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Reflection paper on Immune Tolerance Induction in haemophilia A patients with inhibitors

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1. Introduction

In haemophilia A patients, replacement therapy with factor VIII products has become state of the art. However, a serious complication in the treatment of haemophilia A is the development of neutralizing antibodies against FVIII, causing therapy resistance and increased risk of bleeding. Up to 30% of patients with severe haemophilia A develop antibodies against factor VIII treatment. Several factors (e.g. genetic and environmental) are discussed as possible contributors to inhibitor development. At present, multiple therapeutic options to overcome the immune response to FVIII concentrates and to control bleeding situations are implemented in specialised haemophilia centres.

2. Discussion

Clinical aspects

Treatment of patients with inhibitory antibodies has to focus on bleeding prevention and inhibitor eradication:
Bleeding prevention might be achieved by high amounts of factor VIII or by bypassing agents such as recombinant factor VIIa or activated prothrombin complex concentrate.

Eradication of the inhibitor might be subject to immune tolerance induction (ITI). ITI involves repetitive administration of factor VIII, in some therapeutic regimens in combination with immune-suppressive agents such as chemotherapeutics, corticosteroids or monoclonal antibodies.

The ITI concept was first reported more than 30 years ago by Brackmann and Gormsen, Lancet 1977. They showed that high daily doses of factor VIII gradually eliminated the immune response and the production of anti-FVIII antibodies. The basic principle still applies: repeated intravenous infusion of factor VIII until inhibitors are no longer detectable and the recovery and half-life of FVIII are restored. However, up to now, the exact mechanism of ITI remains unclear. ITI has been shown to induce tolerance in most patients who develop neutralising factor VIII antibodies nevertheless, different treatment protocols and co-medication options are used. ITI protocols cover high-dose and low-dose regimens. High-dose protocols recommend the administration of 100-300 IU/kg of factor VIII daily as one or two doses. Low-dose protocols use 25-50 IU/kg every day or three times/week. Concomitant treatment with bypassing agents may be used to prevent or treat bleeds.

Although several publications are reporting high success rates of about 70% inhibitor eradication following various ITI protocols, those reports reflect heterogeneous data-collections: Patient inclusion criteria in terms of age, type of inhibitor response, various definitions of ITI success etc. might have an impact on study outcome. Multiple risk factors have been identified that may affect the success rate of ITI, e.g. genetic factors, treatment history, infections, period between inhibitor occurrence and start of ITI, duration and interruption of ITI, and type of factor VIII product.

A similar situation is reflected within registry data: a high range of individually justified dosages and therapy durations has been collected. Success of ITI depends on the characteristics of the concerned patient and the experience of the haemophilia centre. All these data support the assumption that inhibitor eradication is a therapeutic approach that has to be tailored for the individual patient.

The principal results of the International Immune Tolerance Study were published in Blood in 2012. This prospective, randomized trial in ITI comparing high- and low-dose regimen (200 IU/kg/day versus 50 IU/kg three times per week) was initiated in 2002 and prematurely closed in late 2009 due to a higher rate of intercurrent bleeding in the low dose arm. Overall success rates did not differ between

the treatment arms. Subjects on high-dose treatment achieved a negative inhibitor titre and normal FVIII recovery more rapidly than subjects on low dose.

Taking the current clinical experience into account, basic scientific aspects remain open. However, studies on single products cannot be expected to answer the still unsolved general questions, for example:

- Are products containing von Willebrand factor more effective than highly purified products for ITI?
- Is there a difference in efficacy when comparing recombinant and plasma-derived products?
- Which patients will have a benefit from which ITI protocol?
- Do high or lower dose regimens have a favorable benefit/risk profile for ITI treatment?
- What is the minimum waiting period before concluding that a treatment failed?
- Are bypassing agents contributing to success?

In summary, the optimal inhibitor eradication strategy has not been established since the management of neutralizing anti-factor VIII antibodies continues to evolve.

Regulatory aspects

Historically, many plasma-derived factor VIII concentrates are only authorised nationally. These products may already have a wording regarding “treatment of inhibitor patients” included in the SmPC. It could be anticipated that the clinical data base supporting this indication claim might be heterogeneous and based rather on individual case reports than on GCP compliant clinical trials. It can be assumed that all plasma-derived and recombinant FVIII products which have a marketing authorisation and are manufactured by well-known processes are used for ITI. There is no experience so far for the new upcoming products (e.g. modified proteins with long-acting performance).

The previous guidelines on the Clinical Investigation of Human Plasma-Derived/Recombinant Factor VIII and IX Products stated that “any request for an indication of induction of immune tolerance in haemophilia A patients with inhibitors should be accompanied by clinical data”. Revision of these guidelines led to deletion of this statement since the wording was considered vague. It has been decided that ITI in haemophilia A patients with inhibitors should be addressed in a separate document. Remaining open scientific questions cannot be solved by clinical data provided for a single product. Clear cut guidance on clinical trials to be performed to endorse an indication claim for ITI cannot be given at present due to the complexity of unresolved scientific questions, the challenging nature of the management of inhibitor patients, the rarity of the condition, and the difficulty to undertake controlled trials.

However, management of inhibitor patients as well as inclusion of ITI experience with a specific product may be reflected in the SmPC. General guidance regarding treatment of bleeding episodes and prophylaxis in inhibitor patients is already included in section 4.2 and 4.4 of the core SmPC. It is now proposed that ITI experience with a specific product may be included in section 5.1 of its SmPC with the following statement:

“Data on Immune Tolerance Induction (ITI) have been collected in patients with haemophilia A who have developed inhibitors to FVIII.” This may be followed by a short description of the number of patients studied, how the data were obtained (e.g. clinical study, registry data), and whether the data show that immune tolerance has been achieved using the product. Success rates from this data, or information on how immune tolerance was induced should not be included unless this information is

robust as such information may not be meaningful in view of the many variables that can influence the observed rate.

3. Conclusion

Treatment of patients with inhibitory antibodies covers bleeding prevention and inhibitor eradication. Bleeding prevention might be successfully achieved by high amounts of factor VIII or by bypassing agents. Eradication of the inhibitor might be subject to several approaches of immune-modulation.

Successful eradication of inhibitors in haemophilia patients through ITI remains an individually tailored therapy which has been subject to reports and discussion over the last 30 years. Longstanding clinical experience shows that ITI significantly contributes to therapeutic success. However, commonly agreed eligibility criteria for concerned patients, treatment regimens regarding dosage and duration as well as success criteria for reproducible documentation of efficacy have not been developed so far. Clinical research to investigate the key clinical questions is encouraged and can be supported by European Scientific Advice. In the meantime, management of inhibitor patients can be reflected in Section 5.1 of the SmPC supported by clinical data. It can be assumed that there is clinical experience with ITI for most of the plasma-derived and recombinant FVIII products. However, there is no ITI experience with the long-acting modified products. Regulatory decision on reflection of ITI in the product information is done on a case by case basis.

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