Observational Immune Tolerance Induction research program (ObsITI) – a multifaceted approach to explore immune tolerance induction

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Introduction

The Observational Immune Tolerance Induction research program (ObsITI) is an international open-label, uncontrolled, non-interventional, multi-centre observational program initiated by the Paediatric Haemophilia Centre of the Johann Wolfgang-Goethe University Frankfurt in 2005, and continued by the Haemophilia Centre Rhine Main (HZRM), Frankfurt-Mörfelden, Germany.

The aim of the program is to evaluate patient and therapy related variables on ITI course, outcome and morbidity in HA patients with inhibitors. Therefore data from patients, who currently undergo ITI or have undergone ITI are collected prospectively and retrospectively. The inclusion criteria are listed in Figure 1.

Patients will be treated preferably according to the Bonn protocol. Subjects with risk factors associated with a poor ITI prognosis are also included, including earlier failures to ITI. The study is open to all FVIII products. The ITI outcome will be correlated to patient therapy and immunological related variables.

Figure 1: Inclusion / Exclusion criteria

Inclusion criteria	1. Male patients of any age 2. Haemophilia A (all severities) 3. Clinical relevant inhibitor levels (> 0.6 BU) 4. ITI for the first time or earlier ITI failure
Exclusion criteria	1. Congenital or acquired bleeding defects other than HA 2. Concomitant immunological diseases 3. Immunosuppressive treatment 4. History of hypersensitivity to blood products and / or FVIII concentrates

Study design

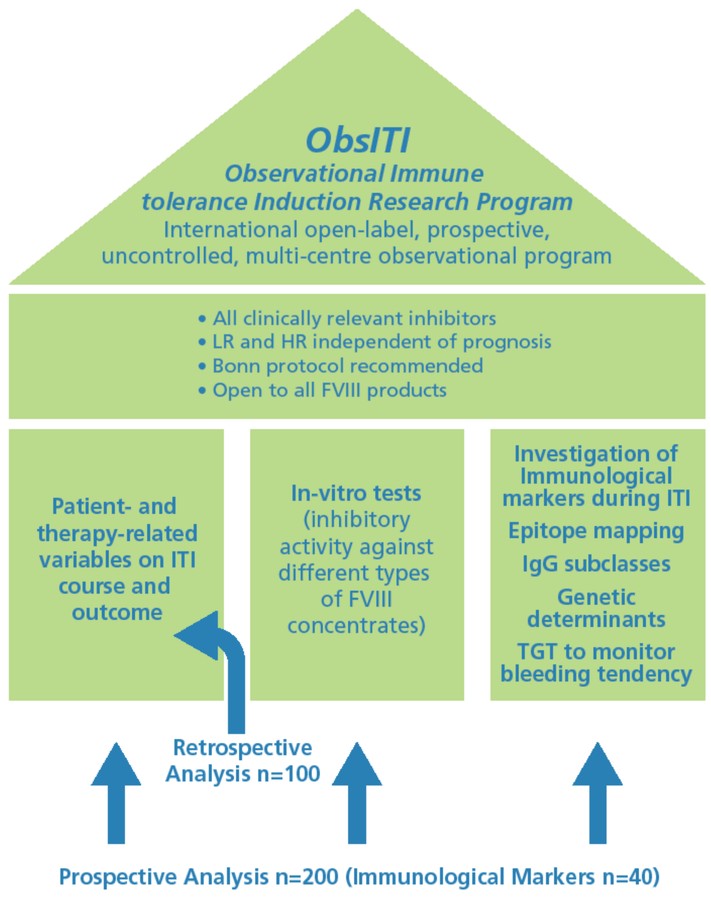
Primary objective

- Evaluation and documentation on the ITI success rate in prospective and retrospective HA patients with newly developed or already existing FVIII-inhibitors, including patients with risk factors associated with a poor ITI prognosis, and those with prior ITI failure.

Secondary objectives

- Investigation of a possible influence of the various factors on ITI duration and outcomes:
  - Genetic factors
  - Therapy regimen (dose and frequency of FVIII administration)
  - Pre-ITI conditions (age at ITI-start, etc.)
  - Time between inhibitor detection and ITI start

Observational Immune tolerance Induction Research program (ObsITI)



Success of ITI in ObsITI

ITI outcome is defined on a cumulative basis, according to the achievement of three stringent individual efficacy criteria:

- **Criterion I:** Inhibitor titer <0.6 BU
- **Criterion II:** FVIII recovery ≥80%
- **Criterion III:** FVIII half-life ≥7 hours

- *Complete success:* all 3 criteria above met
- *Partial success:* 2 of 3 criteria above met
- *Partial response:* 1 of 3 criteria above met
- *Partial failure:* Inhibitor still present, but titre has decreased to <5 BU
- *Failure:* Persistent high titre inhibitor

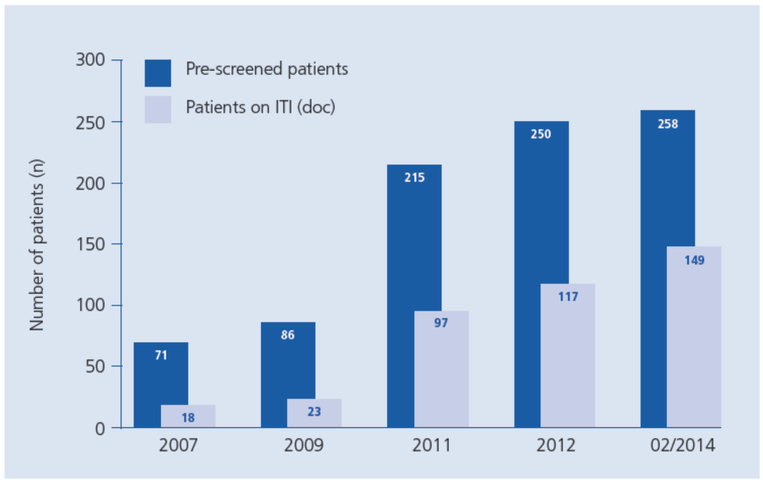
For more information about the study, please visit the website: www.obsiti.com (in English, Russian and Spanish language available) or contact the study co-ordinator, Zeynep Gutowski (zeynep.gutowski@hzrm.de).

The ObsITI study is an investigator-driven study sponsored by the Haemophilia Centre Rhine-Main (HZRM), Frankfurt–Mörfelden, Germany, with funding provided by Octapharma, Baxter, BPL, Biotest and CSL Behring.

Preliminary results

As of February 2014, a total of 258 patients from 22 countries have been screened for ObsITI. In 149 patients ITI has been documented, and 90 patients completed the study (Figure 2).

Figure 2: Patient recruitment status over time



The majority of the patients have been treated according to the Bonn protocol (mean dose of FVIII per kg per day: 201.57 IU; initial frequency of FVIII administration per day: 2 [median]) in this ongoing study.

Satellite studies

The ObsITI research program has become a vivid framework for a growing number of important satellite studies, which look at additional factors related to immune tolerization:

The *thrombin generation test (TGT)* has been initiated in order to predict bleeding risk of a patient. This test correlates the clinical bleeding phenotype and the thrombin generation capacity before and during ITI. Moreover, *the immunogenotyping study* focuses on host genetic factors including *F8* gene defect, polymorphism of the immune response gene and HLA class II alleles; these are thought to act as predictors of ITI outcome. A concentrate-based *thrombin generation assay (TGA)* and *epitope mapping* are also performed. Data of both assessments will be collected, and information on inhibitor antibodies that recognize specific FVIII epitopes will be linked with ITI duration and outcome. In addition to all these evaluations, modification of the immune system and the inflammatory status of the patient are investigated in the *immune monitoring* study.

All of this data provides additional parameters to enhance the prospect of personalized ITI treatment, by correlating individual success rates of ITI with the results obtained in the satellite studies.

Conclusion

ObsITI is the largest prospective ongoing study on ITI with the potential to extend the knowledge on ITI as well as to tailor ITI treatment to each individual. The main goal of the study is to help HA patients with inhibitors to achieve treatment success and have an improved quality of life.

Satellite studies overview

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Product / batch selection for individualised ITI

W. Kreuz and C. Escuriola will investigate the neutralisation activity of FVIII antibodies in the plasma of inhibitor patients against FVIII and different batches of the same FVIII concentrate.

Thrombin Generation Test (TGT) to monitor the haemostatic efficacy of FVIII

C. Négrier and Y. Dargaud will perform TGT of plasma samples from haemophilia A patients with inhibitors before and during ITI. Previous studies have shown a significant correlation between plasmatic FVIII levels and endogenous thrombin potential (ETP) peak and time to peak obtained by TGT. Furthermore, a correlation was found between severe clinical bleeding phenotype and ETP independently of the FVIII plasma level.

F8 gene analysis / Immunogenotyping / HLA genotyping

J. Oldenburg and A. Pavlova will investigate the impact of genetic risk factors (gene defect responsible for haemophilia, HLA genotype, and several immune response genes) on the course and outcome of ITI.

Thrombin generation assay (TGA)

E. Berntorp and J. Astermark will use theTGA to evaluate the potential of different FVIII concentrates to generate thrombin in the patient's inhibitor plasma in order to investigate whether the TGA may be a tool for individualised ITI therapy.

Epitope mapping / IgG isotyping

C. Königs will map inhibitor B-cell epitopes by screening of peptide libraries and will analyse FVIII specific IgG-subclass distribution before and during ITI.

Immune-monitoring of patients undergoing ITI

S. Lacroix-Desmazes will monitor and analyse the modifications of the immune system and the inflammatory status of the patient during the course of ITI in order to identify the clinically relevant immune markers (IMs) that might help to predict the positive or negative outcome of the ITI.

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