

# The International Immune Tolerance Study: Influence of Infection on Outcome.

Charles RM Hay<sup>1</sup>, Jason Keegan<sup>1</sup>, T Abshire<sup>2</sup>, N Ewing<sup>3</sup>, Ilene Goldberg<sup>4</sup>,  
Janet Goldstone<sup>1</sup>, DM DiMichele<sup>4</sup> and the ITI Study Group.

<sup>1</sup>Manchester Royal Infirmary UK. <sup>2</sup>Emory University USA. <sup>3</sup>City of Hope National Medical Centre USA.  
<sup>4</sup>New York Presbyterian Hospital-Cornell Medical Centre



## Introduction:

The international immune tolerance induction (I-ITI) study, started in July 2002, is the only prospective randomized 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 paediatric severe HA patients to high- or low-dose ITI.

## Methods:

### Inclusion Criteria:

- Severe Haemophilia A
- Aged < 8 years.
- Inhibitors present for < 12 months (now <24 months).
- Historical peak titer  $\geq 5$  Bethesda Units (BU)/ml and  $\leq 200$  BU/ml;
- Starting titer of < 10 BU/ml(4).

### Randomisation to :-

High-dose (200 IU/kg/day)  
or  
Low dose (50 IU/kg thrice weekly)

### Successful ITI is defined by :-

- A -ve inhibitor titer .
- Factor VIII (FVIII) recovery of  $\geq 66\%$  of expected.
- A normal FVIII half-life of  $\geq 6$  hours.

Data on treatment given, outcome measures and adverse events is collected electronically, analyzed centrally, and adjudicated prospectively by an independent **Data Safety Monitoring Committee (DSMC)** (Prof LM Aledort, Prof A Giles, Prof I Scharrer). The randomization code will not be broken until the study concludes.

## Results (Analysis conducted January 2006):

- 90 centers in 21 countries (N. America, Europe, Oceania Asia)
- 54 subjects recruited (January 2006).
- 45 subjects randomized (Jan. 2006).
- Median age of 25 months (range: 13-80 months).
- 28/45 (62%) have achieved a negative inhibitor titer
- 23/45 (50%) now have a normal FVIII recovery
- 14 (31%) tolerant after a med. 12 months (range: 5-25) of treatment with a median FVIII  $\frac{1}{2}$ -life of 7 hs (6.5 – 9.9 hrs).
- 7/45 (15%) of subjects failed ITI, according to study criteria.

### Adverse Events:

- 102 serious adverse events (SAEs) reported – All defined by hospitalization.
- 85% determined by the DSMC unrelated to the study or product.
- Hospitalization for 29 bleeds in 14 subjects.
- And 44 catheter infections in 13 subjects.

### Adverse Events:

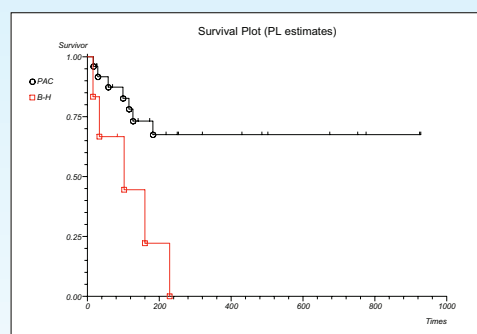
- 52 CVADs inserted in 36 subjects
- 30 Portacaths; 14 Broviac/Hickman catheters; 8 PICC.
  - 6 placed for ITI
  - 28 placed for general venous access
  - 2 placed for unstated reasons.
- Med. 2 (range: 1-5) CVADs placed per subject.
- 13 / 36 pts (36%) developed one or more catheter infections.

### Causitive Organisms:

Gram +ve:	n	Gram -ve:	n
Staph Epidermis	8	Pseudomonas	3
Staph aureus	12	Klebsiella	2
Unspecified	7	Enterobacter	3
		Acinetobacter	3
<b>Others:</b>		Achromobacter	2
Candida	2	Serratia	1
		Unspecified	1

### Influence of Catheter-Type:

- 5/6 patients with Broviac /Hickman catheters became infected.
- 7/26 with Portacaths became infected (Figure 2).
- $p = 0.005$ , Peto log-rank test. (Figure 2).
- The median ages at randomization for 'infected' and 'uninfected' subjects were 19 and 24 months, respectively (NS).



### Catheter survival plot to first infection of first catheter broken down by Portacath (Black) and Broviac/Hickman (Red) Effect of Infection on outcome of ITI: -

- 13 patients have suffered a CVAD infection,
  - 3 (27%) are tolerant.
  - 5 (38%) failed ITI.
  - 5 remain on-study but not tolerant.
  - Only 7 (15%) of the whole group failed ITI.

### Subjects with -ve inhibitors after ITI.

Infection	Yes	No
Number	13	23
N with -ve BU	5 (38%)	17 (74%)
Med. time to -ve BU (months)	14	7.5
Range mths	1-14	1-18

## Conclusion:

- Catheter infection is significantly commoner in patients undergoing ITI using Hickman or Broviac Catheters than those using Portacaths ( $P=0.005$ ).
- The success rate for subjects who have developed CVAD infections is lower, the failure rate higher and response to ITI much slower than for subjects in whom no such infection has yet been observed.
- These preliminary findings suggest that catheter-related infection may have a marked adverse effect on the outcome of ITI.
- Since one of the original objectives of this trial was to study the impact of catheter-related morbidity on ITI outcome, these data will continue to be very actively monitored.

## Acknowledgement:

We would like to acknowledge the hard work and commitment of our Data Safety Monitoring Committee: Prof LM Aledort, Prof A Giles and Prof I Scharrer and of our investigators (Listed alphabetically): ABSHIRE Thomas C – Emory University, Fulton, USA, HAYA Nino – Unidad de Coagulopatías Congénitas, Hospital La Fe, Spain, BARNARD Dr Dorothy – IWK Health Centre, Nova Scotia, Canada, BENNETT Carolyn MD PhD – Children's Hospital, Boston, Massachusetts, USA, CARCAO Manuel – Hospital for Sick Children, Ontario, Canada, COHEN Alice J – Newark Beth Israel Medical Center, NJ, USA, COLLINS Peter – Cardiff and Vale NHS Trust, DEMERS Dr Christine – Centre de l'Hémophilie pour l'Est de Québec, Québec, Canada, EWING Nadia MD – City of Hope National Medical Center, California, USA, GLOMSTEIN Anders – Institute for Rare Disorders, Norway, GOUEMAND Jenny – Haemophilia Centre, Lille, France, HANLEY John – Newcastle Haemophilia Centre, Newcastle Upon Tyne, UK., HEISEL Margaret – Minnesota Children's Hospital, Hennepin, USA, ISHII Eisaburo – Nagano Prefecture Children's Hospital, Japan, KEELING David – Oxford Haemophilia Centre, UK, KENET Gili – The National Hemophilia Center, Israel, KLAASSEN Dr Robert – CHEO, Ontario, Canada, LEISSINGER Cindy A – Tulane University Health Sciences Center, Orleans Parish, USA, LOCKWOOD Lianne – Haemophilia Centre, Queensland, Australia, MATSUSHITA Tadashi – Nagoya University, Aichi, Japan, MONAHAN Paul E – University of North Carolina at Chapel Hill Comprehensive Hemophilia Center, USA, MORFINI Massimo MD – Centro Emofilia, Italy, ALTISENT Carmen – Unitat d'Hemofilia, Hospital Vall d'Hebron, Spain, PEERLINCK Kathelijne – Leuven, Belgium, PIPE Dr Steven – University of Michigan Hemophilia & Coagulation Disorders Program, Washenaw, USA, POON Man-Chiu – Southern Alberta Hemophilia Clinic, Calgary, Canada, REISS Dr Ulrike – St Jude Children's Research Hospital, Tennessee, USA, RITCHIE Bruce – University of Alberta Hospital, Canada, RIVARD Dr Georges-Etienne – Québec Reference Center for the Treatment of Patients with Inhibitors, Canada, SANTAGOSTINO Elena – A Bianchi Bonomi, Italy, SHIMA Midori – Nara Medical University, Nara Prefecture, Japan, SHIMADA Akira – Gunma Children Medical Center, Japan, SHIRAHATA Prof Akira – University of Occupational & Environmental Health, Fukuoka, Japan, SUZUKI Takashi – Tokyo Medical University, Japan, THOMAS Dr A E – Edinburgh Haemophilia Centre, Mid Lothian, UK, VALENTINO Leonard A – Rush HTC, Cook, USA, VAN DE BERG Marieke – Van Crevelkliniek University Medical Center Utrecht, Holland, VORA Dr A J – Sheffield Children's Hospital, South Yorkshire, UK, WATTS Dr Raymond – University of Alabama at Birmingham, Alabama, USA, WERNER Eric J – Bleeding Disorders Center of Hampton Roads, Virginia, USA, WICKLUND Brian MD – The Children's Mercy Hospital & Clinics, Jackson, USA

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