Overcoming Current Challenges in the Treatment and Management of Hemophilia

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Disclosures

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Baxter
Bayer
Biogen Idec
CSL Behring
Novo Nordisk
Octapharma
Pfizer
Topic Outline

1. Overview of hemophilia
2. Clinical challenges
3. Current treatment
4. New treatment options

Magnitude of the Problem

How many people are affected?

- Obesity…………………90,500,000
- Diabetes………………..25,800,000
- COPD…………………..15,000,000
- MS………………………….300,000
- Hemophilia…………………. 20,000

Sources: Centers for Disease Control and Prevention (www.cdc.gov)
National Institute of Neurological Disorders and Stroke (www.ninds.nih.gov)
What is Hemophilia?

- Congenital bleeding disorder
- Due to deficiency or absence of a coagulation cascade protein
- Hemophilia A = factor VIII deficiency
- Hemophilia B = factor IX deficiency
- Clinical phenotypes indistinguishable

Hemophilia affects all racial and socioeconomic groups equally.

- There are ~20,000 hemophiliacs in the United States
- More than 500,000 hemophiliacs worldwide
Genetics of Hemophilia

- Genes for factors VIII and IX are located on the X chromosome
- Females are carriers, males are affected

High rate of spontaneous mutations:

- Unaware female carriers
- New mutation in baby boy
- ~30% have no family history of hemophilia

Age Distribution of the US Hemophilia Population

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 – 19</td>
<td>8584</td>
<td>48%</td>
</tr>
<tr>
<td>20 – 44</td>
<td>6418</td>
<td>36%</td>
</tr>
<tr>
<td>45 – 64</td>
<td>2274</td>
<td>13%</td>
</tr>
<tr>
<td>65+</td>
<td>524</td>
<td>3%</td>
</tr>
</tbody>
</table>

Source: Centers for Disease Control and Prevention
Summary Report of UDC Activity (National)
Report Date – May 30, 2011
Clinical Features of Hemophilia

Severity of bleeding tendency depends on the factor level

<table>
<thead>
<tr>
<th>Severity</th>
<th>Description</th>
</tr>
</thead>
</table>
| Mild ( > 5% ) | • Bleed only after severe injury, trauma, or surgery  
|            | • May not be diagnosed until adulthood           |
| Moderate (1-5%) | • Bleed after injury, surgery                    |
|            | • May have occasional spontaneous bleeding       |
| Severe ( < 1 %) | • Frequent spontaneous bleeding                  |
|            | • Diagnosis made in early childhood              |

Joint bleed (hemarthrosis)

©2009 Rush University Medical Center.
The Clinical Problem of Joint Bleeding

- Hemarthrosis, primarily involving the ankles, knees, and elbows, is the most common complication of hemophilia
- 45% experience first joint bleed within the first year of life
- 90% have at least one joint bleed by 4 years of age
- 90% of those with severe hemophilia have chronic degenerative changes involving at least 1 joint by age 25
- 40% report restricted physical activities due to arthropathy

Lafeber et al., Haemophilia 2008; 14(Suppl. 4):3-9
Valentino et al., Semin Hematol 2008; 45(Suppl. 1):S50-S57
Clinical Features of Hemophilia

Joint bleed (hemarthrosis)

- 36 year old
- Severe hemophilia A
- Recurrent left knee bleeds
- Severe hemophilic arthropathy

Clinical Features of Hemophilia

Joint bleed (hemarthrosis)

- 36 year old
- Severe hemophilia A
- Recurrent left knee bleeds
- Severe hemophilic arthropathy
- Underwent total knee arthroplasty
11/17/2014

47 year old with severe hemophilia B

Standing

Severe hemophilia A, no inhibitor, morbidly obese
• 36 year old, severe hemophilia A, followed by HTC since birth. No history of fVIII inhibitor.
• Target joint in childhood, no longer bleeds (or moves).

44 yo male with severe hemophilia A, right elbow fracture after fall (July 2010)
December 2010 – 4 months s/p TEA, doing well

February 2012 – Resumed truck driving and heavy lifting, not doing so well
August 2014 – Limb threatening progression of hardware failure

October 2014
Clinical Features of Hemophilia

Deep muscle bleeds

- 52 year old with severe hemophilia B
- Spontaneous bleed

Clinical Features of Hemophilia

Intracranial bleeds

- 6 year old
- 52 year old
Clinical Features of Hemophilia

*Intracranial bleeds*

- 58 year old with severe hemophilia A, on regular factor VIII prophylaxis
- Fell at grocery store, didn’t think he had significant injury, refused transfer to ER
- Found unresponsive at home several hours later
- Died of massive subdural hematoma

Inhibitors in Congenital Hemophilia
Inhibitors in Congenital Hemophilia

• Some hemophilia patients “see” factor VIII or factor IX as a foreign protein
• Infusion of factor concentrate to prevent or treat bleeding triggers an immune response
• Antibodies (“inhibitors”) directed against factor VIII or factor IX neutralize the procoagulant effect and render standard treatment useless

Inhibitors in Congenital Hemophilia

• Development of inhibitors is currently the most serious complication of factor replacement therapy
• Typically seen in those with severe hemophilia
• May occur in those with mild or moderate hemophilia, usually after intense factor exposure related to trauma or surgery
• No longer associated with increased mortality

However . . .

➢ Bleeding more difficult to control
➢ Devastating joint disease and disability
➢ Major clinical and economic challenges
Clinical Features of Hemophilia

*Joint bleed (hemarthrosis)*

- 26 yo with severe hemophilia A and fVIII inhibitor
- Recurrent traumatic and spontaneous knee bleeds
- Left side surgically replaced
- Note severe muscular atrophy
- Following right TKA he became fully ambulatory (again)

22 yo male with severe hemophilia A and fVIII inhibitor
Rapid progression of arthropathy

March 2008  May 2010  June 2010
Clinical Features of Hemophilia

*Joint bleed (hemarthrosis)*

- 28 yo severe hemophilia A with inhibitor and end stage arthropathy, severe pain even when non-weight bearing
- Excellent functional outcome with right total hip arthroplasty

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Clinical Features of Hemophilia

*Soft tissue bleeding*
Treatment of Hemophilia

1. Historical perspectives
2. Factor replacement options
3. On-demand vs. prophylaxis
4. Treatment of inhibitor patients
5. New therapeutics

Historical Perspective

*Diabetes vs. Hemophilia*

- First human treated with insulin (1922)
- First human pancreas transplant (1966)
- Commercially available insulin pump (1978)
- Commercially available factor concentrate (1968)
- Viral inactivation of factor concentrates (1985)
- Recombinant factor concentrates (1992, 1997)
Overcoming Clinical Challenges

<table>
<thead>
<tr>
<th>Clinical Challenge</th>
<th>Treatment Advance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achieve clinically meaningful factor levels</td>
<td>Frozen plasma, cryoprecipitate, factor concentrates</td>
</tr>
<tr>
<td>Possibility of home therapy</td>
<td>Factor concentrates</td>
</tr>
<tr>
<td>Virally safe factor concentrates</td>
<td>Recombinant factor products</td>
</tr>
<tr>
<td>Prevent bleeds and maintain healthy joints</td>
<td>Routine use of prophylaxis, long acting factor products</td>
</tr>
</tbody>
</table>

Factor Replacement Therapy

- Plasma derived and recombinant factor VIII and factor IX concentrates are available
- 1\textsuperscript{st}, 2\textsuperscript{nd}, and 3\textsuperscript{rd} generation recombinant factor concentrates
- No documented case of viral transmission in more than 25 years
- Goal is for every child to learn self-infusion
Factor Replacement Therapy

On-Demand
• Treatment of bleeds when they occur
• Good at stopping bleeds after they start, but does not prevent bleeds

Prophylaxis
• Regular administration of factor to prevent bleeds from occurring
• Goal is elimination of all bleeds

Factor Replacement Therapy

On-Demand Treatment

Benefits
• Fewer infusions
• Less annual factor consumption (?)
• Lower factor costs (?)
• More convenient for some patients

Problems
• Bleeds are not prevented
• Joint damage is ongoing
• End stage arthropathy is unavoidable
• Bleeds may become more difficult to control over time
• Long term functional disability
Factor Replacement Therapy

Prophylactic Treatment

Problems
• Requires frequent infusions
• Venous access
• Time / schedule commitment

Benefits
• Proven to prevent bleeds
• Keeps joints healthy
• May delay progression of arthropathy
• Protection from traumatic and unexpected bleeds

Prophylactic Factor Therapy

Children
• Pioneered in Sweden in the 1960s
• Standard of care since introduction of recombinant factor concentrates in the 1990s
• Initiated after first joint bleed or before age 3
• Decreases bleeding frequency AND prevents joint damage

Adults
• Increasingly used, supported by recent clinical trials
• Decreases bleeding frequency and improves QOL, but . . .
• Does it really prevent progression of arthropathy?
• Kids who enter adulthood on regular prophylaxis, with preserved joints, are usually kept on prophylaxis

Economic Burden of Hemophilia

- Factor concentrates account for the majority of the cost of treating hemophilia.
- Routine prophylaxis for severe hemophilia A, dosed at 25-40 u/kg 3x/week:

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Annual factor consumption (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 y</td>
<td>20 kg</td>
<td>78,000 – 124,800</td>
</tr>
<tr>
<td>15 y</td>
<td>60 kg</td>
<td>234,000 – 374,400</td>
</tr>
<tr>
<td>Adult</td>
<td>80 kg</td>
<td>312,000 – 499,200</td>
</tr>
</tbody>
</table>

(Rough estimate of the cost of factor – $1 per unit)

Prophylaxis vs. On-Demand

*Which approach is most cost effective?*

- There are no comprehensive studies or data.
- Many variables . . . Must look beyond just the cost of factor.
- U.S. market unlike any other in the world.

*CAUTION*

Factor is very expensive, but so are the long term costs associated with poorly managed hemophilia!
Ongoing Clinical Challenges

- Managing orthopedic complications in those with already existing arthropathy
- Managing medical co-morbidities (liver disease, HIV, cardiovascular health, weight management)
- The aging hemophiliac
- Inhibitor patients

Treatment of Inhibitor Patients

*Three things you need to know . . .*

1. This is very complicated
2. This can be extremely expensive
3. This absolutely requires HTC expertise

*Why?*

- These patients are rare
- Treatment options have significant limitations
Treatment of Inhibitor Patients

**Immune Tolerance Therapy**
- Costs approximately $1 million per patient
- Only 70% effective, *BUT . . .*
- The effects of a long-term inhibitor can be devastating (clinically and economically)

**Bypassing Agents**
- 2 options: aPCC and rfVIIa
- Efficacy is incomplete (75 – 90%) and unpredictable
- No standard laboratory monitoring exists
- Thrombosis is a real risk

Treatment of Hemophilia

*Where are we headed?*
New Factor Products

- Long-acting factor concentrates have been in development for several years
- Extended half-life should result in similar or improved protection from bleeds with fewer infusions
- Methods to prolong half-life:
  - PEGylation
  - Fc fusion
  - Albumin fusion

<table>
<thead>
<tr>
<th>Degree of success</th>
<th>Old products</th>
<th>New products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII</td>
<td>12 h</td>
<td>18-20 h</td>
</tr>
<tr>
<td>Factor IX</td>
<td>18-24 h</td>
<td>80-90 h</td>
</tr>
</tbody>
</table>

New Factor Products

Where are we now?

- The following all have long-acting factor VIII and/or factor IX products in late stage clinical development:
  - Bayer, Baxter, CSL Behring,
  - Novo Nordisk

- First long-acting factor products recently approved, both made by Biogen Idec:
  - Factor IX – Alprolix (March 2014)
  - Factor VIII – Eloclate (June 2014)
Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A


Blood
Volume 123(3):317-325
January 16, 2014

Phase 3 Study of Recombinant Factor IX Fc Fusion Protein in Hemophilia B

Jerry S. Powell, M.D., K. John Pasi, M.B., Ch.B., Ph.D., Margaret V. Ragni, M.D., M.P.H., Margaret C. Ozelo, M.D., Ph.D., Leonard A. Valentino, M.D., Johnny N. Mahlangu, M.D., M.Med., Neil C. Josephson, M.D., David Perry, M.D., Ph.D., Marilyn J. Manco-Johnson, M.D., Shashikant Apte, M.D., Ross I. Baker, M.D., Geoffrey C. Chan, M.D., Nicolas Novitzky, M.O., Ph.D., Raymond S. Wong, M.D., Snejana Krassova, M.D., Geoffrey Allen, M.D., Haiyan Jiang, Ph.D., Alison Innes, B.Sc., Shuanglian Li, M.D., Ph.D., Lynda M. Cristiano, M.D., Jaya Goyal, Ph.D., Jurgen Sommer, Ph.D., Jennifer A. Dumont, Ph.D., Karen Nugent, M.Sc., Gloria Vigliani, M.D., Aoife Brennan, M.B., B.Ch., Alvin Luk, Ph.D., Glenn F. Pierce, M.D., Ph.D., for the B-LONG Investigators

N Engl J Med
Volume 369(24):2313-2323
December 12, 2013

A-LONG: Study Design

• 165 previously treated patients aged 12-65 years with severe hemophilia A

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Dosing of FVIII:Fc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individualized Prophylaxis</td>
<td>117</td>
<td>25-65 IU/kg every 3-5 days, adjusted to keep trough 1-3% above baseline</td>
</tr>
<tr>
<td>Once-Weekly Prophylaxis*</td>
<td>23</td>
<td>65 IU/kg every 7 days</td>
</tr>
<tr>
<td>On-Demand</td>
<td>23</td>
<td>As required for bleeding episodes</td>
</tr>
</tbody>
</table>

• All subjects eligible for participation in surgery arm

* Not a labeled dosing regimen
A-LONG: Individualized Prophylaxis vs. On Demand

25-65 IU/kg every 3-5 days to keep trough 1-3% above baseline or as needed to prevent bleeds

A-LONG: Once Weekly Prophylaxis vs. On Demand

Fixed dose of 65 IU/kg every 7 days
(Not a labeled dosing regimen)
B-LONG: Study Design

• 123 previously treated patients aged 12-71 years with severe hemophilia B

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Dosing of FIX:Fc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once-Weekly Prophylaxis</td>
<td>63</td>
<td>50 IU/kg weekly, dose adjusted to keep trough 1-3% above baseline</td>
</tr>
<tr>
<td>Individualized Interval</td>
<td>29</td>
<td>100 IU/kg every 10 days, interval adjusted to keep trough 1-3% above baseline</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On-Demand</td>
<td>27</td>
<td>As required for bleeding episodes</td>
</tr>
</tbody>
</table>

• All subjects eligible for participation in surgery arm

B-LONG: Once Weekly Prophylaxis vs. On Demand

1. Start at 50 IU/kg once weekly
2. Adjust dose to keep trough 1-3% above baseline or as needed to prevent bleeds
3. Median weekly dose at study end was 40.7 IU/kg
**B-LONG: Individualized Interval Prophylaxis vs. On Demand**

1. Start at 100 IU/kg every 10 days
2. Adjust interval to keep trough 1-3% above baseline or as needed to prevent bleeds
3. Median interval at study end was 13.8 days

**Treatment of Acute Bleeds**

- **A-LONG**
  - 1 infusion (87.3%)
  - 2 infusions (10.4%)
  - 3 infusions (1.7%)
  - ≥4 infusions (0.5%)

- **B-LONG**
  - 1 infusion (90.4%)
  - 2 infusions (6.9%)
  - 3 infusions (2.7%)

97 – 98% of bleeds are successfully treated with 1 or 2 doses of factor.
Safety of Long Acting Factor

Data from A-LONG and B-LONG
- No surprises
- No anaphylaxis
- No inhibitors
- No thrombotic events

Other products in clinical trials
- So far, so good . . .

Comparison of Factor VIII Concentrates

<table>
<thead>
<tr>
<th></th>
<th>“Original” (pd- and rFVIII)</th>
<th>“New” (FVIII:Fc – Eloctate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery</td>
<td>1 IU/kg increases factor level ~2%</td>
<td></td>
</tr>
<tr>
<td>Half-life</td>
<td>~12 hours</td>
<td>19.7 hours</td>
</tr>
<tr>
<td>Time to 1%</td>
<td>3.3 days</td>
<td>5.1 days</td>
</tr>
<tr>
<td>Prophylactic dose</td>
<td>20-40 IU/kg qod (3-4x/week)</td>
<td>50 IU/kg q4d (Adjust dose: 25-65 IU/kg Adjust interval: q3-5 days)</td>
</tr>
<tr>
<td>Notes</td>
<td>Many patients treat on a MWF schedule; may use larger dose on Friday</td>
<td>~30% achieved dose interval &gt;5 days 65 IU/kg q7d is effective, but not a labeled dose</td>
</tr>
</tbody>
</table>
Comparison of Factor IX Concentrates

<table>
<thead>
<tr>
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<th>“Original” (pd- and rFIX)</th>
<th>“New” (FIX:Fc – Alprolix)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery</td>
<td>1 IU/kg increases factor level ~1%</td>
<td></td>
</tr>
<tr>
<td>Half-life</td>
<td>~18 – 24 hours</td>
<td>86.5 hours</td>
</tr>
<tr>
<td>Time to 1%</td>
<td>5.1 days</td>
<td>11.5 days</td>
</tr>
<tr>
<td>Prophylactic dose</td>
<td>40-60 IU/kg 2x/week</td>
<td>50 IU/kg q7d ~ or ~ 100 IU/kg q10d</td>
</tr>
<tr>
<td>Notes</td>
<td>As with FVIII, personalized dosing adjustments are routinely done</td>
<td>Median dose on q7d arm was 40.7 IU/kg Median interval on q10d arm was 13.8 days</td>
</tr>
</tbody>
</table>

New Factor Concentrates

**What we know . . .**
- Highly effective for prophylaxis, acute bleeds, surgery
- Safety comparable to existing products
- Longer half-life allows for fewer infusions to maintain protective factor levels

**What is expected . . .**
- More effective treatment and improved adherence for a greater number of those with hemophilia

**To be determined . . .**
- How other long acting products will compare
- Role in immune tolerance therapy
- Economic implications (for all involved!)
Management Implications

**Pediatrics**
- Assuming no new safety concerns...
- Less frequent dosing may eliminate need for central venous catheters
- If fewer doses required = more doses actually received, kids on prophylaxis should be better protected
- Anticipate increasing and widespread use

**Adults**
- More complicated discussion
- Heterogeneous population
- Will need individualized approach

**Approach to use of long acting factor products in adults:**
- *On prophylaxis now*
  - Adherent to regimen
  - Rare bleeds
- *Most have little to gain*
  - Interest level generally low
- *Tried prophylaxis in the past*
  - Use prophylaxis, but intermittently, not long term
  - On prophylaxis, but adherence could be better, bleed control suboptimal
- *Have the most to gain*
  - Heterogeneous bunch
  - Need to clearly identify goals and individualize approach
- *Not on prophylaxis*
  - Won’t do prophylaxis
  - Period
- *Not much to talk about*
What’s New for Inhibitor Patients?

**Obizur**
- Recombinant porcine fVIII
- Baxter received FDA approval in October 2014 for use in Acquired Hemophilia
- Hopefully will expand to congenital inhibitor patients

**Factor VII analogues**
- Several in early phase development
- Disappointing results

**Gene Therapy**
- Remains an area of active investigation (for over 20 years)
- Clinical trials are ongoing
- It works in mice and dogs
- Scale up to humans has been a challenge, but progress is being made
- Still expected to be a clinical reality, but not anytime soon
Take Home Points

✓ Hemophilia is a rare condition, with a large economic burden on our healthcare system

✓ We have made great progress in the management of hemophilia, but we still have work to do

✓ We desperately need better treatments for those with inhibitors

✓ New long acting factor products have distinct advantages, but therapeutic and economic implications are not yet fully defined… stay tuned!

Questions and Discussion