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

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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 doses 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 < 8yars.
• Inhibitors present for < 12 months (now <24 months).
• Historical peak titer ≥ 5 Bethesda Units (BU)/ml and ≤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 ≥ 66% of expected.
• A normal FVIII half-life of ≥ 6 hours.

Influence of Infection on Outcome:

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 Aeledert, 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, Oceana 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 half-life of 7 hrs (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 Brovica/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.

Causative Organisms:

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Influence of Catheter-Type:

- 5/6 patients with Brovica/Hickman catheters became infected.
- 7/26 with Portacaths became infected (Figure 2).
- p < 0.005, Peto log-rank test. (Figure 2).

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Conclusion:

- Catheter infection is significantly commoner in patients undergoing ITI using Hickman or Brovica 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 Aeledert, Prof A Giles and Prof I Scharrer, and our investigators listed alphabetically: ABISHA Thomas C. – Emory University, Fulton, USA, PIDIX Nien – Unidad de Coagulopatias Congenitas, Hospital La Fe, Spain, BARNAUX Didier M – I+UZ Inst. de Med. Humana, Namur, Belgium, BERNSTEIN Milton I MD PhD – Children’s Hospital, Boston, Massachusetts, USA, CARACO Manuel – Hospital for Sick Children, Toronto, Canada, CEZARY Anna J – North West Children’s Medical Center, NL USA, COOLLING Peter – Carolfd and Vale NMS Trust, DEMEDS Dr Christine – Centre de l’Hémophilie et des Thrombopathies, Quebec, Canada, EVANS Nicka MD – City of Hope National Medical Center, California, USA, GLOMSTEIN Anders – Institute for Rare Disorders, Norway, GOUDEMAND Jenny – Haemophilia Centre, Lille, France, HARLEY John – Naas Haemophilia Centre, Naas, Ireland, USA, HARVEY James – Professor of Pediatrics, Children’s Hospital, Boston, Massachusetts, USA

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References: