Interchangeability of Coagulations proteins
The treaters perspective

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Introduction (1)

- History of coagulation products; short overview
- Side effects of treatment
- History of transmittable pathogens
- History of immunogenicity
- Switching
- Which product to choose; Treaters perspective
Coagulation factor concentrates: past, present and future

Figure: Historical scheme of FVIII and FIX concentrate development
The effect of viral infections on the Hemophilia community

Human immunodeficiency and hepatitis virus infections and their associated conditions and treatments among people with haemophilia

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Fig. 1. Reconstruction of the HIV-1 epidemic among persons with haemophilia in the USA from Kroner et al. [22], separately for Factor VIII and Factor IX.
Overview of Blood transmittable pathogens

<table>
<thead>
<tr>
<th>Virus</th>
<th>Family/genus</th>
<th>Genome</th>
<th>Geographic area</th>
<th>Blood/organ-donation transmission</th>
<th>Obligatory testing</th>
<th>Antiviral therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Retroviridae/Lentivirus</td>
<td>RNA</td>
<td>Worldwide</td>
<td>Known/high</td>
<td>Yes</td>
<td>Antiretrovirals</td>
</tr>
<tr>
<td>HTLV</td>
<td>Retroviridae/ Deltaretrovirus</td>
<td>RNA</td>
<td>Worldwide; high prevalence in Caribbean, Tropical Africa and Japan</td>
<td>Known/high^*</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepadnaviridae/ Orthohepadnavirus</td>
<td>DNA</td>
<td>Worldwide</td>
<td>Known/high</td>
<td>Yes</td>
<td>PEG-INF; antivirals</td>
</tr>
<tr>
<td>HCV</td>
<td>Flaviviridae/ Hepacivirus</td>
<td>RNA</td>
<td>Worldwide</td>
<td>Known/high</td>
<td>Yes</td>
<td>PEG-IFN + RBV and PI</td>
</tr>
<tr>
<td>HEV</td>
<td>Hepeviridae/ Hepevirus</td>
<td>RNA</td>
<td>Worldwide</td>
<td>Theoretical</td>
<td>No</td>
<td>Ribavirin</td>
</tr>
<tr>
<td>Dengue</td>
<td>Flaviviridae/ Flavivirus</td>
<td>RNA</td>
<td>Latin America and Southeast Asia</td>
<td>Known/low</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>WNV</td>
<td>Flaviviridae/ Flavivirus</td>
<td>RNA</td>
<td>Africa, Europe, the Middle East, west and central Asia, Oceania and North America</td>
<td>Known/low</td>
<td>Yes (only in USA)</td>
<td>No</td>
</tr>
<tr>
<td>Chikungunya</td>
<td>Togaviridae/ Alphavirus</td>
<td>RNA</td>
<td>Central and South Africa, Southeast Asia, Australia, Italy and France</td>
<td>Theoretical</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Human parvovirus B19</td>
<td>Paroviridae/ Erythovirus</td>
<td>DNA</td>
<td>Worldwide</td>
<td>Known/low</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>vCJD</td>
<td>Prion</td>
<td>Prion</td>
<td>UK, USA and Europe</td>
<td>Known/low</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>


Mendoza et al. AIDS Rev. 2012
The effect of viral infections on the Hemophilia community

- HIV epidemic has changed the attitude of doctors and patients
- Patients became active involved in decision making process
Paradigm swift; From sufficient supply to safety

- Concerns have changed from supply to safety
- Safety has become similar with complete safety as an ultimate goal
- How to define?
- Data sufficient prelicensure?
The recognition that certain plasma products had an increased risk for inhibitors led to more frequent testing.

Regulators asked the Recombinant products requested formal PUP studies for registration of new products.

Immunogenicity now greatest concern.
Risk for Inhibitors in PTP patients

- Low inhibitor incidence PTP patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Brand</th>
<th>Sample</th>
<th>FVIII level</th>
<th>ED</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>White et al²³</td>
<td>Recombinate</td>
<td>69</td>
<td>&lt; 0.05</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Schwartz et al²⁴</td>
<td>Kogenate</td>
<td>86</td>
<td>NR</td>
<td>NR</td>
<td>1</td>
</tr>
<tr>
<td>Abshire and Brackmann²⁵</td>
<td>Kogenate-FS</td>
<td>73</td>
<td>&lt; 0.02</td>
<td>&gt; 100</td>
<td>0</td>
</tr>
<tr>
<td>Courter and Bedrosian²⁶</td>
<td>Refacto</td>
<td>113</td>
<td>&lt; 0.02</td>
<td>&gt; 30/y</td>
<td>1</td>
</tr>
<tr>
<td>Tarantino et al²⁷</td>
<td>Advate</td>
<td>108</td>
<td>&lt; 0.01</td>
<td>&gt; 150</td>
<td>1</td>
</tr>
<tr>
<td>Recht et al²⁸</td>
<td>RefactoAF</td>
<td>204</td>
<td>&lt; 0.02</td>
<td>&gt; 150</td>
<td>3</td>
</tr>
</tbody>
</table>

ED indicates exposure day; NR, not reported; and PTP, previously treated patients.

Clotting factor concentrate switching and inhibitor development in hemophilia A

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Blood 2012
Risk for Inhibitors in PTP patients

Total risk from 0.0015 until 0.0080 X 1000 patient years!

<table>
<thead>
<tr>
<th>Year</th>
<th>Author/reference</th>
<th>Study design</th>
<th>Sample</th>
<th>Follow-up, mo</th>
<th>Inhibitors</th>
<th>Rate, × 1000 patient/years</th>
<th>Age, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988</td>
<td>McMillan et al*</td>
<td>Prospective</td>
<td>1306</td>
<td>48</td>
<td>31</td>
<td>0.0080</td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td>Colvin et al†</td>
<td>Prospective</td>
<td>2160</td>
<td>48</td>
<td>32</td>
<td>0.0015</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Darby et al‡</td>
<td>Registry</td>
<td>6078</td>
<td>24</td>
<td>133</td>
<td>0.0020</td>
<td>≥ 15</td>
</tr>
<tr>
<td>2006</td>
<td>Kempton et al§</td>
<td>Prospective</td>
<td>838</td>
<td>48</td>
<td>42</td>
<td>0.0029</td>
<td>5-14</td>
</tr>
<tr>
<td>2011</td>
<td>Hay et al¶</td>
<td>Registry</td>
<td>2258</td>
<td>144</td>
<td>106</td>
<td>0.0053</td>
<td>10-49</td>
</tr>
</tbody>
</table>

*Patient of all severities. A total of 14 inhibitors were in patients > 75 ED; 11 of 14 were low titer, and 6 of 14 were transient. Total patients with > 75 ED not reported but rate likely estimated at 0.0023.
†Only patients with factor VIII < 0.03 U/mL were studied. A total of 13 inhibitors were in patients > 10 years of age. Total patients > 10 years not reported, but the rate was definitely < 0.002.
‡Patients of all severities. 95% confidence interval for ≥ 15 was 0.0017-0.0023. Rate was 0.0052 in severe patients 5-14 years of age and 0.0038 in those ≥ 15 years of age.
§Patients of all severities with negative titer before and at enrollment in UDC. All had > 50 ED. Two additional transient inhibitor were reported; 6 of 7 inhibitors were low titer.
¶Severe patients only. Of the 106 inhibitors in patients 10-49 years of age, 54 were high and 28 were low titer. Of the 11 in patients 50-59 years of age, 9 were high and 9 were low titer.
Reasons for switching of products

- Improved safety
- Fewer side-effects (allergic responses)
- Newer generation product
- Price
- National contracts
- Smaller volumes
- Storage advantage
- Patient/family preference
- Longer-Half-life
Risk for inhibitors after Switching

- No direct correlation to switching products
Surveillance began on 1 October 2008.

Patients included in the surveillance
Haemophilia A
Haemophilia B
von Willebrand’s disease: type 1 severe (<15% VWF:RiCo), type 2, type 3
All inherited rare bleeding disorders
More than > 60 centers participating from > 20 countries
Inhibitor development in PUPs

- Small studies
- Differ
- Different designs and definitions
- Lowest risk for single plasma products

Wight and Paisley
Haemophilia 2003;9:418-35
Larger review than that of Wight and Paisley

Still: recombinant products have higher incidence than plasma products – but less convincing

Problems with outcome definitions and lack of information on confounding factors remained

Most important; studies on average small!!
Prospective registries for PUPs

PedNet

HAEMOPHILIA REGISTRY

The PedNet Haemophilia Registry is a collaborative effort of the European PEDIatric NETwork for haemophilia management. The registry is set up in 2004 by PedNet investigators to promote and facilitate research and healthcare development in children with haemophilia. At this moment 30 Haemophilia Treatment centers (HTC ‘s) from 16 countries are collaborating.

The aim of the PedNet registry is to establish large well-documented birth cohorts of patients with haemophilia enabling studies on side effects and outcome of treatment. Patient data are collected from birth onwards and consist of all data concerning treatment, side effects and outcome of treatment. All newly diagnosed patients with haemophilia A and B until 25% from participating centers are eligible for inclusion.
It all starts with defining the right items to be studied

Courtesy of Gili Kenet
Patients and methods

◆ **CANAL** study (14 centers)
  - Patients with severe haemophilia
  - FVIII < 2%
  - Born between 1990 and 2000
  - Until 50 exposure days

◆ **RODIN** study (29 centers)
  - Patients with severe haemophilia
  - FVIII < 1%
  - Born between 2000 and 2010
  - Until 75 exposure days
CANAL and RODIN combined 1990-2010

- Severe haemophilia A
  - FVIII:C < 1%
  - Follow-up until 50 ED
- Total no. of patients: 921
- Clinically relevant inhibitors
  - ≥ 2 positive titres (>0.3-0.6 BU/ml)
  - Plus decreased FVIII recovery
- High-titre inhibitors
  - Clinically relevant and
  - Peak titre ≥ 5 BU/ml
Cumulative inhibitor incidence
All PUPs 1990-2009

PUPs with severe hemophilia A N=921
Plasma versus Recombinant products

No difference in Class Plasma Versus Class Recombinant products in 921 PUPs with severe Hemophilia A
Reasons for reluctance to Switch products

- Strong psychological link to same concentrate
- Concern for transmittable pathogen; switching prohibit tracking culprit concentrate
- Concern that switching leads to higher change of inhibitors
- Plasma and especially High VWF contain products have a lower risk for inhibitors?
Conclusions (1)

- Safety of Coagulation products; No transmittable pathogens in newer generation plasma and recombinant products
- Although theoretically risk lower in recombinant products patients have been demanding to continue on their “own” plasma product
- Main reason; Lower risk for inhibitors?
- Data to support this claim are weak
More attention is needed for sufficient supply
Majority of the patients still are undertreated
Debates are ongoing on “age to start prophylaxis” and “frequency of dosing”
Main problem is that costs have not decreased despite recombinant technology and larger choice
Future arrival of Biosmilars are promising!...
Factors to consider in the development of new products

Comparability and biosimilarity: considerations for the healthcare provider
Time until Inhibitor development after introduction new Product

Cumulative incidence PUPs

Nr of new inhibitors*/
Nr completed 50 ED + nr new inhibitors

*Inhibitor: 2 positive tests

Fischer K et al
Haemophilia 2012