Starting and stopping ITI?

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Starting and stopping ITI

- Starting and/or stopping ITI is always:
  - Primarily medical decision
  - Decision based on resources available
  - Dependent on patient's compliance and will
  - Facilities/expertise dependent
- It should be based on international and national guidelines/recommendations, though.

WHEN TO START ITI?

International Consensus Panel 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

British guidelines (2012)

- 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

Collins et al., BJH, 2012

Case 1

- Severe haemophilia A
- 2 years old boy
- HR iFVIII (max 50 BU) after 25 ED
  - pdFVIII/vWF concentrate
- No peripheral vein access
- Bleeding at least 2x/months, severe haemarthroses

- What is the best for him regarding:
  - Bleeding treatment?
  - Venous access?
  - ITI (which regimen, if any?, which concentrate?, when to start?)

Case 1

- Bleeding treatment:
  - rFVIIa to lower iFVIII (unless starting ITI upfront)
- ITI with:
  - the same FVIII concentrate (pdFVIII/vWF)
- When to start:
  - Wait until low iFVIII (if possible, up to 1 year)
- Which regimen to choose (HD X LD)
  - LD should be enough
  - HD possible, especially if significant bleeds
- Venous access
  - Due to the age CVAD is very likely

Case 2

- Moderate haemophilia A
- 14 years old boy
- LR iFVIII (1,5 BU, on 2 consecutive visits) after 53 ED in total
  - Previously pdFVIII, now for 5 years (20ED) rFVIII concentrate
- Good peripheral vein access
- Bleeding up to 1/month, needs more rFVIII

- What is the best for him regarding:
  - Bleeding treatment?
  - Venous access?
  - ITI (which regimen, if any?, which concentrate?, when to start, if at all?)

Case 2

- Bleeding treatment:
  - Increase the dose of rFVIII
  - rFVIIa/aPCC if inadequate response to rFVIII
- ITI? Different treatment?:
  - Perhaps watch and wait (iFVIII may be transient, clinically non-relevant?)
  - Prefer by pass therapy to ITI (low success rate)

Case 3

- Severe haemophilia A
- 18 months years old boy
- HR iFVIII (max 250 BU) after 8 ED
  - rFVIII concentrate
- No peripheral vein access
- Bleeding at least 2x/months, severe haemarthroses, GI bleeds

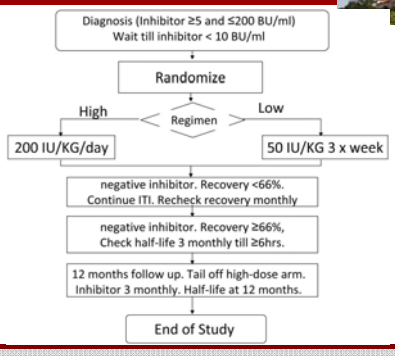
- What is the best for him regarding:
  - Bleeding treatment?
  - Venous access?
  - ITI (which regimen, if any?, which concentrate?, when to start?)

Case 3

- Bleeding treatment:
  - rFVIIa to lower iFVIII (unless starting ITI upfront)
- ITI with:
  - Primarily the same FVIII concentrate (rFVIII)
  - pdFVIII/vWF switch if poor/no response shall be preferred to stopping ITI
- When to start:
  - Wait until low iFVIII (if possible, up to 1 year) unless severe break-through bleeds on proper by-pass treatment
- Which regimen to choose (HD X LD)
  - HD as first choice, consider bleeding prophylaxis with by-pass agents
- Venous access
  - Due to the age and intensity of the treatment, CVAD is almost imperative

WHEN TO STOP ITI?

I-ITI Study



C. Hay, D Di Michelle, Blood 2012 119: 1335-1344

I-ITI study

Criteria to stop ITI:

Negative titre (Nijmegen method) AND
Normal recovery: ≥66% od expected AND
Normal T1/2: ≥6h

	n	LD	n	HD	p
Phase1: Start to negative titre	29	9,2 (4,9-17,0) Mo	31	4,6 (2,8-13,8) Mo	.017
Phase 2: Negative titre to normal recovery	27	13,6 (8,7-19,0) Mo	23	6,9 (3,5-12,0) Mo	.001
Phase 3: Normal recovery to tolerance	24	15,5 (10,8-22) Mo	22	10,6 (6,3-20,5) Mo	.096

C. Hay, D Di Michelle, Blood 2012 119: 1335-1344

I-ITI study success definitions

Table 2. Study definitions of successful tolerance, partial response study failure, and relapse

Successful tolerance	Negative inhibitor titer, FVIII recovery ≥ 66% of expected, and FVIII recovery ≥ 6 h
Partial response	After 33 mo of ITI, negative inhibitor titer but persistently abnormal recovery or half-life; responding clinically to FVIII replacement without an anamnestic increase in inhibitor titer
Study failure	Failure of the inhibitor to decline by ≥ 20% over any 6-mo period after the first 3 mo of immune tolerance induction (ITI); or failure to achieve tolerance or partial response after 33 mo on ITI; or withdrawal from the study for any reason before tolerance was achieved
Relapse	Inhibitor recurrence during the 12-mo follow-up period on prophylaxis after tolerance was achieved, as evidenced by recurrent positive Bethesda titer or a decline in FVIII recovery or half-life below study limits

From the consensus proceedings from the Second International Conference on Immune Tolerance Therapy, Bonn, Germany, 1997 (unpublished).

C. Hay, D Di Michelle, Blood 2012 119: 1335-1344

British guidelines (2012)

- ITI should continue as long as there is convincing downward trend of inhibitor titre
  - 20% in 6 months period after peak titre has been reached
  - Interruptions of ITI should be avoided
- Dose tapering (in good risk patients ONLY)
  - Post-washout BU titre is negative on 2 consecutive occasions AND
  - 24-h trough level is ≥1 IU/dl
  - Reduce FVIII dose, but maintain minimal 24-h trough level ≥1 IU/dl with minimal break-through bleeds
- **Criteria for successful ITI**
  - When FVIII dose is <50 IU/kg on alternate days AND
  - trough level ≥1 IU/dl AND
  - T1/2 > 7h

Collins et al., BJH, 2012

British guidelines (2012)

- If INADEQUATE decrease of inhibitor titre (20% in 6 months period)
  - Alternative strategy to be considered
    - FVIII dose increase AND/OR
    - Introduction of pdFVIII concentrate AND/OR
    - Immune suppression with rituximab (antiCD 20) OR
    - Stopping ITI

Collins et al., BJH, 2012

Case 1

- Severe haemophilia A
  - iFVIII: Max peak 230BU, starting peak 5BU
- 3 years old boy after 10 months of HD ITI
  - 200 IU FVIII/kg/d of rFVIIa
  - On-demand rFVIIa for bleeds
- Currently no excessive bleeds (last 3 mo no bleed at all)
  - His iFVIII 0,4 BU (Nijmegen)
  - His 24-h trough level 1,7%, T1/2 7,8 h
- What is the best for him regarding:
  - Bleeding treatment?
  - What further with his ITI?
  - Further strategy?

Case 1

- Bleeding treatment:
  - rFVIIa to be stopped once trough level measurable
  - rFVIII to be used for bleedings as in “normal” haemophilia
- What further with his ITI?
  - Stop his ITI. His is tolerant now
- Further strategy?
  - Follow him up closely
  - Switch to prophylaxis life long (even in adulthood)
  - Beware of the relapse risk

Case 2

- Severe haemophilia A
  - iFVIII: Max peak 5 BU, starting peak 5 BU
- 7 years old boy after 30 months of LD ITI
  - 50 IU/kg/d of pdFVIII/vWF
  - On-demand aPCC for occasional bleeds
- Currently no excessive bleeds (last 6 mo had only 2 bleeds)
  - His iFVIII 0,35 BU (Nijmegen)
  - His 24-h trough level 1,1%, T1/2 5,5 h
- What is the best for him regarding:
  - Bleeding treatment?
  - What further with his ITI?
  - Further strategy?

Case 2

- Bleeding treatment:
  - rFVIIa to be stopped once trough level measurable
  - FVIII to be used for bleedings as in “normal” haemophilia
- What further with his ITI?
  - Continue with his ITI until normal T1/2 (6-7 h)
- Further strategy?
  - Follow him up closely
  - Switch to prophylaxis life long (even in adulthood) once ITI finished
  - He is still not fully tolerant!

Case 3

- Severe haemophilia A
  - iFVIII: Max peak 100 BU, starting peak 15 BU (after year of waiting)
- 3 years old boy after 20 months of HD ITI
  - 200 IU FVIII/kg/d of rFVIII
  - Prophylaxis with rFVIIa for repeated bleeds
- Currently 1-2 bleeds/month (on rFVIIa prophy)
  - His iFVIII 20 BU (Nijmegen) and has not lowered during last 8 months
  - His 24-h trough level 0,3%, T1/2 very low
- What is the best for him regarding:
  - Bleeding treatment?
  - What further with his ITI?
  - Further strategy?

Case 3

- Bleeding treatment:
  - Continue with rFVIIa prophylaxis
  - Consider aPCC if break-through bleeds on proper rFVIIa treatment
- What further with his ITI?
  - Continue with his ITI but think about switch to pdFVIII/vWF and/or consider rituximab
  - Stopping ITI with by-pass prophylaxis only is unlikely choice in this age group and bleeding pattern
- Further strategy?
  - He has not responded to the therapy given so far
  - Certain change is desirable
  - He may fail an ITI, but give him a chance!