

Prophylaxis in 10 patients with severe haemophilia A and inhibitor: different approaches for different clinical situations

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Summary. The effect of bypassing agents is not as predictable as replacement therapy with the deficient factor in inhibitor patients. Consequently, these patients have more levels of arthropathy than patients without inhibitors. Prophylaxis for inhibitor patients has gained attention over the last decade and some papers have reported that bypassing agents could work in the prevention of arthropathy. However, there is a lack data to support any specific agent or regimen or even to recommend their use in different clinical conditions. We report ten patients with haemophilia A and inhibitors treated prophylactically with bypassing agents (5 with FEIBA and 5 with NovoSeven). The variable conditioning the choice of one agent or the other was the intention to initiate of immune tolerance induction therapy (ITI) in the future. In 8/10 patients (4 in FEIBA group

and 4 in rFVIIa group) there was a decrease of bleeding episodes while 9/10 maintained or increased their joint range of motion (ROM). In the rFVIIa prophylaxis group, prophylaxis can be considered primary since all of them had had less than one joint bleed before prophylaxis. Economic analysis showed that prophylaxis is an expensive treatment. In our experience both agents seem to be safe and effective in reducing the number of bleeds in patients with inhibitors. The anamnestic response provoked by FEIBA could be an issue while awaiting a decline in titres before ITI can be initiated and so rFVIIa may be the best option for prophylaxis in patients with inhibitors who have not yet begun ITI.

Keywords: bypassing agent, haemophilia, inhibitors, prophylaxis

Introduction

Patients with severe haemophilia present recurrent haemorrhages, especially in joints, muscles and soft tissues. Joint haemorrhage predisposes to recurrent haemarthrosis, chronic synovitis and arthropathy. Factor replacement is the mainstay therapy to prevent and control this recurrent joint bleeding. Prophylaxis with the deficient factor can prevent joint damage and decrease the frequency of haemarthrosis and life-threatening haemorrhages [1].

The development of antibodies that inhibit or neutralize replacement therapy with factor VIII (FVIII) or factor IX (FIX) is the most important

complication in haemophilia and its treatment today. Inhibitors occur in 20–30% of patients with severe haemophilia A but in only 5% of patients with haemophilia B [2,3]. Agents that ‘bypass’ the need for FVIII or FIX are the cornerstone in on-demand treatment for acute bleeds: activated prothrombin complex concentrates (aPCC; FEIBA, Baxter Bioscience, Vienna, Austria) and NovoSeven, a recombinant activated Factor VII (rFVIIa; Novo Nordisk, Bagsvaerd, Denmark). However, their effect is not as predictable as replacement therapy with the deficient factor, thus the control of bleeding is more complicated than in patients without inhibitors and consequently the inhibitor patients have higher arthropathy levels than patients without inhibitors [4,5]. Therefore, in recent years interest is growing in establishing the bypassing agent regimens that might prevent bleeding in inhibitor patients in much the same way that prophylaxis works in non-inhibitor patients [3,6].

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However, there is limited data to support any specific agent or regimen or to indicate what would be the best to use in different clinical situations.

Recent emerging data suggest that prophylaxis could be an effective and safe treatment for inhibitor patients in different clinical settings while a waiting antibody levels to decline, after inhibitor development so ITI can be initiated, in patients who failed or who not are candidates for ITI, and, finally, in association with FVIII or FIX during ITI [6–20].

The effect of FEIBA may last longer than that of NovoSeven, because targets in different sites in the thrombin-inducing coagulation cascade inducing a half-life thrombin generation within 4–7 h [21], making the former a more suitable agent for prophylaxis in patients with inhibitors. But FEIBA contains residual FVIII antigen and may provoke an anamnestic response in the inhibitor titre [22].

Several studies have reported that an inhibitor titre of <10 Bethesda Units (BU) immediately before initiating ITI positively affects both the likelihood of success and the time required to achieve tolerance [23–26]. Therefore, based on these considerations the schedule for the future initiation of ITI in patients with an inhibitor titre >10 BU could affect the choice of agent. Cost issues about prophylaxis have hardly been explored [23]. With this perspective, we describe our global experience with the use of rFVIIa and FEIBA as the sole agents for prophylaxis in patients with haemophilia A and inhibitors.

Materials and methods

A retrospective study was conducted in our centre in February 2008 to identify cases and analyse the efficacy, cost and safety of bypassing agents as prophylaxis for patients with haemophilia and inhibitor. The audit covered all inhibitor patients seen over the last 5 years and evaluated only treatments of more than 4 months' duration in which bypassing agents were used as the only haemostatic agent. The following clinical and demographic data were collected from patient's records: age at inhibitor development, type and severity of haemophilia, peak inhibitor titre, age at the start of prophylaxis, prophylaxis agent and regimen, presence of central venous catheter (CVC), duration of treatment and reason for indicating prophylaxis.

The number of months before prophylaxis to be analysed was the same as the number of months that prophylaxis lasted except when prophylaxis had lasted more than a year; in that case only the 12 months prior to prophylaxis were analysed for bleeding episodes.

Orthopaedic status was analysed collecting data on range of motion (ROM) on 10 joints: ankles (normal: dorsiflexion 20°, plantarflexion 50°), knees (normal: flexion 140°, extension 0°), hips (normal: flexion 120°, extension 20°), elbows (normal: flexion 140°, extension 0°) and shoulders (normal: flexion 160°, extension 40°). ROM was measured with a goniometer expressed as degrees and collected from the charts for the patient's regular visits.

Safety was evaluated by the number of complications arising from the use of bypassing agents, especially thromboembolisms and complications associated with the use of CVC. The possible anamnestic response by inhibitor titre was evaluated by comparing inhibitor titre before and at the end of prophylaxis.

The economic analysis has been done under a hospital perspective, evaluating the cost of the factor and the visit to the hospital and doctor. The total cost of all factor regimens used (on-demand bypassing agents, ITI, and on-demand or prophylactic FVIII) and additional factor used to cover bleeding episodes were included for both study periods: before and during prophylaxis.

Results

Patient characteristics

Ten patients with severe haemophilia A and inhibitor with FEIBA or NovoSeven as the only agent administered regularly for more than 4 months were identified from haemophiliac patients treated in our Hospital. Median age was 4 years old (range 1–31 years) and median duration for both groups was 12 months (range 6–24 months) (Table 1).

The aim of prophylaxis in both groups was to prevent or reduce bleeding complications and to slow joint damage or prevent it entirely, in cases without haemarthrosis. Patients under consideration for ITI received rFVIIa.

In 8/10 cases there was a reduction in the bleeding pattern during prophylaxis compared with the situation before prophylaxis. The median number of bleeding episodes per patient was 8.5 (3–19) before prophylaxis and 3 (0–10) during prophylaxis (Table 2).

FEIBA group

The median duration of prophylaxis was 13 months (11–24 months) and median age at initiation of prophylaxis was 11 years old (5–31 years) for patients receiving FEIBA (Table 1). The median

Table 1. Patient characteristics, regimens and duration of prophylaxis.

Patient	Age at development inhibitor (months)	Peak inhibitor titre (BU)	Age at the start of prophylaxis (years)	CVC during prophylaxis (complications)	Regimen	Duration (months)
1	10	297	19	Yes (No)	FEIBA 50 U kg ⁻¹ 3 times week ⁻¹	22
2	11	55	6	Yes (No)	FEIBA 50 U kg ⁻¹ 3 times week ⁻¹	24
3	36	2048	31	No	FEIBA 50 U kg ⁻¹ 48 h ⁻¹	11
4	1	256	7	Yes (no)	FEIBA 50 U kg 48 h ⁻¹	13
5	60	2230	11	Yes (infection)	FEIBA 50 U kg 48 h ⁻¹	11
6	25	440	2	Yes (malfunctioning, infection)	rFVIIa 90 µg kg ⁻¹ day ⁻¹	22
7	2	78	2	Yes (No)	rFVIIa 90 µg kg ⁻¹ day ⁻¹	6
8	34	115	2	Yes (infection)	rFVIIa 100 µg kg ⁻¹ day ⁻¹	9
9	18	11	1	Yes (no)	rFVIIa 100 µg kg ⁻¹ day ⁻¹	8
10	12	2048	4	Yes (no)	rFVIIa 90 µg kg ⁻¹ day ⁻¹	19

BU, Bethesda Units; CVC, central venous catheter.

Table 2. Bleeding pattern and ROM before and after prophylaxis.

Patient	Agent of prophylaxis	Bleeds and ROM before prophylaxis				Bleeds and ROM during prophylaxis			
		Joint	Muscle	Other bleed	ROM	Joint	Muscle	Other bleed	ROM
1	F	14	2	3	Right knee: flex: 130° ext 20° Left knee: flex normal ext 20°	19	1	2	Maintained
2	F	10	0	4	Right knee: flex 95° ext 50°	5	0	1	Right knee: flex 125° ext 20°
3	F	4	2	2	Right knee: flex: 120° ext 20° Left knee: flex 130 ext 30° Right elbow: flex 100° ext 10°	1	0	0	Maintained
4	F	6	2	1	Right ankle dorsiflex 10° plantarflex 10°	3	2	0	Normal
5	F	4	5	6	Normal	1	2	1	Normal
6	N	0	0	5	Normal	0	0	2	Normal
7	N	0	1	3	Normal	0	0	0	Normal
8	N	1	1	2	Normal	0	0	1	Normal
9	N	1	0	2	Right elbow: flex 90° ext 20°	0	0	0	Normal
10	N	1	0	9	Normal	4	0	1	Right knee: flex 75° ext 10

ROM, range of movement (extension-flexion); ext, extension; flex, flexion; dorsiflex, dorsiflexion; plantarflex, plantarflexion; F, FEIBA; N, NovoSeven.

number of bleeds per patient prior to prophylaxis was 14 (8–19) and during prophylaxis 5 (1–22) (Table 2). The number of bleeding episodes decreased in four out of five patients (patients 2, 3, 4 and 5). The total number of bleeding episodes increased in only one patient (patient 1), he had more joint bleeds but fewer bleeds in muscle and other tissues during prophylaxis than before.

Orthopaedic status before FEIBA prophylaxis was: three patients (numbers 1–3) had an important joint arthropathy with different target joints (Table 2). Patient 4 had a less extensive arthropathy with only one target joint (right ankle) and patient 5, despite an important joint bleeding pattern, started prophylaxis without a target joint. At the end of prophylaxis

two patients showed an improvement in ROM (patients 2 and 4) and three patients (1, 3 and 5) had the same ROM as before. Despite the increase in the number of joint bleeds during prophylaxis, ROM was similar in patient 1 to his level before prophylaxis. None of the patients had life-threatening bleeds during prophylaxis.

The median cost per patient per month was €59,398 (€31,495–110,687) prior to prophylaxis and €27,144 (€11,928–44,456) during prophylaxis (Table 3). In patients 1–3, the cost of prophylaxis was less than their previous on-demand treatment (mean cost per patient per month prior to prophylaxis was €63,632 vs. €31,974 per month for prophylaxis in these three patients). In patients 4

Table 3. Cost of treatment and inhibitor titre before and during prophylaxis.

Patient	Agent of prophylaxis	Treatment Schedule before prophylaxis	Cost prior to prophylaxis (euros per month)	Cost of prophylaxis + bleeding treatment (euros per month)	Inhibitor titre at the initiation of prophylaxis (BU)	Inhibitor titre at the end of prophylaxis (BU)
1	F	On-demand bypass agents	110 687	39 494	0.6	3.4
2	F	On-demand FEIBA	31 495	11 928	9.9	3.9
3	F	On-demand FEIBA	48 715	44 500	2048	1802
4	F	ITI + On-demand bypass agents	88 063	27 144	166	15
5	F	ITI+ On-demand bypass agents	59 398	27 144	140	230
6	N	On-demand FVIII	2094	24 404	440	8.8
7	N	ITI + on-demand rFVIIa	49 486	23 544	78	10
8	N	On-demand FVIII	6588	19 794	115	Ongoing (11)
9	N	On-demand FVIII	5044	29 588	11	<0.6
10	N	ITI + short (4 months) FEIBA prophylaxis +on-demand bypassing agents	62 062	26 432	210	16

F, Feiba; N, NovoSeven; BU, Bethesda Units.

and 5, the cost of prophylaxis was less than ITI associated to bypassing agent treatment (mean cost per patient per month prior to prophylaxis was €73,730 vs. €25,774 during prophylaxis).

NovoSeven group

The median treatment duration in this group was 9 months (6–22 months) with a median age of 2 years (1–4 years) (Table 1). The median number of bleeds per patient prior to rFVIIa prophylaxis was 4 (3–10) and during prophylaxis 1 (0–5). In all cases, the total number of bleeds was lower during rFVIIa prophylaxis than before. Patient 10 had more joint bleeds because he developed a target joint (right knee), and, like patient 1, his total number of bleed episodes was lower than before prophylaxis (Table 2).

In three patients (cases 6, 8 and 9) prophylaxis with rFVIIa was started after inhibitors developed.

In another two patients (patients 7 and 10) prophylaxis was started after ITI had failed and in order to reduce bleeds before initiating a second ITI protocol associated to immunosuppression.

Orthopaedic status (ROM) remained normal in three patients (patients 6–8), improved in one case (patient 9) but worsened in one (patient 10) (Table 2).

Patients 6 and 7 had not had any joint bleed before beginning prophylaxis and patients 8–10 had only had one joint bleed, all of five had had less than one haemarthrosis and a normal orthopaedic status when they began ITI. None of the patients had life-threatening bleeds during prophylaxis.

The median cost per patient per month prior to prophylaxis was €6588 (€2,094–62,062) and €23,544 (€19,794–29,588) during prophylaxis (Table 3). In patients 7 and 10, the cost of prophylaxis was less than their previous treatment of ITI plus on-demand bypassing agents (mean cost of per patient per month prior to prophylaxis was €55,774 vs. €23,544 per month for prophylaxis). In patients 6, 8 and 9 the cost of prophylaxis was more expensive than their prior FVIII treatment (mean cost per patient per month prior to prophylaxis €4,575 vs. €24,028 per month during prophylaxis).

Adverse events

No thromboembolic complications were detected in any patient. Patient 6 was treated with rFVIIa, and had difficulty in withdrawing blood from the port on one occasion, which was related to a mechanical problem with the port rather than a thrombotic complication. Nine patients had CVC, one-third (patients 5, 6 and 8) had port-a-cath infection and it was only necessary to replace the port-a-cath in patient 6.

Two patients in the FEIBA group showed an increase in their inhibitor titre after beginning prophylaxis (patients 1 and 5) (Table 3). None of the rFVIIa patients showed increased inhibitor titre with prophylaxis.

Discussion

Prophylaxis with FVIII has recently been shown to be more effective than episodic therapy in reducing the

incidence of joint haemorrhages and lowering the risk of joint damage in boys with severe haemophilia [1,27–29].

Inhibitor patients with an acute bleeding problem do not always respond satisfactorily to treatment with bypass agents [30]. Consequently, inhibitor patients have higher levels of arthropathy and greater difficulties with mobility and daily activities due to pain [4].

The use of prophylaxis for inhibitor patients has gained much interest in the last decade and some reports have supported the idea that bypassing agents could work to help prevent chronic haemophilic arthropathy in the same way as do FVIII/IX in haemophiliacs without inhibitors [6,7,17,19]. However, there are some concerns about efficacy, adverse events and cost and thus the justification for prophylaxis may be even more difficult for patients with inhibitors.

FEIBA has been used in more than 70 haemophilic patients with inhibitors in different clinical situations [8,13–15,17,31–34]. There is a wide variation in dose (23–100 IU) and frequency (two times per day to one week administration). The duration of treatment can be as long as 12 years. No adverse thromboembolic event has ever been published, and the decrease in the number of bleeding complications reported has dropped by 53 as much as 83% [8,13–15,17,31–34].

The aim of prophylaxis in our FEIBA cases was to reduce or prevent bleeding complications in patients in whom ITI had failed or who were not candidates. The FEIBA group were older than the rFVIIa group, and three FEIBA patients already had an important arthropathy with different target joints. In 4/5 patients there was a reduction in the bleeding pattern and one had overall, more bleeding episodes because he had more haemarthroses. This decrease in the number of bleeding complications was accompanied by sustained ROM in three patients and an improvement in the other two. The economic analysis in three patients showed that prophylaxis could be cheaper than on-demand bypassing treatment.

rFVIIa prophylaxis has been reported in nearly 45 patients with haemophilia and inhibitors [7,9–12,16,19,20], of these, 22 were included in a randomized, double-blind study and received prophylactic therapy with 90 or 270 $\mu\text{g kg}^{-1}$ rFVIIa once a day for 3 months. This study, by Konkle *et al.* [7], is the first prospective clinical trial evaluating secondary prophylaxis in patients with haemophilia and inhibitors. As compared to the preprophylaxis period, the frequency of bleeding episodes was reduced by 45% at the 90 $\mu\text{g kg}^{-1}$ dose and by

59% at the 270 $\mu\text{g kg}^{-1}$ dose and this difference between doses was no significant.

The aim of prophylaxis in our rFVIIa cases was to prevent or reduce bleeding complications in patients who were candidates for ITI. The five patients receiving rFVIIa prophylaxis were younger than the FEIBA group, and had not had more than one previous haemarthrosis, if that. Three of them had started the rFVIIa prophylaxis after developing inhibitors and while waiting for inhibitor levels to decline so they could start ITI. In these three patients there was a decrease in the number of bleeding complications and ROM improved in one, and remained the same in the other two. Something that must be underlined is that prophylaxis allowed these three patients to start ITI with less than one joint bleed and a normal ROM, just as they would have if they did not have inhibitors and primary prophylaxis had been possible.

The other two patients initiated rFVIIa prophylaxis after ITI failure and before another ITI with immunosuppression. One had had no prior joint bleeds and maintained his orthopaedic status. Nevertheless, one patient developed a target joint in the right knee during prophylaxis and his joint bleeds increased despite a reduction in the overall bleeding. Prophylaxis can be considered primary since all of them had had less than one joint bleed before starting prophylaxis.

The cost derived from prophylaxis is more expensive than the prior therapy with FVIII but cheaper than a prior ITI. So, despite an important economic cost, rFVIIa allowed 4/5 patients to start a first or second ITI with less than one haemarthrosis and a normal orthopaedic status.

The incidence of serious adverse events associated with the use of both bypassing agent is very low in patients with haemophilia and inhibitor [35,36]. In our experience there have been no thrombotic complications although three patients had a port-a-cath infection.

Our report here has a few caveats. First, our case number is relatively low and a short follow-up for most of them. Second, this report is retrospective, which could affect the accuracy of the data collected. Additionally, two of our patients had not yet developed any joint bleed prior to the initiation of prophylaxis. The age at first joint bleed is reported to range from 0.2 to 5.8 years with a median at 1.8 years [37] and given our patients' phenotype, they would not have had any joint bleeds until later.

In conclusion, our experience suggests that FEIBA and NovoSeven seem to be close in terms of efficacy and safety in decreasing the frequency of bleeding

episodes in patients with haemophilia and inhibitors. The anamnestic response provoked by FEIBA could be an issue while awaiting a decline in inhibitor titres before initiating ITI, so rFVIIa would be the best option for prophylaxis in these patients and would allow some of them to start ITI with a low number of haemarthroses [23]. Although there is an obviously important cost associated to prophylaxis, it has been pointed out by authors like Leissingner [17], that if prophylaxis is initiated early, costs may be similar to those associated with repeated bleeds, hospitalizations, and surgeries in older, larger patients with inhibitors who have joint damage.

Further studies are needed to evaluate the benefits for the orthopaedic outcome of early interventions like primary prophylaxis in patients with inhibitors.

Disclosures

V. Jiménez-Yuste has received a fee for speaking by Novo Nordisk A/S and Baxter. The other authors stated that they had no interests which might be perceived as posing a conflict or bias.

References

- 1 Manco-Johnson MJ, Abshire TC, Shapiro AD *et al.* Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007; **357**: 535–44.
- 2 Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. *Haemophilia* 2003; **9**: 418–35.
- 3 Berntorp E, Shapiro A, Astermark J *et al.* Inhibitor treatment in haemophilias A and B: summary statement for the 2006 international consensus conference. *Haemophilia* 2006; **12**: 1–7.
- 4 Morfini M, Haya S, Tagariello G *et al.* European study on orthopaedic status of haemophilia patients with inhibitors. *Haemophilia* 2007; **13**: 606–12.
- 5 Soucie JM, Cianfrini C, Janco RL *et al.* Joint range-of-motion limitations among young males with hemophilia: prevalence and risk factors. *Blood* 2004; **103**: 2467–73.
- 6 Leissingner CA. Prophylaxis in haemophilia patients with inhibitors. *Haemophilia* 2006; **12**: 67–73.
- 7 Konkle BA, Ebbesen LS, Erhardtson E *et al.* Randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors. *J Thromb Haemost* 2007; **5**: 1904–13.
- 8 Hilgartner MW, Makiperna A, Dimichele DM. Long-term FEIBA prophylaxis does not prevent progression of existing joint disease. *Haemophilia* 2003; **9**: 261–8.
- 9 Brackmann HH, Effenberger E, Hess L, Schwaab R, Oldenburg J. NovoSeven in immune tolerance therapy. *Blood Coagul Fibrinolysis* 2000; **11**: S39–44.
- 10 Cooper HA, Jones CP, Campion E, Roberts HR, Hedner U. Rationale for the use of high dose rFVIIa in a high-titre inhibitor patient with haemophilia B during major orthopaedic procedures. *Haemophilia* 2001; **7**: 517–22.
- 11 Saxon BR, Shanks D, Jory CB, Williams V. Effective prophylaxis with daily recombinant factor VIIa (rFVIIa-Novoseven) in a child with high titre inhibitors and a target joint. *Thromb Haemost* 2001; **86**: 1126–7.
- 12 Young G, McDaniel M, Nugent DJ. Prophylactic recombinant factor VIIa in haemophilia patients with inhibitors. *Haemophilia* 2005; **11**: 203–7.
- 13 Kreuz W, Escuriola-Ettinghausen C, Martinez I, Mentzer D, Figura S, Klarmann D. Efficacy and safety of factor VIII inhibitor bypass activity (FEIBA) for long-term prophylaxis in patients with high-responding inhibitors. *Blood* 2000; **96**: 265a abstract 1140.
- 14 Siegmund B, Richter H, Pollmann H. Prophylactic treatment with FEIBA of a haemophilia A patient with inhibitor: what are the costs, what are the benefits? *Haemophilia* 2005; **11**: 638–41.
- 15 Dimichele D, Negrier C. A retrospective postlicensure survey of FEIBA efficacy and safety. *Haemophilia* 2006; **12**: 352–62.
- 16 Bryant P, Carr M, Martin E, Sutton J. High dose recombinant activated factor VII in a pediatric patient with factor VIII deficiency and high titer inhibitor. *Blood* 2003; **102**: 104b–5b. (abstract 4128).
- 17 Leissingner CA, Becton DL, Ewing NP, Valentino LA. Prophylactic treatment with activated prothrombin complex concentrate (FEIBA) reduces the frequency of bleeding episodes in paediatric patients with haemophilia A and inhibitors. *Haemophilia* 2007; **13**: 249–55.
- 18 Leissingner CA. Prevention of bleeds in hemophilia patients with inhibitors: emerging data and clinical direction. *Am J Hematol* 2004; **77**: 187–93.
- 19 Morfini M, Auerswald G, Kobelt RA *et al.* Prophylactic treatment of haemophilia patients with inhibitors: clinical experience with recombinant factor VIIa in European Haemophilia Centres. *Haemophilia* 2007; **13**: 502–7.
- 20 Jimenez-Yuste V, Quintana M, Alvarez MT, Martin-Salces M, Hernandez Navarro F. Primary prophylaxis with rFVIIa in a patient with severe Haemophilia A and inhibitor. *Blood Coagul Fibrinol* 2008; **19**: 719–20.
- 21 Turecek PL, Varadi K, Gritsch H, Schwarz HP. FEIBA: mode of action. *Haemophilia* 2004; **10**: 3–9.
- 22 Green D. Complications associated with the treatment of haemophiliacs with inhibitors. *Haemophilia* 1999; **5**: 11–7.
- 23 DiMichele DM, Hoots WK, Pipe SW, Rivard GE, Santagostino E. International workshop on immune tolerance induction: consensus recommendations. *Haemophilia* 2007; **13**: 1–22.

- 24 Lenk H. The German Registry of immune tolerance treatment in hemophilia – 1999 update. *Haematologica* 2000; 85: 45–7.
- 25 DiMichele DM, Kroner BL. The North American Immune Tolerance Registry: practices, outcomes, outcome predictors. *Thromb Haemost* 2002; 87: 52–7.
- 26 Haya S, Lopez MF, Aznar JA, Batlle J. Immune tolerance treatment in haemophilia patients with inhibitors: the Spanish Registry. *Haemophilia* 2001; 7: 154–9.
- 27 Nilsson IM, Berntorp E, Lofqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Intern Med* 1992; 32: 25–32.
- 28 Berntorp E, Astermark J, Bjorkman S *et al.* Consensus perspectives on prophylactic therapy for haemophilia: summary statement. *Haemophilia* 2003; 9: 1–4.
- 29 Santagostino E, Gringeri A, Mannucci PM. State of care for hemophilia in pediatric patients. *Paediatr Drugs* 2002; 4: 149–57.
- 30 Mehta R, Parameswaran R, Shapiro AD. An overview of the history, clinical practice concerns, comparative studies and strategies to optimize therapy of bypassing agents. *Haemophilia* 2006; 12: 54–61.
- 31 Valentino LA. FEIBA prophylaxis in patients with haemophilia A and inhibitors results in a 95% reduction in bleeding episodes. *Haemophilia* 2004; 10: 115.
- 32 Schino M, Centra A, Pisedu G, Sbrighi P. APCC (FEIBA) home treatment prophylaxis in inhibitor haemophilia patients. *Haemophilia*. 2000; 6: 294. (abstract 37).
- 33 Escuriola-Ettinghausen C, Martinez-Saguer I, Funk M *et al.* Long-term prophylaxis with FEIBA® in patients with high-responding inhibitors. *J Thromb Haemost* 2003; 1: abstract P1628.
- 34 Ewing NP. Anamnestic responses in hemophilia patients with inhibitors on continuous prophylaxis with factor eight inhibitor bypassing activity, vapor heated (FEIBA VH). *J Thromb Haemost* 2005; 3: abstract P2036.
- 35 Roberts HR, Monroe DM, III, Hoffman M. Safety profile of recombinant factor VIIa. *Semin Hematol* 2004; 41: 101–8.
- 36 Aledort LM. Factor VIII inhibitor bypassing activity (FEIBA) – addressing safety issues. *Haemophilia* 2007; 14: 39–43.
- 37 van Dijk K, Fischer K, van der Bom JG, Grobbee DE, van den Berg HM. Variability in clinical phenotype of severe haemophilia: the role of the first joint bleed. *Haemophilia* 2005; 11: 438–43.