



International Randomized Immune Tolerance (ITI) Study: Progress Report.

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Introduction

The international immune tolerance induction (I-ITI) study, started in July 2002, is the only prospective randomised multi-center trial of immune tolerance therapy. A previously published retrospective meta-analysis of the International (2) and North American (3) immune tolerance registries suggested that the outcome of ITI was independent of dosing regimen in good risk high titer inhibitor patients with severe hemophilia A (HA). The I-ITI trial was designed to test this hypothesis by randomizing a good risk cohort of 150 pediatric severe HA patients.

Methods

Inclusion Criteria:

- Severe haemophilia A
- Age < 8 years
- Inhibitors present for < 12 months (now < 24 months)
- Historical peak titre ≥ 5 BU/ml and ≤ 200 BU/ml
- Starting titre of < 10 BU/ml

Study Design

- Eligible patients are treated with bypass agents until their inhibitor titre declines below 10 BU/ml and they are randomised
- Subjects use the FVIII product of their physician's choice
- Computerised randomisation takes place when the subject's titre declines to < 10 BU using the method of minimisation for product type and inhibitor titre, to balance treatment arms for these variables.
- When tolerant, subjects are followed for a further year on prophylaxis.
- Data is collected electronically, analysed centrally, and adjudicated prospectively by an independent Data Safety Monitoring Committee (DSMC) (Prof LM Aledort, Prof A Giles, Prof I Scharrer).
- The randomisation code will not be broken until the study concludes

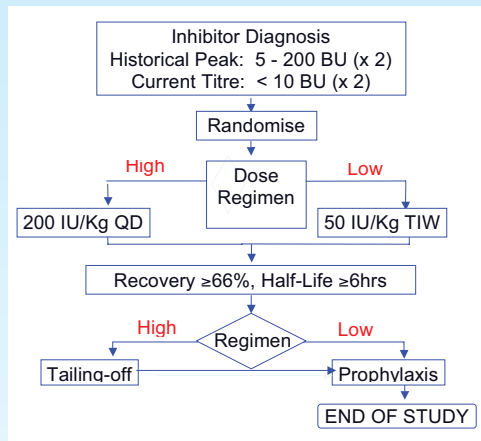


Figure 1: Flow Diagram of ITI Study Design:

Successful ITI is defined by:

- A negative inhibitor titre (< 0.6 BU/ml or < 0.3 BU/ml using the Nijmegen method).
- Factor VIII (FVIII) recovery of $\geq 66\%$ of expected.
- A normal FVIII half-life of ≥ 6 hours.

Failure is defined by:

- Failure of the inhibitor to decline by >20% every 6 months
- Failure to achieve tolerance within 33 months
- Failure to complete the protocol for any reason

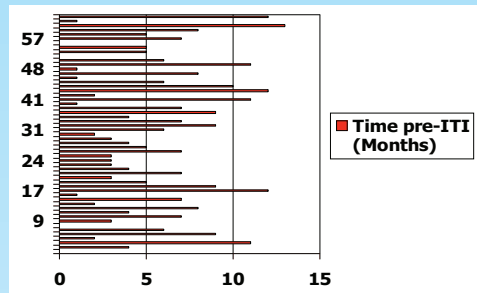
Results

Patient Demographics:

- 90 centers in 21 countries (N. America, Europe, Oceania and Asia)
- 63 subjects recruited so far; 54 have been randomised
- Median age 23 mths (range: 6-80 mths) at time of randomisation

- Median 6 mths (range 0-12 mths) for inhibitor to decline < 10 BU/ml
- Median diagnostic inhibitor titre: 10.6 (20-175) BU/ml
- Median peak historical titre: 21 (7-175) BU/ml
- Median titre at start of ITI: 5 (0.6-9.4) BU/ml

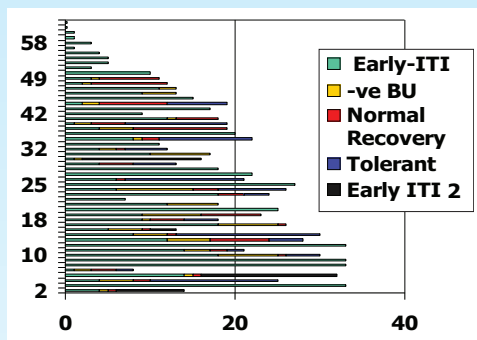
Time taken from inhibitor diagnosis for the inhibitor to decline <10 BU/ml.



Progress on Study:

- 54 subjects are randomised at this time.
 - 37 on-study (3 pre-ITI).
 - 24 off-study (7 pre-ITI, 17 on ITI)
- Median of 23.5 months (range: 1-33) on ITI
- 29/54 have achieved a negative titre
 - after median 8 mths (range: 1-18)
- 23/54 (50%) have a normal FVIII recovery
 - after a median of 9 mths ITI (range: 3-25)
- 15/54 have become tolerant after a median of 11 mths (range: 5-25)
 - Median FVIII half-life of 7 hours (range: 6.5 - 9.9).

Progress on ITI.



Influence of Product Type on ITI Outcome:

Med. Mths (Range):	rFVIII n=45	pdFVII n=9
To -ve inhibitor	7.5 (1-18) (n=19)	9 (3-12) (n=5)
To normal recovery	9 (2-25) (n=19)	8 (4-17) (n=5)
To normal T 1/2	12 (5-25) (n=13)	7 & 13 (n=2)

- The numbers of subjects are too small to make any meaningful comparison at this point, but no obvious difference in response has emerged between subjects tolerised with rFVIII or pdFVIII.

Failure and Relapse:

- 18 patients met end-of-study criteria:
 - 6 met treatment failure criteria
 - 9 failed for other causes; 2 failed venous access; 1 central withdrawal because of protocol violation; 3 subject non-compliance.
 - 2 relapsed.
 - 3 completed 12 months prophylaxis.

Characteristics of relapsed and non-relapsed patients:

2/15 tolerised subjects relapsed 1 and 9 months after achieving tolerance.

	Relapsed n=2	Non-relapsed n=13
Median (range)		
Diagnostic inhibitor (BU/ml)	9 and 175	9 (3.8-100)
Max historical titre (BU/ml)	9 and 175	17.8 (8-160)
Time to <10 BU (mths)	6 (3-9)	4 (1-10)
Peak titre on ITI (BU/ml)	15 and 1300	23 (0-48)
Time to -ve BU (mths)	6 (3-9)	4.5 (1-18)
Time to norm. recovery (mths)	12 (9-15)	8.5 (2-24)
Time to normal T 1/2 (mths)	16.5 (13-20)	9.5 (5-25)
Recovery at end of ITI	89% (80-98)	86% (77-121)
T 1/2 at end of ITI (hrs)	7.22 (7.2-7.26)	6.95 (6.5-9.9)

Adverse Events:

- 102 serious adverse events (SAEs) have been reported
- 85% were judged by the DSMC to be unrelated to the study or product.
- All were hospitalisations.
- Reasons for hospitalisation included 29 bleeding episodes in 14 subjects. and 44 catheter infections in 13 subjects.

Conclusion:

- The start of ITI is not significantly delayed by waiting until the inhibitor titre declines below 10 BU/ml.
- Both treatment regimens appear effective (though the randomisation code has not been broken) and the success rate is comparable with published series.
- Many participants are still at an early stage of ITI.
- Patients who relapsed had similar diagnostic and peak titres, achieved ITI milestones at a similar rate and had similar starting titre, peak titre on ITI and PK at the end of ITI to non-relapsers.

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