New Treatment Modalities; Recombinant Factor VIII Products – “Factor VIII after 2008”

(More Choices)

Gita V. Massey, MD

June 20, 2009
pdFVIII concentrates

Intermediate-purity pdFVIII concentrates

High-purity pdFVIII concentrates

Recombinant FVIII (rFVIII)

Plasma/alumin-free rFVIII

Early 70s

Late 70s

Early 80s

Mid 80s

Late 80s

Early 90s

Late 90s

Early 00s

Donor/plasma screening for HBV starts

Heat treatment starts

Heat-treated FVIII plasma concentrates widely available

Expanded donor/plasma screening: HIV, HCV

Imunoaffinity, solvent/detergent, ion exchange treatments start

Improved donor/plasma screening: HIV, HCV NAT starts

Efforts to minimize presence of animal- or human-derived material in rFVIII agents
The Goals of Safe Therapy

- Promote adequate hemostasis with minimal side effects
- Prevent transmission of viral and “other” pathogens
- Decrease thrombogenicity of concentrates used to treat Factor IX deficiency
- Promote hemostasis in the presence of inhibitors (and minimize inhibitor formation?)
- Cost and ease of use
Safety from Pathogen Transmission

- Donor selection
- Plasma screening
- Viral inactivation
- Recombinant products
Where are we coming from?
Donor Selection

- Recovered plasma from volunteer donors
- Questioning about infectious risks
- Source plasma from apheresis donors
Where are we coming from?
Plasma Screening

- 1940’s – syphilis
- 1972 – hepatitis B surface antigen
- 1985 – HIV antibody
- 1987 – ALT (surrogate marker for hepatitis)
- 1990 – Hepatitis C antibody
- Now – “NAT” (nucleic acid testing) HAV, HBV, HCV, HIV, B-19
Where are we coming from?

Viral Inactivation

- **Heat treatment**
  - Late 1970’s, early 1980’s - “pasteurization” and “dry”
  - Not effective for hepatitis, B-19
  - Fear of increased inhibitors with denatured protein

- **Solvent Detergent**
  - 1985
  - Dissolving lipid envelopes of viruses
  - Not effective against HAV and B-19

- **Increased Purification**
  - Specific activity (increase amount of desired protein)
  - 1980’s – immuno-affinity purification (monoclonal antibodies)
  - High purity does not equal high safety
REMEMBER

- CDC maintains surveillance over viral infections transmitted by plasma products
- Last HIV transmissions from a USA concentrate were in 1987
- No viral-inactivated concentrate made from HIV-Ab screened plasma has transmitted HIV
- No transmission of hepatitis by modern concentrates has been observed
We have arrived!
The Recombinant Products

- 1990’s
- Human genes transfected into nuclei of hamster cells
- Cells replicate and express factor in culture medium
- Factor is extracted from culture medium by chromatography
- Factor stabilized – albumin or sugars
Recombinant Products

- **Advantages**
  - Less viral contamination
  - Production of “designer” molecules

- **Disadvantages**
  - Discordance of labelled units (*in vitro*) vs. recovery in patients (*in vivo*)
  - Laboratory assay methods
  - Cannot absolutely exclude pathogenic viruses in hamster cell cultures
The Product Generations

- **First Generation**
  - Media enriched with human or animal plasma proteins for initial cell culture
  - Albumin in final formulation

- **Second Generation**
  - Sucrose substituted for albumin in final formulation

- **Third Generation**
  - No human or animal plasma proteins in purification or final formulation
The Products

- Recombinate (Baxter – 1\textsuperscript{st} generation)
- HelixateFS/KogenateFS (Bayer/ZLB Behring – 2\textsuperscript{nd} generation)
- ReFacto (Wyeth – 2\textsuperscript{nd} generation) *
- Advate (Baxter – 3\textsuperscript{rd} generation)
- Xyntha (Wyeth – 3\textsuperscript{rd} generation)

*ReFacto will not be available after 5/31/09*
<table>
<thead>
<tr>
<th></th>
<th>RECOMBINA TE</th>
<th>KOGENATE FS HELIXATE FS</th>
<th>REFACTO (*ReFacto will not be available after 5/31/09)</th>
<th>ADVATE</th>
<th>XYNTHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CELL LINE FOR EXPRESSION</td>
<td>CHO</td>
<td><strong>BHK</strong></td>
<td>CHO</td>
<td>CHO</td>
<td>CHO</td>
</tr>
<tr>
<td>FVIII MOLECULE</td>
<td>Full-length</td>
<td>Full-length</td>
<td><strong>B-domain deleted</strong></td>
<td>Full-length</td>
<td><strong>B-domain deleted</strong></td>
</tr>
<tr>
<td>STABILIZER</td>
<td><strong>Human albumin</strong></td>
<td>Sucrose</td>
<td>Sucrose</td>
<td>Trehalose Mannitol</td>
<td>Sucrose Polysorbate 80</td>
</tr>
<tr>
<td>PLASMA ALBUMIN FREE METHOD</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td><strong>Yes</strong></td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>VIRUS INACTIVATION/ PURIFICATION</td>
<td><strong>IA, IE</strong></td>
<td>IA, IE, SD ultrafiltration</td>
<td>IA, IE, SD nanofiltration</td>
<td>IA, IE, SD ultrafiltration</td>
<td>IA, IE, SD nanofiltration</td>
</tr>
</tbody>
</table>
## Clinical Efficacy of Factors

<table>
<thead>
<tr>
<th>STUDIES</th>
<th>RECOMBINATE</th>
<th>KOGENATE FS</th>
<th>REFACTO</th>
<th>ADVATE</th>
<th>XYNTHA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PUP and PTP</td>
<td>PUP and PTP</td>
<td>PUP and PTP</td>
<td>PUP and PTP</td>
<td><strong>PTP</strong></td>
</tr>
<tr>
<td>EFFICACY</td>
<td>92-95% Excellent/good</td>
<td>80-90% Excellent/good 100% surgery</td>
<td>92% Excellent/good</td>
<td>86% Excellent/good 100% surgery</td>
<td>92.5% Excellent/good 100% surgery</td>
</tr>
<tr>
<td>HALF-LIFE</td>
<td>14.6+-/4.9hrs</td>
<td>13.3+-/1.6hrs</td>
<td>14.5+-/5.3hrs</td>
<td>12.0+-/4.3hrs</td>
<td>11.5+-/5.2 hrs</td>
</tr>
<tr>
<td>INHIBITORS</td>
<td>32% in PUP</td>
<td>16% in PUP</td>
<td>30% in PUP</td>
<td><strong>16% in PUP</strong></td>
<td><strong>PUP in progress</strong></td>
</tr>
</tbody>
</table>
## Ease of Use of Factors

<table>
<thead>
<tr>
<th></th>
<th>RECOMBI NATE</th>
<th>KOGENATE FS HELIXATE FS</th>
<th>REFACCTO  (<em>ReFacto will not be available after 5/31/09</em>)</th>
<th>ADVATE</th>
<th>XYNTHA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VIAL RANGES</strong></td>
<td>250, 500, 1000IU</td>
<td>250, 500, 1000, 2000IU</td>
<td>250, 500, 1000, 1500, 2000IU</td>
<td>250, 500, 1000, 1500, 2000, 3000IU</td>
<td>250, 500, 1000, 2000IU</td>
</tr>
<tr>
<td><strong>FINAL VOLUME</strong></td>
<td>10ml</td>
<td>2.5ml</td>
<td>4ml</td>
<td>5ml</td>
<td>4ml</td>
</tr>
<tr>
<td><strong>STORAGE</strong></td>
<td>Refrigerate or room temp</td>
<td>Refrigerate or room temperature for 3 months</td>
<td>Refrigerate or room temp</td>
<td>Refrigerate or room temp</td>
<td>Refrigerate or room temp</td>
</tr>
<tr>
<td><strong>OTHER “PERKS”</strong></td>
<td>Peel-off label Color-coded</td>
<td>Peel-off label Color-coded Butterfly needle</td>
<td>Color-coded Butterfly needle</td>
<td>Peel-off label Color-coded Butterfly needle</td>
<td>Color-coded Butterfly needle</td>
</tr>
</tbody>
</table>
The Issue of Cost

- **Cost of Factor to Family**
  - Co-pays directed by insurance
  - Insurance formularies
  - Insurance caps

- **Cost of Factor to Insurance Company**
  - Average wholesale price of medication
  - Contractual agreements
Evidence Based Use of Recombinant Factors

- **Strong Evidence**
  - rVIIa
    - Inhibitors
    - Allergic reactions to IX
  - Purified IX
    - Patients with increased thrombotic risk

- **“Subjective” Evidence**
  - Consumer perception of risk is serious and valid
  - Newly-diagnosed patients and patients who have only used recombinant factors in the past

Subjective Evidence

Consumer perception of risk is serious and valid

Newly-diagnosed patients and patients who have only used recombinant factors in the past
The Other Recombinant Factors

- **Benefix**
  - Factor IX deficiency
  - Similar production to factor VIII products
  - Problems with calculated dose matching recovered dose

- **NovoSevenRT**
  - Used for Factor VII deficiency, platelet disorders, inhibitors
  - Similar production to factor VIII products
  - Problems include cost, very short half-life, antibodies, and possible thrombogenicity
The Global Picture

- 80% of estimated 400,000 people with hemophilia receive no treatment
The Future – Where are we Going?

- Gene Therapy
- Coagulation factors bioengineered for improved therapeutics – the “designer molecules”
  - Improve biosynthesis and secretion
  - Prolong half-life – Pegylated liposomal products
  - Decrease immunogenicity