# Recent Developments in Immune Tolerance Induction in Haemophilia A

*a report by*

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*DOI: 10.17925/EOH.2007.0.0.6*

Approximately 30% of severe haemophilia A patients suffer an immune response to therapeutically administered factor VIII (FVIII). The formation of inhibitor antibodies is a serious complication in the treatment of haemophilia, and neutralisation of FVIII coagulation activity results in an inadequate response to FVIII infusion.[1] Patients with severe haemophilia A have the highest incidence of inhibitor development. The onset of inhibitors usually occurs during the initial phase of treatment with FVIII (in early childhood, after a median exposure of approximately 15 days),[2] although they have been seen to occur at any time.[3] Several genetic and environmental risk factors have been proposed for the development of inhibitors in previously untreated patients (PUPs): FVIII gene mutation,[4] ethnic origin/race,[5] family history of inhibitors and immunogenotypic differences,[6,7] age at first exposure[8,9] and therapy regimen.[10] The management of bleeding episodes in high-titre inhibitor patients is through the use of bypassing agents, mainly activated prothrombin complex concentrates (aPCCs) and recombinant factor VIIa (rFVIIa). These treatments are satisfactory for achieving haemostasis. However, in arthropathy and disability in long-standing inhibitor patients this is difficult to achieve. Eradication of inhibitors through immune tolerance induction (ITI) is accepted as the superior treatment because it allows the resumption of FVIII replacement therapy and prophylaxis of bleeding episodes.[11] Currently, ITI through various regimens has been successful in approximately 60–90% of patients with inhibitors.[12–17] However, there is not enough scientific evidence to guide a successful ITI regime.

## Immune Tolerance Induction Therapy

ITI is a method of treating inhibitors in patients with haemophilia A that involves several protocols of long-term administration of low- and high-dose FVIII. ITI was first utilised in 1974, when a high-titre inhibitor patient with a serious haemorrhage was treated with a high dose of FVIII concentrate and aPCC. This treatment resulted in control of the haemorrhage and a reduction in inhibitors.[18] Between the late 1970s and 1990, patients were treated with plasma-derived FVIII products for ITI. Since 1990, recombinant and monoclonal products have been introduced and are the most common forms used today. ITI in most institutions involves either the use of the recombinant product and/or the plasma-derived product, depending on patient requirements.

Investigators have also examined alternative unconventional ITI regimens. These regimens include the use of immunosuppressive agents that non-specifically target the humoral or cellular immune system in addition to neutrophils, macrophage and natural killer cells. However, the use of such chemotherapeutic agents is associated with both short- and long-term toxicity. The use of rituximab, a genetically engineered human–mouse chimaeric monoclonal immunoglobulin (Ig)G1 antibody, is now being considered to eradicate inhibitors in haemophilia A and has shown potential in five cases.[19] There are major differences in inhibitor management, and the implementation of ITI regimens varies widely between centres.[20] This reflects a lack of knowledge of a successful ITI regimen.[17,21–23] Studies identify variables affecting ITI, but they do not allow for successful comparison between different regimens. Consequently, an optimal protocol is far from being decided. A consensus agreement is required to define an optimal ITI regimen in terms of both efficacy and pharmacoeconomics.

## Identified Factors Affecting the Outcome of Immune Tolerance Induction Therapy

One of the most important factors affecting the success of ITI is the inhibitor titre at the beginning of treatment, which also has an effect on the time taken to achieve tolerance. An inhibitor titre of less than 10 Bethesda units (BU)/ml at the start of ITI has been correlated with a significantly superior outcome.[24,25] An overall success rate of 85% was noted for patients with <10BU/ml with an average time to tolerance of 11 months compared with 33% tolerance achieved after 15 months in patients with a titre above 10BU/ml. Very high starting titres of more than 500BU/ml are associated with the poorest response to ITI.[16] It is widely thought that ITI should start immediately upon discovery of inhibitors in haemophilia A patients. However, some studies have suggested that a short interval between the start of ITI and inhibitor detection is beneficial for successful tolerance.[24,16] The initiation of ITI as soon as possible after inhibitor development often means that ITI will start shortly after factor VIII replacement therapy. ITI has been demonstrated to be less effective when titre levels are above 10BU/ml; therefore, deliberate deferral of ITI until the inhibitor titre falls below this level is practised in many centres. This is achieved by avoiding any treatment of bleeding episodes with FVIII and using bypassing agents (rFVIIa) as an alternative therapy.

The superior dose to be used in ITI is still controversial. The International Immune Tolerance Registry (IITR) indicated that higher doses are significantly more effective in inhibitor patients with titres of less than 10BU/ml.[24] In contrast, both the North American Immune Tolerance Registry (NAITR) and the German National Immune Tolerance Registry (GNITR) showed no indication that higher doses were more successful.[25,26] In a meta-analysis of all the ITI registries, patients starting inhibitor treatment with <10BU/ml and an historic titre of 50–200BU/ml showed no relationship between the rate of tolerance and the dosage used in ITI.[27] However, higher-titre inhibitor patients may respond better when treated with a higher dose.

## Factor VIII Concentrates

The type of FVIII concentrate used in ITI is of considerable debate. The effectiveness of the recombinant FVIII and plasma-derived vWF/FVIII (pdvWF/FVIII) was first examined in 1996.[28] Four patients who were not responding to treatment with the recombinant concentrate were switched to the pdvWF/FVIII concentrate and all achieved tolerance. Following this

positive result, a further 10 haemophilia A patients were switched to pdvWF/FVIII concentrate with an 88% success rate in a median of 17 months.[29] Similarly, eight high-titre inhibitor patients on a high-dose pdvWF/FVIII regimen had an 85% tolerance rate within eight to 12 months.[30] Recent data from Italy and Spain also suggest that the vWF/FVIII concentrate is successful in patients with poor prognostic factors. Patients with one or more of the negative factors for treatment with ITI still had a positive outcome to the inhibitor treatment.[31]

A study including patients with poor prognostic factors for inhibitor development concluded less beneficial effects of using the vWF concentrate.[32] An explanation for the superior effects seen with vWF-containing concentrate in ITI is that VWF plays an important role in the stabilisation and function of FVIII.[33] VWF may also modulate the immunogenicity affecting the outcome of ITI.[34] However, it it unclear whether a switch from recombinant FVIII to vWF-containing concentrates is responsible for the success of tolerance or if the eradication of inhibitors was due to the extended use of ITI. Meta-analysis of the International ITI study and the NAITR study showed no correlation between the outcome of ITI and the type of concentrate used.[27] To date no prospective randomised trial has directly compared the recombinant and vWF-containing concentrates. Hence, there is no clear evidence for either product being superior in ITI.

## Ongoing Immume Tolerance Induction Therapy Trials

Future trials are aiming to clear up some of the concerns over the most successful ITI regimen. The prospective International ITI study aims to compare the efficacy, response time, morbidity and economics of a high- and low-dose immune tolerance protocol and identify predictors of successful ITI in inhibitor patients with good prognostic factors (aged below eight years, inhibitor present <12 months, historical peak titre ≥5BU and ≤200BU and starting titre <10 BU). The study began in 2002 and has randomised 45 severe haemophilia A patients with an inhibitor. The study hypothesises that a high-dose ITI regimen will achieve tolerance more rapidly than a low-dose regimen; however, the overall success of both will be similar in the long term. It is also proposed that low-dose ITI will be more cost-effective than the higher dose and lower starting inhibitor titres will be associated with greater success than higher titres. Preliminary data from the trial have demonstrated that 62% of the randomised group of patients undergoing ITI have reached a negative titre.[35] The study has also revealed that severe catheter infections are the most common serious adverse effect of the ITI therapy, affecting duration and outcome of ITI. Some reports have noted the success of using vWF/FVIII concentrate as a salvage therapy after failed tolerance with recombinant FVIII, which suggests a role for vWF/FVIII concentrate in patients with poor prognosis.[36] A satellite study of the International ITI study, The Rescue Immunotolerance Study (RESIST), has been designed to examine this hypothesis. This study will enrol ITI-naïve patients who did not qualify for the International ITI study because of poor prognostic factors and patients who have failed to respond to recombinant FVIII. The ITI-naïve participants will be randomised to receive either the vWF/FVIII concentrate or a vWF-free FVIII concentrate at a standard dose of 200IU per kg per day. The salvage patients will receive the vWF/FVIII concentrate at a dose of 200IU per kg per day. The primary study end-point will be partial or complete tolerance to FVIII, with a secondary end-point of time to success and the maintenance of tolerance. The observational research programme on ITI in patients with haemophilia A and F VIII inhibitors (ObsITI) evaluates ITI-naïve patients and ITI failures who qualify for neither RESIST nor the ITI study. ITI courses record and evaluate the impact of frequency and dosage of F VIII, starting inhibitor titre, product type, peak titre, interruption of ITI, surgery, severe bleeds, concomitant medications, concomitant diseases and previous treatment approaches. In addition, the clinical relevance of pre-treatment *in vitro* testing and the F VIII epitopes on ITI course and outcome will be investigated. In order to gain more insight into immune mechanisms during ITI, a substudy on immunological markers is included.

## Future Research Considerations

A highly debated and controversial area in ITI is the success of tolerance through the use of recombinant concentrates or vWF/FVIII concentrate. It has still not been established which concentrate has the overall better success rate. The prospective ITI study, the Rescue Immunotolerance Study (RESIST) and the ObsITI should provide useful insight into this issue. Research is also limited on why the vWF has been shown to be beneficial in addition to FVIII. The mechanisms involved in ITI need to be evaluated to further understanding.

## Summary

Inhibitor development occurs in 30% of all haemophilia patients treated with factor VIII concentrates. ITI is the main model for the eradication of inhibitors in haemophilia A patients. However, ITI procedures fail in a substantial number of patients. Factors have been identified that may affect treatment with ITI, including the level of titre at the start of treatment, the delay from the detection of inhibitor and the start of ITI therapy and the dose of FVIII used. However, the most debated and controversial topic in ITI is the use of either plasma-derived vWF/FVIII or recombinant FVIII concentrates. Early evidence suggests that plasma-derived vWF/FVIII has a higher success rate for tolerance over the recombinant FVIII concentrate; however, later studies have reported conflicting data. The International ITI Study, the RESIST study and the ObsITI are ongoing studies examining the dose regimen success and product differences, and should provide further insight into the future of ITI. ■


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