Perspectives for Joint Health in Patients with Hemophilia and Inhibitors

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A significant difference in bleeding frequency between inhibitor and non-inhibitor patients has not been demonstrated so far but the management of bleeding episodes in the presence of high-titer inhibitors is more problematic.

Inhibitor patients develop chronic and progressive arthropathy earlier and more frequently than non-inhibitor peers.

Prophylaxis as intended for non-inhibitor patients is not possible.

**Clinical examination**

<table>
<thead>
<tr>
<th></th>
<th>Pts with INH (n=38) Mean age 26 yrs</th>
<th>Pts without INH (n=49) Mean age 25 yrs</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major joints</td>
<td>14.6 (+ 12.2)</td>
<td>5.27 (+ 6.2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>All joints</td>
<td>15.4 (+ 13.6)</td>
<td>5.46 (+ 7.1)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Radiological evaluation**

<table>
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<tr>
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<th>Pts with INH (n=38) Mean age 26 yrs</th>
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<tr>
<td>Major joints</td>
<td>22.9 (+ 14.3)</td>
<td>8.0 (+ 10.2)</td>
<td>&lt;0.05</td>
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</table>

Morfini et al. Haemophilia 2007;13:606-12
Delaying treatment of bleeding episodes leads to increased short- and long-term tissue and joint damage and pain. This may lead to unnecessary use of clotting factors, and may impact on daily activities and quality of life.

Clinical guidelines for hemophilia emphasise the importance of rapid bleeding control, ideally by initiating treatment within 2 hours of the onset of bleeding.

European Principles of Hemophilia Care - Colvin et al Haemophilia, 2008; 14:361-374
WFH Guidelines for the management of Hemophilia. 2013
Importance of rapid bleeding control in hemophilia with inhibitors

Delayed treatment is associated with:

- Poorer bleeding control
- Use of more clotting factor concentrates

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose (µg kg⁻¹)</th>
<th>Mean interval from onset of bleeding to first treatment with rFVIIa</th>
<th>Percentage achieving excellent or effective response</th>
<th>Mean number of doses rFVIIa given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compassionate use</td>
<td>60–120</td>
<td>5 days</td>
<td>63.1 (compartment syndrome 73)</td>
<td>13.6 (compartment syndrome 64.8)</td>
</tr>
<tr>
<td>Dose-finding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) 70</td>
<td></td>
<td>9 h</td>
<td>72</td>
<td>3.6</td>
</tr>
<tr>
<td>(b) 35</td>
<td></td>
<td>9 h</td>
<td>53</td>
<td>3.5</td>
</tr>
<tr>
<td>US home treatment</td>
<td>90</td>
<td>1.2 h</td>
<td>92</td>
<td>2.3*</td>
</tr>
</tbody>
</table>

Muscles

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose (µg kg⁻¹)</th>
<th>Mean interval from onset of bleeding to first treatment with rFVIIa (range)</th>
<th>Percentage achieving excellent or effective response</th>
<th>Mean number of doses of rFVIIa given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compassionate use</td>
<td>60–120</td>
<td>2.5 days (0.3–20.7 days)</td>
<td>61</td>
<td>22</td>
</tr>
<tr>
<td>Dose-finding</td>
<td></td>
<td></td>
<td></td>
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<td>13.2 h</td>
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</table>

Joints

Lusher JM Blood Coagul Firbinolysis 2000; 11 (suppl 1): S45-S49
Lusher JM Eur J Haematol 1998;63:7-10
Great inter- and intra-patient variability of treatment efficacy

- rFVIIa: success rates of **74-92%** with 3*90 mcg/kg (mild/moderate joint bleeds; *home*)
- Efficacy and risk of re-bleeding is greatly dependent on the rapidity of treatment onset

![Graph showing time from onset of bleed to first rFVIIa dose (hours) and proportion of re-bleed after 24 hours.](chart)

- Time from onset of bleed to first rFVIIa dose (hours):
  - Effective (79%): 0.6 h, n=42
  - Partially effective/failure (21%): 2.7 h, n=11
  - **p=0.02**

- Proportion of re-bleed after 24 hours:
  - Time to treatment ≤2h: 5.2%
  - Time to treatment >2h: 13.7%

References:

- Sjamsoedin et al. NEJM 1981;305:717-21
- Key et al. TH 1998;80:912-8
- Santagostino et al BJH 1999;104:21-6
- Santagostino et al. JTH 2006;4:367-71
- Kavakli et al. TH 2006;95:600-5
Preventing bleeding recurrence

- Bleeding recurrence leads to the development of *target joints* which are not only difficult to treat but also a relevant cause of morbidity and long-term sequelae in patients with inhibitors, especially in children.

- Preventing re-bleeding may be targeted by prolonging treatment for a finite period of time to cover the vulnerability after bleeding in target joints or muscles.

Treat fast and properly
Criteria for defining joint/muscle bleeding episodes that are non-responsive to bypassing agents (24 h from treatment start)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Subjective assessments*</th>
<th>Objective assessments*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>• Persistence or worsening of pain (with and without analgesics), reported by patient/parent via global self-assessment or VAS</td>
<td>• Persistence or worsening of pain, evaluated by physician assessment</td>
</tr>
<tr>
<td></td>
<td>• Non-responsiveness to analgesics, reported by patient/parent</td>
<td>• Need for analgesics</td>
</tr>
<tr>
<td>Swelling/tension</td>
<td>• Increase or persistence in swelling, reported by patient/parent</td>
<td>• Non-responsiveness to analgesics, evaluated by physician assessment</td>
</tr>
<tr>
<td>Mobility</td>
<td>• Decrease in mobility, reported by patient/parent</td>
<td>• Increase or persistence in swelling or tension relative to baseline, evaluated by size measurements or physician assessment</td>
</tr>
<tr>
<td>Patient perception</td>
<td>• Patient report of the sense of continuance of bleeding</td>
<td>• Decrease in mobility, evaluated by goniometric ROM measurements or physician assessment</td>
</tr>
</tbody>
</table>
**rFVIIa**

- **PROS**
  - Well tolerated
  - Home treatment
  - No anamnestic response
  - Recombinant technology
  - Small volumes

- **CONS**
  - Short half-life (repeated boluses)
  - No optimal dose/regimen
  - No lab monitoring
  - Thrombotic risk
  - High cost

- **Able to trigger a thrombin burst when bound to Tissue Factor**

- **Able to activate FX when bound to activated platelets even in the absence of Tissue Factor**

- **Licensed dosages:** 90-120 mcg/kg every 2-3 h; 270 mcg/kg (single high dose)
• **Dose:** The recommended initial dose is 90-120 μg/Kg repeated at least 3 times. The duration of treatment and the interval between injections will vary with the severity of the haemorrhage.

• **Dose interval:** initially 2-3 hours to obtain haemostasis. If continued therapy is needed, the dose interval can be increased successively once effective haemostasis is achieved to every 4, 6, 8 or 12 hours for as long as treatment is judged as being indicated.

• **Dosing in children:** current clinical experience does not warrant a general differentiation, although children have faster clearance than adults. Therefore, higher doses of rFVIIa may be needed in children to achieve similar plasma concentrations as in adults.
Fast pain relief and early mobilization

- Efficacy was rated on relief of swelling, pain and mobility

- “Effective” treatment courses were started significantly earlier after the onset of bleed (0.6 vs 2.7h; p=0.02)

rFVIIa was given at **90 mcg/kg every 3 +/- 1 hours** for up to 4 injections **starting < 12 hours** from symptoms onset

Reduced risk of re-bleeding

- The risk of re-bleeding into the same joint after home treatment with rFVIIa was 4%-5% after 24 hours.

- Data from the HemoRec registry show a reduced rate of re-bleed when treatment was initiated within 2 hours (5.2 vs 13.7%).

Patients with inhibitors: different challenges at different ages

- Primary prophylaxis as intended for non-inhibitor patients is not possible
- Usually treated with ITI
- May develop arthropathy while waiting for inhibitor eradication

- Chronic synovitis
- Prophylaxis can be attempted
- Chronic pain, stiffness, muscle atrophy

- Severe arthropathy
- Usually treated on demand
- Chronic pain, fixed flexion contracture, stiffness, disability

How to assess MSK status?
What to do?

ITI, immune tolerance induction; MSK, musculoskeletal
Patients with inhibitors: different challenges at different ages

- Regular physical examination (HJHS)
- US/MRI??
- Physical exercise/FKT
- Treat promptly and adequately in case of bleed
- Prophylaxis??

- Regular physical examination (HJHS)
- Assessment of target joints
- X-Rays/US/MRI??
- Regular physical exercise/physiotherapy
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- **Orthopaedic surgery**

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- Assessment of target joints
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HJHS, Hemophilia Joint Health Score; MRI, magnetic resonance imaging; US, ultrasound
By-passing therapy in the surgical setting

✓ rFVIIa has been successfully used to cover major and minor orthopedic and non-orthopedic surgical procedures in inhibitor patients

Hemostatic efficacy in 50 orthopedic procedures [46 major] and 151 non-orthopedic procedures covered with **rFVIIa**

✓ Different dosing regimens have been used
✓ rFVIIa continuous infusion has been used with controversial results

Santagostino et al. Blood Reviews 2015;29(S1):S9–18
Both aPCC and rFVIIa have been used to prevent bleeding episodes and reduce bleeding frequency with good results although not comparable to standard prophylaxis in non-inhibitor patients.

In the PRO-PACT study a 50% reduction in bleeding frequency was observed.

Konkle et al. JTH 2007;5:1904–13
Leissinger et al. NEJM 2011;365:1684–92
Young et al. Thromb Res 2012;130:864-70
By-passing therapy: ongoing issues

Optimal dosing

- HTRS registry – median total dose/bleed
  - < 100 mcg/kg
  - 100-150 mcg/kg
  - 150-200 mcg/kg
  - >200 mcg/kg

- ONE registry – median initial dose
  - <120 mcg/kg
  - 121-249 mcg/kg
  - >250 mcg/kg

Laboratory monitoring

- aPCC U/ml
- rFVIIa mcg/ml

Parameswaran et al. Haemophilia 2005;11:100-6
Turecek et al. Pathophysiol Haemost Thromb 2003;33:16-22