Inhibitors in children and in adults
Why they are different and what do they have common?

Jan Blatny, MD, PhD
Petr Smejkal, MD, PhD

Depts. of Paediatric/Clinical Haematology
Centre for Thrombosis and Haemostasis
University Hospital Brno, Czech Republic

Introduction

Inhibitors in haemophilia

• The development of inhibitors is one of the most serious complications of the treatment in patients with haemophilia
  - Brackmann et al., Eur J Haematol Suppl, 1998
• They develop in 4-20% of HA patients with the percentage rising up to 52% in certain populations
  - Manno, Haemophilia, 1999
• Less frequent in HB: 1,5-3% only –“orphan disease”
  • Lack of useful evidence on treatment outcome predictors, risk factors, diagnosis and treatment
  • Frequent allergic reactions, nephrotic syndrome
  - Di Michele, Br J Haematol, 2007
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

- **Bleeding prophylaxis prior to, during (and perhaps also outside) ITI**
  - rFVIIa
  - aPCC

- **Long-time/life-long on demand (OD) treatment with:**
  - rFVIIa
  - aPCC
  - Porcine FVIII (seldom in these days)
  - High dose of FVIII

Inhibitors in children

**ITI – first line treatment**

- Malmo
  - Cost effective
  - Relatively quick
  - Uses immune adsorption and perhaps immune suppression
  - Not the “treatment of choice” in these days
  - Auerswald et al., Haemophilia 2004
  - Brackmann et al., Blood Coagul Fibrinolysis, 2000
  - Morici et al., Haemophilia 2007

- Bonn
  - Relatively expensive
  - May take up to 3 years
  - Recommended especially for high titre inhibitors
  - Brackmann et al., Blood Coagul Fibrinolysis, 2000

- Low(d)er dose regimen
  - Relatively cheap
  - Effective enough
  - May take long time, but seldom with complications
  - CVL less imperative
  - Di Michelle et al, Thromb Haemost, 2002; Smith, Pathophysiol Haemost Thromb, 2002
  - Bleedings treated with by-passing agents (nowadays rFVIIa, aPCC)

- In average
  - Effective in up to 95% of cases
ICP recommendations – When to start?

The International Consensus Panel (ICP)
Donna DiMichele, Chair

Charles Hay                          Keith Hoots
Thiery Lambert                      Johannes Oldenburg
David Lillicrap                     Mike Recht
Steve Pipe                          Georges Rivard
Mark Reding                         Elena Santagostino
Chantal Rothschild

DiMichele DM et al., Haemophilia. 2007;13 Suppl 1:1-22

International ITI Workshops – (Jun&Sep, 2006)

Preferred start of ITI if titre < 10 BU

When to start?

Wait until Inh titre < 10 BU

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 year
- Severe/life-threatening bleeds occur
- NB: Both (xPC and rFVIIa) recommended if bleeding occurs

DiMichele DM et al., Haemophilia. 2007;13 Suppl 1:1-22

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”

I - ITI study

- Compared two ITI strategies (in HA)
  - HD (200IU/kg daily) vs. LD (50IU/kg thrice/week)
  - In good risk, severe, high titer HA inhibitor pts.
- **No difference in success rate**
  - (24/58 LD vs. 22/57 HD, p=0.909)
  - Shorter time to achieve neg. titer (p=0.027), normal recovery (p=0.002) and tolerance (p=0.018 NS) in HD group
- **Peak inhibitor titers correlated inversely with success rate**
  - Historical peak (p=0.026), on-ITI peak (0.002)
  - ONLY on-ITI peak predicted outcome (p=0.002)
- LD subjects bled more often (p=0.0019, OR 2.2)
  » Ch Hay and D Di Michelle, Blood 2011

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Inhibitors in Haemophilia B

- Rare & less understood disease, mostly in severe HB patients
- High morbidity, difficult to treat
- Severe allergic reactions
  - Difficult to treat with aPCC (contains FIX)
    » rFVIIa only available for bleeding treatment
      » Effective also for prophylaxis
        » Hay et al. BJH 2006
  - Nephrotic syndrome might complicate the disease
- ITI in HB to be considered carefully

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ITI in Haemophilia B

- Poor overall success rate (25%)
- High risk of complication
  - Allergy, anaphylaxis, nephrotic syndrome
- Need for immune suppression to decrease risk of complications and increase success rate
  - E.g. Mycophenolate mofetil (MMF) + dexamethasone (DEXA) + IvIG
    » Wermes et al. Blood 2000
    » Klamann et al. Haemophilia 2008
- Low iFIX titre before the ITI start and some way of bleeding prophylaxis is favourable
Question 1

What will you prefer for the treatment of 2 yrs old severe HA boy with HR inhibitors?
- A) Increase the dose of FVIII
- B) ITI protocol
- C) By-pass medication on demand
- D) Prophylaxis with By-pass, but no ITI

Question 2

Which ITI regimen will you choose for 3yrs old HA boy with peak inhibitor titre 450 BU and pre-ITI titer 15 BU?
- A) I will not go for ITI as this a poor risk patient
  - Will continue on By-pass Tx/Prophy
- B) I will choose LD regimen
- C) I will go for HD regimen

Question 3

Do you have experience with bleeding prophylaxis with By-pass medications?
- Either within or without ITI
- A) Yes
- B) No
Inhibitors in adults

Registries – results and success prediction

<table>
<thead>
<tr>
<th>Registry</th>
<th>N</th>
<th>Dose of FVIII IU/kg/D</th>
<th>Success (%)</th>
<th>Time to remission (months)</th>
<th>Prediction of success ($P &lt; 0.05$)</th>
<th>Age at ITI start (TI start)</th>
<th>Inhibitor titre (TI titre)</th>
<th>FVIII mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITR</td>
<td>314</td>
<td>≤50 - ≥200</td>
<td>51</td>
<td>10.5</td>
<td>Median</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>NAI TR</td>
<td>164</td>
<td>50 - 200</td>
<td>63 HR</td>
<td>16.3</td>
<td>Mean</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>GITR</td>
<td>126</td>
<td>≥ 200</td>
<td>76 HR</td>
<td>7.6-15.5</td>
<td>Mean</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>38</td>
<td>100 - 200</td>
<td>63 HR</td>
<td>9.85</td>
<td>Median</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>PROFIT</td>
<td>103</td>
<td>median</td>
<td>86 HR</td>
<td>Median</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Is ITI accessible for all patients with inhibitor?

- In 1990s – NAITR:
  - 36% (188/518) received ITI
  * Di Michele. Thromb Haemost 2002; 87: 52-7

- After 2000 – Italian ITI Registry:
  - 54% received ITI
    - 88% (65/74) < 14 years
    - 26% (23/88) > 14 years
  * Coppola A. Hemophilia 2012; 18 (Suppl. 3): 88
Prognostic factors of ITI success: Age and time from inhibitor detection to ITI

- **Age:**
  - < 5 years
    - Hay, Pathophysiol Haemost Thromb 2002; (Suppl 1) 19-21
  - < 20 years
    - > 5 years: 70% (38/54)
    - 5 – 10 years: 73% (33/45)
    - 11 – 20 years: 78% (36/46)
  - > 20 years
    - Mafi 2003; Thromb Haemost 2003; 89:75

- **Interval between diag of iFVIII and start of ITI < 5 years**
  - ITF (1997) success
  - iFVIII pre-ITI < 10 BU / ml
  - dose of iFVIII >100 BU / kg / D
  - 65% tolerance till 1 year
  - Without these three criteria:
    - 65% success rate was not achieved for at last 31 months

ITI results in adult patients from the Spanish registry

<table>
<thead>
<tr>
<th>Patient</th>
<th>Inhibitor titre (BU/ml)</th>
<th>Time from inhibitor det. to ITI (months)</th>
<th>Age at start of ITI (years)</th>
<th>FVIII IU/kg/day</th>
<th>Time to inhibitor elimination (months)</th>
<th>Inhibitor after ITI (BU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>-</td>
<td>16</td>
<td>1</td>
<td>25</td>
<td>CR 26/38 (68%)</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>-</td>
<td>21</td>
<td>5</td>
<td>3</td>
<td>CR 67 (86%)</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>8</td>
<td>60</td>
<td>20</td>
<td>4</td>
<td>CR 179</td>
</tr>
<tr>
<td>4</td>
<td>76</td>
<td>17</td>
<td>10</td>
<td>20</td>
<td>4</td>
<td>CR 75</td>
</tr>
<tr>
<td>5</td>
<td>121</td>
<td>7</td>
<td>60</td>
<td>50</td>
<td>7</td>
<td>CR 6</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>2</td>
<td>108</td>
<td>20</td>
<td>8</td>
<td>CR 0.5</td>
</tr>
<tr>
<td>7</td>
<td>192</td>
<td>22</td>
<td>228</td>
<td>39</td>
<td>4</td>
<td>CR 179</td>
</tr>
<tr>
<td>median</td>
<td>41</td>
<td>12</td>
<td>84</td>
<td>32</td>
<td>4</td>
<td>CR 67 (86%)</td>
</tr>
<tr>
<td>All: 1-3B</td>
<td>67</td>
<td>11</td>
<td>25</td>
<td>140</td>
<td>10</td>
<td>CR 26/38 (68%)</td>
</tr>
</tbody>
</table>

*Hay S. Haemophilia 2001; 7:154-159*

ITI results in adult patients with VWF/FVIII: ≥ 1 poor prog: FVIII ≥ 6 years, > 1 year from inhibitor development, 200 BU hist. peak, > 10 BU pre-ITI, previously failed ITI

<table>
<thead>
<tr>
<th>Patient</th>
<th>Inhib. titre (BU/ml)</th>
<th>Time from inhibitor det. to ITI (years)</th>
<th>Age at ITI start (years)</th>
<th>FVIII IU/kg/day</th>
<th>ITI duration (months)</th>
<th>Inhibitor after ITI (BU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>5</td>
<td>6</td>
<td>45</td>
<td>3x weekly 50</td>
<td>11 &lt; 0.5</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>6</td>
<td>18</td>
<td>3x weekly 50</td>
<td>21 1.22 - PR</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>5</td>
<td>13</td>
<td>3x weekly 50</td>
<td>4 &gt; 0.5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>128</td>
<td>6</td>
<td>22</td>
<td>100</td>
<td>33 2.2 - PR</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>737</td>
<td>4</td>
<td>18</td>
<td>53</td>
<td>3x weekly 50</td>
<td>25 &lt; 0.5</td>
</tr>
<tr>
<td>6</td>
<td>110</td>
<td>5</td>
<td>33</td>
<td>54</td>
<td>100 12 &lt; 0.5</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>93</td>
<td>2</td>
<td>14</td>
<td>24</td>
<td>3x weekly 50</td>
<td>9 &lt; 0.5</td>
</tr>
<tr>
<td>8</td>
<td>56</td>
<td>5</td>
<td>1</td>
<td>30</td>
<td>3x weekly 50</td>
<td>12 70 - Failure</td>
</tr>
<tr>
<td>9</td>
<td>94</td>
<td>14</td>
<td>10</td>
<td>31</td>
<td>100 12 &lt; 0.5</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>64</td>
<td>5</td>
<td>14</td>
<td>33</td>
<td>21.3 12</td>
<td>CR 6/9 (67%) PR 2/9 (22%)</td>
</tr>
<tr>
<td>Median children</td>
<td>56</td>
<td>6.5</td>
<td>6</td>
<td>13</td>
<td>100 28.5</td>
<td>CR 3/8 (37.5%) PR 5/8 (62.5%)</td>
</tr>
<tr>
<td>All: 1-17</td>
<td>54</td>
<td>5</td>
<td>8</td>
<td>23</td>
<td>25 23</td>
<td>CR 9/17 (53%) PR 7/17 (41%)</td>
</tr>
</tbody>
</table>
### ITI results in adult patients

**Association of clinical outcome with inhibitor epitope profile**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Inhibitor titre (BU/ml)</th>
<th>Time from inhibitor dg. to ITI (months)</th>
<th>Age at start of ITI (years)</th>
<th>FVIII (IU/kg/week)</th>
<th>ITI duration (months)</th>
<th>Inhibitor after ITI (BU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150</td>
<td>8</td>
<td>210</td>
<td>20</td>
<td>300</td>
<td>9 &lt; 0.6</td>
</tr>
<tr>
<td>2</td>
<td>89</td>
<td>4</td>
<td>4</td>
<td>37</td>
<td>150</td>
<td>28.5 &lt; 0.6</td>
</tr>
<tr>
<td>3</td>
<td>288</td>
<td>1.4</td>
<td>207.5</td>
<td>22</td>
<td>300</td>
<td>16.2 &lt; 0.6</td>
</tr>
<tr>
<td>Median</td>
<td>150</td>
<td>4</td>
<td>207.5</td>
<td>22</td>
<td>300</td>
<td>16.2 CR 3/3 (100%)</td>
</tr>
<tr>
<td>1-7 median</td>
<td>89</td>
<td>5</td>
<td>16</td>
<td>8.2</td>
<td>700</td>
<td>22.75 CR 5/7 (71%) PR 2/7 (29%)</td>
</tr>
</tbody>
</table>

*Gringeri A. Haemophilia 2008;14:295‐302

### ITI results in adult patients - Hungary

<table>
<thead>
<tr>
<th>No.</th>
<th>age (years) mean</th>
<th>Inhibitor titre (BU/ml)</th>
<th>FVIII dose (IU/kg/day) mean</th>
<th>Time to inhibitor elimination (months) success</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>31.8</td>
<td>139.8</td>
<td>52.6</td>
<td>5.4 CR 5/7 (71%)</td>
</tr>
</tbody>
</table>

*Nemes L. 4th Inhibitor Workshop for Opinion Leaders in Haemophilia, Dubrovnik 2006

### Cost of care analysis for ITI in adult patients: comparison with rFVIIa ObsITI study: Russian experience

<table>
<thead>
<tr>
<th>No. of bleeds per year median</th>
<th>Dose of rFVIIa for one bleeding median</th>
<th>ITI dose of FVIII</th>
<th>CR time to CR median</th>
<th>Cost 10 years rFVII (mil. €)</th>
<th>Cost 10 years: rFVII + prophyl (mil. €)</th>
<th>Saved during 10 years (mil. €)</th>
<th>Break-even point ITI + FVIII prophyl. vs. 10 years on demand rFVII</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2</td>
<td>26</td>
<td>4 x 96 μg/kg</td>
<td>100-150 U/kg daily to alter d</td>
<td>3 / 3</td>
<td>6.4</td>
<td>2.2</td>
<td>4.2</td>
</tr>
<tr>
<td>≥ 3</td>
<td>26</td>
<td>100-150 U/kg</td>
<td>6.7 / 10 months</td>
<td>3.8</td>
<td>2.8</td>
<td>1</td>
<td>6.8</td>
</tr>
</tbody>
</table>

* Zozulya N. WFH Congress 2010
ITI results in adult patients with inhibitor:
- rate of success

- Spanish registry + Gringeri 2007:
  - 6/7 + 6/9 = 12/16 (75%)

- + Gringeri 2008 + ObsITI:
  - + 3/3 + 5/7 = 20/26 (77%)

- + Nemes 2006:
  - + 5/7 = 25/33 (76%)

- In total: IITR + Spanish registry + Gingeri 2x + Nemes:
  - 44/80 (55%)

Why immune tolerance induction?

Factor substitution is better than bypassing activities:
- Higher efficiency of haemostatic treatment:
  - Haemostatic effect with FVIII/FIX is kept for longer time than using by-passing activities
- Simple monitoring
- Lower cost of treatment:
  - Treatment of bleeding episodes 10x
  - Surgery 20x
  - Prophylaxis

Treatment of bleeding episodes in patients with inhibitor - registries
(rFVIIa 1 μg = 0.67 €)

<table>
<thead>
<tr>
<th>registry</th>
<th>No. of bleed s</th>
<th>rFVIIa per bleeding episode</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>haemarthroses</td>
<td>children</td>
<td>adults</td>
</tr>
<tr>
<td>HTTRS + Grangeri + FVIIA</td>
<td>2041</td>
<td>median 480 μg/kg</td>
<td>median 480 μg/kg</td>
<td>median 270 μg/kg</td>
</tr>
<tr>
<td>DOSE + Ra + FVIIA</td>
<td>158</td>
<td>Children: median 1245 μg/kg</td>
<td>adults: median 900 μg/kg</td>
<td>median 442 μg/kg</td>
</tr>
<tr>
<td>ONE + Santagostino</td>
<td>494</td>
<td>Children: median 192 μg/kg</td>
<td>Adults: median 270 μg/kg</td>
<td>median 193 μg/kg</td>
</tr>
<tr>
<td>HemosRec + Santagostino</td>
<td>128</td>
<td>median 193 μg/kg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Surgery (major/orthopaedic) in patient with inhibitor (rFVIIa 1 µg = 0.67 €)

<table>
<thead>
<tr>
<th>Initial bolus</th>
<th>Day 1 - 2</th>
<th>Day 3 – 4</th>
<th>Day 5 - 7</th>
<th>Day 8 till 10 – 14</th>
<th>Day 15 - 21</th>
<th>In total</th>
</tr>
</thead>
<tbody>
<tr>
<td>(rFVIIa) 90 – 180 µg/kg</td>
<td>90 µg/kg ä 2 h</td>
<td>90 µg/kg ä 3 h</td>
<td>90 µg/kg ä 4 h</td>
<td>1 080 µg/kg to 2 520 µg/kg</td>
<td>630 µg/kg à 6 h</td>
<td>7 740 µg/kg to 9 120 µg/kg</td>
</tr>
<tr>
<td>In total</td>
<td>90 – 180 µg/kg</td>
<td>2 160 µg/kg</td>
<td>2 160 µg/kg</td>
<td>1 620 µg/kg</td>
<td>90 µg/kg</td>
<td>90 µg/kg à daily</td>
</tr>
</tbody>
</table>

Adult patient, 75 kg – 400 000 - 450 000 €

* Rodriguez-Merchan EC. Haemophilia 2004; 10 (Suppl. 2): 50-52
* Giangrande PLF. Haemophilia 2009; 15: 501-8

Immune tolerance induction (cost)

- adult patient 75 kg
- 1 IU pdFVIII = 0.63 € (price in Germany 2004)
- 1 IU rFVIII = 0.79 €

<table>
<thead>
<tr>
<th>Consumption per 1 year</th>
<th>FVIII (IU)</th>
<th>€</th>
</tr>
</thead>
<tbody>
<tr>
<td>low responder</td>
<td>50 IU / kg / D</td>
<td>1 368 750</td>
</tr>
<tr>
<td>rFVIII: 1 081 312</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pdFVIII: 862 312</td>
<td></td>
<td></td>
</tr>
<tr>
<td>high responder</td>
<td>200 IU / kg / D</td>
<td>5 475 000</td>
</tr>
<tr>
<td>rFVIII: 4 325 250</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pdFVIII: 3 449 250</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cost-effectiveness of ITI, 4 patients, 75 kg, success 75%:
(Czech Republic: FVIII 1 IU = 0.4 €, rFVIIa 1 µg = 0.67 €)

<table>
<thead>
<tr>
<th>Daily dose of FVII</th>
<th>FVIII dose per year</th>
<th>FVIII dose per year per 75 kg</th>
<th>Cost of FVIII per year</th>
<th>Cost of FVIII per 18 months of ITI</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 IU/kg</td>
<td>36 500 IU/kg</td>
<td>2 737 500 IU</td>
<td>1 095 000 €</td>
<td>1 642 500 €</td>
</tr>
<tr>
<td>150 IU/kg</td>
<td>54 750 IU/kg</td>
<td>4 106 250 IU</td>
<td>1 642 500 €</td>
<td>2 463 750 €</td>
</tr>
<tr>
<td>200 IU/kg</td>
<td>73 000 IU/kg</td>
<td>5 475 000 IU</td>
<td>2 190 000 €</td>
<td>3 285 000 €</td>
</tr>
<tr>
<td>300 IU/kg</td>
<td>109 500 IU/kg</td>
<td>8 212 500 IU</td>
<td>3 285 000 €</td>
<td>4 927 500 €</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bleeds / year</th>
<th>rFVII µg per year</th>
<th>Cost of rFVII per 75 kg</th>
<th>Cost of rFVII per 10 years</th>
<th>4 patients, after ITI saved annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1 500 µg</td>
<td>112 500 µg</td>
<td>75 375 €</td>
<td>15 524 €</td>
</tr>
<tr>
<td>10</td>
<td>3 000 µg</td>
<td>225 000 µg</td>
<td>150 750 €</td>
<td>319 000 €</td>
</tr>
<tr>
<td>20</td>
<td>6 000 µg</td>
<td>450 000 µg</td>
<td>301 500 µg</td>
<td>693 900 €</td>
</tr>
<tr>
<td>40</td>
<td>12 000 µg</td>
<td>900 000 µg</td>
<td>603 000 µg</td>
<td>1 598 400 000 €</td>
</tr>
</tbody>
</table>

After ITI prophylaxis FVIII 45 IU/kg/week:

<table>
<thead>
<tr>
<th>FVIII per year</th>
<th>FVIII / year per 75 kg</th>
<th>Cost of FVIII per year</th>
<th>Cost of FVIII per 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 340 IU/kg</td>
<td>175 500 IU</td>
<td>70 200 €</td>
<td>702 200 €</td>
</tr>
</tbody>
</table>
Question 4

What will you prefer for the treatment of 30 yrs old severe HA man with HR inhibitors persistent from his childhood?
- A) ITI protocol
- B) ITI protocol according to bleeding frequency
- C) By-pass medication on demand
- D) Prophylaxis with By-pass, but no ITI

Question 5

Which ITI regimen will you choose for this 30yrs old HA man with peak inhibitor titer 450 BU and current inhibitor titre 15 BU?
- A) I will not go for ITI as this a poor risk patient
  • Will continue on By-pass
- B) I will choose LD regimen
- C) I will go for HD regimen
- D) I will postpone the initiation of ITI until the inhibitor titre drops down to < 10 BU
  • After that I will go for HD ITI

Question 6

What will you prefer for the treatment of 40 yrs old severe HA man with new diagnosed LR inhibitors?
- A) ITI protocol
- B) high dose of FVIII concentrate
- C) By-pass medication on demand
- D) ITI protocol only if:
  • bleeding cannot be treated with FVIII
Question 7

• Which ITI regimen will you choose for this 40yrs old HA man with LR inhibitor but unsuccessful replacement therapy with FVIII?
  – A) I will choose LD regimen
  – B) I will go for HD regimen
  – C) I will go for Malmö protocol
  – D) I will use immune suppression only

Thank you for your kind attention!

Pasqueflower (Pulsatilla grandis) 10 minutes' walk from our CCC

Rime (white frost) on the fence

On demand or prophylaxis with bypassing agents

Low dose prophylaxis or on demand treatment with FVIII concentrate