

Elective Orthopedic Surgery for Hemophilia Patients With Inhibitors: New Opportunities

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We report a series of 108 elective orthopedic surgical procedures in hemophilia patients with inhibitors, comprising 88 cases in which radiosynoviorrhesis was performed and 20 cases in which major orthopedic procedures were carried out. Hemostatic cover was provided by recombinant factor VIIa (rFVIIa, NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark) in 17 cases, and by FVIII anti-inhibitor product (FEIBA, Baxter Corp, Toronto, Canada) in the remaining three procedures. A total of 51 patients from nine centers worldwide were included. The results of the procedures were characterized as good (82 procedures), fair (15), or poor (11). Postoperative bleeding complications requiring further surgical intervention occurred in three (15%) of the 20 major orthopedic procedures; all three procedures used rFVIIa as a hemostatic agent. Despite these complications, however, our study has shown that rFVIIa allows hemophilic patients with high inhibitor titers to undergo elective orthopedic surgery (EOS) with a greater expectation of success, leading to an improved quality of life. Thorough analysis of each case as part of a multidisciplinary team will help to identify further inhibitor patients in whom EOS can be performed both safely and effectively.

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THE DEVELOPMENT of alloantibodies (inhibitors) to factor VIII (FVIII) or factor IX (FIX) is the commonest, and most serious, complication of replacement therapy in patients with hemophilia A or B.²⁸ Inhibitor development results from the use of virus-inactivated, plasma-derived concentrates (such as prothrombin complex concentrates [PCCs], activated prothrombin complex concentrates [aPCCs]) or recombinant products (such as rFVIII or rFIX). When present, the inhibitor neutralizes the biological activity of infused FVIII or FIX, which renders classical substitution therapy ineffective.

It is estimated that inhibitors develop in 10% to 30% of patients with severe hemophilia A^{2,5,7,21} and in 2% to 5% of patients with severe hemophilia B or mild/moderate hemophilia A.¹⁷ The presence of the inhibitor is detected and monitored using the Bethesda assay, which is performed as part of the regular follow-up for all hemophilic patients treated with plasma-derived or recombinant products. In patients with inhibitors, the inhibitor titer decreases and may become undetectable if no FVIII- or FIX-containing products are used for a long period. However, subsequent challenges with such products typically produce an anamnestic response, in which the inhibitor rapidly reappears.

Two approaches for the management of patients with inhibitors have been proposed. The first option is the use of immune tolerance induction, which involves the administration of high-dose FVIII or FIX once or twice daily for a period of a few months to several years. This procedure may completely eliminate the inhibitor, allowing the patient to be treated effectively with FVIII or FIX once again.^{1,4} However,

immune tolerance induction fails in around 20% of cases, and is not recommended for all patients due to the high probability of failure or adverse events. Furthermore, this procedure is very costly.

The second option is to treat bleeding episodes with PCCs or aPCCs, such as anti-inhibitor coagulant complex (Autoplex, Baxter Healthcare Corp, Glendale, CA) and FVIII anti-inhibitor product (FEIBA, Baxter Corp, Toronto, Canada).^{9,12,13} More recently, recombinant activated factor VIIa (rFVIIa; NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark) has presented an effective therapeutic option for inhibitor patients.^{8,10,25,34}

In those situations where aPCCs or rFVIIa are ineffective in controlling life- or limb-threatening bleeds, or where they fail as first-line treatments for major bleeds, human FIX or high-dose human⁶ or porcine³ FVIII may be efficacious if the inhibitor titer

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1. our study has shown that rFVIIa allows hemophilic patients with high inhibitor titers to undergo el...

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is low, or if it can be reduced using plasmapheresis¹⁹ or protein A immunoadsorption.¹¹ Such treatment will, however, provoke an anamnestic response and subsequent rise in inhibitor levels, ensuring that treatment becomes ineffective within a few days. The patient may then become resistant to rescue therapy with FVIII or FIX for months or even years.

The presence of inhibitors presents further complications during surgery in hemophilic patients. Until 10 years ago, major procedures such as elective orthopedic surgery (EOS) were rarely undertaken in inhibitor patients, but recent advances in our knowledge of effective hemostatic agents have addressed the urgent need for products that enable such procedures to take place. Agents such as aPCCs, porcine FVIII, and high-dose human FVIII have all been used during orthopedic surgical procedures in hemophilia patients with inhibitors. Despite the long-standing availability of these products, however, there is little existing information regarding their use during surgical procedures in inhibitor patients. For example, although aPCCs have been available for more than 20 years, the literature contains very few reports of their use in major EOS.^{18,23} Similarly, there are few reported instances in which porcine FVIII has been used to provide hemostatic cover for inhibitor patients undergoing EOS. In one study, porcine FVIII was used in 19 orthopedic procedures in hemophilia A patients with inhibitors. Despite fair or good results, the inhibitor titer for both human and porcine FVIII increased in several patients.⁶

A small number of reports describe the use of high-dose human FVIII in EOS, with or without previous lowering of the inhibitor titer by plasmapheresis or protein A immunoadsorption.^{1,11,34} However, even if the inhibitor titer allows an effective level of circulating FVIII and the treatment provides efficient hemostatic cover, the anamnestic rise in inhibitor levels induces an increased risk of rebleeding in the second postoperative week.^{1,11} Consequently, the number of elective orthopedic procedures carried out using high-dose human FVIII remains low.

These observations imply that there is a clear need for an alternative hemostatic agent, with favorable safety and efficacy profiles, for use during EOS in inhibitor patients. We report a nine-center experience of EOS in hemophilia patients with inhibitors, using either rFVIIa or FEIBA to provide hemostatic cover.

Materials and Methods

Data have been collected on 51 hemophilia patients with inhibitors undergoing EOS in nine centers worldwide. Of 108 surgical procedures examined, 88 involved radiosynoviorthesis and 20 were major or-

thopedic procedures. The average age of the entire patient group was 22.5 years (range, 5 to 40) and the average follow-up period was 2 years (range, 1 to 5).

Radiosynoviorthesis was performed in 88 joints of 41 patients (33 knees, 29 elbows, and 26 ankles). A total of 20 joints were injected with radioactive gold (¹⁹⁸Au), 25 with yttrium (⁹⁰Y), 42 with phosphorus (³²P), and one with erbium (¹⁶⁹Er). The average age of patients in this group was 14.3 years (range, 5 to 40), and the average follow-up period was 6.5 years (range, 1 to 10). Of the 88 joints undergoing the procedure, 31 were covered using rFVIIa (one dose of 150 µg/kg before the procedure, followed by three doses of 150 µg/kg at 2-hour intervals post-surgery), 47 with FEIBA (100 U before surgery, a further 100 U 6 hours later, and 50 U at 12-hour intervals for 4 to 5 days postsurgery), and 10 with other methods (high-dose FVIII or FIX with or without cyclophosphamide, or immune tolerance induction according to the Malmö model with or without protein A adsorption).

A total of 20 major orthopedic procedures were performed in 10 patients, including six total knee arthroplasties, four fixations of bone fractures (one femoral neck fracture, one fracture of the patella, one supracondylar fracture of the femur, and one metacarpal fracture), two total hip arthroplasties, two



Figure 1. Hemophilic pseudotumor of the leg in a patient with inhibitors.

1. A total of 20 major orthopedic procedures were performed in 10 patients, including six total knee a...

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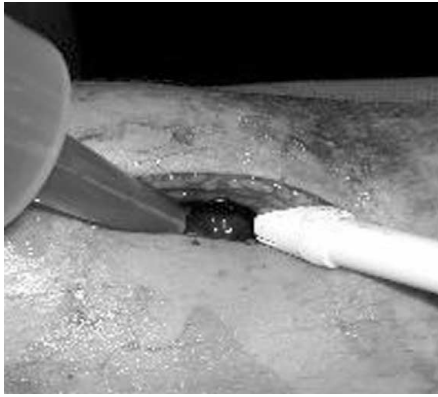


Figure 2. Aspiration of the pseudotumor contents.

removals of pseudotumors (Figs 1 to 4), and one each of the following: hip osteotomy (varus osteotomy); removal of hip osteotomy osteosynthetic material; ankle arthrodesis; elbow synovectomy; forearm fasciotomy; and knee arthroscopic debridement. Recombinant FVIIa was used to provide hemostatic cover in 17 of the surgical procedures (eight patients), and FEIBA was used in the remaining three procedures (two patients). The decision to use rFVIIa or FEIBA was based upon each investigator's preference; rFVIIa was chosen in the majority of cases due to previous experience of greater efficacy during orthopedic procedures.

Follow-up evaluation used the clinical and radiological classification of the Orthopedic Advisory



Figure 4. The pseudotumor 3 months after surgery.

Committee of the World Federation of Hemophilia (WFH).²⁴ This classification considers pain, bleeding, clinical features, and radiographical changes (Tables 1 and 2).

Results

The results of this study are summarized in Table 3. The clinical and radiological condition of the treated joints was evaluated prior to treatment and during follow-up. A good result was considered to be a decrease of more than 5 points on the classification and grading system; a fair result was no change or a decrease of up to 5 points; and a poor result was any increase in the joint score.²⁴ Overall, there were 82 good results, 15 fair, and 11 poor.

In the radiosynoviorthesis group, there were good results in 66 procedures, fair results in 14, and poor results in eight. No complications were encountered in this group (Table 3). Among the 31 procedures using rFVIIa, there were 23 good results, five fair outcomes, and three poor results. FEIBA was used in 47 procedures, leading to 37 good, six fair, and four poor outcomes.



Figure 3. Filling the pseudotumor with hydroxyapatite.

Table 1. Clinical Classification and Grading of the Hemophilic Joint, as Proposed by the WFH¹⁹

Pain		
Grade 0	No pain, no functional deficit	
Grade 1	Mild pain; does not interfere with normal use; occasional analgesia	
Grade 2	Moderate pain; some interference with normal use; occasional analgesia	
Grade 3	Severe pain; interference with normal use; frequent analgesia-narcotic	
Bleeding		
Grade 0	No hemorrhages	
Grade 1	No major hemorrhages; 1-3 minor hemorrhages	
Grade 2	1-2 major hemorrhages; 4-6 minor hemorrhages	
Grade 3	≥3 major hemorrhages; ≥7 minor hemorrhages	
Clinical Features (total score: 0-12)		Score
Swelling		
Nil		0
Present		2
Muscle atrophy		
Nil		0
Present		2
Axial deformity		
Nil		0
20-30° valgus (5° varus)		1
>30° valgus (>5° varus)		2
Joint crepitus		
Nil		0
Present		1
Range of movement (ROM)		
<10% loss of total ROM		0
10-30% loss		1
>30% loss		2
Flexion contracture		
<15°		0
>15°		2
Instability		
Nil		0
Present; function unaffected		1
Present; interferes with function		2

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Of the 20 major orthopedic procedures performed, 16 produced good results, one produced fair results, and the remaining three led to a poor outcome. A total of 17 procedures were undertaken using rFVIIa as a means of hemostatic cover, leading to 14 good results, one fair result, and two poor outcomes (Table 3). FEIBA was used in three procedures, producing two good results and one poor outcome (Table 3).

Postoperative complications were observed following three procedures. In two cases of total knee arthroplasty, postoperative bleeding required further surgical intervention involving surgical drainage of the joint. In one of the four procedures involving fixation of fractures (femoral neck fracture), the presence of a hemophilic pseudotumor in the thigh necessitated surgical removal by means of a second procedure (Table 3).

Discussion

In this multicenter study, 108 elective orthopedic procedures were performed on 51 hemophilic patients with inhibitors. Radiosynoviorthesis was performed on 88 joints of 41 patients suffering from chronic hemophilic synovitis and recurrent hemarthroses. The outcome was considered to be good (66 procedures), fair (14), or poor (8). Of the 88 joints undergoing radiosynoviorthesis, 31 were treated with rFVIIa, resulting in 23 good, five fair, and three poor outcomes. Of 47 procedures performed using FEIBA, there were 37 good results, six fair outcomes, and four poor results. The remaining 10 procedures were covered with other methods (either high-dose FVIII or FIX with or without cyclophosphamide, or immune tolerance induction according to the Malmö model with or without protein A adsorption) (Table 3).

Table 2. Radiographical Classification, as Proposed by the WFH¹⁹

Type of Change	Finding	Score
Osteoporosis	Absent	0
	Present	1
Enlarged epiphysis	Absent	0
	Present	1
Irregular subchondral bone	Absent	0
	Surface partly involved	1
	Surface totally involved	2
Narrowing of joint space	Absent	0
	Joint space >1 mm	1
	Joint space <1 mm	2
Subchondral cyst formation	Absent	0
	1 cyst	1
	>1 cyst	2
Erosions at joint margins	Absent	0
	Present	1
Incongruence of joint surface	Absent	0
	Slight	1
	Pronounced	2
Joint deformity	Absent	0
	Slight	1
	Pronounced	2

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Table 3. Main Results: 108 Cases of EOS¹

Procedure	No. of Procedures	Hematological Treatment	Result*	Complications
Radiosynoviorthesis	88	FEIBA: 47 rFVIIa: 31 Other: 10	Good:66 Fair:14 Poor: 8	None
Major EOS				
Total knee arthroplasty	6	rFVIIa	Good: 3 Fair: 1 Poor: 2	2 postoperative bleedings
Fixation of fractures	4	rFVIIa	Good: 4	Thigh pseudotumor following fixation of femoral neck fracture
Total hip arthroplasty	2	rFVIIa	Good: 2	None
Hip osteotomy (varus osteotomy)	1	FEIBA	Good	None
Removal of osteosynthetic material	1	FEIBA	Good	None
Ankle arthrodesis	1	rFVIIa	Good	None
Elbow synovectomy	1	rFVIIa	Good	None
Removal of pseudotumor	2	rFVIIa	Good: 2	None
Forearm fasciotomy	1	rFVIIa	Good	None
Knee arthroscopic debridement	1	FEIBA	Poor	None

* Good: a decrease of more than 5 points on the classification and grading system; fair: no change or a decrease of up to 5 points; poor: an increase in the joint score.

There were 20 procedures involving major EOS (10 patients). In this group, there were 16 good results, one fair outcome, and three poor results (Table 3). Recombinant FVIIa was used in 17 (eight patients) of the 20 procedures undertaken, leading to 14 good, one fair, and two poor results. The remaining three procedures (two patients) used FEIBA, resulting in two good outcomes and one poor result (Table 3).

We believe that this series of 108 major EOS procedures is the largest ever reported in hemophilic patients with inhibitors, despite the long-standing availability of traditional hemostatic agents, such as aPCCs, porcine FVIII, and high-dose human FVIII. The literature contains few reports in which these agents are used successfully and safely during EOS in inhibitor patients, suggesting that there exists a need for an alternative agent that can be used to provide safe and effective hemostatic cover in this indication.

As the current series confirms, the use of rFVIIa allows such procedures to be performed safely and effectively in patients with high-titer inhibitors (>5 Bethesda units [BU]/mL). Without rFVIIa, the majority of the procedures undertaken in our study may not have been possible, due to the likelihood that even high doses of human or porcine FVIII would have been unable to overcome the inhibitor.

Our study therefore reflects the findings of previous reports describing the successful use of rFVIIa during EOS in hemophilic inhibitor patients. The first such documented case involved a surgical knee synovectomy in a patient with hemophilia A and a

high inhibitor titer.⁹ The procedure was performed under general anesthesia, and without a tourniquet. In addition to rFVIIa, hemostasis was managed using fibrin glue locally along with general antifibrinolytic drugs, but without electrocoagulation. The result was considered to be excellent, with no abnormal bleeding during or after surgery, and no adverse events. Subsequently, two open surgical synovectomies (knee and ankle) were performed using rFVIIa, antifibrinolytic drugs, and fibrin glue, with an excellent outcome.³¹ A complex orthopedic surgical procedure (knee synovectomy, hamstring release, posterior capsulotomy, proximal and distal realignment of the extensor mechanism, and supracondylar extension-varus osteotomy stabilized with a blade-plate sliding screw) was performed in a young hemophilic patient with inhibitors to correct a 90-degree flexion contracture of the right knee associated with a valgus deformity, which rendered the patient unable to walk and confined to a wheelchair.²² The procedure lasted 3 hours, 160 minutes of which were under ischemic conditions. Recombinant FVIIa and antifibrinolytic agents provided hemostatic cover during the pre-, peri-, and postoperative periods. The surgical treatment produced excellent results, and no bleeding complications were observed.

Based on findings from these early case studies on the use of rFVIIa in EOS,^{9,22,31} a recommended dose of 90 µg/kg body weight rFVIIa every 2 hours for 24 to 48 hours was proposed for surgical procedures in hemophilic patients.

Later reports^{14-16,27,29,30} described further experi-

1. Main Results: 108 Cases of EOS

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ences or data analyses of elective orthopedic procedures using rFVIIa in hemophilic inhibitor patients. A total of 53 major surgical procedures were reported. Most were performed using the standard rFVIIa treatment regimen of 90 $\mu\text{g}/\text{kg}$ body weight every 2 hours for 24 to 48 hours,^{16,22,31} with an increasing interval between doses after the first 2 days (as recommended by the European Approval for rFVIIa). In contrast, some procedures used continuous infusion of rFVIIa.^{27,29,30} In most cases, oral antifibrinolytic drugs were used in combination with rFVIIa.

The efficacy and clinical tolerance of rFVIIa were considered to be excellent in the majority of these cases. Moderate bleeding complications were observed in two patients treated with continuous infusion of rFVIIa.^{29,30} Additionally, some moderate bleeding complications were seen in a prospective, randomized trial of rFVIIa in hemophilia patients with inhibitors undergoing EOS. The study compared the efficacy of the standard dosing regimen (90 $\mu\text{g}/\text{kg}$ body weight every 2 hours) with that of a lower dose (35 $\mu\text{g}/\text{kg}$ body weight every 2 hours).³³ In the 90- $\mu\text{g}/\text{kg}$ group, 83% of patients undergoing major surgery demonstrated satisfactory postoperative hemostasis until day 5. However, efficacy of the 35- $\mu\text{g}/\text{kg}$ dose dropped from 80% at postoperative day 1 to 40% at day 5. A hemarthrosis was observed at postoperative day 7 following knee arthroplasty in a patient treated according to the standard regimen, and postoperative bleeding was observed in three patients treated with the lower dose (bleeding in the early postoperative period in two patients, and moderate bleeding at day 19 in a third). Rescue therapy was initiated with aPCCs in the first case (postoperative hemarthrosis), with human or porcine FVIII in the two cases of early postoperative bleeding, and with antifibrinolytic agents in the final case.³³

To date, there have been no reports of serious adverse events associated with rFVIIa use in hemophilic inhibitor patients undergoing EOS, with the exception of one case of disseminated intravascular coagulation in a patient treated with continuous infusion of rFVIIa for excision of an infected pseudotumor.³⁰

The safety and efficacy data available in the current literature on rFVIIa use in hemophilic inhibitor patients undergoing EOS are reflected in the findings of the current study. Radiosynoviothetosis was performed in 88 joints (41 patients), and hemostatic cover was provided by rFVIIa in 31 (35%) procedures. No adverse events or complications were observed.

Of the 20 major orthopedic surgical procedures performed in our series (Table 3), three (15%) resulted in severe complications that required further surgical intervention. All three procedures in which

complications arose were performed under rFVIIa cover. In two cases, development of hemarthroses followed two total knee arthroplasties, necessitating surgical evacuation of the intra-articular bleeding. The third complication involved a hemophilic pseudotumor in the thigh following fixation of a femoral neck fracture. The pseudotumor was removed by a new surgical procedure, with satisfactory results.

Data from the current study support the theory that rFVIIa represents an alternative option for use in major EOS in hemophilia patients with inhibitors.^{14,32} The standard dose is 90 $\mu\text{g}/\text{kg}$ body weight every 2 hours for 24 to 48 hours postoperatively, with increasing intervals between doses after this period. Lower doses appear to be less effective,¹⁵ and administration by continuous infusion is not yet approved, as several bleeding episodes and one case of disseminated intravascular coagulation have been reported following this administration method.^{29,30} A recent study investigating inhibitor patients undergoing orthopedic surgery found that continuous infusion of rFVIIa must maintain plasma FVII:C levels at ≥ 30 IU/mL in order to secure hemostasis.²⁰ This requires an initial bolus dose of 90 $\mu\text{g}/\text{kg}$ followed by continuous infusion of 50 $\mu\text{g}/\text{kg}/\text{h}$, a treatment regimen that is more expensive than the standard bolus dose of 90 $\mu\text{g}/\text{kg}$ every 2 to 3 hours. Additional studies are required to investigate further the safety and efficacy of continuous rFVIIa infusion.

An ongoing study from the Centers for Disease Control and Prevention in the United States is investigating 123 orthopedic procedures performed under rFVIIa cover on 65 hemophilic patients with inhibitors (personal communication with Bruce Evatts). Radiosynoviothetosis has been carried out in 59 cases, and the remaining procedures involved other types of orthopedic surgery (14 joint replacements, 13 arthroscopic synovectomies, seven cases of arthrodesis, six open synovectomies, and 23 other procedures). The results of this large study are eagerly awaited, as they will provide a significant contribution to the current knowledge of rFVIIa use in hemophilic inhibitor patients undergoing EOS. It is expected that such increased knowledge, combined with current data and observations, will facilitate the performance of major EOS in a greater number of hemophilia patients with inhibitors.

Conclusions

Orthopedic surgery requires effective hemostasis in order to reduce the incidence of wound hematomas, which may become infected and jeopardize the long-term outcome. Success depends not only on appropriate drug therapy, but also on the preparations

undertaken prior to surgery as well as adequate surveillance during and after the procedure.

Until a decade ago, major surgery in patients with hemophilia and inhibitors was extremely rare. Since that time, however, substantial experience of various agents that provide hemostatic cover during surgical procedures has been gained, and recent and contemporary advances in the orthopedic and hematological arenas have allowed us to successfully perform major orthopedic operations on hemophilic patients with inhibitors. As shown by our series of cases, and by data in the current literature, provision of effective hemostatic cover facilitates such procedures in hemophilic patients with a success rate that could not have been expected until relatively recently, leading to significant improvements in quality of life. During EOS, however, there still remains a higher risk of bleeding complications in hemophilic patients with inhibitors than in those without.^{14,26,27}

The current study suggests that rFVIIa allows hemophilic patients with high inhibitor titers to safely undergo EOS, with a greater expectation of success. Thorough analysis of the cases presented in this article will help to identify further opportunities in which EOS can be performed both safely and effectively, and will allow a wider range of hemophilic inhibitor patients to receive the EOS that they need. Although these preliminary data are encouraging, a larger, prospective, randomized, multicenter study is needed to confirm the findings of this study.

References

1. Abildgaard CF, Penner JA, Watson-Williams EJ: Anti-inhibitor coagulant complex (Autoplex) for treatment of factor VIII inhibitors in hemophilia. *Blood* 56:978-984, 1980
2. Addiego J, Kasper CK, Abildgaard C, et al: Frequency of inhibitor development in haemophiliacs treated with low-purity factor VIII. *Lancet* 342:462-464, 1993
3. Bona RD, Pasquale DN, Kalish RI, et al: Porcine factor VIII and plasmapheresis in the management of hemophilic patients with inhibitors. *Am J Hematol* 21:201-207, 1986
4. Brackmann HH, Oldenburg J, Schwaab R: Immune tolerance for the treatment of factor VIII inhibitors—Twenty years' 'Bonn protocol'. *Vox Sang* 70:30-35, 1996 (suppl)
5. Bray GL, Gomperts ED, Courter S, et al: A multicenter study of recombinant factor VIII (Recombinate): Safety, efficacy and inhibitor risk in previously untreated patients with hemophilia A. The Recombinate Study Group. *Blood* 83:2428-2435, 1994
6. Brettler DB, Forsberg AD, Lavine PH, et al: The use of porcine factor VIII concentrate (Hyate C) in the treatment of patients with inhibitor antibodies to factor VIII. A multicenter US experience. *Arch Intern Med* 149:1381-1385, 1989
7. Ehrenforth S, Kreutz W, Scharrer I, et al: Incidence of development of FVIII and FIX inhibitors in haemophiliac. *Lancet* 339:594-598, 1992
8. Hedner U, Glazer S, Falch J: Recombinant activated factor VII in the treatment of bleeding episodes in patients with inherited and acquired bleeding disorders. *Transfus Med Rev* 7:78-83, 1993
9. Hedner U, Glazer S, Pingel K, et al: Successful use of recombinant factor VIIa in a patient with severe haemophilia A during synovectomy. *Lancet* 2:1193-1197, 1988
10. Hedner U, Ingerslev J: Clinical use of recombinant FVIIa (rFVIIa). *Transfus Sci* 19:163-176, 1998
11. Heisel MA, Gomperts ED, McComb JG, et al: Use of activated prothrombin complex concentrate over multiple surgical episodes in a hemophilic child with an inhibitor. *J Pediatr* 102:951-954, 1983
12. Hilgartner M, Aledort L, Andes A, et al: Efficacy and safety of vapor-heated anti-inhibitor coagulant complex in hemophilia patients. FEIBA Study Group. *Transfusion* 30:626-630, 1990
13. Hilgartner MW, Knatterud GL: The use of factor eight inhibitor by-passing activity (FEIBA immuno) product for treatment of bleeding episodes in hemophiliacs with inhibitors. *Blood* 61:36-40, 1983
14. Hvid I, Rodriguez-Merchan EC: Orthopaedic surgery in haemophilic patients with inhibitors: An overview. *Haemophilia* 8:288-291, 2002
15. Hvid I, Soballe K, Ingerslev J: Elective orthopaedic surgery in haemophilia patients with high responding inhibitors, in Rodriguez-Merchan EC, Lee CA (eds): *Inhibitors in Patients With Haemophilia*. Oxford, UK, Blackwell, 2002, pp 169-176
16. Ingerslev J, Freidman D, Gastineau D, et al: Major surgery in haemophilic patients with inhibitors using recombinant factor VIIa. *Haemostasis* 26:118-123, 1996 (suppl)
17. Ingerslev J: Efficacy and safety of recombinant factor VIIa in the prophylaxis of bleeding in various surgical procedures in hemophilic patients with factor VIII and factor IX inhibitors. *Semin Thromb Hemost* 26:425-432, 2000
18. Leissinger CA: Use of prothrombin complex concentrates and activated prothrombin complex concentrates as prophylactic therapy in haemophilia patients with inhibitors. *Haemophilia* 5:25-32, 1999 (suppl)
19. Lozier JN, Santagostino E, Kasper CK, et al: Use of porcine factor VIII for surgical procedures in hemophilia A patients with inhibitors. *Semin Hematol* 30:10-21, 1993 (suppl)
20. Ludlam CA, Smith MP, Morfini M, et al: A prospective study of recombinant activated factor VII administered by continuous infusion to inhibitor patients undergoing elective major orthopaedic surgery: A pharmacokinetic and efficacy evaluation. *Br J Haematol* 120:808-813, 2003
21. Lusher JM, Arkin S, Abildgaard CF, et al: Recombinant factor VIII for the treatment of previously untreated patients with hemophilia. A. Safety, efficacy, and development of inhibitors. Kogenate Previously Untreated Patient Study Group. *N Engl J Med* 328:453-459, 1993
22. O'Maricaigh AS, Schmalz BJ, Shaughnessy WJ, et al: Successful hemostasis during a major orthopedic operation by using recombinant activated factor VII in a patient with severe hemophilia A and a potent inhibitor. *Mayo Clin Proc* 69:641-644, 1994
23. Penner JA: Management of haemophilia in patients with high-titre inhibitors: focus on the evolution of activated prothrombin complex concentrate AUTOPLEX T. *Haemophilia* 5:1-9, 1999 (suppl)
24. Pettersson H, Gilbert MS: Clinical and radiological evaluations of hemophilic arthropathy, in Pettersson H, Gilbert MS (eds): *Diagnostic Imaging in Hemophilia*. Berlin, Germany, Springer-Verlag, 1985, pp 56-68
25. Roberts HR: Clinical experience with activated factor VII: Focus on safety aspects. *Blood Coagul Fibrinolysis* 9:S115-S118, 1998 (suppl)
26. Rodriguez-Merchan EC (ed): *The Haemophilic Joints: New Perspectives*. Oxford, UK, Blackwell, 2003
27. Rodriguez-Merchan EC, de la Corte H: Orthopaedic surgery

- in haemophilic patients with inhibitors: A review of the literature, in Rodriguez-Merchan EC, Goddard NJ, Lee CA (eds): *Musculoskeletal Aspects of Haemophilia*. Oxford, UK, Blackwell, 2000, pp 136-142
28. Scharrer I, Bray GL, Neutzling O: Incidences of inhibitors in haemophilia A patients—A review of recent studies of recombinant and plasma-derived factor VIII concentrates. *Haemophilia* 5:145-154, 1999
29. Schulman S, Bech Jensen M, Varon D, et al: Feasibility of using recombinant factor VIIa in continuous infusion. *Thromb Haemost* 75:432-436, 1996
30. Schulman S, d'Oiron R, Martinowitz U, et al: Experiences with continuous infusion of recombinant activated factor VII. *Blood Coagul Fibrinolysis* 9:S97-S101, 1998 (suppl)
31. Schulman S, Lindstedt M, Alberts KA, et al: Recombinant factor VIIa in a multiple surgery. *Thromb Haemost* 71:154, 1994 (letter)
32. Schulmann S: Joint surgery in patients with inhibitors, in Rodriguez-Merchan EC (ed): *The Haemophilic Joints: New Perspectives*. Oxford, UK, Blackwell, 2003, pp 56-62
33. Shapiro AD, Gilchrist GS, Hoots WK, et al: Prospective, randomised trial of two doses of rFVIIa (NovoSeven) in haemophilia patients with inhibitors undergoing surgery. *Thromb Haemost* 80:773-778, 1998
34. White GC 2nd, Taylor RE, Blatt PM, et al: Treatment of a high titer anti-factor-VIII antibody by continuous factor VIII administration: Report of a case. *Blood* 62:141-145, 1983