

Risk of Inhibitor Development in Children with Haemophilia A

a report by

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The development of inhibitors in children with haemophilia A presents a major problem in terms of both the success and the cost of treatment.¹ Inhibitors develop in response to treatment with factor VIII (FVIII), which is administered to haemophilia A patients to overcome bleeding episodes. The risk of inhibitor development is highly dependent on disease severity: it is estimated that between 20 and 52% of patients with severe haemophilia A develop inhibitors compared with approximately 3% of those with mild to moderate disease.²⁻⁹ For the most part, inhibitors develop early in a patient's treatment life – usually after nine to 12 days of exposure to FVIII.¹⁰ Subsequent to inhibitor development, bleeds are treated with bypassing agents, which are less efficient and more expensive than FVIII replacement. Immune tolerance induction (ITI) therapy is used successfully in approximately 70% of haemophilia patients to eradicate inhibitors and allow future treatment with exogenous FVIII.¹¹ Future studies aim to further optimise the ITI treatment regimen. Indeed, the risk of inhibitor development is much greater and more frequent in previously untreated patients, while it is rarer in previously treated patients. In this latter group, inhibitor risk factors are thought to be more treatment-related and in previously treated patients with >150 exposure days to FVIII are considered low-risk.¹²

Alongside disease severity, numerous patient-determined factors have been demonstrated to alter the risk of inhibitor development in haemophilia A patients. These include a family history of inhibitor development, FVIII gene mutations, ethnicity, prophylaxis treatment, the intensity of treatment and the individual FVIII concentrate.^{7,9,12-17} Age at first exposure^{14,18} has also been proposed as a potential risk factor for inhibitor development, although the relative importance of this treatment-related factor is now questioned.^{15,18,19}

Genetic Risk Factors

Severe defects, such as large deletions in the FVIII gene, inversions (particularly intron 22 inversion) and stop mutations, are associated with a higher risk of inhibitor development than small deletions/insertions, missense mutations or splice site mutations.^{7,13,18,20,21} In a recent study of children with severe haemophilia A who were first exposed to FVIII as neonates, 41 of 141 children with severe genetic defects (29%) developed inhibitors compared with 12 of 90 children with non-severe defects (13%; $p=0.006$).⁷ Similarly, in the Concerted Action on Neutralizing Antibodies in severe haemophilia A (CANAL) cohort study, patients with severe defects were nearly three times more likely to develop inhibitors compared with patients with low-risk mutations.¹⁸

The Malmö International Brother Study (MIBS), a large-scale family study, examined the shared host genetic factors between brothers with severe haemophilia A and found a 70% concordance in terms of the presence or absence of inhibitors.¹³ In the study, siblings with severe haemophilia

A and intron 22 inversion showed an inhibitor concordance rate of only 40%. Moreover, the concordance rate for the presence of inhibitors among inhibitor families was only 42.4%. Data from two large registries of unrelated patients with haemophilia – the Haemophilia A Mutation, Structure, Test and Resource Site (HAMSTeRS) and Bonn databases – predicted a concordance among inhibitor families of 20%. The differences between the MIBS study and the HAMSTeRS and Bonn databases suggest that the risk of inhibitor development may involve other factors beyond the FVIII genotype alone.

Indeed, recent evidence points to defects related to the FVIII immune response genes. Major histocompatibility complex (MHC) molecules, which play a central role in the cellular cascade leading to antibody formation, have been evaluated as potential co-determinants. Two studies detected a weak influence from MHC class I/II genotypes,^{22,23} although no association was found in the MIBS cohort.²⁴ The MIBS study also showed that there was a strong association between inhibitor development and a polymorphism located in the promoter region of the IL-10 gene. Patients with this IL-10 genotype had a significantly greater risk of developing an inhibitor compared with patients with other IL-10 genotypes.²⁵ A genetic predisposition to the development of FVIII inhibitors is evident; however, further studies are required.

Ethnic Background

Inhibitor incidence is high in African-American, Hispanic and Latin haemophilia patients compared with Caucasian patients.¹⁴ This is thought to be due to immunogenotypic factors carried in these racial groups. Two prospective trials have reported that African-Americans are twice as likely to develop inhibitors compared with Caucasians, despite a similar level of haemophilia in both ethnic groups.^{3,26} These results suggest a racial risk and hence a genetic risk for the development of inhibitors in haemophilia A.

Intensity of Factor VIII Treatment

In 1970, it was suggested that less frequent exposure to FVIII concentrate in patients with mild haemophilia accounted for a lower incidence of inhibitor development.²⁷ However, the cumulative FVIII exposure was found to be no higher in patients with severe haemophilia who developed inhibitors than in those without inhibitors.²⁸ In the CANAL cohort study, a dose of 35–50IU/kg over five consecutive days was associated with 1.4 times the risk than a normal dose (<35IU/kg). This increased to 3.3 times the risk of a normal dose when FVIII was administered at doses of ≥ 50 IU/kg.¹⁸

The association between inhibitor development and number of exposure days to FVIII was also examined in the CANAL cohort study.¹⁸ It was reported that a higher number of consecutive exposure days

increased the risk of inhibitor development in severe haemophilia patients. In a multicentre cohort study, a shorter duration between exposure days increased the risk of inhibitor development.⁹ In addition, there appeared to be an association between the dose of FVIII and inhibitor development. However, this link lessened after adjustments for other confounding factors were made. Biological evidence indicates that a higher dose of FVIII will lead to an increased risk of inhibitor development.²⁹ Major injuries and surgeries cause tissue damage and inflammation. Damaged cells from injured areas send 'danger signals', which activate FVIII antigen-presenting cells, upregulating co-stimulatory signals to T lymphocytes. Both FVIII-expressing antigen-presenting cells and T lymphocytes enhance the formation of antibodies to FVIII in B lymphocytes.

Prophylaxis Treatment

There is increasing evidence that prophylaxis regimens reduce the risk of inhibitor development compared with bolus on-demand treatment in terms of exposure to FVIII.³⁰ A recent study reported that 78% of previously untreated children with severe haemophilia A treated with on-demand FVIII replacement developed inhibitors compared with 0% in the prophylaxis group.¹⁶ Owing to the similarities in terms of genetic mutations and age in the prophylaxis and on-demand groups, the authors concluded that on-demand therapy represents a clear risk factor for the development of inhibitors. Further support for the use of prophylaxis in children with severe haemophilia A came from a study evaluating environmental risks for the development of inhibitors in children with moderate to severe haemophilia A.³¹ A univariate analysis was used to demonstrate that commencing prophylaxis before the age of 35 months carried an inhibitor risk of 28% compared with a 56% risk in patients treated with on-demand therapy. The protective effect seen from use of prophylaxis remained significant after adjustments for genetic and environmental factors. The results of this study support the use of prophylaxis in children, even in those with a high risk of inhibitor development.

The 'danger theory' of tolerance proposes that the immune system responds to danger signals from both exogenous and endogenous sources.³² If an antigen is not itself perceived as dangerous and no other danger signals – such as cell necrosis or tissue injury – are present, tolerance normally occurs rather than an immune response. Thus, theoretically, a prophylactic regimen may offer a protective effect since the patient is treated in the absence of any additional danger signals, whereas on-demand administration of FVIII may be perceived as dangerous due to danger signals from ongoing bleeding episodes or during physiological stress such as surgery.

Other Treatment-related Factors

Age at First Exposure

Age at first exposure as an independent risk factor has been a subject of much debate. While early studies have reported a link between the development of inhibitors and the age at which children start FVIII treatment,^{15,19} when genetic factors are taken into account the differences are not statistically significant.³¹ In the CANAL cohort study, the risk of inhibitor development in patients treated with FVIII before the first month of age was 41% compared with 18% in those who started FVIII treatment after the age of 18 months.¹⁸ However, once again the link between inhibitor development and age at first exposure became insignificant after accounting for other factors such as ethnicity, gene

mutation type, reason for first treatment and FVIII concentrate product type. Similarly, a study investigating inhibitor development in children first exposed to FVIII as neonates found that the effect of age at first exposure disappeared after adjustment for intensive treatment.⁷

Type of Factor Used

The potential difference between products was first noted with the introduction of virus-inactivated concentrates.^{33,34} With the introduction of recombinant FVIII (rFVIII), the focus has shifted to differences between these products and plasma-derived FVIII (pdFVIII). However, studies with both pdFVIII and rFVIII in previously untreated patients have produced a large range of inhibitor development rates. Moreover, retrospective studies comparing pdFVIII and rFVIII have produced conflicting results. Goudemand et al. reported that rFVIII was associated with a higher risk of inhibitor development compared with high-purity pdFVIII, regardless of other risk factors.⁶ This is in contrast to findings from the recent CANAL study, which showed that there was no significant difference in the risk of inhibitor development between patients who received the pdFVIII and patients treated with rFVIII.³⁵ These results highlight the difficulty in directly comparing data from retrospective studies due to confounding factors such as differences in study design, the inherent heterogeneity of concentrate design, inhibitor diagnostics and diagnostic intervals.

There is increasing evidence that prophylaxis regimens reduce the risk of inhibitor development compared with bolus on-demand treatment in terms of exposure to factor VIII.

More recently, it was reported that inhibitor development was lower in haemophilia A patients treated with a high-purity pdFVIII product containing von Willebrand factor (vWF) compared with those treated with rFVIII.³⁶ However, it is unclear whether the brand of product or the high-purity nature of the pdFVIII used accounts for the lower incidence of inhibitor development. In the CANAL study, patients treated with pdFVIII products containing small concentrations of vWF had a lower incidence of inhibitors, although the patient number was too small to confirm this finding.³⁵ It has been suggested that vWF may protect FVIII from circulating antibodies by altering antibody epitopes on the C2 domain.^{37–39} It has been reported that mice treated with FVIII alone developed higher peak inhibitors compared with those treated with FVIII containing vWF.⁴⁰ However, it should be noted that the validity of the FVIII exon 17 knockout mouse model utilised in the study has been questioned. It has been argued that the vWF/FVIII combination may have induced a dual immunogenic challenge in the murine model, resulting in antigenic competition that could have suppressed the immune response to FVIII.⁴¹

Although it was previously suspected that there might be an impact on inhibitor development, evidence from large-scale studies shows that there was no conspicuous increase in inhibitor development when patients were switched between different products during treatment. The recent CANAL study examined whether changing between FVIII products altered inhibitor risk in 316 previously untreated patients with severe haemophilia A.³⁵ No difference was noted in patients who had

been switched to different products during treatment. This result confirms previous findings in 73 haemophilia patients where the ratio for switching to another product or remaining on the same product was 0.4.⁴² Similarly, no increased risk of inhibitor development has been reported after switching FVIII products in previously treated patients.^{43,44}

Prophylaxis has been found to reduce the development of inhibitors and is recommended for children with severe haemophilia A.

Summary

The development of inhibitors in children with haemophilia A presents a major problem in terms of both the cost and the success of treatment.

Numerous patient-related risk factors are thought to be associated with inhibitor development. For example, a family history of inhibitor development and the presence of specific gene mutations have been linked to a higher risk of inhibitors. Also, the presence of inhibitors in African-Americans has been reported to be twice that in Caucasians. There are also treatment-related risk factors: in several studies a high-intensity treatment regimen was reported to increase the risk of inhibitor development. Prophylaxis has been found to reduce the development of inhibitors and is recommended for children with severe haemophilia A. The effect of the individual factor used on inhibitor incidence needs further study. Some studies report that rFVIII has a significantly higher risk of inhibitor development compared with pdFVIII, while others report no significant risk. Moreover, individual FVIII concentrates have been associated with a wide range of inhibitor development rates. It is yet to be confirmed whether FVIII product choice in general has a significant effect on the development of inhibitors in previously untreated patients. Current evidence points to the development of inhibitors as a multifactorial process that both is polygenic and involves several environmental factors. Further investigation will help to better define the interactions between these risk factors and immune responses. ■

- Bohn RL, Aledort LM, Putnam KG, et al., The economic impact of factor VIII inhibitors in patients with haemophilia, *Haemophilia*, 2004;10:63–8.
- Ehrenforth S, Kreuz W, Scharer I, et al., Incidence of development of factor VIII and factor IX inhibitors in haemophiliacs, *Lancet*, 1992;339:594–8.
- Scharer I, Bray GL, Neutzling O, Incidence of inhibitors in haemophilia A patients – a review of recent studies of recombinant and plasma-derived factor VIII concentrates, *Haemophilia*, 1999;5:145–54.
- Darby SC, Keeling DM, Spooner RJ, et al., The incidence of factor VIII and factor IX inhibitors in the hemophilia population of the UK and their effect on subsequent mortality, 1977–99, *J Thromb Haemost*, 2004;2:1047–54.
- Lusher JM, Is the incidence and prevalence of inhibitors greater with recombinant products? No, *J Thromb Haemost*, 2004;2: 863–5.
- Goudemand J, Rothschild C, Demiguel V, et al., Influence of the type of factor VIII concentrate on the incidence of factor VIII inhibitors in previously untreated patients with severe haemophilia A, *Blood*, 2006;107:46–51.
- Chalmers EA, Brown SA, Keeling D, et al.; Paediatric Working Party of UKHCDO, Early factor VIII exposure and subsequent inhibitor development in children with severe haemophilia A, *Haemophilia*, 2007;13(2):149–55.
- Escuriola Ettingshausen C, Kreuz W, Recombinant vs. plasma-derived products, especially those with intact VWF, regarding inhibitor development, *Haemophilia*, 2006;12(Suppl. 6):102–6.
- Gouw SC, van den Berg HM, le Cessie S, et al., Treatment characteristics and the risk of inhibitor development: a multicenter cohort study among previously untreated patients with severe haemophilia A, *J Thromb Haemost*, 2007;5(7):1383–90.
- Lusher JM, Arkin S, Abildgaard CF, Schwartz RS, Recombinant factor VIII for the treatment of previously untreated patients with haemophilia A. Safety, efficacy, and development of inhibitors. Kogenate Previously Untreated Patient Study Group, *N Engl J Med*, 1993;328:453–9.
- Brackmann HH, Induced immunotolerance in factor VIII inhibitor patients, *Prog Clin Biol Res*, 1984;150:181–95.
- EMEA, Report on expert meeting on FVIII products and inhibitor development, 28 Feb – 2 Mar 2006: www.emea.europa.eu/pdfs/human/bpwg/12383506en.pdf
- Astermark J, Oldenburg J, Escobar M, et al.; Malmö International Brother Study study group, The Malmö International Brother Study (MIBS). Genetic defects and inhibitor development in siblings with severe haemophilia A, *Haematologica*, 2005;90:924–31.
- Aledort LM, Dimichele DM, Inhibitors occur more frequently in African-American and Latino haemophiliacs, *Haemophilia*, 1998;4:68.
- van der Bom JG, Mauser-Bunschoten EP, Fischer K, van den Berg HM, Age at first treatment and immune tolerance to factor VIII in severe hemophilia, *Thromb Haemost*, 2003;89:475–9.
- Sharathkumar A, Lillcrap D, Blanchette VS, et al., Intensive exposure to factor VIII is a risk factor for inhibitor development in mild hemophilia A, *J Thromb Haemost*, 2003;1:1228–36.
- Morado M, Villar A, Jimenez Yuste V, et al., Prophylactic treatment effects on inhibitor risk: experience in one centre, *Haemophilia*, 2005;11:79–83.
- Gouw SC, van der Bom JG, van den Berg H, et al., Treatment-related risk factors of inhibitor development in previously untreated patients with hemophilia A: the CANAL cohort study, *Blood*, 2007;109:4648–54.
- Lorenzo JL, Lopez A, Altisent C, Aznar JA, Incidence of factor VIII inhibitors in severe haemophilia: the importance of patient age, *Br J Haematol*, 2001;113:600–3.
- Hay CR, The epidemiology of factor VIII inhibitors, *Haemophilia*, 2006;12(Suppl. 6):23–9.
- Oldenburg J, Pavlova A, Genetic risk factors for inhibitors to factors VIII and IX, *Haemophilia*, 2006;12(Suppl. 6):15–22.
- Hay CR, Ollier W, Pepper L, et al., HLA class II profile: a weak determinant of factor VIII inhibitor development in severe haemophilia A. UKHCDO Inhibitor Working Party, *Thromb Haemost*, 1997;77:234–7.
- Oldenburg J, Picard J, Schwaab R, HLA genotype of patients with severe haemophilia A due to intron 22 inversion with and without inhibitors to factor VIII, *Thromb Haemost*, 1997;77: 238–42.
- Astermark J, Oldenburg J, Carlson J, et al., Polymorphisms in the TNFA gene and the risk of inhibitor development in patients with haemophilia A, *Blood*, 2006;108:3739–45.
- Astermark J, Oldenburg J, Pavlova A, et al.; MIBS Study Group, Polymorphisms in the IL-10 but not in the IL-1B and IL-4 genes are associated with inhibitor development in patients with haemophilia A, *Blood*, 2006;107:3167–72.
- Bray G, Gomperts ED, Courter S; Recombinate Study Group, A multicenter study of recombinant factor VIII (Recombinate): safety, efficacy and inhibitor risk in previously untreated patients with haemophilia A, *Blood*, 1994;83:2428–35.
- Crowell EB Jr, A factor VIII inhibitor in a mild hemophiliac, *Am J Med Sci*, 1970;260:261–3.
- Strauss HS, Acquired circulating anticoagulants in hemophilia A, *N Engl J Med*, 1969;281:866–73.
- Matzinger P, The danger model: a renewed sense of self, *Science*, 2002;296:301–5.
- Berntorp E, Astermark J, Björkman S, et al., Consensus perspectives on prophylactic therapy for haemophilia: summary statement, *Haemophilia*, 2003;9(Suppl. 1):1–4.
- 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.
- Matzinger P, Tolerance, danger, and the extended family, *Annu Rev Immunol*, 1994;12:991–1045.
- Rosendaal FR, Nieuwenhuis HK, van den Berg HM, et al., A sudden increase in factor VIII inhibitor development in multitransfused haemophilia A patients in the Netherlands, *Blood*, 1993;81:2180–86.
- Peerlinck K, Arnout J, Gilles JG, et al., A higher than expected incidence of factor VIII inhibitors in multitransfused Haemophilia A patients treated with an intermediate purity pasteurized factor VIII concentrate, *Thromb Haemost*, 1993;81:39–44.
- Gouw SC, van der Bom JG, Auerswald G, 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(11): 4693–47.
- Wight J, Paisley S, The epidemiology of inhibitors in haemophilia A: a systematic review, *Haemophilia*, 2003;9:418–35.
- Suzuki T, Arai M, Amano K, et al., Factor VIII inhibitor antibodies with C2 domain specificity are less inhibitory to factor VIII complexed with von Willebrand factor, *Thromb Haemost*, 1996;76:749–54.
- Berntorp E, Ekman M, Gunnarsson M, Nilsson IM, Variation in factor VIII inhibitor reactivity with different commercial factor VIII preparations, *Haemophilia*, 1996;2:95–9.
- Auerswald G, Spranger T, Brackmann HH, The role of plasma-derived factor VIII/von Willebrand factor concentrates in the treatment of hemophilia A patients, *Haematologica*, 2003;88: EREPO5.
- Behrmann M, Pasi J, Saint-Remy JM, et al., Von Willebrand factor modulates factor VIII immunogenicity: comparative study of different factor VIII concentrates in a haemophilia mouse model, *Thromb Haemost*, 2002;88:221–9.
- Reipert BM, Schoppmann A, Schwarz HP, A caution on the use of murine hemophilia models for comparative immunogenicity studies of FVIII products with different protein compositions, *Thromb Haemost*, 2003;89:1110–12.
- Baglin T, Beacham E, Is a change of factor VIII product a risk factor for the development of a factor VIII inhibitor?, *Thromb Haemost*, 1998;80:1036–7.
- Scharer I, Ehrlich HJ, Lack of evidence for increased inhibitor incidence in patients switched from plasma-derived to recombinant factor VIII, *Haemophilia*, 2001;7:346–8.
- Giles AR, Rivard GE, Teitel J, Walker I, Surveillance for FVIII inhibitor development in the Canadian haemophilia A population following the widespread introduction of recombinant FVIII replacement therapy, *Transfus Sci*, 1998;19:139–48.