Bleeding prevention and treatment prior to, during and after ITI

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How to treat inhibitor patients?

- **ITI is the first-line treatment in children**
  - Commenced during 1st year after inhibitor development
  - In adults ITI applied remarkably less often
  - Auerswald et al., Haemophilia 2004
- **Prophylaxis prior to, during (and perhaps also outside) ITI**
  - aPCC
  - rFVIIa
- Long-time/life-long on demand (OD) treatment with:
  - hFVIIIa
  - aPCC
  - Porcine FVIII (seldom in these days)
  - High dose of FVIII
  - Auerswald et al., Haemophilia 2004
  - Bruckmann et al., Blood Coagul Fibrinolysis, 2000
  - Morfini et al., Haemophilia 2007

Bleeding treatment PRIOR to ITI
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”

Recommended dosing: Either 3 x 90ug/kg or 1x270 ug/kg rFVIIa per bleed. Higher single dose may decrease the cost, early administration (<2h) decreases re-bleeding rate

Sahaj et al., Haemophilia 2009; 15(3) 752-9

By-passing agents during ITI

CONTRADICTORY statements?

• Prophylaxis during ITT using rFVIIa failed to show favourable results compared to aPCC
  - Brackmann et al., Blood Coagul Fibrinolysis, 2000

• Prophylaxis with rFVIIa considerably reduced bleedings compared to previous treatment.
  - Eight/nine patients were satisfied or very satisfied with rFVIIa treatment
  - Subjective quality of life (Qol.) was improved, much improved, or significantly improved
  - Morfini et al. Haemophilia 2007
Bleeding prevention during ITI with aPCC

At the time of introduction of Bonn protocol aPCC was the only available bypassing agent.

Oldenburg J. Vox Sang 1999; 77 Suppl 1:49-54.

**Bonn Protocol**

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Phase</th>
<th>FVIII U/kg</th>
<th>aPCC U/kg</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>1</td>
<td>100</td>
<td>50</td>
<td>BID until &lt; 1 OU**</td>
</tr>
<tr>
<td>2</td>
<td>150</td>
<td></td>
<td></td>
<td>BID until normal R/S</td>
</tr>
</tbody>
</table>

* For patients with high bleeding tendency
** Oxford units, correspond to about 1 BU

First report

- 4 year boy, severe haemophilia A with inhibitors (116 BU peak)
- ITI (100 U/kg/d) rFVIII
- 9 weeks with 19 severe bleeds, treated on demand (90 µg/kg/d). Bleds led to immobility (wheelchair)
- 21 weeks on rFVIIa prophylaxis (90 µg/kg/d) resulted in significant decrease of bleedings (7 bleed) and return to kindergarten free of wheelchair

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Frequency of bleeds</th>
<th>Days of immobility</th>
<th>Injections of rFVIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>On demand</td>
<td>2.1</td>
<td>6.0</td>
<td>8.4</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>0.4</td>
<td>1.1</td>
<td>7.8</td>
</tr>
</tbody>
</table>

Saxon et al. Thromb Haemost 2001; 86: 1126-7

By-passing agents out of ITI
Bleeding prophylaxis in inhibitor patients

- rFVIIa administered prophylactically can reduce bleeding rate in 48-52%
  - No matter what is the relation to ITI
  - In adults and children
  - At median individual dose of 133-185 ug/kg
  - At dosing frequency from 3-7 /week
  - No thrombotic complication
    » Young et al., Thrombosis research 2012
- aPCC prophylaxis is well tolerated in children, even when failed ITI
  - 60-100 IU aPCC/dose on different dosing regimens based on bleeding pattern
  - Mean annual bleeding rate of 1.5/year
  - No serious thrombotic complications (only associated with venous access)
    » Ettinghausen et al. Haemophilia 2010 16(1) 90-100

On-demand treatment for inhibitor patients

- rFVIIa
  - 3x90 or 1 x 270 ug/kg
  - See comments related to “prior ITI”
  - More convenient
  - Safe
- aPCC
  - 50-100 IU/kg
  - Many decades of experience
  - Less convenient (?)
  - Safe (?)
- Non responsive bleedings?
  - Combination/alteration of rFVIIa and aPCC

SUMMARY I

Bleeding prevention and treatment prior to ITI

- International Consensus for ITI recommends rFVIIa for treatment of bleeding episodes in haemophilia patients planning to undergo ITI
- rFVIIa may improve the success of ITI by decreasing and maintaining low inhibitor titres prior to initiation of ITI
- Avoiding anamnestic response should be the goal of therapy prior to ITI as it will increase the success rate and cost-effectiveness of ITI.
Bleeding prevention and treatment during/after ITI

- Bypassing agents (both aPCC and rFVIIa) are recommended for the treatment of bleeding episodes during ITI.
- aPCC has been used in that way for many decades successfully and safely.
- Latest reports confirm that rFVIIa is effective and safe for prophylaxis during ITI, decreasing the frequency of bleeds and increasing QoL.
- rFVIIa is recombinant and thus carries no known risk of any blood borne infections and thus might be the treatment of choice for all "plasma naive" children with inhibitors.