Starting and stopping ITI

Jan Blatný
Department of Paediatric Haematology
Children’s University Hospital
Masaryk University
Brno, Czech Republic

Starting and stopping ITI

- Starting and/or stopping ITI is always:
  - Primarily a 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?

- Start ITI regardless of titre (<10 BU) if
  - Waiting period > 1-2 years
  - Severe/life-threatening bleeds occurs

NB: Both (pPCC 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 <15BU
  - If bleeding complications: increase dose in stages up to 200IU/kg FVIII daily to control bleeds
- 100 IU/kg FVIII daily
  - Historical peak <200 BU AND
  - Starting titre <10BU
- 200 IU/kg FVIII daily
  - Historical peak >200 BU AND/O R
  - Starting titre >10BU

Collins et al., B.J.H. 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/PCC 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?)


The best for him regarding:

- 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

Criteria to stop ITI:
Negative titre (Nijmegen method) AND
Normal recovery: ≥66% of expected AND
Normal T1/2: ≥6h

Phase 1: Start to negative titre

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<th>LD</th>
<th>n</th>
<th>HD</th>
<th>p</th>
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<td>29</td>
<td>9.2 (4.9-17.0) Mo</td>
<td>31</td>
<td>4.6 (2.8-13.8) Mo</td>
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Phase 2: Negative titre to normal recovery

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<tr>
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<td>13.6 (8.7-19.0) Mo</td>
<td>23</td>
<td>6.9 (3.5-12.0) Mo</td>
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Phase 3: Normal recovery to tolerance

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<tbody>
<tr>
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<td>15.5 (10.8-22.0) Mo</td>
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<td>10.8 (6.3-20.5) Mo</td>
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I-ITI study success definitions

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

Successful tolerance: Negative inhibitor titre, FVIII recovery ≥90% of expected, and FVIII recovery ≥90%
Partial response: After ≥30 min of ITI, negative inhibitor titre but persistently abnormal recovery or half-life; responding clinically to FVIII replacement without an acute increase in inhibitor titre
Study failure: Failure of the inhibitor to decline by ≥30% over any 60 min period after the first dose of immune tolerance induction (ITI) or failure to achieve tolerance or partial response after two doses or more of ITI or withdrawal from the study for any reason before tolerance was achieved
Relapse: Inhibitor recurrence during the 15 to 60 min follow-up periods after inhibitor tolerance was achieved, as evidenced by recurrent positive Bethesda titre or a decrease in FVIII recovery or half-life below study limits

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 of iFVIII
  - 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:**
  - rFVII 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

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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?

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Case 2

- **Bleeding treatment:**
  - rFVII 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 rFVII
      - Prophylaxis with rFVIII for repeated bleeds
  - Currently 1-2 bleeds/month (on rFVII proph)
    - 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?

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Case 3

- Bleeding treatment:
  - Continue with rFVII 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!