Factor eight inhibitor bypass activity (FEIBA) in the management of bleeds in hemophilia patients with high-titer inhibitors

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Abstract: The development of high-titer inhibitors to FVIII and less often to other coagulation factors are the most serious complication of hemophilia therapy and makes treatment of bleeds very challenging. At present, bypassing agents, such as factor eight inhibitor bypass activity (FEIBA) and activated recombinant factor VII (rFVIIa) are the only coagulation factor concentrates available for the treatment of bleeds in inhibitor patients. Both products are effective and safe, and their efficacy has been found to be comparable (approximately 80%) in a recent prospective study. A significant number of patients report a better effect of one or the other of the products, and in a minority of the patients none of the products are particularly effective. The hemostatic efficacy of bypassing agents is not considered equal to that of coagulation factor replacement in patients without inhibitors by most physicians. An improvement in hemostatic efficacy may be achieved by optimizing the dosing of by passing agents. However, the lack of standardized and validated laboratory assays reflecting the hemostatic efficacy of the bypassing agents is an obstacle to this achievement.

Keywords: hemophilia, inhibitors, bleeds, bypassing agents

Introduction

The risk of blood-borne pathogens in coagulation factor concentrates has been virtually eliminated by the introduction of effective virus inactivation procedures for plasma-derived concentrates and the development of recombinant factor concentrates. At present, the development of inhibitors is the most serious complication to the use of these concentrates in hemophilia care, and patients with inhibitors represent a major therapeutic challenge. Inhibitors develop in 20–30% of patients with severe hemophilia A [factor (F) VIII levels <1%] and in 5% or less of patients with severe hemophilia B (FIX levels <1%) (Scharrer et al 1999; Wight and Paisly 2003; UK Haemophilia Center Doctors' Organization (UKHCDO) 2004). Inhibitors may occasionally also develop in patients with mild or moderate hemophilia. Inhibitors are inhibiting or neutralizing alloantibodies to FVIII/FIX which usually develop after 10–20 exposures to FVIII/FIX concentrates. Inhibitors may be transient or resolve with immune tolerance therapy (ITI), but in 10–15% of hemophilia A patients inhibitors remain clinically significant (high-titer). ITI is far less successful in managing FIX inhibitors than FVIII inhibitors (Key 2004).

Inhibitors to FVIII/FIX preclude the use of standard and effective factor concentrates. Although bleeds do not occur more frequently than in non-inhibitor patients, the bleeds may be much more difficult to control, and the presence of inhibitors increases the risk of uncontrollable bleeding, disability and premature death (Triemstra et al 1995; UK Haemophilia Center Doctors' Organization [UKHCDO] 2004). Progressive and

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disabling joint disease is more prevalent in inhibitor patients than in non-inhibitor patients (Leissinger et al 2001).

Acquired hemophilia is a rare condition characterized by the development of neutralizing or inactivating autoantibodies to FVIII in patients with previously normal FVIII levels. An incidence of 0.2–1 patient per million persons per year has been reported (Shapiro and Hultin 1975; Lottenberg et al 1987; Holme et al 2005). The disease usually develops late in life, and it is associated with high morbidity (life-threatening bleeds in more than 85% of patients) and high mortality varying from 8% to 22% (Green and Lechner 1981; Hay et al 1997; Delgado et al 2003). Although the clinical phenotype of acquired hemophilia differs from that of congenital hemophilia, managing bleeds poses more or less the same challenges to the clinician.

Inhibitors are measured with the Bethesda assay or its modifications, and titers are expressed in Bethesda units (BU).

The development of inhibitors is the most pressing concern in hemophilia care to day, and there is great interest in methods to reduce the risk of inhibitor development, improve on immune tolerance therapy regimens, treat bleeds, provide hemostasis during surgery and develop effective laboratory methods to assess bypassing therapy. In this review we will focus on the management of bleeds and the prevention of chronic joint disease.

Treatment of bleeds

Apart from the severity and location of the bleed, the characteristics of the inhibitor are the most important factors to consider in the management of a bleeding episode in a particular patient. Treatment options are dependent on the inhibitor titer as well as whether the inhibitor is low or high responding. Knowledge of the patient's previous response to specific therapies also provides important information selecting the best hemostatic therapy. Approximately 70% of the inhibitors in hemophilia A patients are due to high-responding antibodies which show a substantial rise in titer (5 BU or higher) within 4–6 days of exposure to FVIII (anamnestic response). In hemophilia B more than 80% are of the high responder type. Low-responding inhibitors (generally <5 BU) are not anamnestic, and they are much more likely to be transient. A bleed in a low-titer, low-responder patient can usually be treated by standard factor concentrates, but much higher doses than in non-inhibitor patients have to be used to overcome the inhibitor. In general, standard factor concentrates, even in higher doses, are not effective in patients with high-titer inhibitors. Hemostatic agents with proven efficacy in the treatment of bleeds in inhibitor patients are presented in Table 1. However, only bypassing agents are currently available. Prothombin complex concentrates (PCCs) and activated prothrombin complex concentrates (aPCCs), plasma-derived products containing FII, FVII, FIX, FX and small amounts of FVIII, have been available for the treatment of inhibitor patients for more than 30 years. aPCCs, in contrast to PCCs, contain activated FVII and small amounts of activated FII, FIX and FX. PCCs have been shown to be less effective than aPCCs and to show a higher rate of adverse reaction (Sjamsoedin et al 1981; Lusher et al 1983; Negrier et al 1997). Currently, PCCs are seldom used to treat inhibitor patients. In the 1990s, recombinant activated FVII (rFVIIa) concentrate were introduced for treatment of inhibitor patients. In clinical trials both aPCCs (factor right inhibitor bypass activity, [FEIBA]; Baxter AG, Vienna, Austria) and rFVIIa (NovoSeven, Novo Nordisk AS, Bagsværd, Denmark) have shown excellent efficacy (80–90%) in the management of bleeding in inhibitor patients (Hilgartner et al 1990; Key et al 1998). The hemostatic actions of these agents are different and still not fully unraveled. Nevertheless, both products appear effective, safe and well tolerated, but clinical evidence from randomized, prospective trials comparing the two agents as a guide to their optimal use in inhibitor patients are still lacking. There are ongoing studies addressing this issue, but the final reports are still pending.

The FENOC (The FEIBA versus NovoSeven Comparative Study) study compared the hemostatic effect of FEIBA on joint hemorrhages with that of rFVIIa. The main objective was to compare the efficacy of a single dose of FEIBA (target dose, 85 IU/kg bw) with two doses of rFVIIa (target dose, 105 μg/kg bw), and enrollment was stopped in December 2004. Preliminary results show that the treatment was effective in 80.9% and 78.7% of the patients with FEIBA and rFVIIa, respectively (Astermark et al 2007). The study also show that a significant number of patients report a better effect of one or the other of the products. A second study is addressing whether a single high dose (270 μg/kg) of rFVIIa is more effective than the currently approved dosing (90 μg/kg for 3 doses). Data from uncontrolled trials suggest that higher doses of rFVIIa are more effective than standard dose (Kenet et al 2003; Seremetis 2003). The results from the prospective, randomized study are pending.

Some patients do not respond well to either FEIBA or rFVIIa. The combined use of FEIBA and rFVIIa has been put forward as an approach for bleeds that are refractory to either agent alone (Key et al 2002). A recent case report on the use

Table 1 Coagulation factor concentrates with proven efficacy in hemophilia patients with high-titer inhibitors

Factor concentrate	Advantage	Disadvantage	Comments
Porcine (p) FVIII	Measurable FVIII levels	Inhibitors often show cross-reactivity with pFVIII or the patients develop pFVIII after 5–10 days of treatment Risk of transmission of porcine viruses	Plasma derived pFVIII are presently not available A recombinant pFVIII concentrate is in clinical development
PPCs	Bypass the need for FVIII Relatively inexpensive	Inferior efficacy compared to aPCCs Potentially thrombogenic High frequency of infusion related adverse events	aPCCs have supplanted the use of PCCs
aPCCs	Long history of use Efficacy of 80–90% in clinical trials Long-half life compared to rFVIIa More effective than PCCs Cost advantage over rFVIIa	Unpredictable hemostatic response Potentially thrombogenic Trace amounts of FVIII leading to anamnesis of the inhibitor Possibility of transmission of human viruses No established laboratory assay to monitor efficacy and optimal dosing	The risk of thrombotic complications with standard doses is low Increase in inhibitor titer does not hamper efficacy
rFVIIa	Efficacy in 80–90% in clinical trials No anamnestic response No risk of transmission of human viruses	Unpredictable hemostatic response Potentially thrombogeneic No established laboratory assay to monitor efficacy and optimal dosing Short half-life making rFVIIa less convenient than aPCCs	The risk of thrombotic complications is low Whether the risk of thrombotic complications differ significantly between aPCCs and rFVIIa is an unresolved issue

of sequential therapy with FEIBA and rFVIIa demonstrated the efficacy and safety of this approach (Schneiderman et al 2004). However, the issue of concomitant use of FEIBA and rFVIIa is a matter of dispute among hematologists (Allen and Aledort 2006).

Several clinical features distinguish FIX inhibitors from FVIII inhibitors. With respect to treatment of bleeds, anaphylaxis or anaphylactoid reactions to FIX-containing concentrates are, although rare, the most important feature in terms of morbidity. A history of anaphylaxis to FIX-containing concentrates was recently shown in a majority of hemophilia B patients with high-titer inhibitors, and rFVIIa seems to be a suitable treatment of choice in these patients (Warrier 2003; Key 2004).

Prophylaxis

In non-inhibitor patients prophylactic treatment with coagulation factor concentrates prevents bleeding and resultant joint damage (Nilsson et al 1992; Funck et al 1998; Kreuz et al 1998). Currently, prophylaxis from early childhood to prevent end-stage joint disease is recommended in most western countries. Inhibitor patients have an even greater probability of developing disabling joint disease than non-inhibitor patients (Leissinger et al 2001). Accordingly, the possibility of prophylaxis with bypassing agents in inhibitor patients is a matter of concern for the hemophilia community. Several small studies suggest that daily or every-other-day doses of FEIBA of less than 100 IU/kg/day are safe (Leissinger 1999; Kreuz et al 2000a, 2000b; Ehrlich et al 2002; Valentino and Salit 2002; Hilgartner et al 2003; Ehrlich et al 2002). The studies show a reduction in the number of annual bleeds, but the results regarding the prevention of progressive joint damage are equivocal (Hilgartner et al 2003). There are two reports describing prophylaxis with rFVIIa in three patients resulting in reduction in severe bleeds and reduced hospitalizations (Saxon et al 2001; Young et al 2005). At present, a recommendation of prophylaxis with bypassing agents in inhibitor patients is not supported by solid clinical evidence. There is an on-going study evaluating the efficacy of FEIBA for prophylaxis in inhibitor patients (PRO-FEIBA study). The primary objective of the trial, which has a cross-over design, is >50% reduction in the number of bleeds during a 6-month period with prophylaxis compared to on-demand therapy.

Monitoring therapeutic efficacy

There is no generally accepted laboratory assay to monitor efficacy or determine an optimal dose of the bypassing agents (Leissinger 2004; Mathew 2006). However, both thromboelastography (TEG) and thrombin generation assay (TGA) may provide some guidance in the treatment of the individual patient. Using these assays it is clearly demonstrated that the ex vivo responses to both bypassing agents are dose-dependent (Ingerslev et al 2003; Turecek et al 2003; Sørensen et al 2004). It is well appreciated

that there is a considerable variation in clinical phenotype among patients with severe hemophilia, and this is reflected by a variation in the results of in vitro testing of hemostatic intervention (Ingerslev et al 2003). A good in vitro response to rFVIIa usually predicts a similar response to FEIBA, but discrepancies are observed in some patients (Ingerslev et al 2003; Sørensen et al 2004). One of our inhibitor patients failed post-surgical prophylaxis with FEIBA following a total knee arthroplasty. He was successfully rescued by rFVIIa. Ahead of a scheduled arthroplasty of the other knee, we have performed in vitro testing of the hemostatic efficacy of FEIBA and rFVIIa by TEG in collaboration with Sørensen and Ingerslev (Center for Haemophilia and Thrombosis, Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark). rFVIIa corresponding to a 100 μg/kg dose normalized the patient's clotting profile. FEIBA corresponding to a 100 IU/kg dose did not normalize the patient's clotting profile, but the clotting profile was normalized by increasing FEIBA corresponding to a 200 IU/kg dose. In the post-surgical prophylaxis setting this would result in a daily dose of FEIBA high above the maximum recommended dose (200 IU/kg/day). Dargaud et al have recently used the TGA to tailor the hemostatic treatment during major surgery in an inhibitor patient in whom rFVIIa was ineffective treating muscle and joint bleeds (Dargaud et al 2005).

FEIBA: mode of action

Testing plasmas deficient in different coagulation factors using TGA, Turecek et al showed that FEIBA improves thrombin generation in all plasmas, except FV-deficient plasma (Turecek et al 1999, 2003). Similar results were accomplished by a complex consisting of activated FX and prothrombin indicating that FXa and prothrombin are the constituents of FEIBA providing the hemostatic efficacy (Turecek et al 1999, 2003).

Adverse effects

FEIBA is usually well tolerated. Infusion-related adverse events like fever, hives and bronchial spasms are rare (<0,04%) (Dimichele and Negrier 2006). FEIBA contains trace amounts of FVIII which may produce an anamnestic response. The first report on this phenomenon appeared in 1977 (Preston et al 1977). Kasper reported a rise in inhibitor level to at least twice the pretreatment value in 21% of patients following the first exposure of prothrombin complex concentrates, and the proportion of patients who mounted an anamnestic response decreased with the number of exposures (Kasper 1979). An anamnestic response to FVIII does not seem to influence the efficacy of FEIBA, and Hilgartner et al reported more recently that the inhibitor titre decreased during long-term FEIBA prophylaxis (Hilgartner et al 2003). FEIBA is a vapour-heated plasma-derived coagulation factor concentrate and a potential for viral transmission exists. Today, no confirmed reports of human immunodeficiency virus, hepatitis A, hepatitis B or hepatitis C transmission have been published.

FEIBA as well as rFVIIa have been associated with thromboembolic complications and disseminated intravascular coagulation (DIC). The most serious complications are myocardial infarction and cerebral infarction. These are rare events associated with large and repeated doses that in most cases exceeded the recommended doses (Ehrlich et al 2002). There is an on-going dispute whether the risk of thromboembolic complications differs between FEIBA and rFVIIa (Aledort 2004; Makris and Veen 2005; Sallah et al 2005).

Conclusion

The development of high-titer inhibitors to FVIII and less often to other coagulation factors makes treatment of patients with severe bleeding disorders difficult. Although bypassing agents, such as FEIBA and rFVIIa, are effective and safe in controlling bleeding in inhibitor patients, their efficacy is not considered equal to that of coagulation factor replacement in patients without inhibitors. Improvements of hemostatic therapies for inhibitor patients are warranted. Patients with high-titer inhibitors are prone to serious bleeding episodes and development of debilitating joint disease, and many physicians still are reluctant to perform surgery in these patients.

Conflict of interest

Dr. Tjønnfjord is an honoraria recipient of both Baxter Healthcare Corporation and NovoNordisk A/S

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