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Advances in bypassing agent therapy for hemophilia patients with inhibitors to close care gaps and improve outcomes

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***Abstract*:** In the past, patients with hemophilia and inhibitors have had less-than-optimal treatment and have experienced more orthopedic complications than patients without inhibitors. Bypassing agents offer the potential to close treatment gaps between inhibitor and noninhibitor patients by helping the former better attain key treatment goals, including: facilitating early initiation of treatment and hemostatic control in hemarthroses; providing effective treatment in serious hemorrhagic episodes; and performance of major surgery. Effective treatment with a bypassing agent minimizes joint and/or muscle damage and potentially can serve as an effective prophylactic agent to minimize the number of hemarthroses experienced per year, thereby mitigating the development of arthropathy. The reported efficacy of the currently available bypassing agents ranges from approximately 50–80% (50–64% in controlled studies) for plasma-derived activated prothrombin complex concentrate (pd-aPCC) and 81–91% (in controlled studies) for recombinant activated factor VII (rFVIIa), including use in major orthopedic surgery. Both bypassing agents have undergone key improvements in their formulation and/or properties in recent years. The nanofiltered, vapor-heated formulation of pd-aPCC has diminished the risk of acquiring blood-borne viral infections and the room temperature stable formulation of rFVIIa allows more convenient storage, increased ease to dissolve and inject, and smaller volumes, thereby increasing overall ease of administration. Use of recommended dosing has been demonstrated to provide effective hemostasis with a minimal number of injections for both agents. In this paper, we review the individual characteristics of pd-aPCC and rFVIIa and discuss clinical data from studies conducted in inhibitor patients that demonstrate the potential benefits of these bypassing agents in this difficult-to-treat population, and underscore the potential opportunities to close the gap in care between inhibitor and noninhibitor hemophilic patients.

***Keywords*:** hemophilia, inhibitors, outcomes, patient care, plasma-derived activated prothrombin complex concentrate, recombinant activated factor VII

Introduction

Hemophilia is a serious bleeding disorder: without appropriate treatment, patients affected with severe hemophilia historically have an average life expectancy of 16 years [Ramgren, 1962]. The characteristic bleeding pattern in affected patients is repeated joint bleeds (hemarthroses), resulting in the development of chronic arthropathy. In the late 1950s and early 1960s, the regular administration of factor VIII/factor IX (FVIII/FIX) concentrates once to several times per week (prophylaxis) was introduced in some patient populations to determine whether the number of spontaneous hemarthroses could be decreased [Ahlberg *et al.* 1965]. Long-term follow up demonstrated a correlation between the number of hemarthroses and the joint score as a measure of joint damage [Manco-Johnson *et al.* 2007; Nilsson *et al.* 1992], thus supporting the concept of prevention of hemarthroses through prophylactic administration of FVIII/FIX concentrates as a mechanism to ameliorate associated sequelae. It is also widely recognized that treatment initiated at the first signs of a hemorrhagic episode results in more efficient hemostasis and is often associated with the need for

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fewer required overall doses of replacement therapy [Salaj *et al.* 2009; Lusher, 1998b]. The establishment of home-based treatment has facilitated early replacement therapy and set the stage for the administration of optimal prophylaxis.

The development of inhibitory antibodies complicates treatment in approximately 20–33% of patients with severe or moderately severe hemophilia A and 1–6% of individuals with severe hemophilia B [DiMichele, 2008]. In patients with inhibitors, the administration of FVIII/FIX concentrates is less effective or, most commonly, ineffective, resulting in failure to achieve adequate hemostasis. Poor control of hemorrhagic episodes is, in turn, associated with increased orthopedic complications. It was demonstrated in a European study that patients with inhibitors, aged 14–35 years and 36–65 years, were hospitalized for orthopedic procedures at rates of 16% and 27%, respectively; these hospitalization rates are in stark contrast to the 4% documented in patients without inhibitors. Furthermore, patient mobility was reduced in these two groups of inhibitor patients (24% and 22%, respectively, used wheelchairs *versus* 4% in the noninhibitor group) [Morfini *et al.* 2007b].

Immune tolerance induction therapy is increasingly employed to achieve antigen-specific tolerance to FVIII administration; however, available information is insufficient to support the superiority of a particular regimen [DiMichele, 2007]. Reported efficacy rates range from 70% to 85% [DiMichele, 2008]. The utility of immune tolerance induction therapy in patients with FIX deficiency is less well established, with an average reported success rate of approximately 30% [DiMichele, 2008].

The bypassing agents plasma-derived activated prothrombin complex concentrate (pd-aPCC; FEIBA NF®, Anti-Inhibitor Coagulant Complex, Baxter Healthcare Corporation, Westlake Village, CA) [Baxter Healthcare, 2010] and recombinant activated factor VII (rFVIIa; NovoSeven®, NovoSeven® RT, Novo Nordisk A/S, Bagsværd, Denmark) [Novo Nordisk, 2010] are the two currently available agents utilized in patients with inhibitors (Table 1). Efficacy rates for resolving mild-to-moderate bleeding episodes in patients with congenital hemophilia with inhibitors ranged from 57% to 79% for pd-aPCC and 87% to 100% for rFVIIa based on studies included in a systematic review [Lyseng-Williamson and Plosker, 2007] that included an external independent review by several experts during the development of the article. When considering data from only controlled trials, the efficacy of pd-aPCC ranges from 50% to 64% [Young *et al.* 2008b; Lusher *et al.* 1983, 1980; Sjamsoedin *et al.* 1981]. Further, pd-aPCC and rFVIIa have been shown to be effective in patients with inhibitors undergoing minor and major surgical and invasive diagnostic and therapeutic procedures, including orthopedic surgery [Balkan *et al.* 2010; Hedner and Ingerslev, 1998; Shapiro *et al.* 1998; Ingerslev *et al.* 1996]. Both products have been used in the home-treatment setting with success [Gomperts, 2006; Negrier *et al.* 2006b; Key *et al.* 1998]. While long-term prophylaxis with both bypassing agents has been shown to reduce joint hemorrhages, there have been mixed results in the prevention of progressive orthopedic damage [Valentino, 2010; Konkle *et al.* 2007; Morfini *et al.* 2007a; Hilgartner *et al.* 2003; Kreuz *et al.* 2000]. In this paper, we discuss the mechanistic characteristics and clinical data of these two bypassing agents, and how and to what extent this evidence demonstrates the capability of either one or both to close the gaps in care between patients with hemophilia with inhibitors and those without inhibitors.

Pathophysiologic basis of bypassing agent activity

The availability of rFVIIa has stimulated research on the role of the tissue factor (TF)–FVII pathway, resulting in a re-evaluation of some concepts of hemostasis. Using a cell-based model including both TF-expressing cells and platelets [Monroe *et al.* 2002], it was recognized that hemostasis is initiated by the exposure of TF, a true receptor protein with an intramembraneous component, at the site of injury and through a complex with its ligand, FVIIa, present in a small amount in the circulating blood. This tight complex maintains a localized process and activates factor X (FX) into activated FX (FXa) on the TF-expressing cell, thereby providing an initial limited amount of thrombin generation. This initial thrombin activates FVIII, factor V (FV), and factor XI (FXI), as well as platelets. After the generation of FXa, a quaternary complex including TF–FVIIa–FXa and TF pathway inhibitor is formed, leading to the inhibition of this initial phase of the hemostatic process. The initial activation of FIX is mediated by the TF–FVIIa complex. Further, full thrombin

Table 1. Comparison of available bypassing therapies in patients with hemophilia and inhibitors.

Property/parameter	rFVIIa	pd-aPCC
Source	Recombinantly produced protein [Novo Nordisk, 2010; Klitgaard and Nielsen, 2008]	Pooled human plasma [Baxter Healthcare, 2010; Turecek *et al.* 2004]
Composition	Highly purified recombinant protein [Novo Nordisk, 2010; Klitgaard and Nielsen, 2008]	Mixture of coagulation proteins (FII, FIX, FX unactivated; FVII activated; trace amounts of FVIII) and other unknown plasma components whose function is unknown [Baxter Healthcare, 2010; Turecek *et al.* 2004]
Mechanism of action	Pharmacological concentrations of rFVIIa bind to platelets activated by a small amount of thrombin generated by the initial TF–FVIIa–FXa complex; further activation of FX converts additional prothrombin to thrombin, forming a tight fibrin hemostatic plug [Novo Nordisk, 2010; Klitgaard and Nielsen, 2008]	Prothrombin complex zymogens present in pd-aPCC; small amounts of thrombin activate prothrombinase complex consisting of prothrombin (FII) and activated FX which generates excess thrombin that triggers a feedback mechanism involving FIX, activated by FXIa and FVIIa, and zymogen FX, activated by FIXa and FVIIa, for coagulation independent of FVIII or FVIIIa [Baxter Healthcare, 2010; Turecek *et al.* 2004]
Storage requirements	Stable at room temperature; reconstituted solution may be stored at room temperature or refrigerated for up to 3 h [Novo Nordisk, 2010; Klitgaard and Nielsen, 2008]	Must be kept refrigerated [Baxter Healthcare, 2010; Turecek *et al.* 2004]
Time to mix	Rapid reconstitution to clear, colorless solution [Novo Nordisk, 2010; Klitgaard and Nielsen, 2008]	Storage vial and diluent must be at room temperature before reconstitution; once diluent added, must be swirled gently until completely dissolved [Baxter Healthcare, 2010; Turecek *et al.* 2004]
Volume of administration	Dependent on dose up to 5.2 ml [Novo Nordisk, 2010; Klitgaard and Nielsen, 2008]	Dependent on dose and kg body weight up to a few hundred ml [Baxter Healthcare, 2010; Turecek *et al.* 2004]
Time to administer	2–5 min as a slow intravenous bolus, depending on dose administered; administer within 3 h after reconstitution [Novo Nordisk, 2010; Klitgaard and Nielsen, 2008]	Maximum infusion rate not to exceed 2 U/kg/min; infusion time dependent on number of units to be administered [Baxter Healthcare, 2010; Turecek *et al.* 2004]
Time to maximum effect	Resolves joint bleeds in ≤5 h [Novo Nordisk, 2010; Klitgaard and Nielsen, 2008]	May involve multiple administrations at 12-h intervals [Baxter Healthcare, 2010; Turecek *et al.* 2004]
Half-life in plasma	2.3 h (range, 1.7–2.7 h) [Novo Nordisk, 2010; Klitgaard and Nielsen, 2008]	4-7 h measured by thrombin generation (TG), peak TG estimated to occur 15-30 min after infusion [Varadi *et al.* 2003; Negrier *et al.* 2006a]; pharmacokinetic data are limited [Baxter Healthcare, 2010; Turecek *et al.* 2004; Franchini and Lippi, 2010]
Dosing interval	90 μg/kg every 2 h until hemostasis is achieved, then posthemostasis every 3–6 h for severe bleeds and surgery; one dose of 90–120 μg/kg or 270 μg/kg is recommended for mild-to-moderate joint bleeds [Novo Nordisk, 2010; Klitgaard and Nielsen, 2008; Young *et al.* 2008b]	A function of type and severity of the bleed; 50–100 U/kg every 6–12 h but limited to a total daily patient exposure of no more than 200 U/kg [Baxter Healthcare, 2010; Turecek *et al.* 2004]

pd-aPCC, plasma-derived activated prothrombin complex concentrate; rFVIIa, recombinant activated factor VII; TF, tissue factor.

generation occurs on the surface of the thrombin-activated platelets that are no longer circulating but are localized to the site of injury, compartmentalizing the hemostatic process. This thrombin burst is mediated by the formation of the FVIIIa–FIXa–FX complex ('tenase-complex') on the negatively charged platelet surface exposed through thrombin activation. This subsequent larger thrombin burst is required for the formation of a tight, well-structured fibrin plug resistant to premature lysis, and thus is required to maintain hemostasis [Hedner and Ezban, 2008]. In patients with hemophilia who lack either FVIII or FIX, no or insufficient 'tenase-complex' is formed on the thrombin-activated platelet surface. As a result, these patients only generate the initial limited amount of thrombin formed by the TF-FVIIa-FXa, a quantity that is insufficient to generate a firm, tight fibrin hemostatic plug. Therefore, patients with hemophilia form loose, bulky, unstable hemostatic plugs that result in surface oozing and rapid dissolution.

The mechanisms by which the two commercially available bypassing agents facilitate hemostasis in patients with hemophilia and inhibitors are different (Table 1). Plasma-derived aPCC (infused as single doses ranging between 50 and 100 U/kg every 6–12 hours not to exceed 200 U/kg/day) is an aPCC-containing vitamin-K-dependent coagulation protein. Prothrombin (factor II) and FXa are purported to be the primary active components (the prothrombinase complex), with other components, including other vitamin-K-dependent proteins, contributing to the overall hemostatic effect [Negrier *et al.* 2006b]. The precise mechanism(s) by which pd-aPCC facilitates hemostasis has not yet been determined but appears to principally involve conversion of prothrombin in the prothrombinase complex (FII–FXa) into thrombin downstream from the point of inhibitor blockade in the coagulation pathway. Thus, pd-aPCC mimics the action of an increased presence of prothrombin combined with sufficient levels of FXa to achieve thrombin generation essential to shortening the time to clot formation and the arrest of bleeding [Turecek *et al.* 2004].

Pharmacologic doses of rFVIIa (ranging from 90 to 300 μg/kg) bind to the activated platelet surface with a low affinity [Franchini and Lippi, 2010; Hoffman and Monroe, 2010; Kenet *et al.* 2003; Monroe *et al.* 1997]. By exploiting this mechanism, thrombin generation on the platelet surface is increased in a dose-dependent manner, although complete normalization does not seem to occur. However, a tight fibrin structure is induced by the addition of rFVIIa, likely representing its core mechanism of action. Thus, pharmacologic doses of rFVIIa enhance thrombin generation on the activated platelet surface and result in a tight fibrin hemostatic plug [Hedner and Ezban, 2008] and bleed resolution, the majority of which occurs within approximately 5 hours [Lusher *et al.* 1998b].

Safety of bypassing agents

Both pd-aPCC and rFVIIa are well tolerated, and adverse events are usually uncommon in inhibitor patients. Owing to their procoagulant actions, both bypassing products have the potential to contribute to the development of thrombosis and thromboembolism (Table 1). For pd-aPCC, the primary adverse event of concern is thrombosis, especially with the administration of doses higher than those recommended (50–100 U/kg every 6–12 hours) or exceeding the daily exposure limit (>200 U/kg/day) and in patients with known cardiovascular risk factors [Gomperts, 2006; Luu and Ewenstein, 2004]. Other adverse events reported for pd-aPCC have included diffuse intravascular coagulation (DIC), injection-site pain, anaphylactic reaction, hypersensitivity, urticaria, hypotension, and hypoesthesia [Baxter Healthcare, 2010]. The overall risk of thrombotic events with pd-aPCC treatment is low, which is supported by pharmacovigilance data analyses reporting incidences of 4.05 and 8.24 per 100,000 infusions, with myocardial infarction (MI) and DIC the most frequent thrombotic adverse events [Aledort, 2004; Ehrlich *et al.* 2002]. The risk of thrombosis with pd-aPCC can be mitigated by prompt recognition of other thrombotic risk factors and adherence to recommended dosing [Ehrlich *et al.* 2002]. An anamnestic inhibitor response due to trace amounts of FVIII has also been reported in 21% of patients with factor VIII deficiency after their first exposure to pd-aPCC; however, this response does not appear to affect efficacy and inhibitor titer reportedly decreases during long-term prophylaxis with pd-aPCC [Hilgartner *et al.* 2003; Kasper, 1979]. In contrast, pd-aPCC contains sufficient factor IX to result in inhibitor anamnesis in patients with factor IX deficiency complicated by inhibitors [Thorland *et al.* 1999; Negrier *et al.* 1997].

Data from clinical trials with rFVIIa in hemophilia patients with inhibitors indicated that thrombotic events associated with its use at a recommended dose (90 μg/kg every 2–3 hours until hemostasis is achieved) had a low incidence of 0.20% [Novo Nordisk, 2010; Abshire and Kenet, 2008]. Other reported adverse events in clinical trials within approved indications have included pyrexia, hypertension or hypotension, injection-site reaction, headache, vomiting, arthralgia, edema, and urticaria. In an analysis of the US Food and Drug Administration's Adverse Event Reporting System database, most of the serious thromboembolic adverse events reported for rFVIIa occurred following its use for unlabeled indications in patients without hemophilia with many experiencing active bleeding [O'Connell *et al.* 2006]. Of 185 thromboembolic events reported, 17 (9.1%) occurred in patients with hemophilia and 151 (81.2%) occurred in patients experiencing bleeds caused by other factors [O'Connell *et al.* 2006]. Stroke, acute MI, other arterial thromboses, and pulmonary embolism were among the most frequently reported thromboembolic adverse events following the use of rFVIIa for unlabeled indications [O'Connell *et al.* 2006]. The authors noted that because this was a case series study performed by passive surveillance a causal link between rFVIIa treatment and the incidence of thromboembolic adverse events could not be established due to the lack of controls for underlying medical conditions that increase thrombotic risk, numerous potential reporting biases, and other limitations [O'Connell *et al.* 2006]. Whether or not the risk of thrombotic complications differs significantly in hemophilia patients treated on label with either pd-aPCC or rFVIIa remains unknown [Tjonnfjord and Holme, 2007]. Unlike pd-aPCC, rFVIIa is a homogeneous product and has not been shown to evoke an anamnestic inhibitor response at any dose studied in clinical trials. For both bypassing agents, the hemostatic responses of patients after treatment are unpredictable due to variability in patient responsiveness. Further, laboratory assays that would be useful for monitoring efficacy or optimizing patient dosing are not yet available [Johansson and Ostrowski, 2010].

Addressing challenges in the treatment of patients with hemophilia with inhibitors

The optimal treatment of patients with hemophilia with inhibitors would be to achieve treatment and outcome goals comparable to those achieved in patients without inhibitors. Key goals for the treatment of hemophilia include: (1) to provide effective treatment for hemorrhagic episodes; (2) to facilitate early initiation of treatment to minimize blood accumulation and its deleterious effects in joints, muscles, and other tissues through home treatment, the availability of treatment drug, and optimal dosing; (3) to provide effective prophylaxis to suppress or minimize hemarthroses, thereby mitigating the development of arthropathy; and (4) to have the ability to perform elective and emergent surgery.

Early treatment initiation

As mentioned previously, individuals with inhibitors commonly experience poorly controlled bleeding episodes that result in increased orthopedic complications. While single doses of pd-aPCC have been shown to effectively treat acute bleeds [Negrier *et al.* 2006b], its use for early treatment of bleeds could be hampered by the time required to infuse this agent (the maximum infusion rate cannot exceed 2 U/kg/min) and the time taken to attain peak hemostatic action and bleed resolution (6–12 hours or longer; Table 1) [Baxter Healthcare, 2010; Tjonnfjord and Holme, 2007]. Another drawback to the use of pd-aPCC for early treatment initiation is the limit on total daily patient exposure (<200 U/kg/day; Table 1) due to concerns with increasing the risk of thrombosis [Baxter Healthcare, 2010; Luu and Ewenstein, 2004]. It is likely that agents with improved portability, and therefore availability, could lead to more efficient treatment and an improvement in bleed control in this population. The importance of early initiation of effective treatment was clearly demonstrated in data from a prospective, observational registry established in 2005. Data reported from the Czech Republic included 15 inhibitor patients treated with rFVIIa for 128 bleeding episodes [Salaj *et al.* 2009]. In patients treated within 2 hours after the appearance of the first symptoms, 5.2% experienced rebleeding, whereas in those treated more than 2 hours after symptom onset, 13.7% experienced rebleeding. When discussing the impact of early treatment on rate of rebleeding, one should also address dosing as a mechanism to achieve early bleed control. Interestingly, in the report of Salaj and colleagues, rebleeding did not occur in patients treated after 2 hours from bleed onset if a dose of >250 μg/kg was utilized as compared with the 15.8% who experienced rebleeding

when a dose of <120 μg/kg was employed. Among the patients given doses of 120–250 μg/kg, 9.1% experienced a rebleed, indicating that an initial higher dose may be important in patients whose treatment is not initiated more than 2 hours after recognition of a bleeding episode. The number of injections required for hemostasis was found to increase as the dose was lowered. As a result, five or more injections were required, with a mean of 663.6 μg/kg of total rFVIIa per bleed, to achieve hemostasis in those patients who received a mean of 99.2 μg/kg of rFVIIa as a first injection. This is in comparison to one injection required in bleeding episodes where a mean first dose of 153.1 μg/kg rFVIIa was employed.

A room temperature stable formulation of rFVIIa (Table 1) was recently made available, an enhancement that improves the potential for early treatment [Novo Nordisk, 2010]. The two rFVIIa formulations were demonstrated to have comparable bioequivalence and pharmacokinetics, including rapid activity (maximal activity 5–10 minutes postdose) [Bysted *et al.* 2007]. The room temperature stable rFVIIa formulation can be stored up to 25°C (77°F) and is supplied in vials of 1, 2, and 5 mg [Novo Nordisk, 2010]. The diluent contains a histidine buffer that allows for rapid dissolution and drug stability up to 3 hours after reconstitution, either refrigerated or at room temperature. Reconstituted room temperature stable rFVIIa also has a higher rFVIIa concentration (1000 μg/ml) than the original formulation (600 μg/ml), and therefore, a smaller infusion volume (1 mg/ml as compared with 0.6 mg/ml, respectively) that can be administered quickly (intravenous bolus over 2–5 minutes). Potentially, both hemostatic efficacy and compliance might be improved with a therapy that supports facilitation of rapid treatment, such as in the case of the room temperature formulation of rFVIIa.

Dose optimization

The reported dosing of pd-aPCC varies based on bleed type and severity. Recommended doses of 50–100 U/kg are typically administered every 6–12 hours (Table 1) [Negrier *et al.* 2006b]. Owing to the potential concern for thrombotic complications, single doses greater than 100 U/kg and total daily cumulative doses greater than 200 U/kg are not recommended [Baxter Healthcare, 2010]. Further investigation of dose optimization for pd-aPCC treatment has not been reported. The recommended dosing for the treatment of acute bleeding episodes with rFVIIa in patients with inhibitors is 90 μg/kg by bolus injection every 2 hours until hemostasis is achieved followed by additional 90 μg/kg doses every 3–6 hours, if needed, to control severe bleeding and bleeding during major surgery, while mild-to-moderate joint bleeds should be treated with a single bolus dose individualized to the patient (Table 1) [Novo Nordisk, 2010]. Dosing regimens and dose optimization have evolved since initial approval and commercialization in the late 1990s.

For both pd-aPCC and rFVIIa, clinical assessment remains the primary method for determining efficacy and the need for additional doses [Negrier *et al.* 2006b]. The concept of utilizing rFVIIa to achieve hemostasis and to compensate for the lack of FVIII or FIX in patients with hemophilia with inhibitors is a relatively recent one. In factor replacement therapy with FVIII or FIX concentrates in noninhibitor patients, dosing can be adjusted by adding FVIII/FIX until the plasma activity reaches a hemostatic level. However, a similar strategy cannot be applied to rFVIIa, as it is not known exactly how much additional FVIIa is required in the circulation to generate a sufficient local quantity of thrombin for the development of a stable, well-structured fibrin hemostatic plug at the site of injury. A method for measuring local thrombin generation is not yet available. Global hemostatic assays such as the prothrombin time and activated partial thromboplastin time are not useful for monitoring rFVIIa therapy, as results do not correlate with clinical outcomes [Key and Nelsestuen, 2004]. It has been suggested that whole blood assays that are able to capture platelet–clotting protein interactions could provide an improved assessment of rFVIIa activity [Key and Nelsestuen, 2004]; however, whole blood thrombin generation assays have not fulfilled this initial promise. Evaluations of these measures have demonstrated significant interpatient and intrapatient variability that limit the ability of these methods to accurately predict a comparable dose response in the clinical setting [Kenet *et al.* 2010; Young *et al.* 2008a].

Key issues in determining the optimal dosing of rFVIIa have been reported to include wide interindividual variation in (1) recovery (plasma level of FVII:C 10 minutes after injection), a well-known characteristic of

vitamin-K-dependent coagulation proteins [Hedner and Erhardtsen, 2003]; (2) clearance rates, especially in children younger than 15 years (where it may be up to three times faster than in adults) [Fridberg *et al.* 2005; Villar *et al.* 2004; Lindley *et al.* 1994], those with cirrhosis with upper gastrointestinal bleeding [Klitgaard and Nielsen, 2008], and in trauma patients with severe bleeding [Klitgaard *et al.* 2006]; and (3) the capacity of thrombin generation on the preactivated platelet surface [Sumner *et al.* 1996]. The initial dosing schedule for rFVIIa in inhibitor patients was based on extrapolation from *in vitro* measurements and dog studies [Hedner *et al.* 1990; Brinkhous *et al.* 1989], and led to the recommended dosing of 90–120 μg/kg, repeated every second hour in surgery or serious hemorrhage for at least 24 hours [Rodriguez-Merchan *et al.* 2004; Hedner and Ingerslev, 1998; Shapiro *et al.* 1998]. In a home treatment study, most participants were found to require more than one dose of 90 μg/kg (mean, 2.2 doses) to achieve hemostasis in mild-to-moderate bleeding episodes indicating that these individuals required doses higher than 90 μg/kg for optimal hemostasis [Key *et al.* 1998].

Optimal hemostasis is best achieved with a single dose, both for convenience but, above all, to minimize damage from accumulated blood. The first patient in whom it was demonstrated that a large dose of rFVIIa (320 μg/kg) administered as one single bolus induced hemostasis in mild-to-moderate joint or muscle bleedings was a 13-year-old boy with hemophilia B and inhibitors found to have a high clearance rate [Cooper *et al.* 2001]. Based on this observation, the administration of a single large dose of rFVIIa (270 μg/kg) corresponding to three separate 90 μg/kg doses, was evaluated in two multicenter, randomized, double-blind, crossover clinical trials [Young *et al.* 2008b; Kavakli *et al.* 2006]. These studies demonstrated a similar effect regardless of whether rFVIIa was given as a single dose of 270 μg/kg or as three injections of 90 μg/kg. Measured as the percentage of patients requiring rescue medication, the efficacy was 90.5% (270 μg/kg) and 85.7% (90 μg/kg for three doses) in the study of Kavakli and colleagues [Kavakli *et al.* 2006]. In the study of Young and colleagues, corresponding efficacy rates were 91.7% and 90.9%, respectively [Young *et al.* 2008b]. No safety issues were observed in these studies. A third study comparing a bolus dose of 270 μg/kg with 90 μg/kg for three doses observed full and partial effect 9 hours after initiating treatment in 81% of those receiving the 270 μg/kg dose and in 90% of those receiving three doses of 90 μg/kg [Santagostino *et al.* 2006]. These data have led to the European Medicines Agency approval of the use of a single injection of 270 μg/kg or two to three injections of 90 μg/kg for mild-to-moderate bleeding episodes. The use of single, high-dose injections is not approved in the United States.

Prophylaxis

The first prospective, multicenter, randomized, double-blind trial to evaluate prophylaxis with bypassing products studied the use of rFVIIa given in daily doses of 90 μg/kg or 270 μg/kg for 3 months following an observation period of 3 months. After the daily administration of rFVIIa was discontinued, the patients were followed for a subsequent 3 months. The number of bleeding episodes was more than five per month during the initial observation time and decreased significantly ($p < 0.0001$) during the treatment period for both dose levels. Interestingly, the number of bleeding events did not achieve the pretreatment values, but stayed significantly decreased ($p < 0.0001$) during the posttreatment 3-month observation period [Konkle *et al.* 2007]. Furthermore, hospitalization and absenteeism from school or work decreased during prophylaxis (from 13.5% to 5.9%, $p = 0.0026$; and from 38.7% to 16.7%, $p = 0.0127$; respectively [two dose groups pooled]). These reductions tended to be maintained during the postprophylaxis observation period. Also, pain decreased in 40.9% of the patients and mobility increased in 27.3% during the postprophylaxis observation period [Hoots *et al.* 2008]. These findings suggest that secondary prophylaxis with rFVIIa may improve patient health-related quality of life in patients with inhibitors who have frequent bleeding episodes.

Data evaluating the use of pd-aPCC for prophylaxis in patients with inhibitors has, until recently, been more limited, consisting of results obtained with a total of 12 inhibitor patients participating in two clinical trials [Hilgartner *et al.* 2003; Kreuz *et al.* 2000]. The first was a prospective study conducted in five pediatric patients with high-responding inhibitors who had previously failed immune tolerance induction [Kreuz *et al.* 2000]. Long-term pd-aPCC administration (50–100 U/kg two or three times weekly for 0.7–12.3 years) in these patients was reportedly safe and well

tolerated. Joint bleeds were 'infrequent' and changes in arthropathy were mild or absent during the treatment period. The second was a retrospective analysis of data from seven patients with severe FVIII deficiency and high inhibitor titers treated with pd-aPCC 50 to 100 U/kg 3–4 times weekly for 3–6.5 years [Hilgartner *et al.* 2003]. Despite prophylactic therapy, arthropathy progressed in all patients, with five developing synovitis and four developing new target joints during treatment. Two of these patients did, however, demonstrate functional improvement.

A recent meta-analysis of six clinical studies involving 34 patients with inhibitors showed that a prophylactic dose (mean dose, 78.5 U/kg) of pd-aPCC infused three to four times per week reduced bleeding episodes by an average of 63.9% irrespective of the type of hemorrhage reported [Valentino, 2010]. A total of 18 patients in three of the studies analyzed were assessed for the prevention of joint bleeds and reported a 74% reduction in the annual number of these events with pd-aPCC prophylaxis. There were no reports of thrombotic complications and while inhibitor anamnesis occurred in some patients, it did not compromise pd-aPCC efficacy. Results from the Pro-FEIBA study evaluating pd-aPCC prophylactic efficacy in a prospective controlled trial have been reported recently [Leissinger *et al.* 2010]. Prophylactic treatment with pd-aPCC at a dose of 85 U/kg administered three times per week in 26 patients with hemophilia A and inhibitors achieved a 62% reduction in bleeds of all types and 61% in joint bleeds *versus* on-demand treatment.

Surgery

In the past, elective surgery in hemophilia patients with inhibitors was avoided due to the risk of uncontrollable bleeding. In the early 1970s, doses of replacement FVIII/FIX sufficient to neutralize the presence of the inhibitor and increase the plasma activity of FVIII/FIX to hemostatic levels were utilized for emergent interventions when the inhibitor titer was sufficiently low to allow this treatment approach. In addition, the use of cytotoxic agents was introduced when treating serious hemorrhagic episodes and/or to cover essential surgery when this approach was utilized to minimize the anamnestic inhibitor response [Hedner *et al.* 1982; Nilsson and Hedner, 1976; Nilsson *et al.* 1973; Green, 1971]. Patients with high inhibitor titers also may have required additional measures such as extracorporeal adsorption to decrease the inhibitor titer to a level that could be neutralized by the administration of exogenous FVIII/FIX concentrates [Hedner *et al.* 1982; Nilsson *et al.* 1981]. Although intermittently useful, these therapies were not without risk and were not uniformly successful [Nilsson *et al.* 1981, 1973; Nilsson and Hedner, 1976; Green, 1971].

Tjonnfjord and colleagues reported a low risk of bleeding complications in patients with FVIII/FIX inhibitors undergoing minor and major elective surgeries after being given a pd-aPCC preoperative loading dose of 100 U/kg followed by postoperative 200 U/kg/day divided into 3 doses given every 8 hours for 3 days then tapered to 150–100 U/kg/day thereafter [Tjonnfjord, 2004; Tjonnfjord *et al.* 2004]. While hemostatic efficacy was rated as good following three of six major surgeries, three patients did have postoperative bleeding complications including one who suffered a MI 3 days after undergoing a sigmoidectomy [Tjonnfjord *et al.* 2004]. However, insufficient hemostasis and signs of a systemic activation of the coagulation system in addition to resultant sequelae, including myocardial infarction, cerebral stroke, and DIC, have been observed in inhibitor patients receiving bypassing therapy with pd-PCC or pd-aPCC, especially in those undergoing major surgery, thereby limiting its use in this setting [Tjonnfjord, 2004; Hedner and Nilsson, 1983; Nilsson *et al.* 1981].

rFVIIa has been used successfully in major surgery, including bilateral hip and knee arthroplasty, with efficacy rates ranging from 88% to 97% [Ludlam *et al.* 2003; Shapiro *et al.* 1998; Ingerslev *et al.* 1996], and its use between 2002 and 2006 was recently reviewed and included 80 orthopedic procedures [Obergfell *et al.* 2008]. Notably, systemic activation of the coagulation system was not reported. A hemostatic agent capable of providing reliable hemostatic coverage for performing major orthopedic surgery in severe hemophilia with inhibitors may also be considered to be a useful therapy for other hemorrhagic episodes [Hedner and Ingerslev, 1998; Lusher *et al.* 1998a].

Discussion and conclusions

In the past, treatment results have been less than optimal for individuals with hemophilia and inhibitors, resulting in increased orthopedic complications and poorer quality of life and overall outcomes relative to patients without inhibitors.

This fact is strongly supported by data obtained from cohorts of male hemophilia patients enrolled in the Centers for Disease Control and Prevention–Universal Data Collection Project which showed that inhibitors, age, non-White race, body mass index (all $p < 0.001$), and orthopedic procedures ($p = 0.02$) were independently associated with loss of joint range of motion in patients with severe disease [Kempton *et al.* 2006; Soucie *et al.* 2004].

In contrast to hemophilia patients without inhibitors whose acute bleeding episodes and/or prophylactic therapy can be suitably managed with FVIII/FIX replacement therapy, the administration of FVIII/FIX concentrates is commonly ineffective, resulting in an ongoing tendency to bleed. This inability to control bleeding episodes effectively results in significant care gaps, leading to poorer patient outcomes compared with patients without inhibitors. These care gaps include progressive deterioration of orthopedic status and mobility, increased risk for serious bleeding complications into muscular and soft tissues, and increased risk for postoperative bleeding complications. The availability of bypassing agents has substantially improved the care of hemophilia patients with inhibitors and served to narrow these care gaps between inhibitor and noninhibitor patients by providing an effective means to overcome the inhibitor-mediated coagulation blockade.

Surgeries and procedures were previously not considered feasible or were rarely undertaken in patients with inhibitors, but the availability of pd-aPCC and rFVIIa have allowed patients with inhibitors increased access to both elective and major surgeries and invasive diagnostic and therapeutic procedures by preventing bleeding during and after surgery. In addition, rFVIIa has specific attributes that are supportive for achieving early and rapid bleed resolution in this population. For example, rFVIIa has a rapid onset of activity (maximal onset within 5–10 minutes of administration); many bleeding events treated with rFVIIa resolve rapidly, often within 5 hours. The availability of a room temperature stable rFVIIa formulation facilitates early treatment due to the convenience of nonrefrigerated medication; it dissolves easily and represents a small injection volume, both serving to improve the treatment of bleeding episodes. Promising results regarding the use of secondary prophylaxis in patients with hemophilia with inhibitors utilizing rFVIIa have been reported. Through the minimization of joint and/or muscle damage associated with repeated prolonged bleeding episodes, effective secondary prophylaxis could potentially mitigate the development of arthropathy in this vulnerable population. In order to optimize therapy, one must individualize treatment by considering the patient, the specific bleeding event, and/or procedure in order to choose the most appropriate therapeutic agent.

In conclusion, bypassing agents have greatly advanced the care of individuals with hemophilia with inhibitors, providing effective treatment in serious hemorrhagic episodes. Both pd-aPCC and rFVIIa have been used successfully in the home-based treatment setting, as well as in long-term prophylaxis. Further, the efficacy of rFVIIa has been demonstrated in prospective trials in patients undergoing major orthopedic surgery. The advent of a room-temperature stable formulation of rFVIIa has provided a more portable therapeutic option that may further facilitate efficient hemostasis in patients with inhibitors.

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Conflict of interest statement

Dr Hedner was previously employed by, and owns stock in, Novo Nordisk A/S, the manufacturer of rFVIIa (NovoSeven), Research and Development; and is currently consulting for Novo Nordisk A/S. Dr Shapiro has received reimbursement for attending symposia, funding for research, and fees for consulting from Novo Nordisk.

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