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Recombinant Factor VIIa (Eptacog Alfa)

A Review of its Use in Congenital Hemophilia with Inhibitors, Acquired Hemophilia, and Other Congenital Bleeding Disorders

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Data Selection

Data Selection Sources: Medical literature published in any language since 1980 on 'eptacog alfa', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE search terms were ('eptacog alfa' or 'recombinant factor VIIa' or 'rFVIIa') and 'hemophilia'. EMBASE search terms were ('eptacog alfa' or 'rFVIIa') and 'haemophilia'. AdisBase search terms were ('eptacog alfa' or 'recombinant factor VIIa' or 'rFactor VIIa') and 'haemophilia'. Searches were last updated 24 Feb 2008.

Selection: Studies in patients with congenital or acquired hemophilia, congenital factor VII deficiency, or Glanzmann's thrombasthenia who received recombinant factor VIIa (eptacog alfa). Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Recombinant factor VIIa, eptacog alfa, hemophilia, factor VII deficiency, Glanzmann's thrombasthenia, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability, pharmacoeconomics.

Contents

Summary

Abstract

Recombinant factor VIIa (NovoSeven®; also known as recombinant activated factor VII or eptacog alfa) is structurally similar to human plasma-derived coagulation factor VIIa, but is manufactured using DNA biotechnology. Recombinant factor VIIa interacts with thrombin-activated platelets to produce a thrombin burst leading to accelerated fibrin clot formation localized to the site of vascular injury. It is approved in many countries for use as an intravenous hemostatic agent in patients with congenital hemophilia with inhibitors, and also for acquired hemophilia, factor VII deficiency, and Glanzmann thrombasthenia in some countries.

Studies have shown it to be effective and generally well tolerated when used intravenously to treat bleeding episodes or provide hemostatic cover during surgery in patients with congenital hemophilia with inhibitors, acquired hemophilia, factor VII deficiency or Glanzmann thrombasthenia. Based on available data, its efficacy in terms of patient-assessed response may be similar to that of activated prothrombin complex concentrate (aPCC), but treatment with a single 270 μg/kg dose of recombinant factor VIIa might reduce the need for rescue therapy compared with aPCC. Recombinant factor VIIa is not immunogenic in patients with hemophilia, does not produce an anamnestic response in hemophilia patients with inhibitors, and has very low thrombogenicity. It is recommended in guidelines as the treatment of choice for bleeds in patients with hemophilia B with high-responding inhibitors and for patients with factor VII deficiency, and is also a first-line therapeutic option for high-responder hemophilia A patients with inhibitors and those with acquired hemophilia. Cost data from pharmacoeconomic analyses support its use in hemophilia patients with inhibitors. Thus, recombinant factor VIIa is a valuable treatment option for patients with these rare, but potentially serious, bleeding disorders.

Pharmacologic Properties

Recombinant factor VIIa is a recombinant protein, similar in structure to coagulation factor VIIa derived from human plasma, but manufactured without using material of human origin. It has effects on both tissue factor-dependent and -independent coagulation. In particular, at pharmacologic concentrations, its main effect is to enhance thrombin generation on the surface of activated platelets, even in the absence of factors VIII and IX, which are deficient in patients with congenital hemophilia A and B, respectively. The thrombin induced by recombinant factor VIIa enhances platelet activation, fibrin formation, and inhibition of fibrinolysis. The effects of recombinant factor VIIa are localized to the site of vascular injury and it does not appear to enhance systemic activation of coagulation. Thrombotic events have been reported rarely. Antibodies to recombinant factor VIIa generally do not develop in patients with hemophilia, although there have been a few reports in patients with factor VII deficiency.

Following a single intravenous dose of recombinant factor VIIa in patients with hemophilia, the area under the plasma concentration-time curve generally increased in a dose-dependent fashion. Volume of distribution at steady state, clearance, elimination half-life, and mean residence time were generally independent of dose in patients with hemophilia. Values for clearance were higher in pediatric patients than in adults with hemophilia, and were also higher in patients with factor VII deficiency than in adults with hemophilia.

Therapeutic Efficacy

In addition to a number of small controlled trials, therapeutic efficacy data for recombinant factor VIIa come from noncomparative studies, and compassionate- or emergency-use programs. The most widely used dosage in these studies was 90 μg/kg every 2–4 hours in patients with congenital hemophilia with inhibitors, acquired hemophilia or Glanzmann thrombasthenia, and 15–30 μg/kg in patients with congenital factor VII deficiency. Hemostatic efficacy was generally evaluated using a global assessment by the patient or the physician.

Recombinant factor VIIa was effective at controlling mild to moderate bleeding episodes in patients with congenital hemophilia with inhibitors during home treatment in noncomparative studies, with efficacy rates of up to 93% after ≈2 doses. Early treatment was more likely to be associated with a successful outcome than late treatment.

In double-blind or open-label comparative trials in hemophilia patients with inhibitors experiencing hemarthroses, the effectiveness of a single dose of recombinant factor VIIa 270 μg/kg was similar to that of a standard regimen of 90 μg/kg every 3 hours. A single 270 μg/kg dose achieved successful hemostasis in >90% of patients with mild to moderate bleeding episodes after 9 hours without the need for additional hemostatic medication.

Two open-label, crossover studies compared recombinant factor VIIa with aPCC in hemophilia patients with inhibitors. One study failed to demonstrate equivalency between the two treatments, possibly due to inadequate patient/bleed numbers. In the other study, patient-assessed treatment response did not differ significantly between recombinant factor VIIa (single dose of 270 μg/kg or standard regimen of three doses of 90 μg/kg at

3-hour intervals) and aPCC 75 U/kg; however, fewer patients required 'rescue' therapy with additional hemostatic agents after a single 270 μg/kg dose of recombinant factor VIIa than after aPCC.

Based on data largely from the compassionate-use program, recombinant factor VIIa was effective in the treatment of major nonsurgical bleeds (e.g. life- or limb-threatening bleeds), and at producing and maintaining hemostasis during surgery, in patients with hemophilia with inhibitors. In a double-blind controlled trial in hemophilia patients with inhibitors undergoing surgical procedures, satisfactory hemostasis was achieved in 13 out of 14 patients (93%) treated with a standard regimen of recombinant factor VIIa.

Data from a limited number of patients with acquired hemophilia, factor VII deficiency or Glanzmann thrombasthenia (mostly from the compassionate-use programs or patient registries) indicated that recombinant factor VIIa was also effective at treating surgical and nonsurgical bleeding in these patient groups. Efficacy rates were generally consistent with those seen in patients with congenital hemophilia.

Tolerability

Recombinant factor VIIa is generally well tolerated and adverse events do not appear to be dose-related. Non-serious adverse events include nausea, fever, injection-site pain, skin rash and increased values for ALT, alkaline phosphatase and lactate dehydrogenase. The overall incidence of serious adverse events with recombinant factor VIIa is ≈1%. Serious events have included thrombotic events (e.g. myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis, disseminated intravascular coagulation); however, they have generally occurred in patients with predisposing risk factors or in patients without hemophilia being treated for non-approved conditions. Recombinant factor VIIa has no risk for transmission of human pathogens, is not immunogenic, and does not induce an anamnestic response in patients with inhibitors.

Pharmacoeconomic Considerations

On-demand treatment with recombinant factor VIIa was associated with improvements in health-related quality of life relative to plasma-derived agents in a cost-utility study in hemophilia patients with inhibitors. Modelled cost analyses in this patient population found that on-demand treatment of mild to moderate bleeds with recombinant factor VIIa was cost neutral or cost saving relative to aPCC. Modelled cost analyses also showed that orthopedic surgery using recombinant factor VIIa to maintain hemostasis was generally cost saving over the medium to long term relative to not having surgery. Modelled analyses were performed from the healthcare payer perspective.

1. Introduction

Congenital hemophilia A and B (deficiency of coagulation factor VIII or IX, respectively), acquired hemophilia, congenital factor VII deficiency and Glanzmann thrombasthenia are all rare disorders. The estimated prevalence in the general population ranges from 1 in 10 000 for hemophilia A to 1 in 1 000 000 for acquired hemophilia and Glanzmann thrombasthenia.[1-4] In congenital hemophilia, bleeding into joints and muscles predominates,[1] whereas in factor VII deficiency and Glanzmann thrombasthenia, mucosal bleeding is more common.[4,5] Bleeding after surgery and dental procedures is seen with all of the disorders.[1,4,5] In addition to the acute effects of bleeds, which can be life-threatening in severe episodes, severe congenital hemophilia can be associated with chronic complications such as disabling arthropathy from recurrent hemarthroses.[6]

Treatment of bleeding disorders using blood products has improved the prognosis of patients.[7] However, there is a risk of immunologic or allergic reactions, thrombogenicity or infection transmission with some agents.[8] The development of inhibitor antibodies to coagulation factors VIII or IX can lead to resistance to clotting factor replacement therapy, and so complicate treatment.[6,9] Two agents have been developed that can be used to treat patients with hemophilia with inhibitors or acquired hemophilia; they consist of recombinant factor VIIa[10] and the activated prothrombin complex concentrate (aPCC) known as factor eight inhibitor bypassing activity (FEIBA).[7] Unlike recombinant factor VIIa, aPCC is prepared from human plasma and, therefore, has some potential to transmit human infectious agents, despite precautionary measures.[7]

Recombinant factor VIIa (NovoSeven®)[1] [also known as recombinant activated factor VII or eptacog alfa] is a hemostatic agent approved for use in the treatment of several bleeding disorders, including congenital hemophilia A or B with inhibitors, acquired hemophilia, congenital factor VII deficiency, and Glanzmann thrombasthenia (with antibodies to glycoprotein [GP] IIb/IIIa and/or human leukocyte antigens [HLA], and refractory to platelet transfusions).[11,12] This article reviews the pharmacology, therapeutic efficacy and tolerability of intravenous recombinant factor VIIa in patients with these bleeding disorders.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table I. Pharmacodynamic properties of recombinant factor VIIa

Mechanism of action
As the concentration of rFVIIa increased, the rate and peak of thrombin generation increased, and the time to peak thrombin generation decreased, in an *in vitro* model of hemophilia.[18] However, rFVIIa did not restore normal levels of thrombin generation,[18,19] although platelet activation became more rapid[19]
In the presence of limited levels of TF, rFVIIa overcame the inhibitory effect of factor VII on FVIIa/TF-initiated thrombin generation which is seen at physiologic ratios of FVII to FVIIa in an *in vitro* model of hemophilia A[20]
In an *in vitro* model of hemophilia B or 'acquired' hemophilia B, the combination of TF, rFVIIa and 3–5 × normal platelet levels restored thrombin to near-normal levels, suggesting that the accumulation of activated platelets at the site of vascular injury would enhance rFVIIa-associated thrombin formation[16]
At pharmacologic concentrations, rFVIIa did not increase thrombin generation in the absence of TF, but did activate platelets, in an *in vitro* hemophilia model.[19] Results suggest that rFVIIa would likely only initiate thrombin generation at the site of a vascular lesion[21]
rFVIIa bound with low affinity to activated platelets, and at high concentrations led to activation of factor X, in the absence of TF and factors VIII or IX, in an *in vitro* model of coagulation[22,23]
rFVIIa-mediated thrombin generation enhanced platelet activation, the exposure of phospholipids, and increased platelet adhesion, in models of normal and platelet-deficient blood[24]
rFVIIa improved clot structure, and improved the rate of clot formation during a fibrinolytic challenge, in an *in vitro* model of hemophilia[25]
rFVIIa normalized fibrin clot permeability *in vitro* and led to a tighter fibrin network in factor VIII- or IX-deficient plasma containing platelets[26]
In factor VIII-[27,28] and IX[28]-deficient plasma, rFVIIa inhibited fibrinolysis by activating thrombin-activatable fibrinolysis inhibitor
Thrombin generation was induced *in vitro* by rFVIIa in plasma that was deficient in factors VIII and IX, provided TF and phospholipids were present. The effect of rFVIIa was increased by the presence of even minute amounts of factors VIII or IX[29]
rFVIIa enhanced fibrin formation at the site of vascular damage in a model of Glanzmann thrombasthenia[30]
rFVIIa supported TF-independent thrombin and fibrin formation, which enabled αIIbβ3-independent platelet aggregation, in a model of Glanzmann's thrombasthenia[31]
Effects on coagulation parameters
rFVIIa 17.5–70 μg/kg had no significant effect on blood levels of fibrinogen, platelet count, antithrombin, α_2-antiplasmin, D-dimers or thrombin-antithrombin complex in nonsurgical hemophilia patients with or without inhibitors in bleeding and nonbleeding states[32]
There were no significant changes in coagulation parameters in hemophilia patients with inhibitors treated with a single bolus of rFVIIa 270 μg/kg or three doses of 90 μg/kg[33]
Changes in coagulation parameters after surgery in hemophilia patients were consistent with expected postoperative changes from surgery-associated tissue damage[34,35]
Significant decreases in PT occurred for up to 24 h and aPTT for up to 4 h after administration of rFVIIa 17.5–70 μg/kg to nonsurgical hemophilia patients with or without inhibitors ($p < 0.007$)[32]
PT decreased postoperatively in hemophilia patients undergoing surgery who received rFVIIa 35 or 90 μg/kg (statistical significance not reported)[34]

aPTT = activated partial thromboplastin time; **PT** = prothrombin time; **rFVIIa** = recombinant activated factor VII; **TF** = tissue factor.

2. Pharmacodynamic Properties

Recombinant human factor VIIa is structurally similar to coagulation factor VIIa derived from human plasma.[12] It is produced by expressing the cloned gene for human factor VII in baby hamster kidney cells without the use of human serum or other human proteins.[12] Recombinant factor VIIa is a vitamin K-dependent glycoprotein of 406 amino acid residues and has a molecular weight of 50 kDa.[12]

Normal hemostasis has two phases.[13] In the initiation (tissue factor [TF]-dependent) phase, a complex forms between TF (exposed as a result of injury to a vessel wall) and activated factor VII (factor VIIa). This complex activates factor X, leading to the formation of a small amount of thrombin which is sufficient to activate platelets as well as factors VIII and V. In the second (TF-independent) phase, which occurs on the surface of the thrombin-activated platelets, complexes form between factors IXa and VIIIa and subsequently between factors Xa and Va, leading to a full thrombin burst.[13] Recombinant factor VIIa has effects on both TF-dependent and TF-independent processes (table I).[14] In the latter process, recombinant factor VIIa binds directly to thrombin-activated platelets and activates factor X, even in the absence of factors VIII and IX. Thus, at pharmacologic (supraphysiologic) concentrations, the main effect of recombinant factor VIIa is that of enhancing thrombin formation on the surface of thrombin-activated platelets.[13,15] The thrombin induced by recombinant factor VIIa enhances platelet activation, fibrin generation and inhibition of fibrinolysis (see table I).

The effects of recombinant factor VIIa appear to be localized to the site of vascular injury,[16] and *in vitro* studies suggest that it

does not enhance systemic activation of the clotting system and is unlikely to induce a hypercoagulable state.[17]

2.1 Antigenicity

There is a theoretical risk of inducing antibodies when administering recombinant proteins, including recombinant factor VIIa, to patients.[36] However, antibody-mediated inhibitory activity could derive from antibodies induced by recombinant factor VIIa itself[36] or from cross-reactivity of antibodies directed against other factors, such as factor IX.[37]

The development of specific anti-recombinant factor VIIa antibodies following treatment with recombinant factor VIIa has generally not been demonstrated for hemophilia patients.[36,38]

There have been only a few reports of antibodies against recombinant factor VIIa in patients with factor VII deficiency, in particular when exposed to extremely high doses of recombinant factor VIIa.[36,39,40] In one report of a patient with severe factor VII deficiency developing inhibitors after treatment with recombinant factor VIIa 20 μg/kg exclusively over the previous 5 years, the inhibitor activity decreased over time without further exposure to recombinant factor VIIa, while re-exposure led to a marked increase in inhibitor levels.[40] However, there was only a slight reduction in the observed hemostatic effect of treatment.

Among patients with hemophilia and high-responding inhibitors treated with recombinant factor VIIa alone for bleeding episodes over a 12-month period, the titer for factor VIII inhibitor decreased by two-thirds compared with baseline.[41] Titers remained unchanged in patients who received treatment with other factors, suggesting that the reduction in titer with recombinant factor VIIa was due to lack of exposure to antigenic products.[41] This contrasts with aPCC, which contains trace amounts of factor VIII and may produce an anamnestic response (i.e. an increase in factor VIII inhibitor levels) in some patients.[42]

3. Pharmacokinetic Properties

The pharmacokinetic properties of intravenous recombinant factor VIIa have been evaluated in healthy volunteers,[43,44] in adult[45,46] and pediatric[46] patients with hemophilia, and in adults with congenital factor VII deficiency.[47] Pharmacokinetic evaluations were based on the factor VII coagulant (FVII:C) assay in all studies; some[46,47] also used the factor VIIa clot activity assay, which is generally more accurate.[48] Key pharmacokinetic parameters are summarized in table II.

Following a single dose of recombinant factor VIIa 90 μg/kg in adult hemophilia patients, the area under the plasma concentration-time curve (AUC) from 0 to 12 hours was 2.16 μg • h/mL using the FVII:C assay (1.71 μg • h/mL with the FVIIa clot activity assay).[46] The AUC generally increased in a dose-propor-

Table II. Pharmacokinetic properties of intravenous recombinant factor VIIa in healthy volunteers and patients. Values are means obtained using the factor VII coagulant (FVII:C) assay, unless otherwise specified

Study	Population (no.)	Dose (μg/kg)	Vd_{ss} (mL/kg)	CL (mL/h/kg)	$t_{½β}$ (h)	MRT (h)
Adult healthy volunteers						
Fridberg et al.[43]	Caucasian/Japanese (29)[a]	40	144.5/164.7	34.3/33.3	5.2/6.0	
		80	132.4/130.1	36.6/33.7	3.9/4.3	
		160	138.5/134.8	37.2/34.5	4.1/4.0	
Girard et al.[44]	Anticoagulated with	5–20	80.0	30.9	2.4	
	acenocoumarol (28)[b]	21–320	93.6	34.5	2.5	
Adult patients						
Berrettini et al.[47][c]	Factor VII deficiency (5)	15	280 [210]	70.8 [64.9]	2.8 [2.5]	3.8 [3.3]
		30	290 [230]	79.1 [67.7]	3.1 [2.6]	3.8 [3.5]
Lindley et al.[45]	Hemophilia, nonbleeding (11)	17.5–70	109.9	32.1	2.8	3.5
	Hemophilia, bleeding (3)	17.5–70	103.5	36.6	2.5	2.7
Villar et al.[46][c]	Hemophilia (5)	90	128 [159]	39 [53]	3.1 [2.3]	3.3 [3.0]
Pediatric patients						
Villar et al.[46][c]	Hemophilia (12)	90 + 180[d]	164 [196]	58* [78*]	2.6 [2.3]	2.8 [2.5]

a Values for Caucasian/Japanese patients; values were comparable across the ethnic groups.

b Population pharmacokinetic study.

c Values in brackets are those obtained using the factor VIIa clot activity assay, rather than the FVII:C assay.

d Patients received two single doses separated by a washout period. Pharmacokinetic values shown are an average of values for the two doses.

CL = clearance; **MRT** = mean residence time; $\mathbf{t_{½β}}$ = terminal elimination half-life; $\mathbf{Vd_{ss}}$ = steady-state volume of distribution; * $p < 0.05$ vs values in adults (39 [53] mL/h/kg).

tional manner for the dosages evaluated in pharmacokinetic studies with recombinant factor VIIa.[43,45-47]

In a population pharmacokinetic study in healthy volunteers, steady-state volume of distribution (Vd_{ss}) appeared to be dose dependent.[44] However, in patients with hemophilia[45] or factor VII deficiency,[47] Vd_{ss}, as well as clearance, terminal elimination half-life, and mean residence time were generally independent of dose (table II).

Clearance values were similar in adults with hemophilia (32–39 mL/h/kg) and in healthy adult volunteers (31–37 mL/h/kg) [table II]. Clearance was significantly higher in children than in adults with hemophilia (58 vs 39 mL/h/kg [FVII:C assay]; $p < 0.05$)[46] and was similarly higher in patients with factor VII deficiency (71–79 mL/h/kg)[47] [table II].

Only limited pharmacokinetic data are available for hemophilia patients experiencing bleeding episodes; however, the minor differences between values for bleeding (5 episodes) and nonbleeding states (25 episodes) [table II] were not considered clinically significant.[45] Values for pharmacokinetic parameters were similar for Caucasian and Japanese healthy volunteers,[43] and there were no significant differences between the sexes.[43] The pharmacokinetic properties of recombinant factor VIIa in patients with cirrhosis were consistent with those in adult hemophilia patients.[49]

4. Therapeutic Efficacy

The bleeding disorders for which intravenous recombinant factor VIIa is indicated are rare conditions. Consequently, while it has been evaluated in a number of small, randomized, double-blind[33,34,38,50] or open-label,[51,52] controlled trials in patients with congenital hemophilia with inhibitors (section 4.1), other data on this indication and on acquired hemophilia (section 4.2), congenital factor VII deficiency (section 4.3) and Glanzmann thrombasthenia (section 4.4) come from noncomparative studies and series of case reports, including compassionate- or emergency-use programs. The data reviewed are from articles that have been published in full.

In most studies, the efficacy of recombinant factor VIIa at producing hemostasis was evaluated using a global assessment by the physician or the patient (or their caregiver). The precise definitions used varied between trials, but generally categories such as excellent, effective, partially effective, or ineffective were included, and the assessment took into account relief of pain/tenderness, size of the bleed, and/or cessation of bleeding. Adults and children could be enrolled in studies. To be eligible for compassionate-use programs, patients had to have failed treatment with an alternative hemostatic agent.

4.1 Congenital Hemophilia with Inhibitors

Randomized trials of recombinant factor VIIa in congenital hemophilia A or B with inhibitors include dose-finding studies[34,38] and some home-treatment studies (in particular, comparisons of recombinant factor VIIa with aPCC[50,52] and comparisons of single high-dose therapy versus standard therapy[33,50,51]). Additional, noncomparative data are available from other home-treatment studies,[53-55] worldwide compassionate- or emergency-use programs in which treatment was provided on a named-patient basis,[56-64] and a series of case reports.[65]

An initial, double-blind, dose-finding study in 78 nonsurgical patients with hemophilia A or B (66 with inhibitors) who attended hospital for treatment, demonstrated that dosages of 35 and 70 μg/kg intravenously every 2–3 hours were similarly effective in the treatment of joint and muscle bleeding, although there was an ≈7.8 hour difference between groups in the average time from onset of bleeding to start of treatment.[38] Among hemarthroses (the most frequent bleed), the global response to treatment was excellent or effective in 71% of each dosage group and the mean number of doses per episode of bleeding was ≈3.[38]

However, another dose-finding study in 29 patients with hemophilia with inhibitors undergoing elective surgery found that recombinant factor VIIa at a dosage of 90 μg/kg every 2–6 hours was significantly more effective than a dosage of 35 μg/kg every 2–6 hours for maintaining postoperative hemostasis from day 3 onward, although they were similarly effective intraoperatively (see section 4.1.3).[34]

Data from the compassionate-use programs also suggested that 90 μg/kg (generally given every 2–3 hours) was more effective than lower dosages[59] and this dosage was used in the majority of studies in congenital hemophilia discussed in the following sections. Single-dose therapy with 270 μg/kg has also been evaluated.[33,50,51]

4.1.1 Home Treatment of Mild to Moderate Bleeds

Intravenous recombinant factor VIIa administered by the patient or their caregiver at home was effective at controlling mild to moderate bleeding episodes in hemophilia patients with inhibitors, in noncomparative studies (table III).[53-55] Recombinant factor VIIa was administered at a dosage of 90[53,54] or 90–100[54] μg/kg every 2–4 hours and, where stated, treatment had to be initiated within 8[53] or 12[55] hours of the onset of bleeding. After ≈2 doses the hemostatic response was rated as excellent or effective in 79–93% of bleeding episodes. After initial resolution, bleeding recurred within 24–48 hours in 4–5% of episodes.

Early treatment with recombinant factor VIIa is more likely to be associated with a successful outcome than late treatment.[55] In one of the noncomparative home-treatment studies, the risk of treatment failure or a partially effective response was significantly lower if treatment was started within 6 hours of the onset of

Table III. Efficacy of recombinant factor VIIa in the treatment of mild to moderate bleeding episodes in patients (pts) with congenital hemophilia with inhibitors. Data are from noncomparative studies of home treatment in which pts self-administered intravenous recombinant factor VIIa 90[53] or 90–100[54] μg/kg every 2–4 hours

Study	No. of bleeds [no. of pts]	Time from bleeding onset to treatment initiation (mean[53] or median[55] h)	No. of injections per bleed[a] (mean[53,54] or median[55])	Treatment response (% of episodes)		Recurrence of bleeding within 24[53,54] or 48[55] h (% of episodes)
				effective[b]	partially effective[c]	
Ingerslev et al.[54][d]	123 [7]		2.1	93[e]		4
Key et al.[53]	614 [52]	1.1	2.2	92	5	5
Santagostino et al.[55]	53 [10]	1.0	2	79	11	5

a Excludes bleeds for which pts were hospitalized.

b Defined as successfully managed entirely at home;[54] bleeding ceased or decreased substantially;[53] or definite relief of pain, swelling and mobility[55] as assessed by the pt/caregiver.

c Defined as bleeding reduced but continued;[53] or an improvement in pain, swelling and mobility.[55]

d This report from the Danish self-management programs did not report time to treatment or partial effectiveness.

e Nine bleeding episodes (7%) required hospitalization; treatment was initiated at home in two of these episodes (1.6%).

bleeding than if it was started later (odds ratio 0.24; 95% CI 0.09, 0.63).[55] Combined analyses of data from a dose-finding study, home-treatment study and compassionate-use study confirmed the benefits of early treatment for patients with acute hemarthrosis[66] or intramuscular hemorrhage,[67] finding that fewer doses were needed and higher response rates were achieved when treatment was initiated early.

The effectiveness of treatment with a single dose of recombinant factor VIIa 270 μg/kg is similar to that of a standard regimen (90 μg/kg every 3 hours for three doses) in hemophilia patients with inhibitors experiencing hemarthroses (table IV).[33,50,51] In double-blind[33,50] or open-label[51] studies, outcomes were similar for the single 270 μg/kg dose and the standard regimen in terms of the treatment response rate, as assessed by patients after 9 hours (25–65% vs 31–70%),[33,50,51] and the proportion of patients not requiring additional hemostatic medication to control a bleeding episode (91% and 92% vs 86% and 91%).[33,50]

In the open-label study, in which patients were not required to use all three doses of the standard regimen unless necessary, the median number of injections used for this regimen was three and so the median quantity of recombinant factor VIIa administered was the same as for the single-dose regimen (270 μg/kg per bleeding episode).[51]

The use of high doses of recombinant factor VIIa is supported by an analysis of data from a registry of patients with congenital hemophilia with inhibitors, which found that bolus doses >200 μg/kg were associated with a significantly higher bleed-cessation rate than seen with lower doses (97% of 119 bleeds vs 84% of 436 bleeds; p = 0.0018).[68] Successful use of bolus doses as high as 300 μg/kg has been reported.[69]

Two randomized, open-label, crossover studies comparing recombinant factor VIIa with aPCC in the home-treatment of hemophilia patients with inhibitors have been reported.[50,52]

In the FENOC (FEIBA NovoSeven Comparative) study, the criterion for equivalency between recombinant factor VIIa (two doses of 90–120 μg/kg) and aPCC (one dose of 75–100 IU/kg) was not met.[52] This equivalence study evaluated 96 bleeding episodes (hemarthroses) in 48 hemophiliac patients with inhibitors; patients were randomized to the order of treatment with recombinant factor VIIa and aPCC. The primary endpoint was the proportion of patients reporting effective or partially effective hemostasis at 6 hours after treatment initiation. Equivalency required the upper and lower limits of the 90% confidence interval (CI) for the difference between treatments to fall within minus or plus 15%. At 6 hours after infusion, the rate of effective plus partially effective responses was 78.7% for recombinant factor VIIa versus 80.9% for aPCC (90% CI −11.42, 15.67; p = 0.059). The efficacy of the two treatments was rated differently by a substantial proportion of patients at all time points up to 48 hours. The percentage of discordant pairs (one treatment effective and the other not effective) ranged from 9.8% to 43.8% at different time points, but was highest during the first 12 hours after treatment.[52] The small number of patients/bleeds evaluated may have meant that the study was underpowered to demonstrate equivalence. In addition, the involved joints were unevenly distributed between treatment groups, with more knee joints in the recombinant factor VIIa treatment arm.[52]

In the second trial, two different regimens of recombinant factor VIIa (a single dose of 270 μg/kg and a regimen of three doses of 90 μg/kg at 0, 3 and 6 hours; administered in double-blind fashion) were compared with a single dose of aPCC 75 U/kg (administered unblinded).[50] There were no significant differences in patient-assessed treatment response between either of the recombinant factor VIIa regimens and aPCC (data are shown in table IV because the study also included a comparison of the two recombinant factor VIIa regimens). However, the proportion of

Table IV. Efficacy of single-high-dose and standard regimens of recombinant factor VIIa (rFVIIa) in the home-based treatment of hemarthroses in hemophilia patients (pts) with inhibitors. Data are from randomized, double-blind[33,50] or open-label,[51] crossover, multicenter trials in which pts received intravenous rFVIIa as a single dose of 270 μg/kg and as a regimen of 90 μg/kg every 3 hours for three doses, for separate bleeding episodes. In one study, pts also received a single dose of activated prothrombin complex concentrate (aPCC) 75 U/kg in open-label fashion[50]

Study	Regimen (dose in μg/kg unless stated otherwise [no. of injections])	No. of bleeds [no. pts]	Treatment response rated as success[a] or effective[b] (% of episodes)		Hemostasis achieved without additional hemostatic medication (% of episodes)[c]
			9 h	48 h	
Kavakli et al.[33]	rFVIIa 270 [×1]	21 [21]	65[d]		90.5
	rFVIIa 90 [×3]	21 [21]	70[d]		85.7
Santagostino et al.[51]	rFVIIa 270 [×1]	36 [18]	25	64	
	rFVIIa 90 [×3[e]]	32 [18]	31	66	
Young et al. [50]	rFVIIa 270 [×1]	24 [24]	37.5		91.7*
	rFVIIa 90 [×3]	22 [22]	54.5		90.9
	aPCC 75 U/kg [×1]	22 [22]	27.3		63.6

a Defined as: treatment rated as effective (i.e. definite relief of symptoms) plus a score ≥70 on a visual analog scale for improvement in signs and symptoms (where 0 is no relief and 100 is complete relief), as assessed by the pt, taking into account joint swelling, pain and functional limitation over the 48-h period after the first dose of rFVIIa.[51]

b Patient assessment using a global treatment-response rating tool taking into account pain and joint mobility and assessed over the 9-h period after the first dose of rFVIIa (or aPCC).[33,50]

c Within 9[50] or 48[33] h of the first dose of rFVIIa.

d Assessed for 20 bleeds in 20 pts.

e Median no. of doses.

* p = 0.032 vs aPCC.

patients needing additional 'rescue' hemostatic therapy within the first 9 hours was significantly lower with the single 270 μg/kg dose of recombinant factor VIIa treatment than with aPCC (8.3% vs 36.4%; p = 0.032), although the difference between the standard three-dose regimen of recombinant factor VIIa and aPCC did not reach statistical significance (9.1% vs 36.4%; p = 0.069).[50]

4.1.2 Major Nonsurgical Bleeds

Data on the use of recombinant factor VIIa in the treatment of serious nonsurgical bleeding come from the noncomparative compassionate- and emergency-use programs. Patients were eligible for enrolment if they had a life- or limb-threatening bleed, required essential surgery (discussed in section 4.1.3), and/or were refractory to other treatments. The majority of patients had congenital hemophilia A or B with inhibitors, but patients with acquired inhibitors or with factor VII deficiency were also included, and reports on the programs generally present data for all patients combined.

Results have been reported for specific types of bleeding, including serious joint/muscle, intracranial, CNS and other internal bleeds.[56-61] The response was rated as excellent or effective in 62–86% of bleeding episodes following treatment with recombinant factor VIIa (table V).

In a report summarizing overall experience with the use of recombinant factor VIIa for 518 serious bleeding episodes in hemophilia patients with inhibitors, which included data from the dose-finding study discussed earlier[38] and an unpublished Japanese study, as well as the compassionate-use program, the hemostatic response was considered excellent or effective in 62–88% of episodes depending on the location of the bleed.[62]

4.1.3 Surgical Hemostasis

Recombinant factor VIIa is effective at producing and maintaining hemostasis during surgical procedures in hemophilia patients with inhibitors.[34,61-65]

In a double-blind, dose-finding study in 29 patients (28 with hemophilia A or B with inhibitors and 1 with acquired inhibitors) undergoing elective surgery for major (mainly orthopedic) or minor (central venous catheter placement) procedures, patients were randomized to receive recombinant factor VIIa 35 or 90 μg/kg immediately prior to surgery, every 2 hours for 48 hours and then 2–6 hourly for 3 days.[34] No other hemostatic agent was permitted in the preceding 48 hours. Among patients who received recombinant factor VIIa 90 μg/kg, satisfactory hemostasis (which included effective and partially effective hemostasis) was achieved in 13 out of 14 (93%) patients intraoperatively, in all patients during the first 48 hours, and in 93–100% of patients during days 3–5. In those receiving the 35 μg/kg dose (n = 15), satisfactory hemostasis was achieved in 100% of patients intraoperatively, 80–93% of patients during the first 48 hours, and 60–67% of patients during days 3–5. The 90 μg/kg dose was

associated with significantly ($p < 0.05$) higher rates of efficacy than 35 μg/kg from day 3 onwards.[34]

In the report summarizing overall clinical experience with recombinant factor VIIa discussed in section 4.1.2,[62] in which the majority of patients received recombinant factor VIIa 90 μg/kg every 2–4 hours, the response to treatment was excellent or effective in 17 of 21 (81%) major surgical bleeds, 49 of 57 (86%) minor surgical bleeds and 23 of 25 (92%) dental bleeds.

Another report summarized data for 12 patients undergoing 13 major surgical procedures from several centers within the compassionate-use program.[63] Patients were treated with recombinant factor VIIa at a mean dosage of 99 μg/kg every 2–3 hours for up to 2 days and then at longer intervals; overall they received between 45 and 160 injections each. No additional hemostatic agents were needed and in all of the 12 cases for which a global evaluation was reported, the outcome was considered excellent or efficient.[63]

Data have also been reported for two individual centers participating in the compassionate-use program.[64] In one center, intraoperative bleeding was absent, or less than or equivalent to normal in 20 of 22 (91%) major and minor surgical procedures, with postoperative bleeding absent or minimal in a similar number of cases.[61] At the second center, the outcome of all 21 major and minor surgical procedures was considered to be excellent.[64]

In addition, a report on a series of 108 elective orthopedic surgery procedures performed in nine centres worldwide indicated that recombinant factor VIIa was associated with beneficial responses in hemophilia patients with inhibitors.[65] Of 88 joints undergoing radiosynoviorthesis, 31 were covered with recombinant factor VIIa and 23 had good outcomes, while 17 of 20 major orthopedic procedures received hemostatic cover with recombinant factor VIIa with 14 good outcomes.[65]

A review of data published during the period 2002–2006 on the use of recombinant factor VIIa in hemophilia patients with inhibitors undergoing orthopedic surgery (80 procedures) likewise concluded that recombinant factor VIIa is safe and effective for providing hemostatic cover during surgery, and suggested that the initial bolus dose should be a minimum of 120 μg/kg, followed by 90 μg/kg bolus injections every 2 hours or a 50 μg/kg/h infusion.[70]

4.2 Acquired Hemophilia

Based on an overview of noncomparative data from the compassionate-use programs, the Hemophilia and Thrombosis Research Society Registry and published reports, recombinant factor VIIa provides effective hemostasis in patients with acquired hemophilia.[71] Treatment was given for episodes of nonsurgical

Table V. Efficacy of recombinant factor VIIa in the treatment of serious nonsurgical bleeding episodes refractory to other treatments, in patients (pts) with congenital hemophilia with inhibitors, acquired hemophilia or factor VII deficiency. Data are from worldwide compassionate- or emergency-use programs

Study	Type of bleeding	No. of bleeds [no. of pts]	Dose (μg/kg every 2–4 h)	Mean no. of injections per bleed	Treatment response rated as excellent or effective (% of episodes)[a]
Arkin et al.[56]	Life-threatening intracranial	13 [12][b]	90–120[c]	91.3[d]	85
Arkin et al.[57]	Limb-threatening joint/muscle	35 [23][e]	90–120	56	86
Bech[58]	Joint/muscle	494 [111]	60–120	11.2–64.8[f]	62–79[f]
Lusher[59]	Internal[g]	51 [43][h]	84	80.1	76
Rice and Savidge[60]	CNS[i]	29 [21][j]	80–100[k]	2–332 (range)	84
Scharrer[61]	Joint and various others	45 [28][l]	90–120[c]	46.8	69

a Where stated, defined as: complete or substantial decrease in hemorrhage;[56,57] significant relief of pain (or cessation of bleeding) and/or decrease in size of bleed and/or significant improvement in joint mobility;[58] cessation of bleeding (and to be 'excellent', include resolution of internal hemorrhage);[59] or significant and substantial reduction in bleeding.[61] Ratings were determined by the investigators.

b Eleven pts had hemophilia A or B with inhibitors and one patient had factor VII deficiency.

c Factor VII-deficient pts received 15–30 μg/kg every 4–6 h.

d Mean 96.9 injections for hemophilia pts and 24 injections for the pt with factor VII deficiency.

e Seventeen pts had hemophilia A or B with inhibitors and six pts had acquired inhibitors.

f Depending on type of bleed (joint, muscle, tense muscle compartment syndrome).

g Iliopsoas, gastrointestinal, renal tract, other intra-abdominal or retroperitoneal bleeds.

h Twenty-eight pts had hemophilia A or B with inhibitors, thirteen had acquired inhibitors and two had factor VII deficiency.

i Cranial subdural, intracerebral, cranial or spinal extradural, subarachnoid bleeds.

j Eighteen pts had hemophilia A or B with inhibitors and three had factor VII deficiency.

k Mean dose in this range for 62% of hemophilia pts; not stated for the remainder. For two of the three factor VII-deficient pts, the mean dose was 24 μg/kg.

l Nineteen pts had hemophilia A or B with inhibitors, four had acquired inhibitors and five had factor VII deficiency.

bleeding in the majority of cases and regimens included bolus injections of 31–197 μg/kg every 2–24 hours or continuous infusions of 8–50 μg/kg/h. Overall, treatment with recombinant factor VIIa was rated as effective or partially effective in 88% of episodes (based on 182 episodes for which efficacy was rated). Results were comparable across the different sources of data. Treatment was rated as effective or partially effective for 90% of nonsurgical bleeds and 86% of surgical cases (and effective in 80% of nonsurgical and 63% of surgical cases). When given as first-line therapy, recombinant factor VIIa was effective or partially effective in 95% of episodes; as salvage therapy after other hemostatic agents had failed, it was rated as 80% effective.[71]

An earlier report of compassionate-use data[72] and a report from the Italian Registry of Acquired Hemophilia[73] (included in the overview discussed above) support the effectiveness of recombinant factor VIIa in patients with acquired hemophilia. During the compassionate-use program, 38 patients with acquired hemophilia received recombinant factor VIIa, with a good response in all 14 bleeding episodes in which it was used as first-line therapy and in 75% of 60 episodes in which it was used as salvage therapy after patients had failed to respond to a median of 4 days of therapy with a blood product.[72] In the latter analysis, recombinant factor VIIa was used in 15 patients (as first-line therapy in 19 severe bleeding episodes and salvage therapy in one episode).[73] It was administered as a bolus of 90 μg/kg every 2–6 hours (total dose 309 μg/kg) in eight patients and as a continuous infusion (loading dose 98 μg/kg followed by 15–30 μg/kg/h; total dose 474.5 μg/kg) in seven patients. Treatment was rated as very effective or effective in 18 of 20 bleeding episodes (90%) within 48 hours.[73]

4.3 Congenital Factor VII Deficiency

An overview of data from the compassionate- and emergency-use programs and from published case reports concluded that recombinant factor VIIa appears to provide effective hemostasis for bleeding episodes in patients with congenital factor VII deficiency.[74]

Among 32 factor VII-deficient patients included in the compassionate-use analysis, 69 episodes (43 nonsurgical bleeds and 26 surgical procedures) were administered recombinant factor VIIa, using a median dose per injection of 22 μg/kg every 4–6 hours for a median of 10 injections. Treatment was rated as effective in 37 of 43 (86%) nonsurgical bleeds and all 25 (100%) surgical cases for which efficacy data were collected (96% including the one patient for whom data was not collected). The main types of nonsurgical bleeding were joint and CNS bleeds.[74]

Among the case reports were 15 patients with congenital factor VII deficiency treated for 19 bleeding episodes. All five acute nonsurgical bleeding episodes resolved satisfactorily; similarly, all 11 surgical procedures were completed without excessive bleeding. An additional three cases of childbirth or Caesarian section also reported successful use of recombinant factor VIIa.[74]

Data from the *haemostasis.com* registry on 39 cases among 30 patients indicated that treatment with recombinant factor VIIa was associated with cessation of bleeding or markedly reduced bleeding.[75] The median dose was 13.3 μg/kg administered for a median of three doses. Among cases that reported bleeding response, there was no excessive bleeding among nine elective surgery cases, bleeding stopped in all four cases of emergency surgery, and bleeding stopped or was markedly reduced in all eight cases of trauma-associated bleeding.[75]

4.4 Glanzmann Thrombasthenia

An international survey of patients with Glanzmann thrombasthenia summarizes available data on this indication.[5,14] The analysis included 108 nonsurgical bleeding episodes and 34 surgical procedures among 59 patients, 29 of whom had current or past antiplatelet antibodies (anti-GP IIb/IIIa, anti-HLA, or both) and 23 of whom had a history of refractoriness to platelet transfusion. Regimens of recombinant factor VIIa varied; the median bolus dose was 92–109 μg/kg in successfully treated bleeds/procedures. When continuous infusion was used, the median initial bolus dose was 49–88 μg/kg followed by continuous infusion at a median rate of 5–12 μg/kg/h.[5]

Treatment was rated as successful (bleeding stopped and did not recur within 48 hours) in 85% of surgical episodes (94% if episodes without evaluable efficacy data were excluded) and 64% of nonsurgical bleeding episodes (75% of evaluable episodes).[5,14] Treatment with bolus recombinant factor VIIa at doses ≥80 μg/kg and intervals ≤2.5 hours was associated with significantly higher response rates than lower dose/frequency regimens in severe (77% vs 55%; p = 0.01), but not moderate (80% vs 82%), bleeding episodes.[5]

Included in the survey data were two small noncomparative studies.[76,77] In one study (n = 5), treatment with recombinant factor VIIa 89–116 μg/kg every 2 hours was effective in 23 of 24 episodes (96%),[76] while in the second study (n = 5), the response was reported as excellent or good for 12 of 25 bleeding episodes (48%) following treatment with recombinant factor VIIa 100–200 μg/kg every 90 minutes.[77] In the latter study, the response was good or excellent in 10 of 14 (71%) episodes treated within 12 hours of bleeding onset compared with 2 of 11 (18%) of those treated after 12 hours, suggesting that early treatment was more effective.[77]

5. Tolerability

The majority of tolerability data relate to patients with hemophilia with inhibitors, and recombinant factor VIIa is generally well tolerated by these patients.[11,78,79] Based on post-marketing

data, adverse drug reactions are rare, occurring at a rate of <1 per 1000 standard doses.[11] There is no apparent link between adverse events and dose of recombinant factor VIIa,[79] including a single dose of 270 μg/kg.[33,50,51]

Non-serious adverse events reported with recombinant factor VIIa include nausea, fever, injection-site pain, skin rash and increased ALT, alkaline phosphatase, and lactate dehydrogenase (overall incidence of each event <1 per 10 000 standard doses).[11] In the home-treatment trials in congenital hemophilia, the incidence of non-serious adverse events was <3%,[53,55] and in the randomized trial in patients undergoing surgery, 1 of 29 patients (3%) had a clinically significant adverse event (thrombosis after a difficult central venous catheter placement).[34]

Serious adverse events reported with recombinant factor VIIa have included thrombotic events, such as myocardial infarction, stroke, pulmonary embolism, deep venous thrombosis and disseminated intravascular coagulation.[78] However such events are rare; the incidence is given as ≈1% in hemophilia patients in one review,[79] whilst according to post-marketing data in the manufacturer's prescribing information individual serious events occur at a rate of <1 per 10 000 standard doses.[11] Most thrombotic events occurred in hemophilia patients with predisposing risk factors, such as diabetes mellitus, atherosclerotic disease, obesity and cancer,[78,79] and it was not possible to establish a definite causal relationship with recombinant factor VIIa.[79] In the period from the licensing of recombinant factor VIIa in 1996 through to 2003, there were 16 thromboembolic events (10 arterial and 6 venous) and two cases of disseminated intravascular coagulation spontaneously reported from over 700 000 standard doses administered to patients with congenital hemophilia with inhibitors or acquired hemophilia.[78] A review of serious thromboembolic adverse events reported to the FDA between 1999 and 2004, found that the majority occurred in patients receiving recombinant factor VIIa for non-approved indications in patients without hemophilia (151 of 168 reports); only 17 events occurred in patients with acquired hemophilia.[80]

Tolerability data are limited for patients with factor VII deficiency or Glanzmann thrombasthenia treated with recombinant factor VIIa. Thromboembolic events have been reported rarely,[5,74,75] and alloantibody development has been reported occasionally for factor VIIa-deficient patients;[74] however, there are currently insufficient data to determine the precise risk of such events in these particular patients.[14,74]

There was no difference in the tolerability of recombinant factor VIIa and aPCC in the only direct comparison to report safety data.[50] Based on data from the US MedWatch pharmacovigilance program, the incidence of thrombotic adverse events was reported to be higher with recombinant factor VIIa than with aPCC.[81] However, the author noted that this finding should be interpreted with caution because of differences in the reporting patterns for the agents, and discussion in the medical literature confirmed that conclusions on the comparative tolerability of these agents could not be drawn from these data.[82-84]

Since recombinant factor VIIa is manufactured without exposure to human tissue or plasma, there is no risk of transmission of human pathogens.[9] The formulation does not contain any factor VIII or IX and, therefore, does not induce an anamnestic response (increase in inhibitor titer) in patients with inhibitors.[9]

6. Pharmacoeconomic Considerations

Pharmacoeconomic data relating to the use of recombinant factor VIIa in hemophilia patients with inhibitors has been reviewed in depth recently.[85] This section briefly summarizes key data on this patient population. Pharmacoeconomic data on the use of recombinant factor VIIa in patients with other bleeding disorders are not available.

In a cost-utility analysis performed in Australia, on-demand treatment (generally at home) with recombinant factor VIIa 90 μg/kg was associated with improvements in health-related quality of life relative to previous treatment with plasma-derived agents (aPCC, porcine factor VIII, human factor VIII and/or prothrombin complex concentrate).[86] Utility values were determined using the EuroQOL multi-attribute utility valuation instrument. Costs included medication and other healthcare services (year of costing not reported). The incremental increase in quality-adjusted life-years (QALYs) with recombinant factor VIIa relative to plasma-derived agents was 0.58, while the cost of 6 months' treatment was $A29 901 higher with recombinant factor VIIa than with plasma-derived products. The incremental cost per QALY gained with recombinant factor VIIa treatment relative to plasma-derived agents was $A51 533.[86] By way of comparison, the incremental cost per QALY for hospital dialysis in Australia between 1993 and 1996 was estimated to be $A57 053.[86]

In a number of well designed, decision-model, cost analyses conducted in several countries, the use of on-demand treatment with recombinant factor VIIa for mild to moderate bleeding episodes was found to be cost saving or cost neutral relative to on-demand treatment with aPCC (reviewed by Lyseng-Williamson and Plosker[85]).

In some studies, the acquisition cost was higher for recombinant factor VIIa than aPCC; however, the greater efficacy of recombinant factor VIIa led to lower medical costs overall. The analyses used a cost-minimization approach and took the healthcare payer perspective. Costs included country-specific costs for recombinant factor VIIa or aPCC, direct medical costs of hospital or outpatient care, and in some studies concomitant medications, ambulance transport, and routine tests.[85]

One analysis looked at lifetime costs and found that the lifetime cost of treating bleeding episodes was ≈£200 000 lower with a recombinant factor VIIa-only regimen than with regimens that

used aPCC as first-line or first- and second-line treatment (2001 costs).[87]

Other analyses found that the cost of treating a minor to moderate bleeding episode was lower when only recombinant factor VIIa was used compared with regimens that used aPCC for initial treatment (followed by recombinant factor VIIa), and that first-line treatment with recombinant factor VIIa was more effective and less expensive than aPCC when the cost per resolved bleeding episode was analyzed.[85] The results of these cost analyses were generally robust in sensitivity analyses.

In modelled cost analyses from a healthcare payer perspective in the US[88,89] and UK, [90] orthopedic surgery using recombinant factor VIIa to maintain hemostasis was generally found to be cost saving relative to no surgery, over the medium to long term.

In the US analyses of lifetime costs (including costs for surgery, recombinant factor VIIa, hospital stay and physiotherapy; discounted at 3% per annum), the difference in costs favored orthopedic surgery over no surgery (difference of $US2 015 910 to $US2 325 101 depending on the surgical procedure performed).[88,89] Although the initial cost of surgery was high, the reduced number of bleeding episodes in patients who had surgery led to reduced costs in the longer term, with the time to break even estimated to be 5–9 years depending on the type of surgery.[88,89]

In the UK analysis, which evaluated the cost of recombinant factor VII therapy over a 5-year horizon, the cost saving for surgery versus no surgery was £13 931 to £359 908 (depending on the type of surgical procedure) in patients who received initial treatment with recombinant factor VIIa at home, whereas for patients who received initial recombinant factor VIIa treatment in a specialist center, the difference varied from a cost saving of £304 708 to a cost increase of £41 269.[90] Year of costing was not stated for these analyses.

7. Dosage and Administration

Recombinant factor VIIa is approved for use in many countries for the treatment of bleeding episodes, and the prevention of bleeding during surgery, in patients with congenital hemophilia A or B with inhibitors to factors VIII or IX. In some countries, including European countries and the US, it is also indicated for use in patients with acquired hemophilia or congenital factor VII deficiency.[11,12] In Europe it is also indicated for use in patients with Glanzmann thrombasthenia.[11] Recombinant factor VIIa is administered intravenously by bolus injection.

In patients with congenital hemophilia, acquired hemophilia or Glanzmann thrombasthenia, the usual initial dosage is 90 μg/kg, generally every 2–3 hours, until hemostasis is achieved.[11,12] If continued therapy is needed, the dosing interval can be increased. In Europe, hemophilia patients with inhibitors experiencing mild to moderate bleeding may be given a single bolus dose of 270 μg/kg instead.[11] In the US, the unit dose for acquired hemophilia is 70–90 μg/kg.[12]

For patients with factor VII deficiency, the initial dosage is 15–30 μg/kg every 4–6 hours until hemostasis is achieved.[11,12]

Local manufacturer's prescribing information should be consulted for full details of indications, dosage regimens, administration method, precautions, and warnings.

8. Place of Recombinant Factor VIIa in the Management of Hemophilia with Inhibitors and Other Bleeding Disorders

Although congenital hemophilia, acquired hemophilia, factor VII deficiency and Glanzmann thrombasthenia are rare disorders, they can be associated with significant morbidity,[6,91] impaired quality of life,[2] and considerable healthcare expenditure.[85]

The type of bleeding seen most frequently varies between the disorders. Congenital hemophilia carries a high risk of recurrent joint and muscle bleeding, whereas mucosal bleeding, such as epistaxis and menorrhagia, is more common with other disorders.[1,4,5] Although bleeding into muscles occurs in acquired hemophilia, hemarthroses are not common.[42] The risk of bleeding varies between individual patients. For example, patients with mild hemophilia (factor concentration 5–40% of normal) tend to bleed only after surgical procedures or trauma; those with moderate hemophilia (factor concentration 1–5% of normal) may bleed after minor injuries; while those with severe hemophilia (factor concentration <1% of normal) experience recurrent spontaneous bleeding into their joints and muscles, which can lead to disabling arthropathy.[6]

Neutralizing alloantibodies (inhibitors) develop against coagulation factors VIII or IX in approximately one-third of patients with severe hemophilia A and up to 3% of hemophilia B patients.[6,9] Patients without congenital hemophilia can also develop inhibitory autoantibodies to these factors (acquired hemophilia).[9] The presence of inhibitors can lead to resistance to clotting factor replacement therapy, and so make treatment more difficult.[6,9,18] In addition, patients with inhibitors appear to be at greater risk of developing arthropathy and orthopedic complications than those without inhibitors, and this has a negative effect on their quality of life.[91] Patients with inhibitors are more likely to be hospitalized and to have reduced mobility than those without inhibitors.[91]

Treatment of bleeding disorders generally involves the use of blood products.[7] Hemophilia patients without inhibitors usually respond well to coagulation factor VIII or IX concentrates, as recommended by guidelines.[7,92] Similarly, factor VII concentrates are recommended for patients with factor VII deficiency.[2,7] Where available, recombinant products are generally preferred over plasma-derived concentrates, in order to minimize the risk for transmission of infectious agents.[7] Hence, recombinant factor

VIIa is the replacement therapy of choice for both surgical and nonsurgical bleeds in patients with factor VII deficiency.[2,7]

In hemophilia patients with inhibitors, bypassing agents, such as recombinant factor VIIa and aPCC, are useful treatment options.[42,92] aPCC is a multicomponent agent derived from plasma and undergoes controlled surface activation during manufacture;[7] it is thought that the active moiety of aPCC may be a complex of factor Xa and prothrombin.[93] The roles of other protein components of aPCC remain more speculative.[93] In contrast, recombinant factor VIIa is manufactured using DNA technology without the use of material of human origin, hence avoiding the risk of transmission of human infectious agents. At pharmacologic doses it enhances thrombin generation on activated platelet surfaces via a factor VIII/IX-independent route (section 2).

For patients with hemophilia A or B with inhibitors who are low responders (i.e. inhibitor level <5 Bethesda units [BU]/mL and no anamnestic response to factor VIII/IX exposure), an increased dose of factor VIII or IX concentrate may be sufficient to achieve a response,[42,94] although bypassing agents can be used as an alternative.[42] For high responders with hemophilia A (i.e. inhibitor level >5 BU/mL and an anamnestic response to factor VIII exposure), both recombinant factor VIIa and aPCC are recommended as treatments of choice.[42] Patients not responding to one agent may respond to the other,[42] but an increase in dose or frequency of the initial agent should be tried before considering switching,[95] and concurrent use of the two agents should be avoided because of a potential increased risk of thromboembolic events.[11,12] Recombinant factor VIIa may be preferred in high responders with a low initial titer who have previously experienced an anamnestic response when exposed to aPCC.[42] Some patients with hemophilia B with inhibitors develop allergic reactions to factor IX; therefore, since aPCC contains some factor IX,[42] recombinant factor VIIa is the preferred option for hemophilia B patients with high-responding inhibitors.[94] The UK guidelines also recommend that recombinant factor VIIa be used to treat bleeding episodes in patients with congenital hemophilia with inhibitors awaiting immune tolerance induction, since this will allow inhibitor titers to decline to appropriate levels prior to commencement of the process and avoid an anamnestic response.[42] Lastly, most patients with acquired hemophilia are resistant to factor VIII replacement, so recombinant factor VIIa and aPCC are the recommended first-line options.[42] According to the Nordic guidelines for the management of acquired hemophilia, tranexamic acid is not recommended when using aPCC because of the risk of thrombosis, and switching from aPCC to recombinant factor VIIa may increase the risk of thromboembolic complications.[96] Therefore, recombinant factor VIIa might be considered the preferred initial agent.

The standard treatment for Glanzmann thrombasthenia, an inherited platelet disorder in which there is a defect of the platelet membrane GP IIb/IIIa complex, is platelet transfusion.[5,14] However, compatible concentrates may not always be available.[5] In addition, after repeated transfusions, antibodies to GP IIb/IIIa and/or HLA, and platelet refractoriness, can develop,[5] and in Europe recombinant factor VIIa has been approved for use in these particular patients.[11]

Large-scale, well designed clinical trials are difficult to conduct in patients with bleeding disorders, because of the rarity of the conditions. Consequently, the majority of data on recombinant factor VIIa come from noncomparative trials or compassionate-use programs. Most data are from patients with congenital hemophilia with inhibitors, and show that recombinant factor VIIa is effective for the treatment of acute bleeding episodes and for providing hemostatic cover during surgery in these patients (section 4). The limited data available for patients with acquired hemophilia, factor VII deficiency or Glanzmann thrombasthenia with antiplatelet antibodies and/or refractoriness, indicate it is also effective in these populations (section 4).

The standard dosing regimen for recombinant factor VIIa in patients with hemophilia with inhibitors is generally a bolus injection of 90 μg/kg every 2–3 hours (section 7). However, it has been shown that a single injection of 270 μg/kg is as effective as the standard regimen in mild to moderate bleeds in hemophilia patients (section 4.1), with no negative effect on tolerability (section 5). In Europe, this is now an approved alternative dosage for such bleeds, including use as home therapy.[11] A single-dose regimen might be more convenient for patients than multiple injections and could also be useful for those with difficult venous access.

Treatment at home, whether with standard multiple 90 μg/kg injections or a single 270 μg/kg injection of recombinant factor VIIa, is considered a reasonable option for mild to moderate bleeds in hemophilia patients with inhibitors.[11] Home usage allows prompt treatment of bleeding episodes, which can be associated with a better outcome (section 4.1), and is convenient for patients and their caregivers.[97]

Recombinant factor VIIa is generally well tolerated, including the 270 μg/kg dose (section 5). Thromboembolic events have been reported, but they are rare and have generally occurred either in hemophilia patients with other risk factors for such events, or in patients being treated for off-label indications. There have been no reports of antibody formation against recombinant factor VIIa in patients with hemophilia, although rare instance have been reported in patients with factor VII deficiency (section 2).

There are few clinical trials directly comparing recombinant factor VIIa and aPCC. The available data in patients with congenital hemophilia do not demonstrate the superiority of either agent in terms of patient-assessed response. However, in one study, 'rescue' hemostatic therapy was less likely to be required after a single 270 μg/kg bolus dose of recombinant factor VIIa than after aPCC

(section 4.1), although the study limitations of low patient numbers and differences in blinding should be considered when interpreting the results.[50] At present, the choice between these agents may be determined by previous clinical response, the likelihood of an anamnestic or allergic response, and the likelihood of adverse events in particular patients.[42] For example, aPCC contains trace amounts of factor VIII and may induce an anamnestic response to this factor.[42] As mentioned earlier, it also contains factor IX, to which some hemophilia B patients become allergic.[42] aPCC has been associated with thromboembolic events, some in patients lacking other risk factors; however, there is presently no conclusive evidence about the comparative thrombogenicity of aPCC and recombinant factor VIIa, and the risk is low with either agent.[42]

Bleeding disorders are associated with lifelong costs for the healthcare system and society.[85] In addition, the cost of managing patients with inhibitors is higher than for those without inhibitors.[85] Available pharmacoeconomic data support the use of recombinant factor VIIa as a treatment that is at least cost neutral relative to aPCC in treating mild to moderate bleeds in hemophilia patients with inhibitors, and indicate that orthopedic surgery using recombinant factor VIIa to maintain hemostasis is generally cost saving over the medium to long term relative to not having surgery (section 6).

A limitation of the available formulation of recombinant factor VIIa is that it must be kept at a temperature of 2–8°C, necessitating storage in a refrigerator.[11] A room temperature-stable version of recombinant factor VIIa is being developed, which might facilitate treatment away from home and enable immediate access to treatment. The room temperature-stable formulation has been shown to be bioequivalent to the current formulation of recombinant factor VIIa.[98]

In conclusion, studies have shown recombinant factor VIIa to be effective and generally well tolerated when used intravenously to treat bleeding episodes or provide hemostatic cover during surgery in patients with congenital hemophilia with inhibitors, acquired hemophilia, factor VII deficiency or Glanzmann thrombasthenia. Based on available data, its efficacy in terms of patient-assessed response may be similar to that of aPCC, but treatment with a single 270 μg/kg dose of recombinant factor VIIa might reduce the need for rescue therapy compared with aPCC. Recombinant factor VIIa is not immunogenic in patients with hemophilia, does not produce an anamnestic response in hemophilia patients with inhibitors, and has very low thrombogenicity. It is recommended in guidelines as the treatment of choice for bleeds in patients with hemophilia B with high-responding inhibitors and for patients with factor VII deficiency, and is also a first-line therapeutic option for high-responder hemophilia A patients with inhibitors and those with acquired hemophilia. Cost data from pharmacoeconomic analyses support its use in hemophilia patients with inhibitors. Thus, recombinant factor VIIa is a valuable treatment option for patients with these rare, but potentially serious, bleeding disorders.

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