Immune Tolerance Induction (ITI) options to eradicate inhibitors in patients with hemophilia: starting time and dose regimen

This document prepares the clinician to discuss scientific evidence with the patient (or carer) so they can make an informed decision together.

What is ITI?

Immune tolerance induction (ITI) aims to eradicate factor inhibitory antibodies, to allow recommencement of FVIII or FIX concentrate infusion. ITI remains the optimal treatment for eradicating inhibitors.

What patient population might consider this tool?

Persons with congenital hemophilia A or B, of all ages, who have developed inhibitory antibodies and have not previously undergone ITI.

Decision 1: What are the options for ITI starting times?

Immediate start: shortly after detection, irrespective of titer level and trends
Delayed start: sometime after detection, allowing for opportunity for spontaneous titer reduction to happen.

Why do parent and patient preferences matter when making this decision?

There are pros and cons to *delayed compared to immediate start:*

Pros of delayed start:

- Increased chance of success
- Later implant of port if needed
- More time to consider decision and prepare for treatment
- Other:_____

Cons of delayed start:

- Increased anxiety about bleeding
- Need for alternative treatment to manage intercurrent bleeding for a longer time
- Other:_____

Selection of the best available studies (as of January 2013)

Benefits
of delayed start

People who have **lower pre-titer level** at start may have **25% higher chance of success** compared to people who have higher levels at start, and their titer level may spontaneously decrease over time.

Outcomes in 174 patients:

	Pre-titer level	Individuals with Success[1]	Time to success[2] (months)
Delayed	≤10 BU/mL	75%	11
Immediate	>10 BU/mL	50%	15

86% patients required a central venous access device (CVAD) for ITI administration; therefore, can **delay CVAD** if required.[3]

Risks
of delayed start

By delaying treatment, people with inhibitors may experience **higher rates of bleeding episodes** and **lower quality of life**.[4]

Exposure to FVIII must be discontinued to avoid anamnestic inhibitor increase; therefore, **alternative treatment for bleeding** is required.[1,5]

Decision 2: What are the options for ITI dosing regimens?

High dose with immunosuppressant (i.e, Malmo protocol): large daily doses (i.e. >100 IU per kg per day) of factor concentrates plus oral immunosuppressant (i.e. cyclophosphamide or prednisone)
High Dose (i.e. Bonn protocol): large daily doses (i.e. > 100 IU per kg per day) of factor concentrate
Low Dose (i.e. Dutch protocol): lower doses (i.e. < 100 IU per kg per day) of factor concentrate administered 2-3 times per week.

Why do parent preferences matter when making this decision?

There are pros and cons to *different dosing regimens*

- Addition of immunosuppressant may increase success
- High dose may provide better joint protection
- Lower doses require fewer injections with less volume per injection
- Lower doses may **not** require venous access devices.

Selection of the best available studies (January 2013)

High dose with immuno-suppressant (Malmo protocol)

Benefits

60 to 85% of people receiving **high dose** of ITI with immunosuppressant **achieved tolerance** within 40 days. [6,7]

Risks

High dose of ITI with immunosuppressant is 55% **less successful in children younger than 5 years old** compared to children older than 5 years.[5]

Common adverse effects of immunosuppression.

High dose (Bonn Protocol)

Benefits

For 50 to 90% of people receiving high dose FVIII, treatment is **successful** (inhibitors are undetectable, FVIII recovery and half-life are normal).[1]

Risks

40 to 60% **withdraw** from treatment for the following reasons:
-too demanding
-poor compliance.[3]

Low dose

Benefits

Comparable success rates but **less demanding**:[3]

	Low dose*	High dose**
Success	41%	39%

Comparable success rates with **low-responding** inhibitors:[7]

	Dose (IU/Kg)	Full success	Partial success	Failure
High titer	High (100)	100%	0%	0%
	Low (30)	33%	33%	33%
Low titer	Low(30-50)	91%	10%	0%

Can be administered **without a CVAD:**[3]

	Low dose*	High dose**
Patients without CVAD	18%	9%

*Low dose = 50 IU/kg 3 times/week
**High dose = 200 IU/kg/day

Risks

More frequent bleeding events until tolerance:[3]

	Low dose*	High dose**
% patients without bleeding	14%	37%

Longer time to tolerance:[3]

	Low dose*	High dose**
Median # months	9.2	4.6

*Low dose = 50 IU/kg 3 times/week
**High dose = 200 IU/kg/day

How much confidence can we have in these results for these 2 decisions?

The evidence is **low to moderate** for the following considerations:

Item decreasing confidence in evidence:

- No evidence comparing ITI with natural history of inhibitors not undergoing ITI.

Items increasing confidence in evidence:

- One randomized controlled trial comparing different regimens[3]
- Two large retrospective registries[2,5], one multinational.[1]

References: [1]Mariani G *Haematologica* 2001; [2]Kroner B *Vox Sang* 1999; [3]Hay C *Blood* 2012; [4]Gringeri A *Blood* 2003; [5]Benson G *European J Haemotology* 2012; [6]Freiburghaus C *Haemophilia* 1999; [7]Lin P *Pediatr Blood Cancer* 2011; [8]Carlborg E *Haemophilia* 2000