

## Inhibitor treatment in haemophilias A and B: summary statement for the 2006 international consensus conference

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**Summary.** Participants in an international conference on the management of haemophilia patients with inhibitors developed a jointly authored summary of the findings and conclusions of the conference. Current knowledge of the genetic and immunologic mechanisms underlying inhibitor development was briefly summarized. Concerning the purported treatment-related risk factors, conference participants commented on the limitations of the available evidence and the need for more rigorous prospective research in a fully genotyped population. Other clinical considerations discussed included the unproved utility of routine surveillance, the need for assay standardization, the management of acute

bleeding and approaches to joint disease prophylaxis and immune tolerance induction (ITI). A number of issues were identified as needing further investigation in larger prospective studies, ideally through international cooperation. Such studies should enrol cohorts that have been scrupulously defined in terms of mutation status and treatment exposure. Finally, conference participants urged their colleagues to participate in the currently ongoing international trials of ITI.

**Keywords:** diagnosis, guidelines, haemophilia, inhibitors, treatment

### Introduction

The International Consensus Conference on Inhibitor Treatment in Hemophilia A and B, held in Cambridge, Massachusetts, 24–25 March 2006, was convened with the goal of formulating recommendations on the management of the patient with inhibitors to factor VIII (FVIII) or factor IX (FIX)

where sufficient evidence exists to guide clinical practice, and of identifying priorities for research where the data are inadequate. The conference format combined brief presentations with extended periods of open discussion. The conclusions reached over the course of the 2-day conference are summarized briefly below and presented at greater length in the individual papers and accompanying discussions that constitute the conference proceedings.

The development of inhibitors is today the most serious complication of haemophilia and its treatment. Inhibitors occur in 20–30% of patients with haemophilia A but in only 5% of patients with haemophilia B. In haemophilia B, however, inhibitors

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may develop concurrent with life-threatening allergic responses to FIX infusion. Haemophilic patients who develop an inhibitor have a different, and far more severe, disease course than the patient without inhibitors. Their treatment options and the potential complications, as well as the costs of treatment, all differ from those of the patient with haemophilia uncomplicated by inhibitors.

### **Inhibitor biology**

An inhibitor is a polyclonal inhibitory immunoglobulin G antibody directed against FVIII or FIX. As clinicians caring for patients with haemophilia are already aware, there is a high-risk period for the development of inhibitors during the first 50–100 days of exposure to infused factor. It is not so commonly appreciated that there is another period of increased risk later in life. In the UK database of inhibitor patients, 27% of inhibitors were first detected in adulthood, with a peak incidence in the fifth and sixth decades. A number of prognostic factors, both genetic and environmental, have been proposed, and some clinicians currently base their management decisions (e.g. type of concentrate) on these reported risk factors. However, the evidence to support them is sometimes drawn from retrospective studies in small numbers of patients, and the inhibitor incidence rates associated with these treatment variables have sometimes differed markedly from one report to another.

#### *Genetic risk factors*

Inhibitor risk is to a considerable degree genetically determined. Inhibitor prevalence in haemophilias A and B is influenced by mutation type; in particular, the severity and the localization of the factor gene defect. Despite the small population available for study, there are data to suggest that inhibitors in haemophilia B are especially associated with large deletions in the FIX gene, and that these patients are also at higher risk of severe anaphylactoid reactions. For patients with haemophilia A, there is a 15-fold or greater difference between the lowest and highest risk levels associated with specific FVIII gene mutations, e.g. large multidomain deletions vs. missense mutations. However, for most patients with haemophilia A, there is only a twofold difference in the range of risk (17–41%) of inhibitor development. Thus, at this point in time, genotyping provides a significant prediction of the inhibitor risk for about 20% of patients with severe haemophilia A, while for the other 80% of

patients, there is only a twofold risk difference which limits the power of assessing the average patient's risk of inhibitor development by genotyping. However, in haemophilia B, a genetic analysis of the FIX gene directly after diagnosis is strongly recommended because the result may point to patients at risk for developing an allergic reaction. In those patients, the first 20 FIX concentrate substitutions should only be given in the presence of a physician or haemophilia nurse.

Aside from the factor gene defect itself, mutations and polymorphisms in immune response genes are likely involved in determining inhibitor risk. HLA polymorphisms appear to have a relatively weak effect on inhibitor development. Polymorphisms in the IL-10 but not in the IL-1 $\beta$  and IL-4 genes are associated with inhibitor development in patients with haemophilia A. In the genetics of inhibitor development, immune response genes may prove to be as significant as the specific factor gene mutation. The genetic component of inhibitor risk may well result from a complex interaction of multiple immune response gene polymorphisms in addition to the FVIII or FIX gene mutation. If that proves to be the case, then the genetic profile may be too complex to allow for clinically useful interpretation of an individual patient's risk of inhibitor development. However, further research to delineate the genetic determinants of inhibitor risk may nonetheless benefit patient care by clarifying the impact of environmental variables and thus providing a better knowledge base for instituting preventive strategies.

Although genetic testing can be important for families who wish to know carrier status, conference participants concurred that the family history and ethnic origin are still the most powerful and best validated approach to estimate the individual patient's lifetime risk of inhibitor development. For patients with a positive family history of inhibitors, the risk of an inhibitor is 48% overall; however, the risk is only 9% for an extended family member vs. 50% for a sibling. Risk is also known to vary with ethnicity, and the incidence of inhibitors is notably increased for patients of African descent.

#### *Environmental influences on inhibitor development*

Putative non-genetic influences on inhibitor development include age at first infusion; immune system challenges, such as immunization, inflammation and trauma or surgery; and treatment-related variables, including type of concentrate and mode of administration.

In the opinion of conference participants, the data to implicate age at start of treatment as an independent risk factor for inhibitor development are unconvincing. Patients who require factor infusion in infancy most likely have more severe disease and are at greater risk regardless of the time of first treatment. Thus, there is no scientific evidence at this time to say that clinicians should avoid treating very young patients.

There is a possible mechanistic basis for an effect of immune system challenges on inhibitor risk. Activation and modulation of cytokines and other immune regulatory elements via infections, immunization or bleeding may facilitate the formation of an inhibitor. In mild haemophilia, inhibitors most often arise in conjunction with surgery. However, at this point, there are no data to show a significant influence of infections, vaccination, surgical events or central nervous system bleeding on inhibitor risk.

A rationale can also be put forward to account for the putative product-related factors. Manufacturing processes may modulate immunogenicity, and potentially important variables include the possible protective roles of von Willebrand factor and immunomodulatory peptides in plasma-derived concentrates. Some conference participants felt that it will not be possible to arrive at definitive data on this issue without studying each FVIII product individually, commenting that existing studies have reported very wide ranges of inhibitor incidence within the category of plasma-derived concentrates. Recombinant concentrates have not been well enough studied to permit conclusion about their purported impact on inhibitor risk. For progress in elucidating the effects of product on inhibitor risk, compliance with the existing voluntary systems for reporting of adverse effects needs to be improved. There is a clear need for a more effective pharmacovigilance system that would gather all relevant patient data to identify product-related patterns in inhibitor development.

Overall, the impact of non-genetic factors on inhibitor development is still unclear. To date, it has not been possible to perform a true evaluation of non-genetic factors because of the lack of a study population that has been sufficiently well characterized with respect to genetic risk profile. Conference participants concluded that insufficient data are available to support recommendations on assessing and minimizing any treatment-related influences on inhibitor development. As a corollary, there is currently no scientific evidence to say that clinicians should avoid specific treatment approaches that would otherwise constitute good clinical practice.

## Diagnosis of inhibitors

### *Inhibitor assays*

It is widely recognized that the Nijmegen method is the most sensitive and specific assay for inhibitors currently available. However, the Nijmegen method is performed differently from one country to another and even from one laboratory to another. Participants felt that centralized testing alone would not be sufficient to ensure that multicentre data are truly comparable. Both research and clinical assessment would benefit if an international standard could be developed from careful study of reference material, as it is currently performed to validate other assays, such as the international normalized ratio and the standard for prothrombin time. More data are needed to establish the sensitivity and specificity of the Nijmegen method for FIX inhibitors and to demonstrate that the low titres reported with this assay are in fact measuring inhibitory antibodies.

### *Surveillance*

Inhibitors may be found by routine screening but are more commonly diagnosed because of a sudden lack of response or poor response to standard replacement therapy. Surveillance studies are important, but they should be carefully designed with well-defined questions and utilizing standardized methodology. Routine clinical surveillance schedules for paediatric haemophilia A patients during high-risk incidence periods, although widely employed, have not been sufficiently well studied either to determine the optimal schedule or to demonstrate a clinical benefit to early detection and intervention. However, in the views of the conference participants, surveillance of inhibitors seems to be primarily justified as a component of a research effort. In the clinical setting, the occurrence of poorly controlled bleeding is more relevant for identifying the patient in need of an intervention. To aid in prompt diagnosis and intervention, the physician should advise the patient or parents to report any poor response to treatment, as such an observation merits inhibitor testing.

Conference participants commented that genotyping may be preferable to routine inhibitor screening for patients with haemophilia B. The group recommended that those patients identified as high risk for anaphylactic/anaphylactoid reactions in association with inhibitor development because of large deletion mutations in the FIX gene receive their first 10–20 treatments under very close medical supervision. Given that 95% of patients with FIX deficiency never

develop inhibitors, in the absence of a high-risk mutation or a positive family history, routine surveillance may not always be helpful for these patients.

Although both the research and the clinical emphasis have been on screening previously untreated patients (PUPs) in their high-risk period, it is important for physicians to be aware that older adults with haemophilia also have an increased risk of inhibitors, especially those with mild or moderate disease severity. There is a need to develop and validate an inhibitor monitoring strategy for the high-risk older population. These patients should be monitored closely for inhibitor development in the event of surgery or bleeding. When these patients are seen before a surgical procedure, or when there is unexplained or poorly controlled bleeding, a baseline FVIII assay is inadequate; a specific inhibitor titre must be assayed whether their FVIII is detectable or not. Although the risk of inhibitor development in mild and moderate haemophilia A is only about 5%, risk level should not preclude careful evaluation of the surgical or trauma patient. All patients with mild and moderate haemophilia should have an inhibitor titre determined prior to any surgical intervention or at the earliest time feasible during intensive times of treatment, with follow-up as appropriate.

### Treatment of acute bleeding

All bleeding events in the patient with inhibitors must be treated in as timely a manner as possible. Options include bypassing agents, factor replacement, desmopressin and antifibrinolytic agents. Extracorporeal immunoadsorption is yet another option and is described in detail within the conference proceedings; however, the procedure requires a highly trained team and as a consequence is not widely available. None of these therapeutic options is optimal, and there is no universally effective haemostatic agent. Clinicians with a significant number of inhibitor patients have observed that some patients respond better to the activated prothrombin complex concentrate FEIBA<sup>TM</sup> and others to activated recombinant factor VII (rFVIIa). This was also a striking finding in the FENOC trial. Indeed, some patients respond sometimes better to one product and sometimes to another.

Thus, no general recommendations are possible; the choice of product should be based upon the patient's past responses, current inhibitor titre and the severity of the bleed. For acute treatment of severe bleeds, the most effective approach is factor replacement whenever feasible. When the inhibitor titre is low ( $\leq 10$  Bethesda units), it is often possible

to obtain haemostasis by giving an increased dose of the concentrate following the published algorithms for dose calculation. High-dose immune tolerance induction (ITI) sometimes reduces bleeding frequency even in patients with high titres.

There are anecdotal published reports describing improved efficacy with combination regimens of FEIBA and rFVIIa administered on an inpatient basis in haemophilia treatment centres. Conference participants did not feel that sequential or combined use of these two agents can be recommended as a strategy to control bleeding, given the limited data to support it and the serious and as yet unstudied risks of thromboembolic complications. Such an approach may have potential therapeutic efficacy in life-threatening circumstances when all other options to stop bleeding have failed, but it cannot be recommended as standard practice.

Because of the special challenges of controlling bleeding in the patient with inhibitors, these individuals are optimally treated in a specialist centre or in close consultation with such a centre if the patient is unable to travel. Response to treatment should be ascertained by sensitive and objective assessment approaches including imaging studies when necessary; treatment should be continued until bleeding cessation is certain. For most types of deep tissue bleeding, including muscle haematomas, it may be necessary to continue some form of prophylaxis until tissue healing, not merely bleeding cessation, has been demonstrated.

### Joint prophylaxis

Inhibitor patients have substantially greater joint morbidity than patients without inhibitors. Accordingly, there is considerable clinical and research interest in establishing effective regimens for prevention of bleeding in inhibitor patients, particularly those who fail ITI. However, there is a general lack of good data to support any specific regimen. For the individual patient, the clinician should individualize the prophylactic regimen using bleeding as an endpoint.

Prophylaxis studies are currently underway with the two bypassing agents FEIBA and rFVIIa (NovoSeven<sup>®</sup>, Nova Nordisk, Inc., Princeton, NJ, USA). The ProFEIBA trial has a randomized crossover design in which all patients receive 6 months of on-demand treatment and 6 months of prophylactic therapy with FEIBA 90 U kg<sup>-1</sup> thrice weekly. The initial NovoSeven prophylaxis trial had a randomized double blind design that utilized a 3-month lead in observation period of on-demand therapy,

followed by 3 months of prophylaxis at one of two doses,  $90 \mu\text{g kg}^{-1} \text{ day}$  vs.  $270 \mu\text{g kg}^{-1} \text{ day}^{-1}$ . The primary endpoint for both the studies is the number of bleeds. Preliminary data from the NovoSeven prophylaxis study were presented at the World Federation of Haemophilia meeting in May of 2006, showing reduced frequency of bleeding with both dosing regimens when compared with the number of bleeds occurring during the 3-month lead-in period.

No data are thus far available from the ProFEIBA study. These results, as well as the full published data of the NovoSeven prophylaxis trial, are awaited with great interest. It is worth noting that these two products have never been compared head to head, and the current studies are unlikely to provide data that would guide the clinician in choosing between them. Moreover, judging from the preliminary NovoSeven results, some patients will continue to experience serious bleeding episodes on prophylaxis despite the statistically significant reduction in bleeding frequency.

Although there are currently insufficient data to make recommendations in regard to routine prophylaxis for patients with inhibitors, there are clinical circumstances, such as postsurgery or following intracranial haemorrhage, where prophylaxis is clearly indicated. Patients with frequent joint bleeding who have failed ITI are also candidates for prophylaxis, but the risks and benefits of radioisotopic synovectomy, if appropriate, may also be considered as a cost-effective strategy.

### Immune tolerance induction

Given that a patient's long-term morbidity is substantially worse if complicated by inhibitor development, a majority of conference participants felt that an attempt at tolerization is reasonable for most such patients, with the potential exception of haemophilia B patients, given the risk of severe anaphylactoid reactions. Participants agreed that tolerization should be tried in all haemophilia A patients with inhibitors of recent onset. Tolerization is best undertaken at centres with an interest in the procedure and a commitment to data collection, or in consultation with such a centre if the patient cannot travel. To aid progress in this field, all patients in whom ITI is attempted should be either in a trial or in a registry. Two multicentre prospective randomized studies will examine the impact of dosing regimen and product purity on outcome: the ongoing I-ITI study, which is comparing ITI outcome using either high (FVIII,  $200 \text{ U kg}^{-1} \text{ day}^{-1}$ ) or low ( $50 \text{ U kg}^{-1}$  thrice weekly),

dose ITI regimens in a good risk severe haemophilia A cohort, and the planned RESIST (Rescue Immunotolerance Study) study, which will evaluate ITI outcome with respect to type of product used (rFVIII vs. a von Willebrand factor containing plasma-derived FVIII product) in a poor prognosis inhibitor population. Conference participants concurred in recommending that all eligible patients be enrolled in these important studies.

Among the various ITI regimens currently in use, the Bonn ITI protocol utilizes FVIII  $100\text{--}150 \text{ U kg}^{-1}$  every 12 h, along with FEIBA concentrates, in patients with a history of severe bleeding or when frequent bleedings are complicating the ITI course. Although thrombosis has not been observed as a complication of this particular regimen, some conference participants expressed concern that some clinicians are using bypassing agents in conjunction with high doses of FVIII (e.g.  $200 \text{ U kg}^{-1}$ ). Because of potential thrombogenicity, titres should be regularly checked and FEIBA should be discontinued as soon as any FVIII level is achieved on such a high-dose regimen.

In considering the merits of alternative strategies for achieving immune tolerance, conference participants discussed at some length the Malmö regimen for ITI via immunoabsorption of inhibitor. Although technically difficult to perform, it has the advantage of a very rapid 3-week median response time. The potential advantages of immunoabsorption for rapid elimination of inhibitors in haemophilia B patients, thereby minimizing risk of the nephrotic syndrome, should receive further study. Technological advances, including the development of inhibitor-specific columns, could enhance the procedure's clinical utility, particularly for patients with long-standing inhibitors who have failed conventional ITI.

### *Rituximab*

Although numerous case reports have suggested that rituximab may benefit some patients who have previously failed immune tolerance therapy, there is likely a reporting bias in the literature in that therapy failures are rarely presented or published. The potential utility of rituximab for suppressing antibody levels in patients with haemophilia B and the allergic phenotype should also be investigated. Participants commented that caution is appropriate, particularly in treating children, as this agent has not been approved for use either in haemophilia or in the paediatric population. One such trial is underway in the United States.

*Venous access*

Conference participants felt that use of central venous access devices (CVADs) has become too routine in haemophilia, given the complication rates associated with these devices. Studies have shown that at least 80% of the children can start thrice weekly prophylaxis without any implantable device. The recommendation of conference participants is that clinicians avoid the routine use of CVADs, but if required, the catheter should be removed as soon as feasible. This is particularly important in the inhibitor population, as these patients have an increased incidence of infection with these devices. Totally implantable CVADs (ports) are preferred over external CVADs as the risk of complications, especially infections, is much higher with external devices. While arteriovenous fistulae may prove to be an important option because of the low rate of infection, there is a risk in small children of differential limb growth. The approach requires a highly specialized and experienced surgeon who is aware of this risk and can create fistulae with relatively low flow. In children, this procedure should only be performed in specialized centres in the context of a study, which includes an informed consent procedure detailing the possible sequelae.

*Economics of inhibitor treatment*

The costs of care for the patient with an inhibitor are substantially greater than the costs of treating persons with haemophilia who do not have inhibitors. Those costs are variable from patient to patient but range up to several million US dollars a year. In this context, immune tolerance is expensive but may be economically justifiable in the long-term as, if successful, it reduces the lifetime costs of treating that patient. Inclusion of an economic substudy in ITI trials would be important to clarifying costs and benefits, specifically the cost per quality-of-life gain.

**Research priorities**

Continued basic research in the immunologic aspects of inhibitors may yield insights into more effective intervention and prevention strategies. In particular, inhibitor biology in the haemophilia B population is poorly understood. It is also still unknown whether clotting factor concentrates have differential immunogenicity; this important question cannot be answered by additional small retrospective series, as these are biased by historical shifts in treatment patterns. Formal prospective studies are needed of

rituximab and other immunosuppressive interventions to determine whether they might enhance inhibitor eradication in individuals initially refractory to standard immune tolerance regimens. All future studies of environmental and treatment variables must control for mutation genotype. The well-designed I-ITI study is currently open, as detailed above, but has not yet made its accrual goal. Conference participants urge investigators to join these studies and enrol their eligible patients.

Conference participants were in substantial agreement on these research priorities. They concluded that additional publications of case reports and small retrospective series will not take the field further. Advances in inhibitor prevention and treatment will only come from a global commitment on the part of large haemophilia treatment centres to participate in trials and to gather registry data in a uniform and consistent fashion. Moreover, to answer questions concerning product differences in immunogenicity, there will need to be a commitment by each participating centre to use a specific product throughout a patient's high-risk period for inhibitor development.

In this context, there was considerable discussion of the impact of the European directive on research in this field, which mandates that all study medications be provided free of charge. The costs of doing studies in haemophilia rapidly become prohibitive under these restrictions. For example, had the I-ITI study been initiated under the European directive, it would have required funding to cover the cost of approximately 500 million units of FVIII. Conference participants commented that they understand the ethical motives that underlie the European directive; however, they felt these restrictions should not be applied to research where investigators wish to randomize patients to different regimens of standard therapies or to gather prospective data on therapies that the patients would be receiving in the absence of a formal research effort. It is vital for improving patient care and allocating very costly interventions in a rational and equitable fashion that research not be impeded.

*Defining populations for study*

Conference participants agreed that, for research purposes, the PUP should be defined strictly as a previously untransfused patient, i.e. one with no prior antigen exposure. The previously treated patient is defined as having more than 150 exposure days. Some participants felt that PUP studies should not include an intermediate group of minimally

treated patients, as this distinction may be invalid for the purposes of studying inhibitor biology or product immunogenicity. Other participants objected that, in the setting of a clinical trial, it may not be possible to accrue sufficient numbers of strictly defined PUPs. However, the trial entry criteria may be expanded without broadening and confusing the definition. Going forward, studies should specify their population as clearly as possible.

#### *Registries and data collection aims*

Conference participants debated the feasibility of organizing an effort to maintain an international registry of inhibitor patients. Although an international registry might seem ideal, conference participants commented on the shortcomings of past initiatives. As the registries are voluntary and require an informed consent process, it is not possible to know how many patients might have been excluded or, indeed, whether there might be duplication when patient data are entered into multiple national and international registries. There are now more regulations designed to protect patient confidentiality, which may vary from one country to another in

how they mandate informed consent for data collection for research purposes, and there may be additional restrictions on data sharing. However, many of the important unresolved research questions, such as product immunogenicity, require patient numbers so large that no single national database can provide them. If the registries remain national, then it is important for the large centres to communicate across borders in an effort to harmonize data collection and publication. All clinicians caring for patients with inhibitors should make a commitment to furthering this research by reporting adverse effects of treatment and by participating in clinical trials and patient registries whenever possible.

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