

Factors Affecting Choice of Hemostatic Agent for the Hemophilia Patient With an Inhibitor Antibody

Paul E. Monahan,^{1*} and Louis M. Aledort,² for the ad hoc Hemophilia Inhibitor Study Group[†]

¹Department of Pediatrics, University of North Carolina at Chapel Hill, North Carolina

²Department of Medicine, Mount Sinai School of Medicine, New York City, New York

Achieving adequate hemostasis in patients with hemophilia and high-titer inhibitor antibodies remains a challenge despite the development of plasma-derived and recombinant therapies to bypass the inhibitory effect. A group of hemophilia treaters met to examine the factors that influence physician choices among the very costly and cumbersome available therapies. Specific knowledge deficits in need of prospective research were identified with respect to the rational treatment of inhibitor patients. Am. J. Hematol. 77:346–350, 2004. © 2004 Wiley-Liss, Inc.

Key words: inhibitor; factor VIII; factor IX; recombinant factor VIIa; aPCC

INTRODUCTION

The treatment of hemophilia complicated by a humoral immune response against the congenitally deficient clotting factor (an “inhibitor” antibody) remains challenging despite the development of several clotting factor concentrates designed specifically for this clinical scenario. The majority of such inhibitor antibodies in patients with severe hemophilia are of high titer, as defined quantitatively by a Bethesda inhibitor assay level of >5 BIU [1]. This correlates in practice to an anticoagulant activity great enough to make treatment with even high doses of the deficient factor usually ineffective. To discuss the issues influencing treatment choice for high-titer inhibitor patients, a group of hemophilia treaters from the United States gathered for a one-day meeting in March 2002, convened and supported by Baxter Healthcare, Inc. Two previous ad hoc Hemophilia Inhibitor Study Groups (HISG) have defined the currently available treatment options for inhibitor patients [2,3]. A focus of the HISG discussion was to examine the factors that influence physician choices and practical use of available therapies for acute bleeding in inhibitor patients.

TREATMENT OPTIONS

Efficacious agents for the treatment of hemorrhage in patients with hemophilia A and inhibitors include

© 2004 Wiley-Liss, Inc.

high-dose human factor VIII concentrates, porcine factor VIII, and bypassing agents including the activated prothrombin complex concentrates [aPCCs, e.g., Autoplex T (Nabi, Boca Raton, FL), and FEIBA (Baxter Healthcare, Glendale, CA)], prothrombin complex concentrates (PCCs), and recombinant factor VIIa (rFVIIa, Novoseven brand, Novo Nordisk, Copenhagen, Denmark). It is worth noting that a recent systematic evidence-based review of inhibitor therapy has been compiled [4].

Participating treaters agreed that aPCCs or rFVIIa were used in most clinical scenarios, to avoid antigenic anamnestic stimulation of IgG inhibitor antibodies by

Dr. Monahan is an educational consultant (honoraria/consulting fees) for Baxter Healthcare, Inc., Speakers Bureau (honoraria) for NovoNordisk, Speakers Bureau (honoraria) for Aventis-Behring, and clinical advisor and educational consultant (consulting fees) for Bayer. Dr. Aledort is the DSMC chairman for NovoNordisk and Baxter BioScience.

*Correspondence to: Paul E. Monahan, M.D., CB#7220, 418 MacNider Bldg., UNC-CH School of Medicine, Chapel Hill, NC 27599-7220. E-mail: Paul_Monahan@med.unc.edu

[†]Panelists of the ad hoc Hemophilia Inhibitor Study Group are named in the Appendix.

Received for publication 6 March 2004; Accepted 22 June 2004

Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ajh.20204

factor VIII. This strategy reserves the ability to use factor VIII for life-threatening emergencies, in those patients whose antibody titers fall in the absence of factor VIII stimulation. As no controlled head-to-head trial of aPCCs versus rFVIIa has been completed, there was not a perception among the treaters present that one treatment has superior efficacy versus the other. Two head-to-head trials of FEIBA versus rFVIIa have been initiated. One of these two trials will also examine dosing intervals for rFVIIa administration. The approved treatment dose for rFVIIa requires three infusions, usually given at intervals of 2–3 hr because of the factor VIIa plasma half-life of 2 hr. Following the initial three-infusion treatment, additional doses may be given every 2–3 hr if needed for hemostasis. Dosing with aPCCs is similar to factor VIII or IX treatment, so that an initial dose may be repeated in 8–24 hr as needed for hemostasis.

Porcine factor VIII, which has significant sequence variation from the human factor VIII molecule, provides selected patients with excellent hemostasis. Cross-reacting antibodies between human and porcine factor VIII occur commonly in individuals with congenital factor VIII deficiency and inhibitors (up to 15%) [4,5]. Anamnestic increases in anti-human or anti-porcine factor VIII with repeated porcine factor VIII dosing are even more common [4]. As a result, this agent is often reserved for potential one-time use in the treatment of congenital hemophilia and inhibitors and is rarely the treatment of choice for pediatric patients. Most participants used porcine factor VIII primarily for the treatment of adults with acquired hemophilia. Allergic reactions and transient thrombocytopenia may occur with porcine factor VIII. Although supplies of the porcine plasma-derived product have been inconsistent, a recombinant porcine factor VIII is presently in clinical trials.

Hemophilia B patients develop inhibitors with much less frequency than hemophilia A patients. Nevertheless, therapy with factor IX-containing products may result in allergic or anaphylactic responses in the presence of factor IX inhibitors. Although factor IX (in the setting of low-titer, low-responding inhibitors) and bypassing agents can be used in patients who do not have allergic reactions, recombinant factor VIIa is the safest treatment option in the patient with factor IX inhibitors and anaphylactic reactions.

In most instances, an attempt is made to achieve immune tolerance induction (ITI) for newly developed inhibitor patients and elimination of the inhibitor is the ideal outcome. Strategies for ITI were not discussed in favor of focusing discussion on the management of acute bleeding challenges. For the treatment of hemorrhage (prior to or during ITI, or after failed ITI), the panel as a whole did not feel that a significant difference in efficacy has been demonstrated in clinical trials that

influence the choice of aPCCs versus rFVIIa for bypassing agent therapy. (An excellent concise review of controlled (for aPCCs) and uncontrolled (aPCCs, rFVIIa) trials is available [6] as well as a comprehensive review [4].) Instead, the choice of agent for any given treatment is influenced by considerations falling into the following general areas: (i) safety considerations; (ii) practical issues that limit availability of product or reliable delivery; and (iii) experience of the individual treater.

INFECTIOUS RISK CONSIDERATIONS

For treatment of the subset of inhibitor patients who are plasma-naïve (generally pediatric patients), the stated preference of a number of participating treaters or their patients was the use of a recombinant product (recombinant factor VIIa) to minimize the risk of infectious contaminants that may be present in pooled plasma-derived clotting products. The entire panel agreed that modern donor and plasma pool screening, combined with specific virus-inactivation steps, result in an extraordinarily low risk of contamination of aPCCs by lipid enveloped viruses (including hepatitis B, hepatitis C, and HIV) [6,7]. The use of recombinant FVIIa does minimize the small chance of a clinically significant non-enveloped virus transmission (hepatitis A, parvovirus B19), but most treaters agreed that this consideration alone did not sway them to choose this more expensive product, especially in patients previously exposed to plasma-derived product [6]. Compared to these relatively well-characterized infectious risks, the risk of prion disease (e.g., variant Creutzfeldt-Jakob disease, vCJD) through plasma-derived clotting factor- or albumin-containing products is much less well understood [7]. The only case of vCJD likely resulting from a transfused blood product from a donor with vCJD has recently been reported [8]. vCJD is concentrated in the cellular components of blood rather than in plasma (the vCJD transmission just mentioned was via packed red blood cell transfusion), and multiple steps in plasma clotting concentrate manufacture each lead to removal of prions [7,8]. Therefore it is difficult, based on this case, to extrapolate a risk of vCJD transmission from clotting factor concentrates. Given the absence of a blood screening test for vCJD and the extraordinarily lengthy incubation periods of these agents, some treaters felt avoiding plasma-derived products was prudent whenever possible.

To avoid plasma-derived products, treaters of pediatric hemophilia were more likely to attempt recombinant factor VIIa as front-line therapy than were treaters of adults; nevertheless, the additional challenges of venous access for repeated rFVIIa dosing in children can dictate a change to aPCCs in children

as well. Several participating treaters expressed that their patients, who preferred recombinant products prior to the development of an inhibitor, nevertheless accepted plasma-derived products as an important option for treating the inhibitor complication.

THROMBOTIC RISK CONSIDERATIONS

Thrombotic complications have been described with the use of aPCCs and rFVIIa. Over 20 years' experience with aPCCs in patients with congenital hemophilia has been reviewed by Leissenger [9]; other reports review separately the experience with FEIBA [10] and Autoplex [11]. Myocardial infarction (MI) and laboratory or clinically evident disseminated intravascular coagulation (DIC) are reported. In each case, thrombosis was associated with doses exceeding 200 units/kg/day or with pre-existing conditions associated with MI or thrombotic disease. This maximum dose, therefore, represents a ceiling below which thrombosis is unlikely [9]. MI and DIC have not been reported with the use of Autoplex T as a single agent in hemophilia. The incidence of reported thrombotic adverse events temporally associated with FEIBA administration (all indications) is 16 per 395,000 infusions [10].

Thromboses with rFVIIa also occur infrequently, as reviewed by Roberts [12]. Currently recommended doses reportedly lead to minimal changes in systemic markers of activation of coagulation (e.g., prothrombin activation peptide F1 + 2) [13], although as with aPCCs, fibrinogen decreases have been reported. Ongoing post-marketing studies with rFVIIa are seeking to establish efficacy and safety of giving larger doses on different schedules than those currently approved for this drug; a "ceiling" dose for safe administration has not been established. Many panelists stated the opinion that they preferred using rFVIIa for specific settings associated with high thrombotic risk, e.g., concurrent active liver disease. A general feeling was that a longer clinical experience with this drug is needed to establish the relative thrombogenicity of this bypassing agent. Roberts et al. recently published that the number of spontaneously reported thrombotic events temporally associated with rFVIIa administration (all indications) is 18 per 400,000 standard doses [12].

All participants agreed that no one agent is efficacious in all hemorrhagic episodes, and switching between the use of aPCCs and rFVIIa is commonplace and appropriate during a bleeding episode that does not respond to initial treatment. A beneficial synergistic hemostatic effect of rFVIIa use following PCC/aPCC therapy has been suggested recently based on clinical responses and *in vitro* modeling [14,15]. If confirmed, these investigations suggest that a prospective trial of

mono versus dual therapy with bypassing agents may yield important efficacy and safety data. While the potential efficacy of sequential use of activated products has been suggested [14,16], the potential exists to aggravate thrombosis [12,17], and approaches to such combined use are not established. As an example, some panelists voiced the opinion that they prefer to use rFVIIa as the initial agent for inpatient bleeding treatment, because the shorter circulating half-life of rFVIIa allows substitution of aPCCs, if necessary, after a shorter "wash-out" period without risking interaction of the two drugs. An unmet need is the establishment of safety guidelines for transitioning from the use of one product to another without activating thrombosis.

IMMUNOGENICITY CONSIDERATION

All PCCs and aPCCs contain minute amounts of factor VIII, and exposure to these products carries some risk of an anamnestic rise in anti-factor VIII inhibitor titers [6]. This complication has been seen in less than 10% of treatments with Autoplex, but has been reported in 15–32% of patients following FEIBA [4,6,9]. An anamnestic increase in anti-factor VIII titer does not appear to correlate with decreased hemostatic efficacy of the aPCC but clearly affects the ability to use human FVIII if clinically required, and may correlate with increased clinical bleeding. Anamnestic responses reportedly occur 25–35% of the time with porcine FVIII and are associated with loss of hemostatic efficacy [5]. There is no evidence that rFVIIa treatment of hemophilia is associated with a rise in inhibitor antibodies directed against factor VII, VIII, or IX [4,6].

COST AND ACCESS CONSIDERATIONS

Although safety issues related to viral transmission or thrombogenicity influence case-specific product choice for inhibitor patients, practical issues of treatment access and cost significantly overshadow initial and subsequent choices of therapy. Bleeding in the presence of inhibitor does not require inpatient admission *per se*. The majority of treaters rely on inhibitor patients treating at home with bypassing agents and state confidence that both rFVIIa and aPCCs are efficacious for home therapy when given promptly and at recommended dosing intervals [3,6,18,19]. Reliable venous access is often a limitation in the home treatment setting, however. Participating treaters used aPCCs more frequently than rFVIIa for home treatment because of the requirement for repeated dosing of rFVIIa at short dosing intervals. Many treaters used rFVIIa as initial therapy in the inpatient setting, citing confidence that the requirement for every 2- to 3-hr dosing with rFVIIa could be reliably

accomplished in hospital. Nevertheless, aPCCs were used as initial therapy by the majority of treaters in this HISG panel, and at least one panelist stated that his hospital dictated that rFVIIa could only be used after other treatment options had been exhausted. Treaters of pediatric (plasma-naïve) patients, however, were more likely to rely on rFVIIa as initial inpatient therapy.

Venous access remains for many treaters less of a restriction than access limitations related to the cost and supply of bypassing agents; the latter limitations were a critical determinant in choice of product for almost half of the participating treaters. Many treaters noted that their large public hospitals have established stringent rules for approval of use of rFVIIa. These measures parallel similar decisions made after the introduction of aPCCs in the 1980s. U.S. hospitals that do not have a Hemophilia Treatment Center will not uniformly stock any form of bypassing agents. Other institutions have made an effort to separate pharmacy costs of clotting factors from other inpatient pharmacy expenses to insulate the pharmacy from the rapidly explosive costs that a single inhibitor patient can incur. The amount of support for hemophilia services from state to state within the U.S. varies widely and directly affects the product choice for treaters in less well supported states and hospital systems. Unfortunately, some off-label use of bypassing agents has resulted in expenditures that have affected a given hospital's ability to stock these products even for approved use in hemophilia. Many hospitals choose to have a coagulation consult service oversee and approve any off-label use of bypassing agents.

UNRESOLVED ISSUES AFFECTING CLINICAL CHOICES (Table I)

A number of specific knowledge deficits as regards the rational treatment of inhibitor patients were

TABLE I. Unresolved Issues That Impact Choice of Hemostatic Agent for Inhibitor-Related Bleeding

How do the efficacies of aPCCs and rFVIIa compare in controlled clinical trials?
Is prophylactic treatment with aPCCs or rFVIIa safe and efficacious?
What doses and schedules are appropriate for prophylaxis?
How are bypassing agents best dosed in the perioperative setting?
Is there a role for continuous infusion of bypassing agents?
What are the appropriate dosing intervals to maintain clot after initial hemostasis using bypassing agents? (Is plasma half-life the principal determinant of hemostatic efficacy?)
How can clotting factors and bypassing agents safely be used in combination or sequentially for the bleeding inhibitor patient?
How is the efficacy of bypassing agents best monitored?
How is the safety of bypassing agents best monitored?

identified. This particular area of treatment is in danger of having treatment approaches codified that have resulted from relatively anecdotal experiences rather than careful prospective clinical trials. Ongoing prospective trials compare efficacy of aPCCs versus rFVIIa, and results are awaited eagerly. One area identified as needing careful study is secondary prophylactic treatment of inhibitor patients, whether with aPCCs or with rFVIIa. Many participants shared the opinion that prophylactic approaches are being used without a mechanism to collect or compare the success or complications of the approach [9,20]. Another identified area for study is the perioperative management of inhibitor patients, particularly with recombinant factor VIIa. The use of rFVIIa for perioperative hemostasis for central line placement in inhibitor patients is a common and uniform surgical scenario that could be expected to accrue patients rapidly and yield evaluable results in a clinical trial [21]. Is an every 2- to 3-hr dosing schedule feasible or necessary with this drug following initial hemostasis? Although the recommended dosing intervals for rFVIIa have been based on the circulating half-life of this agent, hemostatic activity of this agent may result in part from mechanisms independent of the initiation of thrombin generation [22–24], so that less frequent dosing may prove to be efficacious and cost-effective. Alternatively, the question of whether rFVIIa as a continuous infusion achieves equivalent efficacy or cost savings when compared to repeated bolus dosing is the subject of an ongoing clinical trial. While clinical trial information addresses these questions, laboratory understanding of the mechanisms of action of bypassing agents continues to advance and will likely suggest improved dosing approaches or formulations based on current bypassing agents [23–27].

A choice of relatively effective treatment options for patients with inhibitors now exists, so that evaluation of quality of life and cost/efficacy endpoints may now be incorporated into clinical studies to complement the clinical outcome data. Regardless, issues of cost and availability emerge as primary influences on current treatment choice. Until uniform treatment doses and schedules have been prospectively established for the available agents, it will be difficult to model the appropriate cost–benefit analyses to guide treatment choice.

ACKNOWLEDGMENT

The ad hoc Hemophilia Inhibitor Study Group panel discussion was supported by an unrestricted educational grant from the Baxter Healthcare.

APPENDIX

Panelists of the ad hoc Hemophilia Inhibitor Study Group (HISG), 20 March 2002. Louis M. Aledort, M.D., Mount Sinai Medical Center, New York, NY; Lisa N. Boggio, M.D., Northwestern Medical School, Chicago, IL; Eric H. Kraut, M.D., Ohio State University Hospital, Columbus, OH; Cindy A. Leissinger, M.D., Tulane Medical Center, New Orleans, LA; Edward N. Libby, M.D., University of New Mexico Hospital, Albuquerque, NM; Brian McDonald, R.Ph., H.O.S.S., Oldsmar, FL; Paul E. Monahan, M.D., University of North Carolina at Chapel Hill, Chapel Hill, NC; Nkechi Onwuzurike, M.D., Hurley Medical Center, Flint, MI; Rajiv K. Pruthi, M.D., Mayo Clinic, Rochester, MN; Shirley E. Reddoch, M.D., Walter Reed Army Medical Center, Washington, DC; Swayam Sadanandan, M.D., The Brooklyn Hospital Center, Brooklyn, NY; Raymond G. Watts, M.D., University of Alabama, Birmingham, AL; Eric J. Werner, M.D., Children's Hospital of the King's Daughters, Norfolk, VA.

REFERENCES

- White GC 2nd, Rosendaal F, Aledort LM, et al. Definitions in Hemophilia. Recommendations of the Scientific Subcommittee on Factor VIII and Factor IX of the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis. *Thromb Haemost* 2001;85:560.
- Tarantino M, Aledort L. On the treatment of hemorrhage in patients with hemophilia and associated inhibitors. *Transfusion* 2001;41:1628–1629.
- Kulkarni R, Aledort LM, Berntorp E, et al. Therapeutic choices for patients with hemophilia and high-titer inhibitors. *Am J Hematol* 2001;67:240–246.
- Jones ML, Wight J, Paisley S, Knight C. Control of bleeding in patients with haemophilia A with inhibitors. *Haemophilia* 2003;9:464–520.
- Lee CA. The evidence behind inhibitor treatment with porcine factor VIII. *Pathophysiol Haemost Thromb* 2002;32(Suppl 1):5–8.
- Teitel JM. Recombinant factor VIIa versus aPCCs in haemophiliacs with inhibitors. Treatment and cost considerations. *Haemophilia* 1999;5(Suppl 3):43–49.
- Farrugia A. Evolving perspectives in product safety for haemophilia. *Haemophilia* 2002;8:236–243.
- Llewelyn CA, Hewitt PE, Knight RSG, et al. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. *Lancet* 2004;363:417–421.
- Leissinger CA. Use of prothrombin complex concentrates and activated prothrombin complex concentrates as prophylactic therapy in haemophilia patients with inhibitors. *Haemophilia* 1999;5(Suppl 3):25–32.
- Ehrlich HJ, Henzl MJ, Gomperts ED. Safety of factor VIII inhibitor bypass activity (FEIBA(R)): 10-year compilation of thrombotic adverse events. *Haemophilia* 2002;8:83–90.
- White II GC. Seventeen years' experience with Autoplex®/Autoplex®-T: evaluation of inpatients with severe haemophilia A and factor VIII inhibitors at a major haemophilia centre. *Haemophilia* 2000;6:508–512.
- Roberts HR, Monroe DM 3rd, Hoffman M. Safety profile of recombinant factor VIIa. *Semin Hematol* 2004;41(Suppl 1):101–108.
- Ingerslev J, Holm M, Christiansen K, Knudsen L, Negrier C. Levels of prothrombin activation peptide F1+2 in patients with a bleeding tendency. *Blood Coagul Fibrinolysis* 1998;9(Suppl 1):S129–S134.
- 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.
- Allen GA, Monroe DM 3rd, Roberts HR, Hoffman M. The effect of factor X level on thrombin generation and the procoagulant effect of activated factor VIIa in a cell-based model of coagulation. *Blood Coagul Fibrinolysis* 2000;11(Suppl):S3–S7.
- Hough RE, Hampton KK, Preston FE, Channer KS, West J, Makris M. Recombinant VIIa concentrate in the management of bleeding following prothrombin complex concentrate-related myocardial infarction in patients with haemophilia and inhibitors. *Br J Haematol* 2000;111:974–979.
- Rosenfeld SB, Watkinson KK, Thompson BH, Macfarlane DE, Lentz SR. Pulmonary embolism after sequential use of recombinant factor VIIa and activated prothrombin complex concentrate in a factor VIII inhibitor patient. *Thromb Haemost* 2002;87:925–926.
- Santagostino E, Gringeri A, Mannucci PM. Home treatment with recombinant activated factor VII in patients with factor VIII inhibitors: the advantages of early intervention. *Br J Haematol* 1999;104:22–26.
- 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;6:912–918.
- 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.
- O'Connell N, McMahon C, Smith J, Khair K, Hann I, Liesner R, Smith OP. Recombinant factor VIIa in the management of surgery and acute bleeding episodes in children with haemophilia and high responding inhibitors. *Haemophilia* 2002;116:632–635.
- Lisman T, Mosnier LO, Lambert T, et al. Inhibition of fibrinolysis by recombinant factor VIIa in plasma from patients with severe hemophilia A. *Blood* 2002;99:175–179.
- Kjalke M, Ezban M, Monroe DM, Hoffman M, Roberts HR, Hedner U. High-dose factor VIIa increases initial thrombin generation and mediates faster platelet activation in thrombocytopenia-like conditions in a cell-based model system. *Br J Haematol* 2001;114:114–120.
- He S, Blomback M, Jacobsson Ekman G, Hedner U. The role of recombinant factor VIIa (FVIIa) in fibrin structure in the absence of FVIII/FIX. *J Thromb Haemost* 2003;1:1215–1219.
- Turacek PL, Varadi K, Gritsch H, et al. Factor Xa and prothrombin: Mechanism of action of FEIBA. *Vox Sang* 1999;77:72–79.
- Turacek PL, Varadi K, Keil B, et al. Factor VIII inhibitor-bypassing agents act by inducing thrombin generation and can be monitored by a thrombin generation assay. *Pathophysiol Haemost Thromb* 2003;33:16–22.
- Tomokiyo K, Nakatomi Y, Araki T, et al. A novel therapeutic approach combining human plasma-derived Factors VIIa and X for haemophiliacs with inhibitors: evidence of a higher thrombin generation rate in vitro and more sustained haemostatic activity in vivo than obtained with Factor VIIa alone. *Vox Sang* 2003;85:290–299.