ITI Risk Stratification in Children

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ITI – three main regimens

- Malmo
  - Cost effective
  - Relatively quick
  - Uses immune adsorption and perhaps immune suppression
- Bonn
  - Relatively expensive
  - May take up to 3 years
  - Recommended especially for high titres inhibitors
- Low(er) dose regimen
  - Relatively cheap
  - Effective enough
  - May take long time, but seldom with complications
- In average
  - Effective in up to 80% of cases
    - Di Michelle et al, Thromb Haemost, 2002; Smith Pathophysiol Haemost Thromb, 2002
  - Bleedings treated with by-passing agents (nowadays aPCC, rFVIIa)

ITI OUTCOME PREDICTORS

ITI outcome predictors

Inhibitor titres and FVIII dose I.

Pre-ITI Historical Titers / Dose			
Historical Titer (BU)	Pre-ITI Titer (BU)	Dose (U/kg/d)	# Successes (%)
< 50	< 10	< 50	30 /36 (83%)
		50-99	33 /38 (87%)
		100-199	18 /19 (95%)
		≥ 200	23 /24 (96%)
	10 – 20	< 50	2 /3 (67%)
		50 – 99	11 /14 (79%)
		≥ 200	3 /4 (75%)
	> 20	50 – 199	3 /9 (39%)
		≥ 200	1 /3 (33%)

Marianni and Kroner; Immune Tolerance Study Group (ITSG) Haematologica; 2001:86(11):1186-93

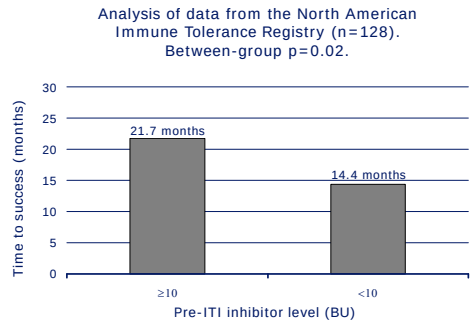
ITI outcome predictors

Inhibitor titres and FVIII dose II.

Pre-ITI and Historical Titers / Dose			
Historical Titer (BU)	Pre-ITI Titer (BU)	Dose (u/kg/d)	# Successes (%)
> 200	< 10	< 50 – 199	5 /11 (45%)
		≥ 200	7 /7 (100%)
	10 - 20	< 50 – 199	1 /3 (33%)
		≥ 200	3 /4 (75%)
	> 20	< 50 – 199	1 /23 (4%)
		≥ 200	12 /18 (6%)

Marianni and Kroner; Immune Tolerance Study Group (ITSG) Haematologica; 2001:86(11):1186-93

Duration of successful tolerance is dependant of pre-ITI inhibitor level

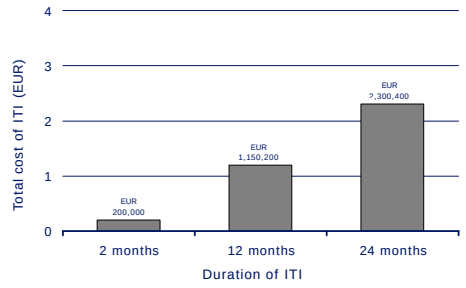


DiMichele DM et al., Thromb Haemost 2002; 87:52-57.

WHAT ABOUT COSTS?

Costs related to duration of ITI therapy

German cost-of-illness study
Data shown for 15 kg high-responder child on ITI protocol



Auerswald G, et al., Haemophilia 2004; 10:499-508

The International Consensus Panel (ICP)
Donna DiMichele, Chair

Charles Hay
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Steve Pipe
Mark Reding
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Keith Hoots
Johannes Oldenburg
Pia Petrini
Mike Recht
Georges Rivard
Elena Santagostino

DiMichele DM et al., Haemophilia. 2007;13 Suppl 1:1-22

ICP recommendations – When to start?

Based on: International ITI Workshops – (Jun&Sep, 2006)

Preferred start of ITI if titre < 10 BU

When to start?

Wait until Inh titre < 10BU

- Pre ITI treatment of inh patients with by-passing agents
- Recommended : rFVIIa (90-270µg/kg/d)

Start ITI regardless of inh titre (<10 BU) if

- Waiting period > 1-2 years
- Severe/life-threatening bleeds occurs

NB: Both (aPCC and rFVIIa) recommended if bleeding occurs

DiMichele DM et al., Haemophilia. 2007;13 Suppl 1:1-22

WHAT HAVE WE LEARNED FROM I-ITI STUDY?

I - ITI study

- **Compared two ITI strategies (in HA)**
  - HD (200IU/kg daily) vs. LD (50IU/kg thrice/week)
  - In good risk, severe, high titer HA inhibitor pts.
- **Good risk patients (inclusion criteria)**
  - Severe Haemophilia A
  - Aged <8 years
  - Inhibitors present for <12 Mo
  - Historical peak ≥5BU and ≤200BU
  - Starting titre <10 BU

I-ITI Study: Results

- **No difference in success rate**
  - **(24/58 LD vs. 22/57 HD, p=0,909)**
    - HD is either 200IU/kg/d or 100 IU/kg/d
  - **Shorter time to achieve neg. titer (3x;p=0,027), normal recovery (p=0,002) and tolerance (p=0,116 NS) in HD group**
- **Peak inhibitor titers correlated inversely with success rate**
  - **Historical peak (p=0,026), on-ITI peak (0,002)**
  - **ONLY on-ITI peak predicted outcome (p=0,002)**
    - If >36 IU – longer time to achieve tolerance and lower percentage of tolerance achieved in 3 years (cca 2x)
- **LD subjects bled more often (p=0,0019, OR 2,2)**
  - **However ONLY until negative BU test**

» Ch Hay and D Di Michelle, Blood 2011

UK GUIDELINES (4TH EDITION, 2012)

ITI outcom predictors

- **Good risk**
  - **Historical peak of iFVIII<200 BU**
  - **iFVIII at the start of ITI<10 BU**
- **Poor risk**
  - **Historical peak of iFVIII>200 BU**
  - **iFVIII at the start of ITI>10 BU**

Wait with ITI until iFVIII<10 (up to 1 year)
Then start ASAP

If no success in lowering the iFVIII<10BU for one year, consider commencing on ITI despite of that

ITI regimens to choose for severe HA…

- **50 IU/kg FVIII on alternate days**
  - Historical peak <5BU
  - If bleeding complications: increase dose in stages up to 200IU/kg FVIII daily to control bleeds
- **100 IU/kg FVIII daily**
  - Historical peak <200BU AND
  - Starting titre <10BU
- **200 IU/kg FVIII daily**
  - Historical peak >200BU AND/OR
  - Starting titre >10BU

Reflecting more bleeds in LD group in I-ITI study.

ITI regimen for HB?

- **Careful consideration of ITI**
- **Relatively poor response rate**
- **Many risks (see before)**
- **Immune supression often needed**

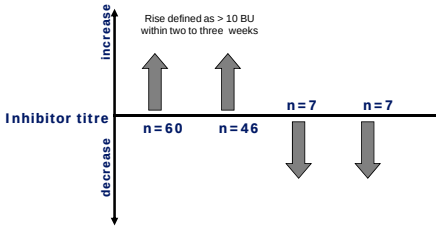
ITI in mild to moderate HA?

- **Mild/Mod HA with iFVIII**
  - On-demand by-passing therapy should precede ITI
  - Very low ITI success rate
- **Acquired like bleeding phenotype**
  - Consider immune suppression

HOW TO GET FVIII INHIBITORS LOW?

Anamnestic potential of aPCC

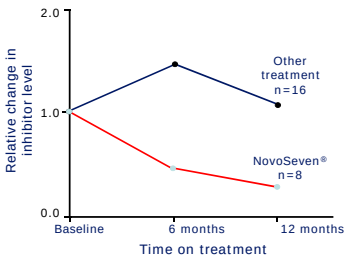
Results from four available studies recording inhibitor titre responses following aPPC infusion



Hilgartner M, et al. Blood 1983; 61:36–40.
Hilgartner M, et al. Haemophilia 2003; 9:261–268.
Negrier C, et al. Thromb Haemost 1997; 77:1113–1119.
Zwahlen H, Beck EA. Acta Haematol 1980; 64:12–17.

rFVIIa and dynamics of inhibitor level

Inhibitors levels declined by two-thirds in high responder patients on rFVIIa



Johannessen M et al., Blood Coagul Fibrinoanalisis 2000; 11:239-242

Use of rFVIIa to optimise conditions for ITI

"The exclusive use of rFVIIa in acute bleeding episodes prior to commencing ITI is an effective method of decreasing inhibitor titre, thereby optimizing conditions for ITI"

Brackmann H, et al., Bood Coagul Fibrinolysis 2000; 11(Suppl 1):S39-44

Fair to say, that there are centres, who use aPCC from very beginning succesfully.

They, however, often do not wait with ITI start for low iFVIII titres (e.g. Frankfurt centre)

Summary

Severe Haemophilia A

- **It worth to wait (up to one year) for iFVIII<10BU**
  - **If not waiting, high risk protocols should be used upfront**
- **In low/good risk patients both ITI regimens can be used with similar success**
  - **"Different" definitions of low/good risk patients in different reports**
  - **Low dose regimen (50IU FVIII trice a week) may be accompanied by more bleedings**
    - These may not be too serious from the clinical point of view, though
- **High risk patients (historical peak >200 BU, starting titre>10 BU)**
  - **High dose (Bonn like) protocol is often recommended**
  - **Certain centres recommend to commence every patient wit historical peak >5BU on HD protocol to minimize intercurrent bleedings**
  - **Consider always resources available, compliance etc… (HD protocol is quicker, perhaps safer, but often far more expensive)**
- **ITI study showed**
  - **200IU/kg/d FVIII equally effective to 100 IU/kg/d FVIII**
  - **the on-ITI peak more predictive for the outcome**
  - **No influence of CVADs in good risk patients**

Summary

Mild/Moderate Haemophilia A

- **ITI is not the first line treatment**
  - **Very low success rate**
- **If "Acquired-like" bleeding phenotype – consider immune suppression**

Haemophilia B

- **Careful consideration of ITI**
- **Relatively poor response rate**
- **Many risks associated**
- **Immune suppression often needed**