

# **ObsITI – Immune tolerance induction in haemophilia A**

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**ObsITI**

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# **Inhibitor development – today's most serious complication in the treatment of haemophilia**

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- **Around 25% of severe haemophilia A patients**
- **Reduction of efficacy of haemostatic therapy with F VIII and increased morbidity**

- Bleedings are more difficult to control
- Progressive and severe joint disease
- Disability
- High treatment costs

## Treatment options in inhibitor patients after inhibitor development

Optimal treatment option  
in inhibitor patients after  
inhibitor development



**Immune tolerance induction**

### **Benefits of successful ITI**

- Regular FVIII administration for bleeds/surgery
- Regular FVIII prophylaxis to prevent bleeds/haemophilic arthropathy
- Increase QoL

# Patient and treatment predictors of ITI outcome

## Patient related

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Inhibitor titre at start of ITI  
( $</>10$ BU)

Maximum inhibitor titre  
( $</>200$ BU)/ Peak titre on ITI

F-VIII genotype

Race/ethnicity

Immunogenotype

Bleeds / Inflammation

Inhibitor epitope profile

## Therapy related

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Age at start of ITI

Interval dx and start of ITI  
( $</>2$  years)

Therapy regimen  
(dosage/frequency)

F VIII product type/  
content of VWF

Concomitant bleeding  
prophylaxis with bypassing  
agents during ITI

Interruption of ITI

Immune modulation

# ***ObsITI – Observational Immune Tolerance Induction Research Program***

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- International open-label, prospective, uncontrolled, multi-centre observational program initiated by the Paediatric Haemophilia Center, Frankfurt, Germany (started in 12/2005)
- All haemophilia patients with clinical relevant inhibitor (LR and HR) independent of prognosis for ITI
- The use of the Bonn Protocol is recommended
- Open to all FVIII products



**ObsITI**

***ObsITI –  
Observational Immune  
Tolerance Induction  
Research Program***



ObsITI

Documentation of patient- and  
therapy-related variables on ITI  
course and outcome



Evaluation of patient- and therapy-  
related variables / predictors of ITI



*Sub-studies*

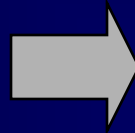
Identify genetic and immunological  
predictors,  
predictive tests



*Individualization of ITI*

# ObsITI

**Documentation and evaluation of patient- and therapy-related variables on ITI course and outcome**



- The success rates of different types of products selected for ITI, especially those of pure and vWF-stabilized F VIII concentrates
- Time necessary to achieve complete or partial success
- The long-term effect in case of complete or partial effect
- Patient age at start of Immune tolerance induction
- Number of EDs between inhibitor development and start of ITI
- Inhibitor titres (both at start of ITI and peak titres)
- Dose and frequency of F VIII administration
- Vaccination
- Surgical procedures and large bleeds
- Inflammatory status during ITI (CVL infections)

(University Hospital Frankfurt, W. Kreuz/C. Escuriola)

## **Correlation of patient and therapy related variables with success of ITI**

- Complete Success (Inhibitor titre  $<0.6$  at least at 2 consecutive times; normal recovery and half-life)
- Partial Success (2 of 3 criteria above met)
- Partial response (1 of 3 criteria above met)
- Failure (none of the criteria above met)

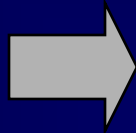


**ObsITI**

# ObsITI

## In-vitro tests

(inhibitory activity against different types of F VIII concentrates)



**Variation of inhibitory reactivity with different F VIII concentrates:** Different types of concentrates are mixed with patient inhibitor plasma. After 2 hrs of incubation at 37° C the F VIII:C activity of the test mixture is measured, compared with a control mixture and calculated by a standard Bethesda log units scale.

(University Hospital Frankfurt, W. Kreuz/C. Escuriola)

**Haemostatic role of variation of inhibitor reactivity with different F VIII concentrates:** Different types of concentrates are mixed with patient inhibitor plasma and thrombin generation is measured

(Malmö University Hospital, E. Berntorp, J. Astermark)

- Lower inhibitory activity against FVIII complexed with VWF compared to recombinant FVIII in inhibitor plasmas with anti-C2-specificity [Berntorp et al., Suzuki et al., Kallas et al. Astermark et al.]
- Higher recovery with F VIII / VWF in patients with haemophilia A and inhibitors against the light chain of F VIII [Berntorp et al. Inoue et al.]

- Correlation with epitope profile
- Correlation with clinical outcome of ITI



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Immunological  
markers during  
ITI

Epitope mapping

IgG subclasses

Genetic  
determinants

## Investigation of 20 ITI naïve and 20 patients after ITI failure

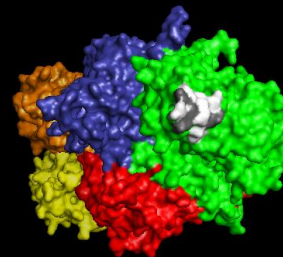
- Different subpopulations of circulating T cells
- Number, maturation state and endocytosing capacity of different antigen presenting cells (APCs)
- Identity of the circulating cells that have endocytosed F VIII
- Numbers of F VIII-specific B-cells
- Inflammatory potential of the patients' plasma
- Expression of different Cytokines

INSERM, Paris: S. Lacroix-Desmazes/Kingston, Canada: D. Lillicrap

## Influence of genetic determinants on course and outcome of ITI

- F VIII mutation type
- HLA-type
- Immunogenotype (TNF- $\alpha$ , IL-10, CTLA-4)

Bonn (J. Oldenburg/A. Pavlova)



- **Epitope mapping** using  
Biopanning method

Frankfurt: C. Königs

## Prediction of outcome of ITI analysing **IgG Subclasses**

Frankfurt: C. Königs



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# *ObsITI*

**Patient- and  
therapy-  
related  
variables on  
ITI course and  
outcome**

**In-vitro tests**  
  
(inhibitory  
activity against  
different types  
of F VIII  
concentrates)

**Investigation of  
Immunological  
markers during  
ITI**  
  
**Epitope mapping**  
  
**IgG subclasses**  
  
**Genetic  
determinants**

**Identify therapy-related, genetic and  
immunological predictors, predictive  
tests**



*Individualization of ITI*



**ObsITI**

ObsITI (February/2011)  
Recruitment status

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## Participating Countries (n=26)

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- Argentina (1)
- Belgium (1), Brazil (5)
- Canada (10), Columbia (1), Croatia (1), Czechia (1)
- England (2), Estonia (1)
- Finland (1), France (1)
- Germany (6)
- Kazakhstan (1)
- Italy (2)
- Mexico (24)
- Poland (2), Portugal (1)
- Romania (1), Russia (7)
- Saudi Arabia (1), Serbia (1), Slovakia (1), Slovenia (2), Spain (3)
- Turkey (1)
- Uruguay (2)



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## Patient status over time

	Number of pre screened patients [n]	Number of patients on ITI (doc) [n]	Number of patients completed [n]
06/2007	71	47	22
05/2008	71	62	30
02/2009	86	86	37
02/2010	186	86	37
02/2011	215	97	51



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## Success rates and ITI duration for completed/discontinued patients and for patients with ongoing ITI

ITI result	N	%
COMPLETE SUCCESS	45	88.23
PARTIAL SUCCESS	2	3.92
TREATMENT FAILURE	4	7.84
<i>Total</i>	<i>51</i>	<i>100</i>

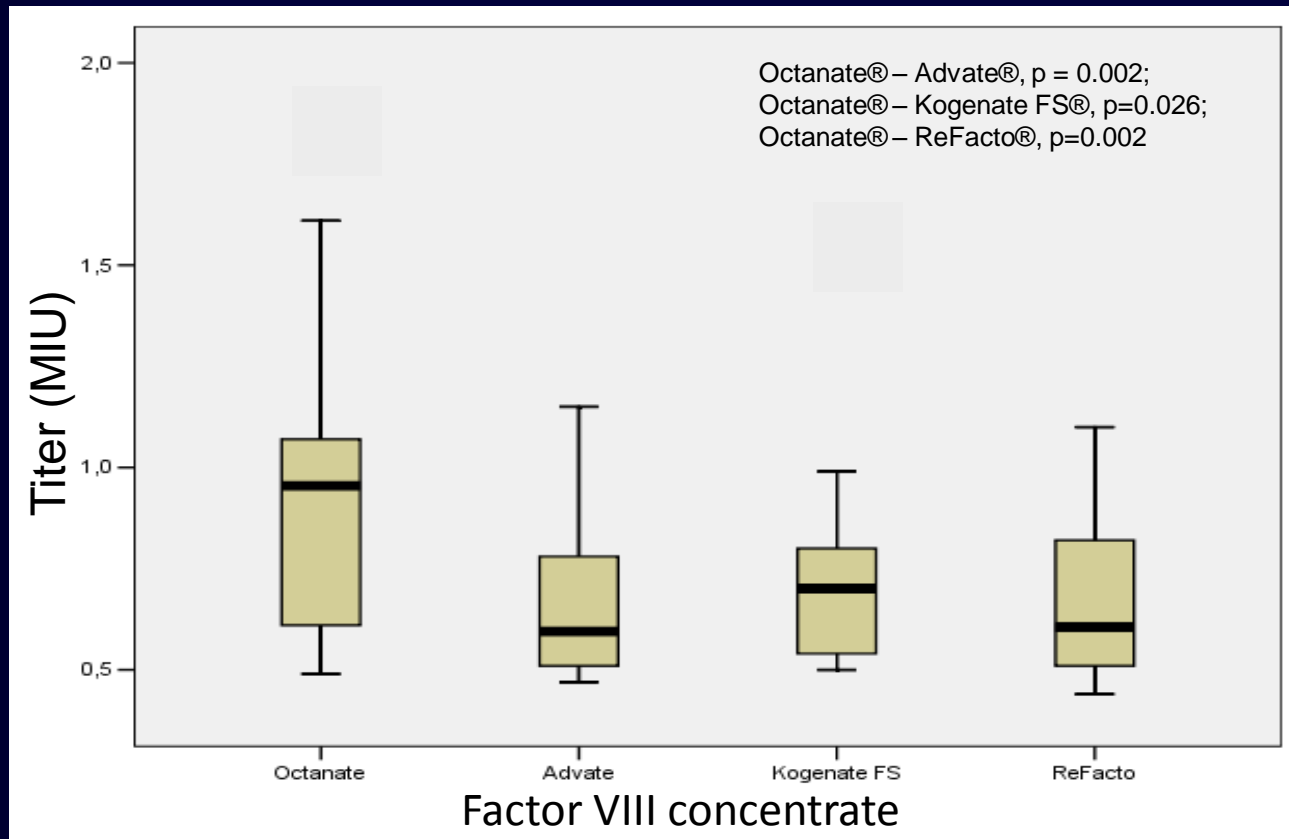
ITI duration [months]	N	Mean	Median	Range
Completed	47	24.42	20.47	3.77-64.7
Failure	4	16.45	18.63	11.2-18.97

ITI duration [months]	N	Mean	Median	Range
Ongoing	43	15.35	14.7	0.03-42.03



# ObsITI – in vitro tests

## Thrombin generation with different concentrates



**VWF containing concentrates added to FVIII-inhibitor plasma generate more thrombin than purified FVIII concentrates**

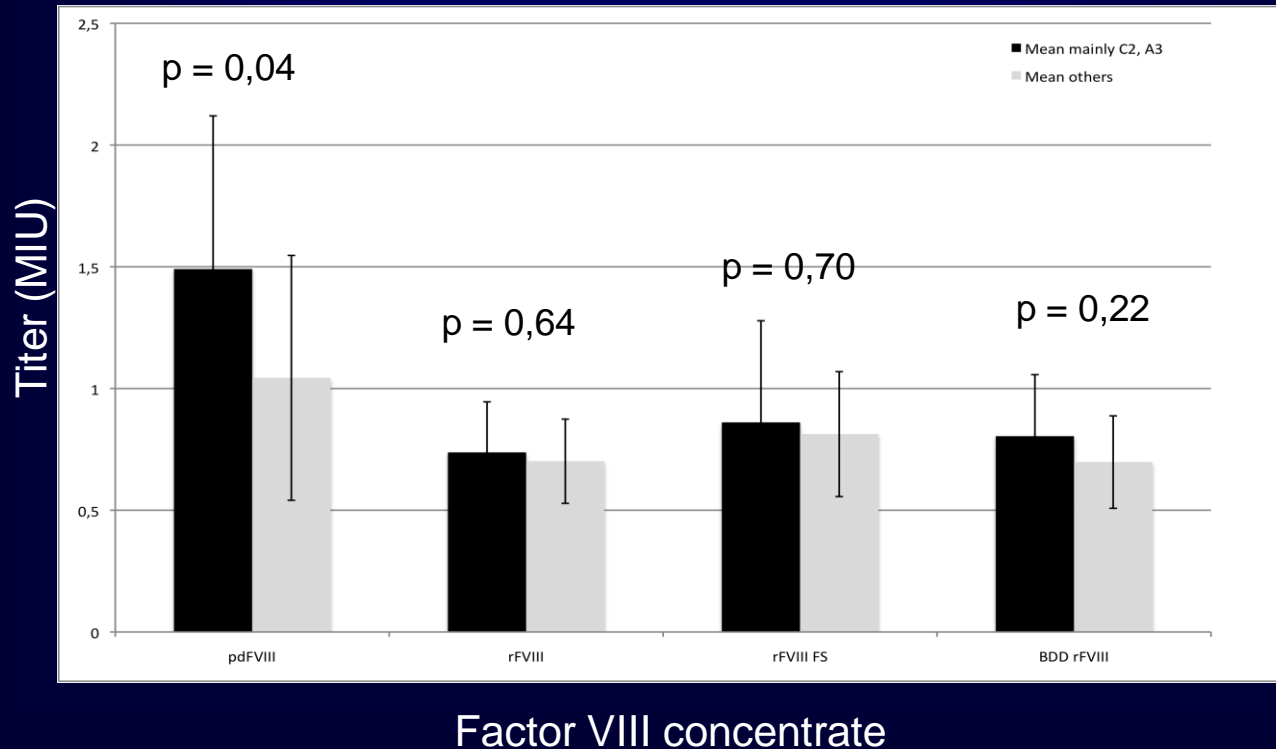
Berntorp, Astermark et al



ObsITI

# ObsITI

## Influence of epitopes on TGA



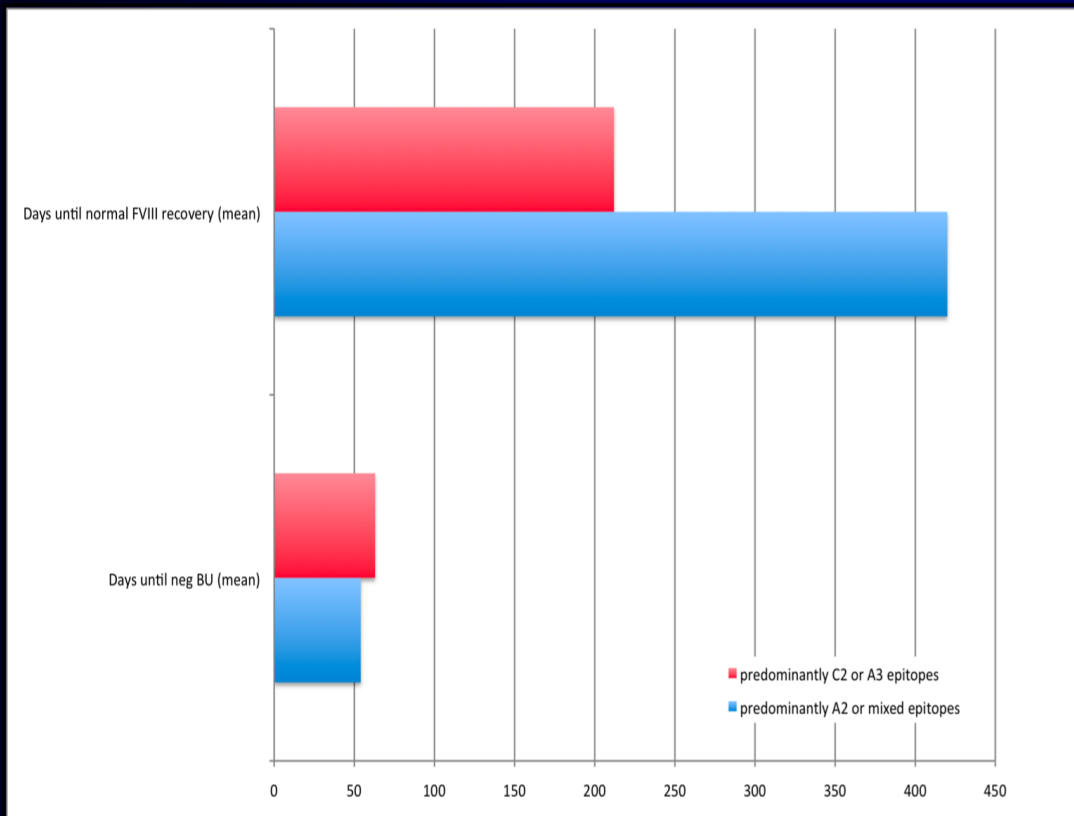
VWF containing concentrates added to FVIII-inhibitor plasma with inhibitory activity directed mainly against the C2, A3 domain generate more thrombin than purified FVIII concentrates



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# ObsITI

## Influence of epitopes on ITI course



- Haemophilia A patients with inhibitors that recognize mainly the C2, A3 epitopes of F VIII and treated with VWF/FVIII concentrate achieved normal F VIII recovery twice as fast than those with A2 or mixed epitopes (n=9, trend, not significant)




# www.obsiti.com

**ObsITI**

**Observational Immune Tolerance Induction research program**

International open-label, uncontrolled, non-interventional, multi-centre observational program initiated by the Paediatric Haemophilia Centre, Frankfurt, Germany.



**GOETHE**  
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- ObsITI website in English, Russian and Spanish
- Find information on how to enrol patients, whom to contact and how the study is progressing



