Management of Patients with Haemophilia and Inhibitors in Australia

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Inhibitors

- Following the widespread introduction of recombinant clotting factor concentrates, development of inhibitors is the most significant complication affecting the patients with haemophilia.
Inhibitor Patients In Australia

- ABDR data (January 2007)
- Total of patients with past or current inhibitor
  - High 74
  - Low 39
  - Transient 3
  - Total 116
- Tolerised 31
Inhibitor Patients In Australia

- Approximate incidence of High Titre Inhibitors in Australia
  - Severe haemophilia A 14.0%
  - Severe haemophilia B 2.6%
Inhibitors

- Presence of an inhibitor renders clotting factor replacement ineffective

- Management of patients with inhibitors focused on
  - Management of bleeding episodes
  - Eradication of inhibitors (immune tolerance)
Management of Bleeding Episodes

- Bypassing agents
  - Novo VII
  - FEIBA

- Common to these agents
  - Difficult to monitor
  - Risk of thrombosis
  - Reported as being effective in 80 – 90% of bleeding episodes
Management of Bleeding Episodes

FEIBA NovoVII comparative study (FENOC)

- Cross over non blinded trial of single dose FEIBA versus 2 doses Novo VII 2 hours apart
- Primary outcome; patient report of efficacy at 6 hours to be the primary outcome

Table 2. Rates of efficacy by treatment and time point. Efficacy is defined as effective or partially effective by subject rating. The 6-hour time point is the primary outcome.

<table>
<thead>
<tr>
<th>Hours after infusion (N)</th>
<th>FEIBA® (%)</th>
<th>NovoSeven® (%)</th>
<th>90% Confidence Interval§</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2* (48)</td>
<td>75.0</td>
<td>60.4</td>
<td>-0.73%, 29.90%</td>
<td>(p=0.482)</td>
</tr>
<tr>
<td>6 (47)</td>
<td>80.9</td>
<td>78.7</td>
<td>-11.42%, 15.67%</td>
<td>(p=0.059)</td>
</tr>
<tr>
<td>12 (45)</td>
<td>80.0</td>
<td>84.4</td>
<td>-18.08%, 9.19%</td>
<td>(p=0.101)</td>
</tr>
<tr>
<td>24 (42)</td>
<td>95.2</td>
<td>85.7</td>
<td>-1.29%, 20.33%</td>
<td>(p=0.202)</td>
</tr>
<tr>
<td>36 (41)</td>
<td>100.0</td>
<td>90.2</td>
<td>2.13%, 17.38%</td>
<td>(p=0.129)</td>
</tr>
<tr>
<td>48 (41)</td>
<td>97.6</td>
<td>85.4</td>
<td>2.05%, 22.34%</td>
<td>(p=0.325)</td>
</tr>
</tbody>
</table>

*Prior to the second dose of NovoSeven®.

§The 90% confidence interval for the difference in the proportions of subjects’ rating of efficacy for each of the treatments (columns 2 and 3). Rejecting the null hypothesis at the 0.05 level is equivalent, in this setting, to showing that the upper and lower limits of the confidence interval for the difference in efficacy fall within plus or minus 15%.
FENOC study


**Conclusion**

- Similar effect of two products
  - Efficacy may be assessed differently
Management of Bleeding Episodes


- Non responding patients
  - Sequential FEIBA / NOVO VII (within 6 hours of each dose)
    - Retrospective report of 5 children unresponsive to single therapy all had bleeding controlled with sequential therapy
Management of Bleeding Episodes - Surgery


- **Major Surgery**
  - FEIBA 75–100 U/kg every 8 h (not to exceed 200 U/kg per 24-h period.
  - Novo VII 90 μg/kg every 2 h on the day of surgery, then every 4 h for 3 days or as long as necessary.

- **Minor Surgery**
  - FEIBA 75–100 U/kg daily as needed (plus antifibrinolytic for oral surgery) 6 h after the last dose of FEIBA
  - rFVIIa 90 μg/kg every 2 h for three doses (plus antifibrinolytic for oral surgery) 6 h after the last dose of FEIBA
Management of Bleeding Episodes - Prophylaxis

- Reports of both successful reduction in bleeding events for patients managed with prophylaxis with FEIBA and Novo VII

- Pro-FEIBA study
  - Randomised cross over trial comparing 6 months on demand versus 6 months three times per week FEIBA @ 85 units / kg per dose
Immune Tolerance Induction (ITT)

- First described in 1977 with numerous protocols subsequently being developed
  - All rely on frequent exposure to FVIII/FIX +/- immune modulation
  - According to the results from three large ITT registries, 56–79% of patients ultimately respond to ITT
### ITT registries

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Success rate (95% CI)</th>
<th>Reported failure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITR</td>
<td>126</td>
<td>78.6%</td>
<td>16%</td>
</tr>
<tr>
<td>IITR</td>
<td>263</td>
<td>48.7%</td>
<td>25%</td>
</tr>
<tr>
<td>NAITR</td>
<td>130</td>
<td>69.2%</td>
<td></td>
</tr>
<tr>
<td>SR</td>
<td>38</td>
<td>68.4%</td>
<td></td>
</tr>
</tbody>
</table>
ITT Success

Favourable outcome associated with

1. Low titre inhibitor immediately prior to ITT
2. Historical low titre inhibitor
3. Young age?
4. Duration from inhibitor to commencement ITT

Uncertain

- Factor VIII / IX dosage
- Type of clotting factor concentrate
ITT – Dose of FVIII

- International Immune Tolerance Study
  - High dose versus low dose
  - World wide study
  - < 7 years, < 12 months from inhibitor diagnosis
  - Peak titre 5 – 200 BU
  - Randomised to 50 U/kg three times per week or 200 U/kg per day
  - www.itistudy.com
Case reports and small case series of Mabthera (anti CD20 molecule) being effective in the eradication of inhibitors
Potential for immune dysregulation (and lymphoproliferative disorders in later life)

Should not be used as first line ITT (may be helpful in difficult ITT cases)
Inhibitors in FIX deficiency

- Lower frequency (4 – 5%)
- Most are high responder inhibitors
- Occur after a shorter median period
- Unusual clinical features
  - Anaphylaxis to FIX containing products
  - More difficult to ITT
  - May develop nephrotic syndrome during ITT
Tolerisation Advisory Committee (TAC)

- Sub-committee of AHCDO
- To provide clinical advice on cases of immune tolerisation for clinicians managing patients with haemophilia and inhibitors in Australia
- To monitor the ongoing progress of cases of patients with haemophilia and inhibitors within Australia
- To liaise with the supplying agencies (NBA) regarding upcoming cases immune tolerisation cases
- Encourage cases of immune tolerance to be included in clinical trials
- Telephone conferences will be held between members of the TAC every month and arranged by the Chair of the TAC with assistance from the Project Officer AHCDO.