Recent Developments in Immune Tolerance Induction in Haemophilia A

a report by
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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,\(^5\) 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.\(^12,13\) 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.\(^14\) 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.\(^15\) There are major differences in inhibitor management, and the implementation of ITI regimens varies widely between centres.\(^16\) This reflects a lack of knowledge of a successful ITI regimen.\(^17,21,22\) 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.\(^18,19\) 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.\(^20\) 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.\(^21,22\) 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 108BU/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 108BU/ml.\(^23\) 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.\(^24,25\) In a meta-analysis of all the ITI registries, patients starting inhibitor treatment with <108BU/ml and an historic titre of 50–200BU/ml showed no relationship between the rate of tolerance and the dosage used in ITI.\(^26\) 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.\(^27\) 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
pooled vWF/FVIII concentrate with an 88% success rate in a median of 17
months.22 Similarly, eight high titre inhibitor patients on a high-dose
pooled vWF/FVIII regimen had an 85% tolerance rate within eight to 12
months.23 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.21

A study including patients with poor prognostic factors for inhibitor
development concluded less beneficial effects of using the vWF
concentrate.22 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.23 vWF may also modulate the
immunogenicity affecting the outcome of ITI.24 However, it is 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.25 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 Immune 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.26 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.27 A satellite study of the International ITI
study, The Rescue Immunotolerance Study (RESIST), has been designed to
taxamine this hypothesis. This study will enrol ITI-naive 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-naive 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-naive 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,
comitant 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 sub-study on
imunological markers is included.

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.