

REVIEW ARTICLE

Paediatric haemophilia with inhibitors: existing management options, treatment gaps and unmet needs

E. SANTAGOSTINO,* M. MORFINI,† G. K.-H. AUERSWALD,‡ G. M. BENSON,§ S. Z. ŠALEK,¶
T. LAMBERT,** P. SALAJ,†† V. JIMENEZ-YUSTE‡‡ and R. C. R. LJUNG§§

*Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre, IRCCS Maggiore Hospital, Mangiagalli and Regina Elena Foundation, University of Milan, Milan, Italy; †Agency for Hemophilia – Reference Center for Inherited Bleeding Disorders of Tuscany, Department of Emergency and Reception, Azienda Ospedaliero Universitaria Careggi, Florence, Italy; ‡Klinikum Bremen-mitte, Professor Hess Children's Hospital, Bremen, Germany; §Northern Ireland Haemophilia Comprehensive Care Centre, Belfast, Northern Ireland; ¶National Haemophilia Centre, University Hospital Centre, Rebro, Croatia; **Hemophilic Care Center, Bicêtre AP-HP Hospital and Faculté de Médecine Paris XI, Paris, France; ††Institute of Hematology and Blood Transfusion, Prague, Czech Republic; ‡‡Haematology Department, Hospital Universitario La Paz, Madrid, Spain; and §§Department of Paediatrics and Coagulation Disorders, University Hospital Malmö, Malmö, Sweden

Summary. Development of inhibitors is a severe complication of haemophilia posing many management challenges. While a long-term goal in inhibitor patients is eradication of inhibitors through immune tolerance induction, bypassing agents such as recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrate (aPCC) are essential for control of bleeding episodes. Paediatric patients with haemophilia and inhibitors are at particular risk of recurrent haemarthroses, and management of these patients should seek to avoid joint damage and support the child's full social and physical development. Current options for management of bleeding complications include on-demand treatment of acute bleeding episodes, secondary prophylaxis to avoid recurrent bleeds and surgery to treat affected joints. There is also a rationale for

adopting prophylactic approaches to prevent bleeding in inhibitor patients, allowing this group similar opportunities for protection against arthropathy development as are given to non-inhibitor patients. This paper, based on a roundtable meeting of haematology experts at the first Zürich Haemophilia Forum in May 2008, reviews the current evidence supporting more intense and prophylactic approaches to manage bleeding risk in paediatric haemophilia patients with inhibitors, and highlights the need for investigations of primary prophylaxis in this vulnerable patient group, to support best long-term outcome.

Keywords: activated prothrombin complex concentrate, haemophilia, inhibitors, paediatric, prophylaxis, recombinant activated factor VII

Introduction

Management of the rare, inherited bleeding disorder of haemophilia characterized by the deficiency of either factor VIII (FVIII) (haemophilia A) or factor

IX (FIX) (haemophilia B), requires life-long replacement treatment with clotting factor concentrates [1]. The development of neutralizing antibodies (inhibitors) to factor replacement therapy is, therefore, a serious complication of haemophilia treatment, compromising on effective management of haemorrhage and resulting in an increased risk of disability [2]. Factors thought to be important in inhibitor formation include genetics, challenges to the immune system and other environmental influences [3]. It is known that treatment-related determinants may have a relevant impact on inhibitor development. In haemophilia A, it has been reported that exposure

Correspondence: Elena Santagostino, MD, PhD, Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre, IRCCS Maggiore Hospital Mangiagalli and Regina Elena Foundation, University of Milan, Via Pace 9, 20122 Milan, Italy.
Tel.: +39 025 503 5308; fax: +39 025 45 7074;
e-mail: hemophilia_ctr@policlinico.mi.it

Accepted after revision 16 January 2009

to FVIII therapy very early in life may be linked to subsequent inhibitor development [4], and recent studies have shown that early and intensive FVIII treatment is associated with an increased inhibitor risk, while early initiation of FVIII prophylaxis may reduce the risk of developing inhibitors [3,5]. It should, however, be noted that age alone is not thought to impact on inhibitor development, as the association with age largely disappeared after adjustment for treatment intensity in the CANAL study [5].

It is estimated that 30% or more of children with severe haemophilia A and around 2–5% of patients with severe haemophilia B are at risk of developing inhibitors [6,7]. Inhibitors may be diagnosed during routine patient surveillance or may come to light as a result of a bleeding episode that responds poorly to standard dose replacement therapy.

While the ideal would be to predict and prevent the development of inhibitors in the very young child [6], the current reality is that the day-to-day management of patients with high-titre inhibitors continues to pose a number of clinical challenges. All patients with inhibitors, and children in particular, face the threat of severe bleeding complications such as limb- or life-threatening bleeds, and are at risk of developing target joints and progressive arthropathy that may lead to permanent disability [6,8].

The European Study on Orthopaedic Status of haemophilia patients with Inhibitors (ESOS study [9]) has provided useful insights into the clinical burden posed by inhibitor development by demonstrating quantitatively that these patients have more orthopaedic complications and a lower quality of life than haemophilia patients without inhibitors. For example, 16% of inhibitor patients aged 14–35 years were hospitalized for orthopaedic procedures compared with only 4% of non-inhibitor patients. This study has shown that a significantly greater proportion of patients with inhibitors suffer joint pain and reduced mobility, with a greater requirement for walking aids, than non-inhibitor haemophilia patients. Radiological evidence also highlights the higher burden of joint damage in young patients with inhibitors compared with young non-inhibitor patients [9].

Once high-titre inhibitors develop in a child with haemophilia, current therapeutic approaches include treatment with bypassing agents to control acute bleeding episodes [10], immune tolerance induction (ITI) treatment to eradicate inhibitors and restore responsiveness to replacement therapy [11,12] and strategies aimed at arthropathy prevention.

The overview presented in this paper is based on the deliberations of an expert forum of haematologists

involved in haemophilia care. The first Zürich Haemophilia Forum, held in May 2008, focussed particularly on the management and unmet clinical needs of haemophilic children with inhibitors. The authors provide a summary of the evidence that supports current clinical approaches to the management of children with haemophilia and inhibitors, and highlight some of the current treatment gaps and unmet needs in the management of these patients.

Current management options for children with inhibitors

Permanent eradication of inhibitors is the ultimate goal and this can be achieved by means of ITI in 60–80% of children with inhibitors [11]. However, clinical management may be problematic during the time interval required to achieve ITI success and in cases of failure. Furthermore, ITI is not viewed as a viable option for patient management in many countries, owing to its high cost and the availability of factor concentrate, as well as the potential for central venous access issues and psychological stress on patients and their families for this highly demanding treatment [11,13,14]. Despite efforts to implement ITI to restore the efficacy of replacement therapy, a sizeable minority of haemophilia patients (~20%) will have life-long inhibitors [15].

Nevertheless, all children with haemophilia who develop high-responding inhibitors (historical peak titre ≥ 5 Bethesda units [BU] mL^{-1}) should be considered for ITI, and current advice in many centres, at least in cases with low bleeding tendency, is that initiation of ITI should be deferred until inhibitor titre has decreased to below 10 BU mL^{-1} [11,16,17]. Although there have been several established protocols developed over recent decades, the optimal schedule for ITI in terms of clinical efficacy is yet to be determined [11,18].

When a paediatric patient develops inhibitors, the key aims of management are similar to those for any child with haemophilia. Management aims to treat acute bleeding episodes promptly, to manage complications, to prevent recurrent bleeds and to conserve or restore joint function. The overall goal is to support a child's healthy development favouring full integration into a normal social life. In order to achieve this, inhibitor patients should have access to the same treatment options as non-inhibitor patients.

There is an increased acceptance that recombinant factor concentrates should be the treatment of choice in children with haemophilia whenever possible [1,17]. Treatment options for children with haemophilia and inhibitors include on-demand therapy

with bypassing agents, recombinant activated factor VII (rFVIIa; NovoSeven[®]; Novo Nordisk, Bagsvaerd, Denmark) or plasma-derived activated prothrombin complex concentrate (aPCC; FEIBA[®]; Baxter Bioscience, Vienna, Austria) [16], and—in patients with very low inhibitor titres—high-dose replacement therapy with FVIII concentrates [16,19]. Prevention of recurrent bleeds may be targeted by using bypassing agents according to secondary prophylaxis regimens [20,21]. Surgery may be required to treat affected joints [22].

This paper considers evidence and unanswered issues concerning each of these options, and how these management options could be integrated with plans for ITI.

On-demand treatment of acute bleeding episodes with bypassing agents

Prompt infusion of bypassing agents, on demand, in the home setting, allows treatment of haemorrhages at early onset, reducing the incidence of complications and improving the quality of life [17].

On-demand treatment of acute bleeds with either rFVIIa or aPCC has been widely practised [13,23–27]. The literature includes papers that provide guidance on how to use on-demand therapy in a systematic fashion in order to optimize outcome in patients with inhibitors [10], but the need for well-designed comparative studies remains in order to optimize the use of by-passing agents [13].

Nevertheless, the ESOS study [9] showed that, despite a similar number of bleeds, young patients with inhibitors have worsened joint scores and poor quality of life when compared with non-inhibitor patients of similar age, suggesting that current on-demand approaches for the management of bleeding episodes in inhibitor patients are either not effective enough or not intensive enough.

Alternative strategies: early intense on-demand therapy with bypassing agents

Early and intense on-demand therapy has been used in inhibitor patients to relieve pain promptly and achieve bleeding control with a reduced number of infusions. These clinical benefits have been reported in studies of single-dose rFVIIa [24,28,29]. Recent evidence to support the observation that intensity of treatment influences the time to success, comes from registry data on haemophilia patients with inhibitors in the Czech Republic [30; Peter Salaj, unpublished data]. While patient numbers are small, this national registry suggests that use of high single doses of

rFVIIa ($>250 \mu\text{g kg}^{-1}$) is more successful in achieving bleeding control than repeated standard dosing. Additionally, early infusion of rFVIIa was a key determinant of treatment success and bleeds treated later than 2 h after onset required more rFVIIa infusions (Peter Salaj, unpublished data).

More studies are needed, particularly in the paediatric population, in order to determine the most effective strategy to ensure rapid resolution of bleeds and minimization of the risk of rebleeding and bleeding-related joint damage.

Prophylaxis: emerging role in inhibitor patients

Rationale: experience in non-inhibitor patients

Prophylaxis with FVIII or FIX is the recommended mode of treatment for acute bleeds in haemophilia patients without inhibitors, reducing the occurrence of bleeds and slowing the rate of joint destruction [31]. Indeed, a report of 25 years' experience using FVIII or FIX prophylaxis in 60 non-inhibitor patients in Sweden suggests that this approach reduces bleeding frequency, pain, incidence of arthropathy, emergency visits, hospitalizations and absenteeism, while also improving patients' physical function, capacity for self-care and quality of life [32]. Similarly, the benefits of prophylactic treatment have also been reported in 38 children with severe haemophilia without inhibitors in the UK, in terms of a decrease in the number of joint bleeds, low clinical joint scores and improved quality of life [33].

More recently, a randomized study in 60 boys with severe haemophilia A compared FVIII prophylaxis with enhanced on-demand treatment with at least three FVIII doses (minimum total dose for on-demand treatment of 80 IU kg^{-1} [40 IU kg^{-1} at the time of joint haemorrhage and 20 IU kg^{-1} at 24 h and 72 h after the first dose]). This study found that by the age of 6 years, 93% of boys on prophylaxis showed normal index-joint structure on magnetic resonance imaging, compared with 55% of boys treated on demand [34]. Prophylaxis treatment also significantly reduced the mean annual number of joint haemorrhages per participant vs. on-demand treatment (mean \pm standard deviation 0.63 ± 1.35 and 4.89 ± 3.57 , respectively; $P < 0.001$). This study, therefore, demonstrates that through prevention of acute bleeds it is possible to avoid long-term joint damage in children with severe haemophilia. In addition, a recent publication by an expert panel states that the studies available to date on prophylaxis in patients without inhibitors do offer a hope that extrapolation may be feasible to patients with inhibitors [35].

The issue of how best to provide prophylaxis in children with haemophilia is a current topic of debate that requires further study and closer definition [18]. The European Paediatric Network for Haemophilia Management (PedNet) has proposed that primary prophylaxis is regular continuous therapy initiated before a patient reaches 2 years of age, with the treatment started after the first joint bleed or given to an individual with no previous joint bleeds. Secondary prophylaxis describes regular continuous (long-term) therapy initiated in a patient aged >2 years or in an individual who has experienced ≥ 2 joint bleeds. Secondary prophylaxis can also include intermittent regular (short-term) treatment administered as a result of frequent bleeds.

Prophylaxis in inhibitor patients The advantages of prophylactic approaches to bleeding control, which have been demonstrated in haemophilia patients without inhibitors, are likely to apply to patients with inhibitors. However, definitions of primary and secondary prophylaxis in inhibitor patients, and in particular in children with inhibitors, may need to be revised taking into account the age at inhibitor development.

Nevertheless, there is growing experience from clinical practice to support a prophylactic approach to the management of bleeding risk in patients with inhibitors [36,37]. Retrospective data have suggested that prophylaxis with aPCC (50–75 U kg⁻¹ three times weekly in four patients; one patient received 100 U kg⁻¹ daily) may be a viable option for reducing the number of bleeding episodes and preventing joint damage or its progression in inhibitor patients, when instituted early, before significant joint damage has occurred [21]. To date, the literature on prophylaxis in inhibitor patients is still limited and evidence for this approach in children is scarce. As such, the dosing and frequency of bypassing agents needed to provide protection against bleeds is still being debated. For example, it has been suggested that aPCC can be given at doses of 50–100 U kg⁻¹ every other day [36], and the best prophylactic dose of rFVIIa to use in children with inhibitors remains to be determined. Clinical experience from European centres managing inhibitor patients using prophylactic rFVIIa has also identified wide variation in administered doses, ranging from 200 to 250 $\mu\text{g kg}^{-1}$ per week to up to 220 $\mu\text{g kg}^{-1}$ per day, with many patients given doses of rFVIIa that were less than the recommended on-demand dose of rFVIIa [38].

The potential benefits of prophylaxis vs. on-demand therapy were highlighted in a pan-European

study of health outcomes in over 1000 haemophilia patients with or without inhibitors [39]. Multiple regression analyses found that patients managed with on-demand therapy had, on an average, 5.15 more joint bleeds over a 6-month period than patients treated with prophylaxis, with benefits being more marked in younger patients. While the study excluded patients undergoing ITI, 15% of the patient cohort described were subjects with inhibitors who did receive prophylaxis with either rFVIIa or aPCC. In general, these agents have been used at different doses and according to different schedules (rFVIIa 90–270 $\mu\text{g kg}^{-1}$ or aPCC 80–100 U kg⁻¹ given twice daily [for aPCC only], daily, every other day or three-times weekly); so optimal treatment regimens for prophylaxis still need to be established.

Proof of concept: benefits of rFVIIa secondary prophylaxis in inhibitor patients A recent study of secondary prophylaxis in patients with inhibitors has provided key clinical data on the potential benefits of preventing bleeding episodes using rFVIIa. In this randomized, uncontrolled trial of rFVIIa prophylaxis in 22 patients with inhibitors (median age 15.7 years [range: 5.1–56.1]), the effects of either rFVIIa 90 or 270 $\mu\text{g kg}^{-1}$ administered daily for 3 months were evaluated over a 9-month study period [20]. Bleeding frequency during active prophylaxis was compared with that seen in a 3-month pre-prophylaxis period of on-demand treatment and in a 3-month postprophylaxis follow-up period of on-demand treatment. The frequency of bleeds was reduced by 45% and 59% during prophylaxis with rFVIIa 90 and 270 $\mu\text{g kg}^{-1}$ doses, respectively ($P < 0.0001$), vs. prior on-demand therapy. The benefits of prophylaxis were most pronounced for spontaneous joint bleeds, although all types of bleeds assessed were reduced (including muscle, soft-tissue, traumatic bleeds). It was noted that a relevant reduction in the bleeding frequency was maintained during the postprophylaxis period. rFVIIa prophylaxis was well tolerated and there were no reports of thromboembolic complications [20].

A further analysis of this key proof-of-concept study reported that rFVIIa prophylaxis more than halved the need for hospitalization vs. on-demand therapy during the preprophylaxis period ($P = 0.0026$) [40]. Absenteeism from school/work also fell significantly ($P = 0.0127$); the median number of days absent from work or school decreased from 18.5 days (19%) in the preprophylaxis period to 4.5 days (5%) during prophylaxis, and remained lowered at 8.5 days (11%) in the postprophylaxis period. These benefits of prophylaxis

were also recorded as improvements in objectively measured health-related quality of life [40].

Unanswered questions: a focus on paediatric patients with inhibitors

For the future, potential therapeutic innovations that might change haemophilia management and the outlook for children with inhibitors include the development of genetically modified FVIII derivatives and new routes for drug administration. Advances such as the development of room temperature stable rFVIIa [41] and therapeutic enhancements to rFVIIa derivatives will allow less frequent dosing. Through innovative research and well-planned clinical studies, it should be possible to determine the optimal approaches to managing and controlling bleeds in children with haemophilia and inhibitors.

The results of the rFVIIa secondary prophylaxis trial [20] strongly support further investigation of prophylactic approaches to management of haemophilia patients with inhibitors. As observed in non-inhibitor patients, there are concerns that secondary prophylaxis may not be as effective as true primary prophylaxis in preventing arthropathy in inhibitor patients.

Irreversible joint damage may have already occurred when secondary prophylaxis is adopted because joint bleeds are already recurrent. In this setting, the child's performance and quality of life may already have suffered. Primary prophylaxis could potentially avoid these situations and allow more children with inhibitors to be spared target joint damage.

It would be important to evaluate the role for prophylactic therapy from the onset of inhibitors in order to determine whether an early preventive strategy can both reduce the frequency of bleeding episodes and have an impact on long-term joint status in children.

Research is needed to provide answers to a number of questions on prophylactic use of bypassing agents when an inhibitor has developed:

1. Should prophylactic therapy be started at the onset of inhibitors?
2. Should prophylaxis be continued during ITI?
3. What is the best treatment regimen for optimal prophylaxis?
4. How should we best manage the issue of adequate venous access to deliver treatment?
5. What is the cost and cost-benefit of prophylaxis?
6. What are the potential drawbacks of prophylaxis?

There is a need for scientific debate and study on how best to protect patients against bleeds before

and during ITI. There is a rationale for prophylaxis using bypassing agents before and during ITI—to improve patient quality of life and to avert major haemorrhage. Such approaches may help restrict the potential for joint damage and allow children to function well enough to continue with their schooling, education and social activities.

The ideal clinical study should allow comparison of the long-term efficacy and safety of bypassing agents when used in a primary prophylactic regimen compared with on-demand therapy in young children who develop high-responding inhibitors and who are candidates for ITI. In this way, the effects of both prophylaxis and on-demand treatment could be evaluated in the pre-ITI stage, during ITI and until restoration of therapeutic response to FVIII. Measures of efficacy should include assessment of the bleeding frequency and joint status during the follow-up period. This controlled study could provide much-needed information on key aspects of children's function and quality of life, adherence to therapy and costs of different treatment regimens.

Acknowledgements

This work was sponsored by an unrestricted grant from Novo Nordisk Region Europe A/S. The authors wish to thank Winnie McFadzean of PAREXEL for medical writing services in the preparation of this manuscript.

Disclosures

E. Santagostino has acted as a paid speaker for Novo Nordisk, Bayer Schering, Baxter, CSL Behring and Wyeth, as paid consultant to Novo Nordisk and has received funding for research from Novo Nordisk. M. Morfini has acted as a paid consultant to the advisory board of Novo Nordisk and as a speaker at the Satellite Symposium of World Federation of Haemophilia, Istanbul, June 2008. G. K.-H. Auerswald has received reimbursement for attending a symposium together with a fee for speaking (CSL Behring, Novo Nordisk, Bayer and Baxter), has received funds for research for member of staff (Baxter, Novo Nordisk and CSL Behring) and has received fees for consulting (Novo Nordisk, Bayer, CSL-Behring and Biotest). G. M. Benson has received speaker's fees on behalf of Boehringer Ingelheim. P. Salaj has acted as a paid speaker during scientific events organized by Novo Nordisk and has received a reimbursement for attending the scientific symposiums. V. Jimenez-Yuste has acted as a paid speaker

for Novo Nordisk and Baxter. R. C. R. Ljung has received a consulting fee from Novo Nordisk as expert in a workshop related to the topic of this paper. The other authors stated that they had no interests which might be perceived as posing a conflict or bias.

References

- Keeling D, Tait C, Makris M. Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. *Haemophilia* 2008; **14**: 671–84.
- 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**(Suppl 6): 1–7.
- Santagostino E, Mancuso ME, Rocino A *et al.* Environmental risk factors for inhibitor development in children with haemophilia A: a case-control study. *Br J Haematol* 2005; **130**: 422–7.
- Chalmers EA, Brown SA, Keeling D *et al.* Early factor VIII exposure and subsequent inhibitor development in children with severe haemophilia A. *Haemophilia* 2007; **13**: 149–55.
- Gouw SC, van der Bom JG, Marijke van den Berg H. Treatment-related risk factors of inhibitor development in previously untreated patients with hemophilia A: the CANAL cohort study. *Blood* 2007; **109**: 4648–54.
- Dimichele D. Inhibitors: resolving diagnostic and therapeutic dilemmas. *Haemophilia* 2002; **8**: 280–7.
- Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. *Haemophilia* 2003; **9**: 418–35.
- 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.
- Morfini M, Haya S, Tagariello G *et al.* European Study on Orthopaedic Status of haemophilia patients with inhibitors. *Haemophilia* 2007; **13**: 606–12.
- Teitel J, Berntorp E, Collins P *et al.* A systematic approach to controlling problem bleeds in patients with severe congenital haemophilia A and high-titre inhibitors. *Haemophilia* 2007; **13**: 256–63.
- DiMichele DM, Hoots WK, Pipe SW, Rivard GE, Santagostino E. International workshop on immune tolerance induction: consensus recommendations. *Haemophilia* 2007; **13**(Suppl 1): 1–22.
- Unuvar A, Kavakli K, Baytan B *et al.* Low-dose immune tolerance induction for paediatric haemophilia patients with factor VIII inhibitors. *Haemophilia* 2008; **14**: 315–22.
- Astermark J, Rocino A, Von Depka M *et al.* Current use of by-passing agents in Europe in the management of acute bleeds in patients with haemophilia and inhibitors. *Haemophilia* 2007; **13**: 38–45.
- Blatny J, Kohlerova S, Zapletal O, Fiamoli V, Penka M, Smith O. Prophylaxis with recombinant factor VIIa for the management of bleeding episodes during immune tolerance treatment in a boy with severe haemophilia A and high-response inhibitors. *Haemophilia* 2008; **14**: 1140–2.
- Barnes C, Rivard GE, Poon MC *et al.* Canadian multi-institutional survey of immune tolerance therapy (ITT) – experience with the use of recombinant factor VIII for ITT. *Haemophilia* 2006; **12**: 1–6.
- Hay CR, Brown S, Collins PW, Keeling DM, Liesner R. The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation. *Br J Haematol* 2006; **133**: 591–605.
- Santagostino E, Gringeri A, Mannucci PM. State of care for hemophilia in pediatric patients. *Paediatr Drugs* 2002; **4**: 149–57.
- Kurnik K, Thomas AE. Meeting report: ninth and tenth workshops of the European Paediatric Network for Haemophilia Management (PedNet). *Haemophilia* 2007; **13**: 658–62.
- Lloyd Jones M, Wight J, Paisley S, Knight C. Control of bleeding in patients with haemophilia A with inhibitors: a systematic review. *Haemophilia* 2003; **9**: 464–520.
- 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.
- Leissinger 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.
- Obergfell A, Auvinen MK, Mathew P. Recombinant activated factor VII for haemophilia patients with inhibitors undergoing orthopaedic surgery: a review of the literature. *Haemophilia* 2008; **14**: 233–41.
- Key NS, Aledort LM, Beardsley D *et al.* Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (Novoseven) in haemophiliacs with inhibitors. *Thromb Haemost* 1998; **80**: 912–8.
- Kavakli K, Makris M, Bulent Z *et al.* Home treatment of haemarthroses using a single dose regimen of recombinant activated factor VII in patients with haemophilia and inhibitors. A multi-centre, randomised, double-blind, cross-over trial. *Thromb Haemost* 2006; **95**: 600–5.
- Sjamsedin LJ, Heijnen L, Mauser-Bunschoten EP *et al.* The effect of activated prothrombin complex concentrate (FEIBA) on joint and muscle bleeding in patients with hemophilia A and antibodies to factor VIII. A double-blind clinical trial. *N Engl J Med* 1981; **305**: 717–21.

- 26 Negrier C, Goudemand J, Sultan Y *et al.* Multicenter retrospective study on the utilization of FEIBA in France in patients with factor VIII and factor IX inhibitors. *Thromb Haemost* 1997; 77: 1113–9.
- 27 Astermark J, Donfield SM, DiMichele DM *et al.* A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study. *Blood* 2007; 109: 546–51.
- 28 Santagostino E, Mancuso ME, Rocino A, Mancuso G, Scaraggi F, Mannucci PM. A prospective randomized trial of high and standard dosages of recombinant factor VIIa for treatment of hemarthroses in hemophiliacs with inhibitors. *J Thromb Haemost* 2006; 4: 367–71.
- 29 Young G, Shafer FE, Rojas P, Seremetis S. Single 270 microg kg(-1)-dose rFVIIa vs. standard 90 microg kg (-1)-dose rFVIIa and APCC for home treatment of joint bleeds in haemophilia patients with inhibitors: a randomized comparison. *Haemophilia* 2008; 14: 287–94.
- 30 HemoRec registry web site. Available at: <http://www.hemorec.com> (last accessed on 28 October 2008).
- 31 Fischer K, van der Bom JG, Molho P *et al.* Prophylactic versus on-demand treatment strategies for severe haemophilia: a comparison of costs and long-term outcome. *Haemophilia* 2002; 8: 745–52.
- 32 Nilsson IM, Berntorp E, Löfqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Intern Med* 1992; 232: 25–32.
- 33 Yee TT, Beeton K, Griffioen A *et al.* Experience of prophylaxis treatment in children with severe haemophilia. *Haemophilia* 2002; 8: 76–82.
- 34 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.
- 35 Rodriguez-Merchan EC, Hedner U, Heijnen L *et al.* Prevention of haemophilic arthropathy during childhood. May common orthopaedic management be extrapolated from patients without inhibitors to patients with inhibitors? *Haemophilia* 2008; 14(Suppl 6): 68–81.
- 36 Leissing CA. Prevention of bleeds in hemophilia patients with inhibitors: emerging data and clinical direction. *Am J Hematol* 2004; 77: 187–93.
- 37 Young G, McDaniel M, Nugent DJ. Prophylactic recombinant factor VIIa in haemophilia patients with inhibitors. *Haemophilia* 2005; 11: 203–7.
- 38 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.
- 39 Schramm W, Royal S, Kroner B *et al.* Clinical outcomes and resource utilization associated with haemophilia care in Europe. *Haemophilia* 2002; 8: 33–43.
- 40 Hoots WK, Ebbesen LS, Konkle BA *et al.* Secondary prophylaxis with recombinant activated factor VII improves health-related quality of life of haemophilia patients with inhibitors. *Haemophilia* 2008; 14: 466–75.
- 41 Bysted BV, Scharling B, Møller T, Hansen BL. A randomized, double-blind trial demonstrating bioequivalence of the current recombinant activated factor VII formulation and a new robust 25 degrees C stable formulation. *Haemophilia* 2007; 13: 527–32.