Assessment of long term safety and efficacy of clotting factor concentrates

Alfonso Iorio, MD, PhD
Health Information Research Unit & Hemophilia Program
McMaster University
Canada
Disclosures for: Alfonso Iorio

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<table>
<thead>
<tr>
<th>CONFLICT</th>
<th>DISCLOSURE — IF CONFLICT OF INTEREST EXISTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESEARCH SUPPORT</td>
<td>Baxter (Bayer, Biogen Idec, NovoNordisk, Pfizer - No conflicts)</td>
</tr>
<tr>
<td>DIRECTOR, OFFICER, EMPLOYEE</td>
<td>CHESS/CHR/CHARMS, WFH Data &amp; Demographics Committee</td>
</tr>
<tr>
<td>SHAREHOLDER</td>
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<td>HONORARIA</td>
<td>Bayer, Baxter, Biogen Idec, CSL, NovoNordisk, Octapharma, Pfizer – No conflicts</td>
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<tr>
<td>ADVISORY COMMITTEE</td>
<td>Bayer, Baxter, Biogen Idec, CSL, NovoNordisk, Octapharma, Pfizer – No conflicts</td>
</tr>
<tr>
<td>CONSULTANT</td>
<td>Bayer (NovoNordisk – No conflicts)</td>
</tr>
</tbody>
</table>

* European Accreditation Council for Continuing Medical Education
Assessment of long term safety and efficacy of clotting factor concentrates

- Vision
- A few key technical aspects
- State of the art
- Future perspectives
Assessment of long term safety and efficacy of clotting factor concentrates

• **Vision**
  • Safe, effective, convenient and affordable treatment for as many patients as we can wherever they happen to be born

• **Technical aspects**

• **State of the art**
Assessment of efficacy and safety

• Setting the stage:
  ① Efficacy and effectiveness
  ① Long versus short term
  ① Absolute versus relative
  ① Concentrates versus regimens
  ① Individuals versus populations
Donor/plasma screening for HBV

Viral inactivation through heat treatment

Heat-treated concentrates widely available

Intermediate-purity concentrates

High-purity concentrates

HIV screening

rFVIII available

Manufacturing changes for rFVIII product

rFIX available

Viral partitioning via chromatography

HCV screening

Nanofiltration

Solvent/detergent available

Modified concentrates

Cryoprecipitate

Low-purity pd concentrates

Intermediate-purity concentrates

Mid 1960s

Early 1970s

Early 1980s

Mid 1980s

Late 1980s

Early 1990s

Late 1990s

Early 2000s

Late 2000s

Today

A more realistic representation..
The reality is slightly different..

- Study design
- Study setting
- Study size
- Outcome measure(s)
- Comparator(s)
Study design

• Administrative databases
  • National health care systems / insurance databases
  • Disease registry
• Dedicated research databases
  • Prospective targeted research projects

• Comprehensiveness
• Risk of bias reduction techniques
Canadian Hemophilia Assessment Resource Management System (CHARMS)

Over 10 years

- 2260 patients
- FC units tracked
- FVIII: 1 009 097 765
- FIX: 272 406 859

The EUHASS study

• **Strengths**
  - Prospective, very large inception cohort
  - Controlled (parallel, head-to-head)

• **Limitations**
  - Minimal information collected
  - No multivariable approach
  - Confounding still possible
  - Dynamic cohort not always at steady-state
EUHASS: Inhibitors in PTPs

<table>
<thead>
<tr>
<th>Product</th>
<th>Inhibitors</th>
<th>Pt/yr</th>
<th>Rate</th>
<th>(95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>4656</td>
<td>0.11</td>
<td>(0.03-0.25)</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1987</td>
<td>0.05</td>
<td>(0.00 - 0.28)</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>3519</td>
<td>0.17</td>
<td>(0.06 - 0.37)</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>2338</td>
<td>0.13</td>
<td>(0.03 - 0.37)</td>
</tr>
</tbody>
</table>

Data from the EUHASS annual reports to the Investigators
## Inhibitor rates, selected recombinant FVIII

<table>
<thead>
<tr>
<th>Product</th>
<th>Studies</th>
<th>Rate (x 100 py)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advate</td>
<td>9</td>
<td>0.10</td>
<td>0.05-0.18</td>
</tr>
<tr>
<td>Kogenate</td>
<td>9</td>
<td>0.12 (0.04-0.33)*</td>
<td></td>
</tr>
<tr>
<td>Refacto</td>
<td>8</td>
<td>0.19</td>
<td>0.11-0.34</td>
</tr>
<tr>
<td>PD factor VIII</td>
<td>4</td>
<td>0.09</td>
<td>0.02-0.45</td>
</tr>
</tbody>
</table>

* 0.26 (0.16 - 0.44) at fixed effect model

<table>
<thead>
<tr>
<th>Year</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhib</td>
<td>8</td>
<td>34</td>
<td>63</td>
<td>96</td>
</tr>
<tr>
<td>Exposed</td>
<td>59</td>
<td>121</td>
<td>221</td>
<td>336</td>
</tr>
<tr>
<td>Proportion</td>
<td>0.31</td>
<td>0.28</td>
<td>0.29</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Data from the EUHASS annual reports to the Investigators
<table>
<thead>
<tr>
<th></th>
<th>EUHASS</th>
<th></th>
<th>EUHASS - RODIN</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>LCI</td>
<td>UCI</td>
<td>P</td>
</tr>
<tr>
<td>Plasma D</td>
<td>0.22</td>
<td>0.11</td>
<td>0.35</td>
<td>0.21</td>
</tr>
<tr>
<td>Recomb</td>
<td>0.26</td>
<td>0.22</td>
<td>0.31</td>
<td>0.24</td>
</tr>
<tr>
<td>A</td>
<td>0.26</td>
<td>0.19</td>
<td>0.34</td>
<td>0.26</td>
</tr>
<tr>
<td>B</td>
<td>0.32</td>
<td>0.18</td>
<td>0.50</td>
<td>0.33</td>
</tr>
<tr>
<td>C</td>
<td>0.30</td>
<td>0.22</td>
<td>0.40</td>
<td>0.22</td>
</tr>
<tr>
<td>D</td>
<td>0.29</td>
<td>0.17</td>
<td>0.43</td>
<td>0.27</td>
</tr>
</tbody>
</table>
Stakeholders and barriers

- Manufacturers
  - Accessibility to data – comparative effectiveness
- Patients
  - “Disease” denial – burden of data generation
- Treaters
  - Time commitment – applied science
- Researchers
  - Small return
Patient data meta-analysis of Post Authorization Safety Surveillance (PASS) studies of hemophilia A patients treated with rAHF-PFM


<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n 1,188)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia-PASS</td>
<td>34 (2.9)</td>
</tr>
<tr>
<td>Europe-PASS</td>
<td>419 (35.3)</td>
</tr>
<tr>
<td>Japan-PASS</td>
<td>361 (30.4)</td>
</tr>
<tr>
<td>Italy-PASS</td>
<td>281 (23.6)</td>
</tr>
<tr>
<td>US-PASS</td>
<td>93 (7.8)</td>
</tr>
</tbody>
</table>
## Patient Characteristics & ABR

<table>
<thead>
<tr>
<th>Characteristics, n (%)</th>
<th>Num (%)</th>
<th>ABR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;150 previous EDs</td>
<td>1016 (85.5)</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis at enrolment</td>
<td>743 (62.6)</td>
<td></td>
</tr>
<tr>
<td>≥ twice/week during the study</td>
<td>587 (49.4)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics, n (%)</th>
<th>Num</th>
<th>Median (Q1, Q3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1,140</td>
<td>3.83 (0.60, 12.90)</td>
</tr>
<tr>
<td>On demand at enrolment</td>
<td>421</td>
<td>10.38 (2.27, 27.29)</td>
</tr>
<tr>
<td>On prophylaxis (on study, any frequency)</td>
<td>710</td>
<td>2.00 (0, 6.73)</td>
</tr>
<tr>
<td>On prophylaxis (on study, ≥ twice/week)</td>
<td>557</td>
<td>1.66 (0, 4.78)</td>
</tr>
</tbody>
</table>

Median dose per infusion of 27 IU/kg (Q1 20, Q3 34).
Stakeholders and barriers

• Manufacturers
  • Accessibility to data – comparative effectiveness

• Patients
  • “Disease” denial – burden of data generation

• Treaters
  • Time commitment – applied science

• Researchers
  • Small return
Effectiveness outcomes

• Cure (as a synonym for normal life)
  • Healthy functional joints
    • Bleeding (annualized bleeding rate)
      – Pain
      – Working capability
      – School attendance
Ways to higher effectiveness

• Improving concentrates
• Improving adherence
• Reducing cost
  • Tailoring dose
• Simplifying treatment
• Investigating social and cultural components
Safety outcomes

• Inhibitor development
  • Laboratory variability
• Blood borne infections

• Unexpected events
  • Long term toxicity of modified molecules
  • Drug interactions
  • “Clots”?
Safety outcomes

Inhibitor event rate in PTPs – so what?

As a result of our systematic review, we identified:

- **39 de novo inhibitors** reported in **19 publications**.

Individual patient data has been collected for:

- **29 (74%) inhibitor cases overall**
  - **14 (36%) from CRFs** completed by study investigators
  - **15 (39%) extracted** from patient-level information available in the published reports.
Interim results – inhibitor characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at inhibitor diagnosis (years)</td>
<td>?</td>
</tr>
<tr>
<td>Peak titre level (BU/ml)</td>
<td>??</td>
</tr>
<tr>
<td>Last know titre level (BU/ml)</td>
<td>???</td>
</tr>
<tr>
<td>Patient follow-up (mo)</td>
<td>????</td>
</tr>
</tbody>
</table>

Barbara, A. Care until Cure grant competition, CHS
Paradigm shift in trial design

  - Efficacy and safety of prophylaxis with once-weekly BAY 79-4980 compared with thrice-weekly rFVIII-FS in haemophilia A patients. A randomised, active-controlled, double-blind study..

  - A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management.

  - Randomized, controlled, parallel-group trial of routine prophylaxis vs. on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A (SPINART).

  - Multicentre, randomized, open-label study of on-demand treatment with two prophylaxis regimens of recombinant coagulation factor IX in haemophilia B subjects.

  - Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors.
# Long term comparison of different regimens

<table>
<thead>
<tr>
<th></th>
<th>NL Median (IQR)</th>
<th>SW, Median (IQR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint bleeds, 5 yr</td>
<td>10 (4 -18)</td>
<td>2.5 (0.93)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Nr joints</td>
<td>2 (1-4)</td>
<td>3 (2-3)</td>
<td>.47</td>
</tr>
<tr>
<td>HJHS (max144)</td>
<td>9.0 (2.0 – 18.)</td>
<td>4.0 (2.0 – 6.0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Activity (max 100)</td>
<td>93 (81-98)</td>
<td>99 (93-100)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>EQ-D5 utility</td>
<td>0.04 (0.81 – 1.00)</td>
<td>1.00 (0.81 – 1.00)</td>
<td>.93</td>
</tr>
<tr>
<td>Factor cost</td>
<td>851 (647-1048)</td>
<td>1474 (1154-1778)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Lost production</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>.82</td>
</tr>
</tbody>
</table>

New study design

• Interrupted time series

• Paired availability design

• Randomized registry trial
  • Lauer & D’Agostino *NEJM* 2013; 369(17), 1579–81.
Figure 1. The effect sizes estimated by time series regression analysis of an interrupted time series design.
Prospective urban rural epidemiology (PURE) study

Innovation

- Bailey, SD. Diabetologia, 2014,57;4:738-45

- Huffman, MD and Yusuf, S. JAMA. 2014,63;14:1368-70
Conclusions

• Clear need for surveillance
• Clear evidence of progress
• Need for harmonization
• Need for guidance
Thanks

hemophilia.mcmaster.ca