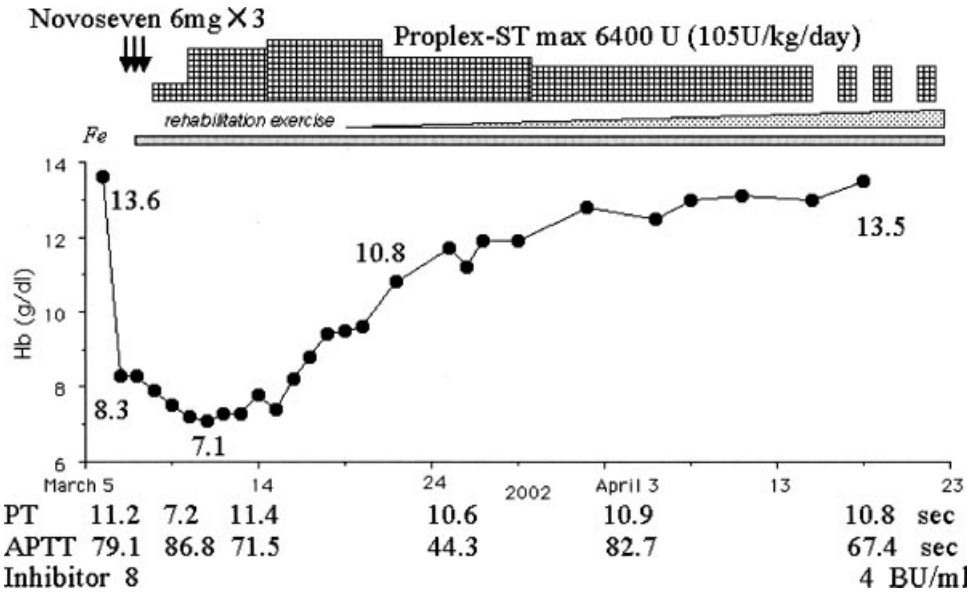

Fig. 3. Treatment course of intramuscular hematoma with Novoseven® and Proplex-ST. Treatment with Novoseven and Proplex-ST are indicated. Because of the progression of anemia 10 days after admission, the daily dose of Proplex-ST was increased up to 105 U/kg/day. Graph shows hemoglobin levels over time. The lower insets show PT, APTT, and inhibitor levels.

dose of PROPLEX-ST was increased up to 105 U/kg/day (Fig. 3). This treatment effectively controlled bleeding in the thigh and allowed normalization of the hemoglobin levels. He was discharged from the hospital with no disability. Nevertheless, the patient experienced frequent bleeding episodes during the next 41 months of prophylaxis with PROPLEX-ST (80–100 U/kg/day, three times per week) (Fig. 1).

At age 14 years, the patient began treatment with FEIBA (50 U/kg, three times per week) by drip infusion over 30 min using a syringe pump (TE-331S, Terumo Co. Tokyo, Japan) in the hospital, with monitoring of coagulation parameters. The patient was instructed in self-infusion FEIBA to allow home-based treatment, and was advised that antifibrinolytic agents should not be used within

12 hr of FEIBA infusion. Subsequent home-based FEIBA prophylaxis has continued for 24 months. During this time, the patient has experienced no bleeding or thrombotic events, and the inhibitor level has decreased to 1 BU/mL (Fig. 1). No adverse events have been reported, and no extra-infusion of FEIBA or other agents have been required. The controlled hemostasis reduced the frequency of hospital admissions and outpatient visits. It was associated with improved quality of life, particularly with respect to school (high attendance rate comparable to healthy schoolers; and participation in light exercise at school), and psychological well being.

DISCUSSION

Clinical management of patients with hemophilia and inhibitors is one of the most challenging issues in modern hemophilia practice. Home-based prophylactic regimens are well established for the prevention of serious bleedings and joint diseases in patients without inhibitors [13], whereas prophylactic replacement in inhibitor-positive patients has been reported for a limited number of patients [6,8–12]. The current report describes successful self-infusion of an APCC, FEIBA, at a dose of 50 U/kg, three times per week, by a 14-year-old Japanese boy with severe hemophilia A and a high-titer inhibitor, who had experienced recurrent bleeding during long-term prophylaxis with a PCC. FEIBA infusion was carried out with a syringe pump, and the adolescent and his family received careful instructions regarding the need for adherence to the prescribed dosing and with respect to thrombogenic risk factors. No extra-infusion of FEIBA or other agents was required during the observation period. Notably, the patient has not experienced bleeding episodes or adverse events over 2 years of therapy to date. Thus, this home-based FEIBA prophylaxis regimen appears to be more effective compared with previous PCC prophylaxis in this patient.

While this case represents a novel experience in the treatment of inhibitor-positive patients in Japan, the findings are consistent with data from other patients treated prophylactically with FEIBA [6,8–12], which reported low or decreased (relative to pretreatment) bleeding episode frequencies for patients treated with a variety of FEIBA regimens, including 50–100 U three or four times per week, or 50 or 100 U/kg/day. Treatment duration across these studies varied from a few months to several years. Consistent with the current case report, two of the previous studies also found decreased inhibitor titers during FEIBA prophylaxis [8,10]. Notably, studies by Escuriola-Ettingshausen et al. [9], Valentino and Salit [12], and Leissinger [7] also showed maintenance or improvement of existing arthropathy. In the present patient, effects of FEIBA on arthropathy could not be determined, as he had no joint disease at the start of FEIBA. Additionally, Ewing [10] suggested that FEIBA prophylaxis was effective even in patients who developed an anamnestic response, as the inhibitor titers decreased over time and patients experienced fewer bleeds and improved physical function.

During FEIBA prophylaxis, adverse events reported catheter port infections/sepsis, decreased fibrinogen, and peripheral thrombophlebitis, but no thrombotic complications or disseminated intravascular coagulation (DIC) [9]. No life-threatening bleeding episodes or thrombotic complications were observed in the other published prophylactic studies. A similar safety profile has been expected in our patient as long as he strictly adheres to the regimen. In three clinical studies of on-demand FEIBA therapy, adverse events including chills, fever, nausea, dizziness, unusual taste in the mouth, chest pain, drowsiness, and discomfort in breathing were recorded in 1.2% to 3.7% of all FEIBA infusions [2]. Concern remains, however, regarding the potential for thrombosis following long-term prophylaxis with APCCs. Pharmacovigilance reports for worldwide FEIBA use during the 10-year period 1990–1999 showed an overall adverse event rate of 55 events per 100,000 infusions [14]. Of these, 17 events in 16 patients were thrombotic, with an incidence of 4.05 thrombotic events per 100,000 infusions; the most frequently reported events were DIC (7/16 patients) and myocardial infarction (5/16 patients; one fatal). Notably, risk factors for thrombosis were present in 13 of the 16 patients (FEIBA overdosing, 8/16; obesity, 3/16; hyperlipemia, 2/16).

Although numerous reports have documented control of hemostasis and bleeding episodes with FEIBA, treatment with APCC may not be successful in some patients [15]. Thus, as an alternative to APCC therapy, successful control of hemostasis by rFVIIa was documented in patients with inhibitors [16]. The short half-life of rFVIIa (3.5 hr) [17], however, makes it difficult to optimize the interval of regular infusion for prophylaxis. Sequential administration of APCC and rFVIIa has been effectively used on occasion. Hayashi et al. [17] and Schneiderman et al. [18] reported that a regimen that alternated between APCC and rFVIIa was effective for treatment of inhibitor-positive patients with refractory bleeding that was not effectively controlled with either agent alone. However, the sequential use of PCCs/APCCs and FVIIa may be problematic, as illustrated by the development of thrombotic events, one of which was fatal, in two patients receiving PCCs and rVIIa [19]. The synergis-

tic effects of these agents is supported by the results of in vitro study that showed dramatic shortening of clotting times when rFVIIa was added to whole blood of patients receiving an APCC. Because limited post-marketing data are available for rFVIIa, long-term thrombogenicity of combined use of the two agents remains to be determined. The continued efficacy and safety of self-infusion of FEIBA may depend on the ability of patients to strictly adhere to dosing guidelines and to recognize the risk, preventive strategies, and signs of thrombosis. Long-term strategies for improving FEIBA prophylaxis should be focused on preventing bleeding episodes as well as the occurrence or progression of hemophilic arthropathy. Future studies of bypassing agents should be aimed at minimizing the total dosage while maximizing hemostatic effects, identifying patients unlikely to respond, and formally addressing the pharmacoeconomics of long-term prophylaxis.

ACKNOWLEDGMENTS

We are grateful to Huong Luu, PharmD, and Bruce Ewenstein, MD, PhD (Baxter BioScience, Westlake Village, CA, USA), for helpful comments and discussion.

REFERENCES

1. Ingerslev J. Hemophilia. Strategies for the treatment of inhibitor patients. Haematologica 2000;85(Suppl. 10):15–20.
2. Luu H, Ewenstein B. FEIBA safety profile in multiple modes of clinical and home-therapy application. Haemophilia 2004; 10(Suppl. 2):10–16.
3. 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;30:626–630.
4. 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;77:1113–1119.
5. Sjamsoedin LJ, Heijnen L, Mauser-Bunschoten EP, et al. The effect of activated prothrombin-complex concentrate (FEIBA) on joint and muscle bleeding in patients with hemophilia A and antibodies to factor VIII. A double-blind clinical trial. New Engl J Med 1981;305:717–721.
6. Kreuz W, Escuriola-Ettinghausen C, Mentzer D, Martinez I, Becker S, Stoll H. Factor VIII inhibitor bypass activity (FEIBA) for prophylaxis during immune tolerance induction (ITI) in patients with high-responding inhibitors. Blood 2000;96:266a.
7. Leissinger CA. Prevention of bleeds in hemophilia patients with inhibitors: Emerging data and clinical direction. Am J Hematol 2004;77:187–193.
8. Hilgartner MW, Makipernaa A, Dimichele DM. Long-term FEIBA prophylaxis does not prevent progression of existing joint disease. Haemophilia 2003;9:261–268.
9. Escuriola-Ettingshausen C, Martinez Saguer I, Funk MB, et al. Long-term prophylaxis with FEIBA in patients with high-responding inhibitors. J Thromb Haemost 2003;1(Suppl. 1): Abst. 1628.
10. Ewing N. Anamnestic responses in hemophilia patients with inhibitors on continuous prophylaxis with factor VIII inhibitor bypassing activity, vapor-heated (FEIBA VH). J Thromb Haemost 2005;3(Suppl. 1): Abst. 2036.
11. Leissinger CA, Becton DL, Ewing NP, Valentino LA. Prophylaxis with factor VIII inhibitor bypassing activity, vapor heated (FEIBA VH) decreases bleeding frequency and maintains or improves joint status. J Thromb Haemost 2005;3(Suppl. 1): Abst. 1436.
12. Valentino LA, Salit MG. Prophylactic use of FEIBA in children with hemophilia complicated by high-titered inhibitors. Blood 2002;100:102b.
13. Dimichele D, Rivard G, Hay C, Antunes S. Inhibitors in haemophilia: Clinical aspects. Haemophilia 2004;10(Suppl. 4):140–145.
14. Ehrlich HJ, Henzl MJ, Gomperts ED. Safety of factor VIII inhibitor bypass activity (FEIBA): 10-year compilation of thrombotic adverse events. Haemophilia 2002;8:83–90.
15. Cooper HA, Jones CP, Campion E, Roberts HR, Hedner U. Rationale for the use of high dose rFVIIa in a high-titre inhibitor patient with haemophilia B during major orthopaedic procedures. Haemophilia 2001;7:517–522.
16. Shirahata A, Kamiya T, Takamatsu J, et al. Clinical trial to investigate the pharmacokinetics, pharmacodynamics, safety, and efficacy of recombinant factor VIIa in Japanese patients with hemophilia with inhibitors. Int J Hematol 2001;73:517–525.
17. Hayashi T, Tanaka I, Shima M, et al. Unresponsiveness to factor VIII inhibitor bypassing agents during haemostatic treatment for life-threatening massive bleeding in a patient with haemophilia A and a high responding inhibitor. Haemophilia 2004; 10:397–400.
18. Schneiderman J, Nugent DJ, Young G. Sequential therapy with activated prothrombin complex concentrate and recombinant factor VIIa in patients with severe haemophilia and inhibitors. Haemophilia 2004;10:347–351.
19. Key NS, Christie B, Henderson N, Nelsestuen GL. Possible synergy between recombinant factor VIIa and prothrombin complex concentrate in hemophilia therapy. Thromb Haemost 2002;88:60–65.