

Haemophilia Treatment – Current and Future Challenges

a report based on presentations at the Bayer Schering Pharma-sponsored satellite symposium at the European Haemophilia Consortium, September 2008

J Blatný,¹ J Ingerslev,² A Huth-Kühne,³ T Lambert⁴ and J Windyga⁵

1. Children's University Hospital, Brno; 2. Aarhus University; 3. Kurpfalzkrankenhaus Hemophilia Centre, Heidelberg;

4. Assistance Publique, Hôpitaux de Paris; 5. Institute of Transfusion Medicine, Warsaw

DOI: 10.17925/EOH.2008.02.1.21

The management and treatment of haemophilia is a complex process requiring a lifelong commitment from patients, family members and care providers alike. Recent decades have seen the goals of haemophilia treatment changing beyond solely maintaining prevention of acute bleeds towards the inclusion of improved patient quality of life by preventing severe debilitating outcomes such as joint damage and haemophilic arthropathy. Although the management of haemophilia has improved dramatically with the introduction of prophylactic therapy and the increased safety of clotting factor products, patients and clinicians still face the complication of inhibitor development, which can impede the clotting activity of factor concentrates and therefore hamper treatment. In order to examine these issues, a satellite symposium, sponsored by Bayer Schering Pharma, was presented to patients and physicians at the XXI Annual General Meeting of the European Haemophilia Consortium. The symposium reviewed recent evidence for prophylactic treatments and the management of inhibitor development and explored new therapies on the horizon for haemophilia.

The Rationale for Prophylaxis in Children – Scientific Evidence and Clinical Experience

Dr Jan Blatný of the Czech Republic provided background on the rationale for prophylaxis in children. This strategy involves treatment with an intravenous injection of factor concentrate in anticipation of, and in order to prevent, any bleeding episodes.¹ As this well-practised procedure was first introduced over 30 years ago,² prophylaxis treatment is now considered the gold standard for children with severe haemophilia worldwide.

Prophylaxis is categorised into two main types: primary and secondary prophylaxis. Primary prophylaxis is initiated before the development of any joint bleeds, ideally prior to the second year of life and the second bleeding episode; secondary prophylaxis is instigated after significant bleeding (including multiple bleeds) or the onset of joint damage. The importance of immediate prophylaxis after the initial bleeding episode is well documented: the longer the delay in prophylactic treatment following the first bleed, the higher the risk of developing arthropathy.³

There are many prophylactic treatment regimens to choose from, and Dr Blatný outlined the three main models: Swedish, Dutch and Canadian. The earliest model originates from Sweden and promotes a progressive start with greater emphasis placed on age rather than intensity of treatment, although it is possible to individualise and adjust treatment based on the patient's bleeding patterns.^{4,5} Clotting factor doses range from 25 to 40IU/kg, twice weekly for haemophilia B and three times a week for haemophilia A. The Dutch model recommends that prophylaxis start as soon as possible after the first bleed, although a lower dosage may be sufficient to prevent joint damage.³ Under this

model, patients adopt a more liberal and tailored approach to prophylaxis. Infusion doses range from 15 to 30IU/kg in response to the severity of bleeding episodes, as the model suggests that the frequency of infusion may not be associated with the prophylactic effects. Similarly, the Canadian model advocates tailored prophylaxis.⁶ Studies have shown that this approach uses less factor VIII (FVIII) compared with traditional prophylaxis. Patients escalate their dose and frequency in a stepwise manner only if the initial once-weekly dosage proves insufficient in controlling bleeding. This model presents a positive cost/benefit ratio – an attractive characteristic in countries with limited resources and limited access to factor concentrates.

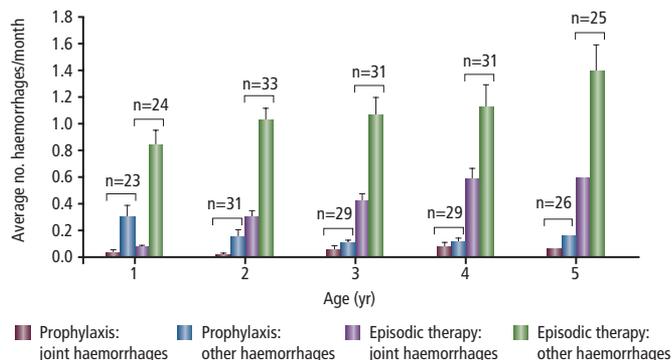
Potential Obstacles in Prophylaxis

Any prophylactic treatment faces potential barriers and problems, and haemophilia is no different. In addition to patient compliance, which can be affected by issues such as impact on lifestyle and the costs of treatment, there are a number of clinical concerns relating to venous access, transmission of pathogens, allergic reactions and the development of inhibitors. Fortunately, many of these issues can be avoided or overcome, often with the individualisation of a treatment regimen.

Venous access can be difficult in young children, but can be facilitated by use of central venous lines (CVLs). However, the use of CVLs has been linked to a risk of infection of 0.2–1 per 1,000 days, and possible thrombosis.⁷ Although the occurrence of thrombosis has historically been underestimated, it is now understood that it can occur in 15–53% of patients with CVLs, even with a diagnosis of haemophilia. In response to this potential risk, Dr Blatný suggested adopting a patient-tailored approach with a gradual introduction to prophylaxis. This view is supported by a study in which children received stepwise escalations of FVIII in accordance with the Canadian model.⁶ The study showed that these patients required fewer infusions of factor concentrate than those under a traditional prophylaxis regimen, reducing the need for CVLs and therefore reducing the risk of infection or thrombosis. Unfortunately, there is a population of patients – such as those requiring immune tolerance treatments – in whom CVLs will be unavoidable.

Both plasma-derived and recombinant FVIII (PD-FVIII and rFVIII, respectively) are currently recommended for prophylactic use in children. While modern production methods for plasma-derived concentrates are fairly safe, pharmacovigilance remains of the utmost importance. Parvovirus B19 (PVB19) can exhibit resistance to the heat treatment and solvent/detergent treatment used for viral inactivation or elimination in the manufacture of plasma-derived products,⁸ and the transmission of PVB19 has been documented in German patients.⁹

Figure 1: Boys with Severe Haemophilia Experience Significantly Fewer Bleeding Episodes with Prophylaxis Compared with Episodic Treatment



Source: Manco-Johnson et al., 2007.¹²

In this respect, the potential for unknown blood-borne infections remains a valid possibility. In comparison, the recombinant concentrates resulting from genetic engineering are the safest available alternative in factor replacement therapy, and their usage should be encouraged.

Allergic reactions to prophylactic FVIII have the potential to be quite severe, where the patient may have to withdraw from using the particular concentrate. Fortunately, safety and efficacy studies have shown that rFVIII can have a rate of allergic reaction as low as 0.004 per infusion.¹⁰

In spite of the aforementioned issues with prophylaxis, the primary concern for physicians nowadays is undeniably the development of inhibitors. Much research has focused on this aspect; studies have shown that although there are elements that can increase the risk of inhibitor development,^{9,11} there is a notable benefit for prophylaxis, where the risk of inhibitor development is 60% lower compared with that seen with on-demand treatment.¹¹

Benefits of Prophylaxis

The obvious benefit in adopting a prophylactic regimen is the reduction of joint bleeds. Recently, the Joint Outcome Study has shown that prophylaxis, compared with enhanced on-demand treatment, was associated with an annual reduction of 87% in joint bleeds ($p < 0.001$) and an annual reduction in the total number of bleeds by 81.5% ($p < 0.001$) (see Figure 1).¹² Furthermore, structural joint damage as determined by magnetic resonance imaging (MRI) occurred in only 7% of boys on prophylaxis compared with 45% of boys receiving on-demand therapy ($p < 0.002$).

The benefits of prophylaxis are evident once the regimen is initiated. Using the Czech Republic as an example, Dr Blatný explained that all children with severe haemophilia began prophylactic treatment with factor concentrates under the Dutch model in 1991. Seventeen years later, these Czech children with haemophilia – even the 2.6% with inhibitors – experience a median of 4.5 bleeds per year.¹³ This should be a prime example for countries that still do not use prophylaxis routinely, as these dramatic differences can emerge within 15–18 years. Indeed, a study of children four to 16 years of age in

western Europe showed that not only did prophylaxis improve orthopaedic outcome, but a survey of these patients showed a high level of health-related quality of life as well.¹⁴

Prophylaxis in children with haemophilia therefore presents a beneficial outcome in terms of preventing joint damage, reducing the risk of inhibitor development and, as a result, improving overall quality of life, allowing children to be children and to live the lives they choose. The use of recombinant concentrates not only maintains these advantages, but offers the safest available option in factor replacement therapy.

Prophylaxis in Adults – Benefits and Challenges

Today's population of adult patients with severe haemophilia can be categorised into two groups: those in whom treatment has been sufficient and those in whom treatment has been insufficient, i.e. those who have received early prophylaxis and those who have not. Dr Jørgen Ingerslev of Denmark spoke of his own experiences with adults who had received no early prophylaxis; many are now disabled to various degrees due to repeated joint and muscle bleeds and today suffer from chronic joint disease, and have had to undergo orthopaedic joint surgery. However, the majority of patients who had received early prophylaxis – of dosages varying between the Swedish and Dutch dosage schemes – now have almost completely normal joint function. A few still experience minor difficulties with the weight-bearing ankle joints. Therefore, it appears that prophylaxis plays a significant role in preventing disability.

There are four different types of prophylaxis for adults. Some may choose to continue on their prophylactic treatment from childhood. Others may also choose to continue secondary prophylaxis, utilising the same principles as adopted in childhood and adolescence. Alternatively, periodic prophylaxis may be chosen for a certain period of time in order to prevent recurrent bleeds or joint pains caused by synovitis. Lastly, patients can choose an on-demand, self-adjusted treatment regimen of episodic prophylaxis.

Prophylaxis in adults with severe or moderate haemophilia is growing in popularity. A survey of 21 haemophilia centres in Europe showed that approximately 35% of adolescent patients currently continue on their treatment from childhood prophylaxis, with 39% able to successfully reduce or discontinue their treatment programme for a short period of time; 30% of patients discontinue treatment permanently.¹⁵ Nearly 20% of patients over 50 years of age currently receive some form of prophylaxis, and this number is gradually increasing.

Benefits and Evidence of Prophylaxis

The goal of prophylaxis is to improve a patient's health and general wellbeing, with the ultimate objective of improving overall quality of life. In the younger patient, the aim of prophylaxis is to prevent joint- and muscle-related disabilities. This can reduce the number of days away from school or work, or allow the patient to participate in sports and exercises, thereby improving quality of life. In the older patient who has not received previous prophylaxis, prophylactic treatment may offer an opportunity to reduce the likelihood of further disability. Although unlikely to fully reduce the amount of pain in the patient, it is likely that prophylaxis can instigate some reduction, allowing patients to take better care of themselves, therefore improving their quality of life.

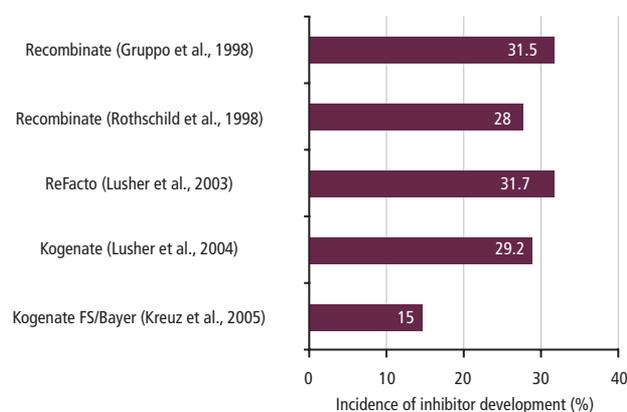
In contrast to the ample medical evidence in support of childhood prophylaxis, the continuation of prophylaxis into adulthood has not been as well documented, and there is still a need for further investigation into the benefits of introducing prophylactic treatment in adult and elderly patients who have had no previous prophylaxis. A recent publication of a retrospective study investigated the role of secondary prophylaxis in 84 patients in Italy with severe haemophilia.¹⁶ These patients had switched from episodic to prophylactic treatment during adolescence (n=30) or adulthood (n=54), and were evaluated in their consumption of clotting factor concentrates, the number of total and joint bleeds, quality of life and disease-related morbidity. Although patients on prophylaxis had higher use of factor concentrates compared with those receiving on-demand treatment, their quality of life was better. This cohort of adolescent and adult patients experienced marked clinical benefits under prophylactic treatment, with a significant reduction in the mean annual number of total bleeds (35.8 versus 4.2; $p<0.01$), joint bleeds (32.4 versus 3.3; $p<0.01$) and days away from school or work (34.6 versus 3.0; $p<0.01$). Joint status was also improved with prophylaxis, but only significantly so with the younger patients.

The current information pertaining to prophylaxis presents an interesting and challenging perspective. Available data in adults suggest that although prophylaxis is unable to restore existing impairments, it may have a role in preventing further joint deterioration and decline in mobility, while also reducing the frequency of bleeds. Ultimately, prophylaxis in adults may be shown to improve overall quality of life. Indeed, there is a need to further document the role of secondary prophylaxis in patients with severe haemophilia through more prospective studies. One such upcoming study is Spinart, where a target number of 80 patients between 20 and 50 years of age will be randomised to prophylactic or episodic treatment with rFVIII over a three-year period. The primary objective is to evaluate the effect of prophylaxis on bleeding frequency, and the secondary objective will evaluate the effect of prophylaxis on structural joint status as assessed by MRI.

Risk Factors for Inhibitor Development

Significant improvements have been made in the treatment and management of haemophilia with the advances in the safety and efficacy of factor concentrates in recent decades. However, concomitant with these developments was the emergence of inhibitors, which remains the most serious of complications in modern factor replacement therapy. Studies have shown that the incidence of previously untreated patients developing alloantibodies in response to FVIII infusions ranges between 15 and 32%, with newer products exhibiting progressively decreasing incidences (see *Figure 2*).^{17–22} These inhibitors impede the clotting activity of the factor concentrates and, as a result, patients with a high titre of inhibitors have a reduced responsiveness to treatment, which may lead to an increased risk of severe, and potentially life-threatening, bleeds, as well as more hospitalisation events and immobilisation due to extensive joint bleeding and severe pain. Dr Angela Huth-Kühne of Germany explained that this development of inhibitors not only decreases the patient's quality of life, but also the following treatment – including immune tolerance therapy and the treatment of bleeds – becomes more complex, with an estimated three-fold increase in therapeutic costs.²³

Figure 2: Incidence of Inhibitor Development in Previously Untreated Patients with Severe Haemophilia A



Factor VIII Inhibitor Development – A Multifactorial Immune Response

Over recent years, emerging data have indicated that the development of FVIII alloantibodies is a multifactorial immune response, including genetic, environmental and treatment-related risk factors. Studies have suggested a role for ethnicity in inhibitor development: patients of African or Latino descent have a higher risk of developing inhibitors than Caucasians.^{24,25} Furthermore, patients with a family history of inhibitor development are at significantly higher risk than those with no family history (48% risk versus 15% risk; relative risk 3.2).²⁵ Studies have also shown that specific types of mutations in the FVIII gene can influence a patient's likelihood of developing inhibitors: those with severe molecular gene defects such as large deletions and non-sense mutations have an estimated seven- to 10-fold increased inhibitor prevalence compared with patients displaying milder molecular gene defects such as small deletions and missense mutations.²⁶ Polymorphisms in the promoter regions of immunomodulatory genes such as those controlling interleukin 10 (IL-10), tumour necrosis factor alpha (TNF- α) and cytotoxic T-lymphocyte-associated protein-4 (CTLA4) have also been shown to increase the risk of inhibitor development.^{27–29}

Extrinsic factors also influence the immune response to FVIII. A patient's age at the start of treatment has been proposed as an environment-related risk factor. Some small studies have shown that initiating treatment with factor concentrates is associated with a cumulatively greater incidence of inhibitor development with younger patients, although the incidence declines with age.^{30,31} However, other studies have shown no such association between inhibitor development and age at first treatment, instead showing that patients who start regular prophylaxis at an early age have fewer inhibitors than those receiving episodic treatment.²⁸ There may also be other triggers acting as a challenge to the immune system during FVIII therapy, such as vaccinations or immunisations, severe infections and surgery or trauma leading to tissue damage, Dr Huth-Kühne added.

Unlike the aforementioned genetic and environmental risk factors, there are treatment-related risk factors that clinicians can influence. Studies have shown that on-demand treatment is associated with significantly higher incidences of inhibitors compared with prophylactic treatment.³² Much discussion has centred on whether the type of concentrate used, either plasma-derived or recombinant, has an impact on inhibitor development, and some researchers have

when treating for haemophilia, to carefully monitor the patient for the onset of inhibitors over the first 50 exposure days – the very high-risk period. Upon discovery of an inhibitor, not only must the physician always consider the possibility of ITI, but he must also inform the family of the high level of treatment adherence that will be required, and take into account the availability of healthcare resources such as care-giver and home care support into his decision.

When should one consider initiating ITI? Ideally, ITI should be started at the onset of inhibitor development. However, inhibitors often develop in a young child with very little treatment experience, and the patient and the family may find the high constraints of treatment difficult. Nevertheless, it is important to try to initiate ITI at such a time. Another occasion to start ITI is when patients require FVIII for surgery or for treatment of a serious bleeding episode; in these cases, ITI is started immediately following the procedure. In some instances, ITI can be started if the objective is well-defined and there is sufficient support for the patient and family.

Treatment of bleeding episodes during the initiation of ITI is of great concern, as FVIII alone may not be sufficient in controlling the bleed. In such a situation, data have indicated that factor VIIa (FVIIa) can be used: it is a pre-haemostatic agent that lacks any FVIII antigen and does not produce any anamnestic response.^{48,49} The use of PCCs or aPCCs are alternative possibilities. However, these plasma-derived products contain traces of antigenic FVIII and have the potential to change the immunogenic presentation of FVIII during ITI. This might be considered in the choice of bypassing agent used to treat bleeding episodes during the ITI initiation phase.

While undergoing ITI, Dr Lambert continued, it is important to be observant and monitor inhibitor titres monthly, and to keep supporting and encouraging the patient and family in adherence. Importantly, interruption of ITI and accidental changes in the FVIII concentrate used must be avoided, as this can adversely influence the success of ITI and delay the time to achieve tolerance.^{49,50} When inhibitor titres decrease below 2BU, treatment should be reassessed: an inhibitor titre of <2BU should indicate cessation of aPCC or FVIIa prophylaxis, as FVIII concentrates may have recovered their efficacy, and the use of these bypassing agents in conjunction with FVIII may present a risk of thrombosis. Significantly, the Bicêtre Hospital has seen a success rate of over 70% in patients undergoing ITI with Kogenate. Out of seven patients between 1.2 and 45 years of age and a treatment duration up to five years, five patients successfully achieved complete remission and one failed treatment; one patient is said to have partial remission as complete remission has not yet been demonstrated (see *Table 1*).⁵¹

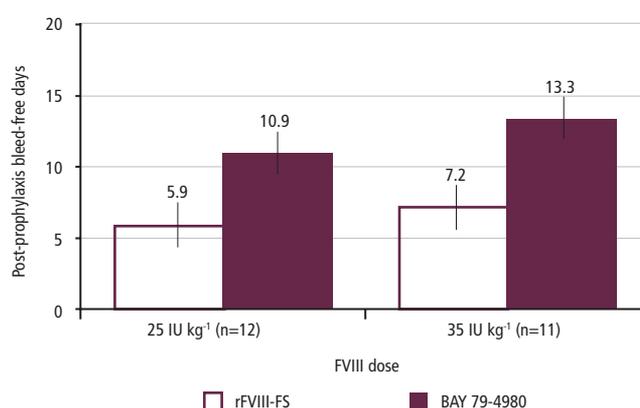
ITI faces a number of potential obstacles in practice. Venous access has already been addressed briefly with respect to prophylaxis and is also an important issue in ITI owing to the need for repeated daily infusions. There is also the issue of treatment duration: daily infusion is required over a long period of time, requiring lengthy attention from the patient, family and care-givers to maintain treatment adherence. Furthermore, short-term costs of ITI can be an issue. The restrictive treatment regimen for ITI can be a major constraint for the patient and his or her family, as well as requiring a high level of support from a comprehensive care centre. Moreover, Dr Lambert does not

Table 1: Immune Tolerance Induction at Bicêtre Hospital – Seven Experiences with Kogenate Bayer

Age at Start (yr)	Prev/ITI Max Titre	Titre at Start	Regimen U/Kg	Outcome Months	Current Treatment U/Kg Frequency (Time Since Start)
1.2	12/600	12	100 TIW	FAIL/switch	Wd FVIII a PCC failure (5 yr)
4.5	2.6/16	<0.4	138 TIW	PR 2/CR 50	87, EOD (5 yr)
10	29/64	0.5	111 EOD	PR 3/CR 4.5	RELAPSE M 8 ...
14	30/56	27	200 QOT	PR 2/CR 4.5	60, EOD (1.5 yr)
19	4.2/5.2	0.6	94 QOT	PR 1/CR?	73, QOT (16 month)
29	19/140	0.95	100 QOT	PR 1.5	90, QOT (month 9)
45	20/2.6	<0.5	100 QOT	PR 0/CR 7	55, EOD (2 yr)

TIW = twice a week; EOD = every other day; QOT = daily; PR = partial remission; CR = complete remission.

Figure 5: Post-prophylaxis Bleed-free Days with BAY 79-4980 versus Recombinant FVIII



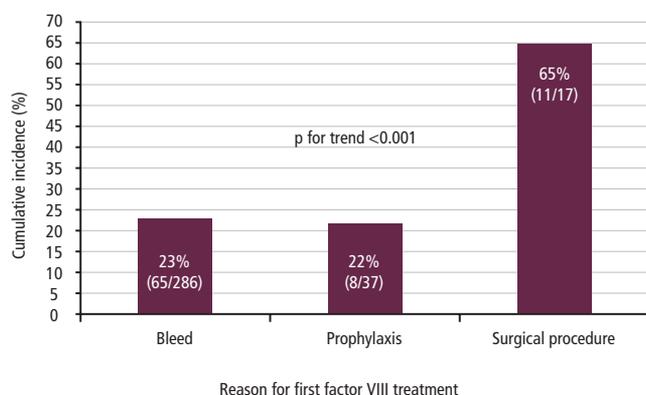
recommend carrying out ITI when there is no reliable biological surveillance for assaying FVIII and inhibitor titres, or if long-term availability of the chosen FVIII concentrate is not guaranteed. The lack of evidence and lack of standardised optimal approach to ITI justifies the enrolment of patients into a protocol or registry. Although some studies have shown high rates of success in ITI, there is still no real individual predictability of the success rate of ITI.

New Perspectives in the Treatment of Haemophilia A – The Next Generation of Coagulation Factors

In light of the discussion of the benefits of prophylaxis in children and adults, and of the risk factors and management for inhibitors, Dr Jerzy Windyga of Poland discussed the outlook for clotting factor concentrates. The second half of the 20th century has witnessed rapid development of replacement therapy in haemophilia. Treatment has evolved from the crude plasma fractionates of the 1950s through lyophilised clotting factor concentrates of increasing purity to cloning of the FVIII gene and, ultimately, development of rFVIII in the 1990s.

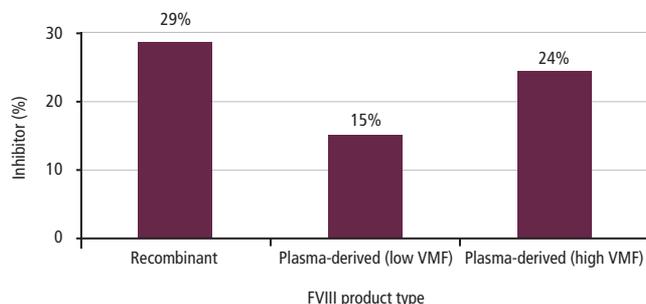
Nowadays, patients have a selection of very safe and effective lyophilised, plasma-derived or recombinant clotting factor concentrates to choose from. However, these products have their limitations. Significantly, only 20% of the world's haemophilia patients have access to treatment with clotting factor concentrates owing to their high price, which presents an economic challenge for healthcare systems even in developed countries. Availability is also an issue: the popularisation of primary prophylaxis has led to a systematic

Figure 3: Incidence of Inhibitor Development by Treatment Purpose



Source: Gouw et al., 2007.¹¹

Figure 4: Inhibitor Development by Type of FVIII Concentrate



VWF = von Willebrand Factor. Low VWF content was defined as less than 0.01 IU VWF antigen per IU factor VIII antigen; high VWF content was defined as more than 0.01 IU VWF antigen per IU factor VIII antigen.

Source: Gouw, 2007.³⁹

suggested that plasma-derived products containing high amounts of von Willebrand factor may induce a lower incidence of inhibitors. However, data are not yet conclusive.^{17,33,34} Mode of administration may also play a role, as patients receiving continuous infusion have been reported to develop *de novo* inhibitors.³⁵

The CANAL study

A large retrospective multicentre cohort study, Concerted Action on Neutralizing Antibodies in severe hemophilia A (CANAL) further investigated the relationship between treatment characteristics and the development of inhibitors, defined as two positive inhibitor titres combined with a decreased recovery.

Of the 366 previously untreated patients born between 1990 and 2000 who were enrolled, 87 (24%) developed inhibitors, including 69 (19%) of high titre. The study showed a correlation between inhibitor development and age at first treatment, with the incidence decreasing from 41% when treatment was initiated at <math><1</math> month of age to 18% for those receiving treatment after 18 months of age.¹¹ However, this association disappeared after adjusting for treatment intensity and other confounding factors, consistent with other studies.^{22,36–38} Furthermore, patients who received treatment for five or more consecutive days for bleeding or surgery were found to be statistically more likely (a 3.3-fold increase) to develop inhibitors than those treated for no more than four days.¹¹ Indeed, patients who were treated for surgical procedures faced a markedly higher risk of

developing inhibitors (65%) compared with patients being treated for bleeds (23%) or those receiving prophylactic treatment (22%; see Figure 3) Notably, patients undergoing regular prophylaxis experienced a 60% lower cumulative risk of developing inhibitors compared with those receiving on-demand treatment.

Researchers also found that switching between recombinant and plasma-derived products produced no clinically significant difference in inhibitor development.³⁹ There is no evidence supporting the superiority of any one type of FVIII product over the others in terms of inhibitor development: the risk was comparable between rFVIII and PD-FVIII (see Figure 4).³⁹ Studies such as CANAL are essential to better understand how clinicians can tailor therapy to prevent the development of inhibitors in patients with haemophilia A.

Clinical Experience of Immune Tolerance Induction – Managing and Overcoming Inhibitor Development

Current management of the development of inhibitors is by immune tolerance induction (ITI), explained Dr Thierry Lambert of France. When initially developed in 1976, the regimen consisted of regularly scheduled and systematic infusions of FVIII at high doses in association with activated prothrombin complex concentrates (aPCCs), the aim being to eradicate inhibitors and restore the clinical and biological efficacy of factor concentrates.⁴⁰ This procedure has since diversified and evolved into many forms, which vary in their overall success rate of 30–96%, and take anywhere from three to 42 months to achieve tolerance.^{41–46} However, studies on ITI are limited by a lack of randomisation and short study duration, and have low overall comparability.

The greatest success with ITI has been shown in patients who historically exhibit a low titre of inhibitor, have a low titre of inhibitor when initiating ITI and who start ITI soon after inhibitor development, although individual predictability is low. Infusions of FVIII at high doses have also been suggested to shorten time to a successful outcome. The use of concomitant aPCC appeared to increase the success of ITI, but to date this aspect remains entirely circumstantial; although ITI acts by modification of the human immune response, the precise mechanism is still unclear.

With an obvious need for greater understanding of ITI, the international Immune Tolerance Induction study was established with the objective of comparing the efficacy, response time, morbidity and economics of high-dose and low-dose immune tolerance protocols, as well as to identify the predictors of successful ITI.⁴⁷ Enrolment criteria are patients with severe haemophilia A who have developed inhibitors in the past 12 months and who have a historical peak inhibitor titre of >5BU but <math><200</math>BU. Since enrolment began in 2002, only 112 patients have been enrolled. It is important for any patient with immune tolerance to be informed of, if not involved in, this study, Dr Lambert stressed.

Starting, Maintaining and Enduring Immune Tolerance Induction

Outlining the difficulties and challenges in ITI, Dr Lambert spoke of the practicalities involved in the development and management of inhibitors in light of his own experiences on ITI with Kogenate at the Bicêtre Hospital in Paris, as well as his own personal recommendations. At diagnosis with haemophilia, it is advisable to inform the patient's family about the risks and consequences of inhibitor development and,

Table 2: Clinical Studies of BAY 79-4980 to Date

Study	Country	Number of Patients	Design	Primary Goal
Unpublished data (pilot)	Portugal	6	Open-label, uncontrolled, single-centre	First data on safety and efficacy; limited pharmacokinetic data
Spira et al., 2006 (dose-finding I)	Russia	24	Patient-blinded, controlled, two-way cross-over, multicentre	Doses of rFVIII of 25IU/kg or 35IU/kg, fixed liposome dose of approximately 22mg/kg
Spira et al., 2008 (dose-finding II)	Russia	16	Patient-blinded, randomised, four-way cross-over, multicentre	Fixed dose of rFVIII at 35IU/kg, varying liposome dose of 0, 4.2, 12.6 or 22.1mg/kg
Martinowitz et al., 2008 (rapid infusion)	Israel	18	Open-label, randomised, parallel-group, single-centre	Safety of 35IU/kg FVIII with 13mg/kg liposomes at increasing rates of infusion (20, 15, 10 and 5 minutes)
Powell et al., 2008 (phase I)	US	26	Double-blind, randomised, parallel-group, cross-over	Safety and pharmacokinetics of 35IU/kg FVIII in 2 liposome dose groups (22 or 13mg/kg)

increase in the consumption of clotting factor concentrates. Other disadvantages lie in the pharmacological properties of the factor concentrates. FVIII has a relatively short half-life of about 12 hours, so patients require frequent intravenous infusions. This is even more inconvenient for younger patients because of difficulties related to venous access, which may lead to the increased use of CVLs and their associated risks of thrombosis and infection. Lastly, the clotting factor concentrates present only a solution for the symptoms of bleeding episodes, not a cure for haemophilia.

There are several directions that the future treatment of haemophilia can take. The ultimate goal of research, and the great anticipation of patients, is a cure – which is potentially offered by gene therapy. Transgenic animals have been of great utility in many genetic diseases, and there is hope that they can be used to increase the production capacity of coagulation factors, thereby reducing the price while increasing availability. Alternative delivery routes are another area of interest: for instance, oral formulations would be much more convenient than intravenous infusions. However, the most imminent development is treatment with a prolonged half-life. Notably, many clinical trials are currently studying pegylated liposomes as a plasma carrier for FVIII.

A Role for Pegylated Liposomes in Haemophilia A Treatment

Various drugs have been encapsulated in liposomes as these small lipid vesicles provide the advantages of improved drug targeting to therapeutic sites, enhanced efficacy and decreased degradation of the active compound in the bloodstream. This method has been adapted for haemophilia treatment: for example, there is the novel compound BAY 79-4980, which involves a non-covalent binding of sucrose-formulated rFVIII (rFVIII-SF) to the surface of pegylated liposomes. This new product possesses the same enzymatic activity and von Willebrand factor levels as conventional rFVIII-SF, differing only in that it is reconstituted in an aqueous solution of pegylated liposomes in lieu of water for injection.⁵² The non-covalent interaction between rFVIII-SF and pegylated liposomes must be formed prior to infusion: sequential injections of rFVIII-SF and PEGylated liposome exhibit no difference in efficacy from injections of FVIII alone.⁵³

Initial *in vivo* studies were performed in the haemophilia mouse tail-cut model. An injection of BAY 79-4980, rFVIII-SF or placebo was given to the mice, followed by a tail cut 24 hours afterwards. Control mice died within 10 hours of having their tails cut. Of the rest, a significantly greater

percentage of mice receiving BAY 79-4980 were still alive after 24 hours (85%) compared with mice that had received rFVIII-SF (50%; $p < 0.01$).⁵⁴ Incremental recovery, clearance and volume of distribution was found to be comparable between the two clotting factor concentrates. However, BAY 79-4980 has shown a modest but significant (13%; $p = 0.024$) increase in terminal half-life – a characteristic that has been attributed to the observed improvements in efficacy.⁵³

Early clinical studies of BAY 79-4980 in adult patients with severe haemophilia A have been promising. The bleed-free interval following a prophylactic infusion of BAY 79-4980 was significantly longer than following an infusion of rFVIII-SF at dosages of 25IU/kg (10.9 versus 5.9 days; $p = 0.02$), a result that was further enhanced at an increased dose of 35IU/kg (13.3 versus 7.2 days; $p < 0.001$; see *Figure 5*).⁵⁵ The specific mechanism of action of BAY 79-4980 is still not clear: pharmacokinetic assessments by one-stage coagulation assays and chromogenic assays have shown no statistically significant differences between the two factor concentrates in their activity with time.⁵⁶ There is speculation that the pegylated liposomes may localise to specific cells such as platelets, and injury sites might instigate platelet activation, leading to platelet aggregation at the site of vascular injury and, by affiliation, concentrating the associated rFVIII-SF.

Previous experiences with lipid emulsions and other liposomal drugs have sometimes encountered hypersensitivity reactions. Although the incidence of these hypersensitivity reactions can reach 45%, severe reactions affect only 2% of patients.⁵⁷ Often, the first dose induces tolerance to lipid emulsions or liposomes, resulting in no anamnestic responses from secondary and tertiary exposure.

An adverse event characteristic of lipid emulsions or liposomal drugs is complement activation-related pseudoallergy (CARPA), in which the complement system is activated for the purpose of liposomal clearance. Notably, the phase I study of BAY 79-4980 saw transient C3a elevations in 69% of patients treated; however, as only one of 26 patients experienced a hypersensitivity reaction consistent with CARPA (increased breathing frequency, flushing), there may be no prognostic value in measuring C3a levels as a diagnostic marker for CARPA.⁵⁶ Although C3a levels increased, there was no corresponding increase in total complement activity CH50, suggesting no evidence in support of gross complement activation or consumption.

In clinical trials to date involving 90 patients and 150 injections in total, BAY 79-4980 has exhibited increased efficacy and prolonged half-life,

as well as similar tolerance levels to its pegylated liposome-free counterpart (see *Table 2*).^{56–59} Notably, the development of inhibitors in subjects receiving BAY 79-4980 has yet to be observed. A phase II study recently began in August 2008 to determine whether once-weekly administration of BAY 79-4980 is tolerable and sufficient to prevent bleeds in patients with severe haemophilia A. This double-blind multicentre study across 66 treatment centres in 14 countries will randomise patients to receive either BAY 79-4980 at 35IU/kg once a week or rFVIII three times a week over the course of one year. With promising safety and efficacy data thus far, it is hoped that this new development of rFVIII-SF in combination with PEGylated liposomes will usher in the next era of progress in haemophilia treatment. ■

- Berntorp E, Astermark J, Björkman S, et al., Consensus perspectives on prophylactic therapy for haemophilia: summary statement, *Haemophilia*, 2003;9(Suppl 1):1–4.
- Nilsson IM, Hedner U, Ahlberg A, Haemophilia prophylaxis in Sweden, *Acta Paediatr Scand*, 1976;65:129–35.
- Fischer K, van der Bom JG, Mauser-Bunschoten EP, et al., The effects of postponing prophylactic treatment on long-term outcome in patients with severe haemophilia, *Blood*, 2002;99:2337–41.
- Nilsson IM, Berntorp E, Löfqvist T, et al., Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B, *J Intern Med*, 1992;232:25–32.
- Berntorp E, Prophylactic therapy for haemophilia: early experience, *Haemophilia*, 2003; 9(Suppl. 1):5–9.
- Feldman BM, Pai M, Rivard GE, et al., Tailored prophylaxis in severe haemophilia A: interim results from the first 5 years of the Canadian Hemophilia Primary Prophylaxis Study, *J Thromb Haemost*, 2006;4:1228–36.
- Petrini P, Identifying and overcoming barriers to prophylaxis in the management of haemophilia, *Haemophilia*, 2007;13(Suppl. 2):16–22.
- World Federation of Hemophilia, Guidelines for the management of hemophilia, 2005. Available at: www.wfh.org/2/docs/Publications/Diagnosis_and_Treatment/Guidelines_Mng_Hemophilia.pdf (last accessed 13 October 2008).
- Giangrande PL, Adverse events in the prophylaxis of haemophilia, *Haemophilia*, 2003;9(Suppl. 1):50–54, discussion 55–6.
- Giangrande PL, KOGENATE Bayer study group, Safety and efficacy of KOGENATE Bayer in previously untreated patients (PUPs) and minimally treated patients (MTPs), *Haemophilia*, 2002;8(Suppl. 2):19–22.
- Gouw SC, van der Bom JG, van den Berg M for the CANAL Study Group, Treatment-related risk factors of inhibitor development in previously untreated patients with haemophilia A: the CANAL cohort study, *Blood*, 2007;109:4648–54.
- Manco-Johnson MJ, Abshire TC, Shapiro AD, et al., Prophylaxis versus episodic treatment to prevent joint disease in boys with severe haemophilia, *N Engl J Med*, 2007;357:535–44.
- Hemophilia: Information System (HemIS) registry, 2006 annual report, unpublished.
- Gringeri A, von Mackensen S, Auerswald G, et al., Health status and health-related quality of life of children with haemophilia from six West European countries, *Haemophilia*, 2004;10(Suppl. 1):26–33.
- Richards M, Altisent C, Batorova A, et al., Should prophylaxis be used in adolescent and adult patients with severe haemophilia? An European survey of practice and outcome data, *Haemophilia*, 2007;13:473–9.
- Tagliaferri A, Franchini M, Coppola A, et al., Effects of secondary prophylaxis started in adolescent and adult haemophiliacs, *Haemophilia*, 2008;14:945–951.
- Wight J, Paisley S, The epidemiology of inhibitors in haemophilia A: a systematic review, *Haemophilia*, 2003;9:418–35.
- Gruppo R, Chen H, Schroth P, et al. for the Recombinate PUP Study Group, Safety and Immunogenicity of recombinant factor VIII (Recombinant™) in previously untreated patients (PUPs): a 7.3 year update, *Haemophilia*, 1998;4:228, abstract 291.
- Rothschild C, Laurian Y, Satre EP, et al., French previously untreated patients with severe haemophilia A after exposure to recombinant factor VIII: incidence of inhibitor and evaluation of immune tolerance, *Thromb Haemost*, 1998;80:779–83.
- Lusher JM, Lee CA, Kessler CM, et al. for the Refacto phase 3 study group, The safety and efficacy of B-domain deleted recombinant factor VIII concentrate in patients with severe haemophilia A, *Haemophilia* 2003;9:38–49.
- Lusher J, Abildgaard C, Arkin S, et al., Human recombinant DNA-derived antihemophilic factor in the treatment of previously untreated patients with haemophilia A: final report on a hallmark clinical investigation, *J Thromb Haemost*, 2004;2:574–83.
- Kreuz W, Gill JC, Rothschild C, et al., Full-length sucrose-formulated recombinant factor VIII for treatment of previously untreated or minimally treated young children with severe haemophilia A, Results of an international clinical investigation, *Thromb Haemost*, 2005;93:457–67.
- Goudemand J, Treatment of patients with inhibitors: cost issues, *Haemophilia*, 1999;5:397–401.
- Aledort LM, Dimichele DM, Inhibitors occur more frequently in African-American and Latino haemophiliacs, *Haemophilia*, 1998;4:68.
- Astermark J, Berntorp E, White GC, et al., The Malmö International Brother Study (MIBS): further support for genetic predisposition to inhibitor development in hemophilia patients, *Haemophilia*, 2001;7:267–72.
- Oldenburg J, El-Maarri O, Schwaab R, Inhibitor development in correlation to factor VIII genotypes, *Haemophilia*, 2002;8(Suppl. 2):23–9.
- Astermark J, Oldenburg J, Pavlova A, et al., Polymorphisms in the IL10 but not the IL1beta and IL4 genes are associated with inhibitor development in patients with haemophilia A, *Blood*, 2006;107:3167–72.
- Astermark J, Basic aspects of inhibitors to factors VIII and IX and the influence of non-genetic risk factors, *Haemophilia*, 2006;12(Suppl. 6):8–13.
- Astermark J, Wang X, Oldenburg J, et al., Polymorphisms in the CTLA-4 gene and inhibitor development in patients with severe haemophilia A, *J Thromb Haemost*, 2007;5:263–5.
- Lorenzo JJ, Lopez A, Altisent C, et al., Incidence of factor VIII inhibitors in severe haemophilia: the importance of patient age, *Br J Haematol*, 2001;113:600–603.
- van der Bom JG, Mauser-Bunschoten EP, Fischer K, et al., Age at first treatment and immune tolerance to factor VIII in severe haemophilia, *Thromb Haemost*, 2003;89:475–9.
- Morado M, Villar A, Jiménez Yuste V, et al., Prophylactic treatment effects on inhibitor risk: experience in one centre, *Haemophilia*, 2005;11:79–83.
- Goudemand J, Inhibitor development in haemophilia A: the role of von Willebrand factor/factor VIII concentrates, *Haemophilia*, 2007;13(Suppl. 5):47–51.
- Escurioloa Ettingshausen C, Kreuz W, Recombinant vs. Plasma-derived products, especially those with intact VWF, regarding inhibitor development, *Haemophilia*, 2006;12:102–6.
- von Auer CH, Oldenburg J, von Depka M, et al., Inhibitor development in patients with haemophilia A after continuous infusion of FVIII concentrates, *Ann N Y Acad Sci*, 2005;1051:498–505.
- Chalmers EA, Williams MD, Richards M, et al., Early FVIII exposure and subsequent inhibitor development in children with severe haemophilia A, *J Thromb Haemost*, 2005;3, abstract OR092.
- Fontes E, Carvalho S, Amorim L, Age at the beginning of factor VIII replacement is not a risk factor for inhibitor development in hemophilia A, *Haemophilia*, 2004;10(Suppl. 3), abstract 120C14.
- Kreuz W, Auerswald G, Budde U, et al., Inhibitor incidence in previously untreated patients (PUP) with haemophilia A and B – a 10-year follow up of the prospective multicenter study, *Blood*, 2004;104, abstract 3983.
- Gouw SC, van der Bom JG, Auerswald Gunter, et al., Recombinant versus plasma-derived factor VIII products and the development of inhibitors in previously untreated patients with severe haemophilia A: the CANAL cohort study, *Blood*, 2007;109:4693–7.
- Brackmann HH, Gormsen J, Massive factor-VIII infusion in haemophiliac with factor-VIII inhibitor, high responder, *Lancet*, 1977;2:933.
- Freiburghaus C, Berntorp E, Ekman M, et al., Tolerance induction using the Malmö treatment model 1982–1995, *Haemophilia*, 1999;5:32–9.
- Smith FP, Spence KJ, Walters EL, et al., Immune tolerance therapy for haemophilia A patients with acquired factor VIII alloantibodies: comprehensive analysis of experience at a single institution, *Thromb Haemost*, 1999;81:35–8.
- Rocino A, Papa M, Capasso F, et al., Immune tolerance induction in haemophilia A patients with high responding inhibitors to factor VIII : experience at a single institution, *Haemophilia*, 2001;7:33–8.
- Gruppo RA, Valdez LP, Stout RD, Induction of immune tolerance in patients with hemophilia A and inhibitors, *Am J Pediatr Hematol Oncol*, 1992;14:82–7.
- Mauser-Bunschoten EP, Rosendaal FR, Niewenhuis HK, et al., Clinical course of factor VIII inhibitors developed after exposure to a pasteurized Dutch concentrate compared to classic inhibitors of hemophilia A, *Thromb Haemost*, 1994;71:35–8.
- Brackmann HH, Oldenburg J, Schwaab R, Immune tolerance for the treatment of factor-VIII inhibitors – twenty years 'Bonn protocol', *Vox Sang*, 1996;70(Suppl. 1):30–35.
- Immune Tolerance Induction Study. Available at: www.itistudy.com
- Morfini M, Auerswald G, Kobelt RA, et al., Prophylactic treatment of haemophilia patients with inhibitors: clinical experience with recombinant factor VIII in European Haemophilia Centres, *Haemophilia*, 2007;13:502–7.
- Brackmann HH, Effenberger W, Hess L, et al., Immune tolerance induction: a role for recombinant activated factor VII (rFVIIa)?, *Eur J Haematol Suppl*, 1998;63:18–23.
- Kreuz W, Ehrenforth S, Funk M, et al., Immune-tolerance therapy in paediatric haemophiliacs with factor VIII inhibitors: 14 years follow-up, *Haemophilia*, 1995;1:24–32.
- Lambert T, Clinical Experience of ITI in overcoming inhibitor development, Presented at the 21st Annual European Haemophilia Consortium, Dublin, Ireland, 12–14 September 2008.
- Powell JS, Liposomal approach towards the development of a longer-acting factor VIII, *Haemophilia*, 2007;13(Suppl. 2):23–8.
- Pan J, Liu T, Kim J-Y, et al., Enhanced efficacy of recombinant factor VIII in non-covalent complex with PEGylated liposome in hemophilia A mice, *Blood*, 2007;110:3149.
- Baru M, Carmel-Goren L, Barenholz Y, et al., Factor VIII efficient and specific non-covalent binding to PEGylated liposomes enables prolongation of its circulation time and haemostatic efficacy, *Thromb Haemost*, 2005;93:1061–8.
- Spira J, Plyushch OP, Andreeva TA, et al., Prolonged bleeding-free period following prophylactic infusion of recombinant factor VIII reconstituted with pegylated liposomes, *Blood*, 2006;108:3668–73.
- Powell JS, Nugent DJ, Harrison JA, et al., Safety and pharmacokinetics of a recombinant factor VIII with pegylated liposomes in severe haemophilia A, *J Thromb Haemost*, 2008;6:277–83.
- Szebeni J, Complement activation-related pseudoallergy: a new class of drug-induced acute immune toxicity, *Toxicology*, 2005;216:106–21.
- Spira J, Plyushch OP, Andreeva TA, et al., Evaluation of liposomal dose in recombinant factor VIII reconstituted with pegylated liposomes for the treatment of patients with severe haemophilia A, *Thromb Haemost*, 2008;100:429–34.
- Martinowitz U, Lalezari S, Luboshitz, et al., Infusion rates of recombinant FVIII-FS with PEGylated liposomes in haemophilia A, *Haemophilia*, 2008;14:1122–4.