Hemophilia Care Delivery in 2016: New factors and beyond factors - Where do we go from here?

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Objectives

1. To understand the evolving developments of enhanced half-life factor VIII and factor IX preparations for hemophilia A and B respectively, and how they differ.

2. To be able to evaluate the relative value and costs of longer-half life factors (particularly the very-long-acting factor IX products).

3. To gain an understanding of upcoming developments in hemophilia pharmacy, including the factor VIIIa-mimetic, emicizumab and the promise of gene therapy.

4. To appreciate the role of comprehensive hemophilia treatment centers and their 340B pharmacies in provision of hemophilia care in 2016.
Financial Disclosure

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• DSMB: Bayer
• Grant Support to my institution: Baxalta, Octapharma
Enhanced half-life factors and how we think about their properties

• Hemophilia management overview
• VIII vs IX
• Brief look at trial data
• Thinking about the pharmacokinetic impacts
Hemophilia A Severity

Severe (< 1%)
- ‘Spontaneous’ bleeding
- Intracranial bleeding
- Inhibitors
- New mutations (inversions)

Moderate (2-5%)
- Fewer spontaneous bleeds,
- But bleeds are as bad as severe
- Less arthropathy than severe

Mild (5-40+%)
- Bleeding with surgery/trauma
- Inhibitors uncommon

No FVIII

Normal FVIII Level
Adult vs. Pediatric Hemophilia A

**Children**
- Risk of inhibitors
- PK, dosing
- Adherence
- Activity

**Adults**
- Hep C was the major killer
- Prior Tx/switching
- Adherence
Managing Active Persons With Hemophilia

- **Adequate hemostasis range**
  - May help prevent activity-related bleeds
- **Area under the curve**
  - May help prevent subclinical bleeding
- **Trough**
  - May help prevent spontaneous bleeding

# FVIII Products in US as of 2014

<table>
<thead>
<tr>
<th>Name</th>
<th>Maker</th>
<th>Class</th>
<th>Gen</th>
<th>Molecular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphanate SD</td>
<td>Grifols</td>
<td>Plasma-Derived</td>
<td>NA</td>
<td>Full length</td>
</tr>
<tr>
<td>Koate DVI</td>
<td>Talecris</td>
<td>Plasma-Derived</td>
<td>NA</td>
<td>Full length</td>
</tr>
<tr>
<td>Recombinate</td>
<td>Baxter</td>
<td>Recombinant</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>Full length</td>
</tr>
<tr>
<td>Kogenate FS (Helixate FS)</td>
<td>Bayer</td>
<td>Recombinant</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>Full length</td>
</tr>
<tr>
<td>Advate</td>
<td>Baxter</td>
<td>Recombinant</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>Full length</td>
</tr>
<tr>
<td>Xyntha</td>
<td>Pfizer</td>
<td>Recombinant</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>B-domain deleted</td>
</tr>
</tbody>
</table>
Latest Therapies with EHL

- **Eloctate (efraloctacog)**
  - B-domain truncated (BDD) rFVIII-Fc fusion
  - Human cell line
- **Adynovate (FVIII-rurioctacog alfa pegol)**
  - PEGylated rFVIII
- **Nưuiq (simoctocog alfa)**
  - BDD rFVIII expressed in a human cell line
- **Afstyla (CSL-627)**
  - Single chain FVIII

Fc or Albumin Fusion

rFVIII-Fc Individualization → Fewer Bleeds

A-LONG Trial: 165 PTP aged ≥ 12 years

1. Individualized prophylaxis
   (25-65 IU/kg every 3-5 days, n = 118)
   ABR = 1.6

2. Weekly prophylaxis
   (65 IU/kg, n = 24)
   ABR = 3.6

3. Episodic treatment
   (10-50 IU/kg, n = 23)
   ABR = 33.6

Time course of fIX Activity with rFIX and rFIXFc, Dose: 50 IU per Kg (Study goal trough >1%)

- Adult terminal t1/2 approx 86 hours, but initial decay is much faster
- Error bars reflect individual variability – lots of interesting biology lies here
- In the published trial, interval adjusted to keep trough >1% in this study arm
- The slope varies on a log scale. This is complicated kinetics

1 wk = 168h
FIX activity after injection of a single dose of rIX-albumin FP or previous FIX product (PK population).
Marked person to person variability: Pilot rVIII-Fc measures, Region I, variable sampling
Questions of value vs cost for longer-acting factors

• What is the “value proposition” of longer-acting factors?
  – Less infusions? Less ports in infants?
  – Better coverage with prophylaxis?

• How much is “better” worth?
• Imagine a factor that lasts four times as long, would 4X price make sense? More than 4X?
Complicated Relationships

- Pivotal Trial Results
- Pricing
- Package Insert (Label)
Cost considerations for FIX-Fc regimens

<table>
<thead>
<tr>
<th>Price/Unit</th>
<th>Standard Factor Prophylaxis Regimens</th>
<th>EHL Factor Label Prophylaxis Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost/year (70kg patient)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparative cost</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusions saved/year</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Strategy #1</strong></td>
<td><strong>Strategy #2</strong></td>
<td><strong>Strategy #1</strong></td>
</tr>
<tr>
<td>40 IU/kg twice weekly</td>
<td>67 IU/kg twice weekly</td>
<td>50 IU/kg once weekly</td>
</tr>
<tr>
<td>$1.06</td>
<td>$1.06</td>
<td>$2.85</td>
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<tr>
<td>$308,672</td>
<td>$517,026</td>
<td>$518,700</td>
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<tr>
<td>1</td>
<td>1.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Baseline</td>
<td>----</td>
<td>52</td>
</tr>
</tbody>
</table>

Croteau, S. E. and Neufeld, E. J. Haemophilia, 2015
### Challenge of the high-dose strategy

**EHL Factor Label Prophylaxis Regimens**

<table>
<thead>
<tr>
<th></th>
<th>Strategy #1</th>
<th>Strategy #2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost/year (70kg patient)</strong></td>
<td>50 IU/kg once weekly</td>
<td>100 IU/kg every 10 days</td>
</tr>
<tr>
<td></td>
<td>$ 518,700</td>
<td>$ 728,175</td>
</tr>
<tr>
<td><strong>Comparative cost</strong></td>
<td>X 1.7</td>
<td>X 2.4</td>
</tr>
<tr>
<td><strong>Infusions saved/year</strong></td>
<td>52</td>
<td>67</td>
</tr>
</tbody>
</table>

- Label strategy #1 and #2 differ by 15 infusions per year
- Premium cost for #2 is **$13,900 per dose saved**
- Annual factor usage 2600 IU/kg for #1 vs. 3650 IU/kg for #2
- Unnecessarily high peaks, lower troughs with 10 day regimen
- This is a problem for the community

Croteau, S. E. and Neufeld, E. J. Haemophilia, 2015
Summary: EHL-VIII vs EHL-IX products

• Improvements in VIII half-life are *incremental*.
  – Many patients may not achieve meaningful prolongation of interval with 1.5X longer half-life
  – So far true for all brands from all manufacturers

• Improvements in IX half-life are *ground breaking*, and allow substantial prolongation of intervals (weekly or less frequently)
  – Properties of two available types (factor IX-Fc and factor IX-albumin) differ, though they use the same mechanism for recycling, the neonatal Fc receptor.

• “Value Proposition” – incremental cost for better products
Big changes coming in hemophilia pharmacy and care

- SIPPET study and what are we going to do about it?
- Factor VIII mimetic - emicizumab
- Inhibit the inhibitors – fitusiran, concizumab
- Gene therapy
  - Factor IX in AAV
  - Factor VIII in AAV
  - Others
SIPPET

• Mulitnational Randomized Clinical Trial in patients not previously treated with factor concentrates (PUPs)
• Trial based on data from meta analysis of all other PUP studies to date, suggesting more inhibitors in recombinant products
• Within each country, one brand of recombinant factor VIII (available before 2011) vs one brand of VWF-containing plasma-derived factor VIII
• High fraction of patients from Egypt and India
• Careful and convincing subgroup analyses.
SIPPET Results

High titer (peak > 5 BU/ml)
- pdFVIII: 18.6%
- rFVIII: 28.4%
- HR: 1.69

SIPPET implications

• New Year 2016: newborn with circumcision bleeding, Dx severe factor VIII deficiency
  – Treatment options?
    • plasma-derived
    • Old recombinant
    • New recombinant (on a clinical trial)

• Neufeld opinion: SIPPET is “practice-changing,”

• Does NOT implicate newest factor products

• Formal statements from MASAC and WFH do not solve the problem of what to do today
  – Special cases –
    • Kovaltry (Bayer) – data on package insert
    • Nuwiq – forthcoming data ASH, 2016
Antibody Analog of Factor VIII (FVIII): Emicizumab

Emicizumab Pilot Efficacy Study

• 18 Japanese patients with severe hemophilia A
• N = 6 per cohort group
• Cohorts: 0.3, 1.0, or 3.0 mg/kg
• Weekly sc dosing for 12 weeks
• Results
  – Dose-dependent PK
  – APTT remained short
  – FXIa-triggered thrombin generation detected at all assessments
  – No serious adverse events
• Extension study results reported at 2016 WFH congress

Emicizumab Impact on ABR

All Bleeding

- 73% of patients with FVIII inhibitors
- 71% of patients without factor VIII inhibitors

No bleeding

Emicizumab summary

• “Bi-functional” antibody that replaces factor VIIIa (factor VIII or VIIIa mimetic)
• Phase 1 trials – no significant adverse events, patients had markedly less bleeding
• Subcutaneous, every one-to-few weeks
• Not affected by inhibitors to factor VIII!
• Could it become a standard in both inhibitor and non-inhibitor patients?
• No role in factor IX deficiency
"Inhibit-the-Inhibitor" Strategies

“Intrinsic” pathway

“Extrinsic” pathway

Initiation
Amplification
Propagation

Feedback

Cross-talk

TFPI

Antithrombin

Thrombin

Fibrinogen

Fibrin

HMWK

XII

XIIa

PreK

Xla

Ca++

PL

IXa

Ca++

PL

VIII

V

TF

PL

Ca++

VIIa

VII

"Intrinsic" pathway

"Extrinsic" pathway

"Intrinsic" pathway

"Extrinsic" pathway
Balancing Coagulation

Hemophilia

Factor Replacement

TFPI Inhibition

Safety and PK of Anti-TFPI Antibody Concizumab

• Dose-dependent procoagulant effect
  – Increased levels of D-dimers and drugs
  – Not associated with coagulation factor inhibitors
  – Good solubility and stability
  – Long plasma $T_\frac{1}{2}$
  – High selectivity and specificity

• Others in Phase 1
  – BAY 1093884
  – PF 6741086

Phase 1 Antithrombin RNAi Results
ALN-AT3/Fitusiran

**Bleeding By AT Quartile**

**ALN-AT3/Fitusiran**

<table>
<thead>
<tr>
<th>AT Lowering</th>
<th>Patients</th>
<th>Cumulative Days</th>
<th>Cumulative Bleeds</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25%</td>
<td>24</td>
<td>602</td>
<td>43</td>
</tr>
<tr>
<td>25-50%</td>
<td>21</td>
<td>838</td>
<td>34</td>
</tr>
<tr>
<td>50-75%</td>
<td>18</td>
<td>862</td>
<td>35</td>
</tr>
<tr>
<td>&gt;75%</td>
<td>9</td>
<td>304</td>
<td>3</td>
</tr>
</tbody>
</table>

Inhibitors summary

- Is it possible that these agents can dramatically reduce bleeding, require no factor, and cause no harm? [need trial results]
- How will this fit into treatment models?
- If there is a thrombotic risk, then what?
FVIII Gene Therapy

- Adeno-associated viral vectors
- 3 clinical trials for hemophilia B show evidence of clinical efficacy
- Hemophilia A trial of BMN 270 is recruiting (N ~ 12)
  - B-domain replaced with spacer
  - Press release:
    - 2 high dose patients \( \rightarrow \) Factor VIII > 50%
    - 5/6 high dose patients \( \rightarrow \) Factor VIII > 5%
- DTX201 in preclinical phase

340B pharmacy, comprehensive hemophilia treatment centers and integrated care models

• Unknowns, November 2016
  – Covered Outpatient Drug (COPD) rules and 340B factor
  – OPA “Mega Guidance” at OMB

• Known challenges November 2016
  – Medicaid Managed Care carve-outs
  – Rebates vs HTC 340B – which is really a better deal for you, your clients, and taxpayers?
  – Antipathy to 340B from various angles and for various reasons
  – 340B and new treatment paradigms?
THE HTC COMPREHENSIVE MODEL OF CARE

The National Hemophilia Foundation Medical and Scientific Advisory Council (MASAC) recognizes the HTC’s emphasis on early diagnosis and intervention as the optimal health care delivery model for this complex chronic disease.

CDC recognizes hemophilia as a complex disorder requiring good quality medical care from HTC doctors, nurses, social workers, physical therapists, and other health care professionals specialized in caring for people with bleeding disorders.

*The National Hemophilia Foundation’s (NHF) Medical and Scientific Advisory Council (MASAC) Standard 132- http://www.hemophilia.org
THE HTC COMPREHENSIVE MODEL OF CARE

REFERRAL

CLINICAL ASSESSMENT
Assessment includes:
- Patient/Caregiver
- Physician
- Nurse
- Psychosocial Professional
- Physical Therapist
- Pharmacist
- Other HTC Team Members

INTERDISCIPLINARY CARE PLAN
Components include:
- Clinical Care
- Pharmacy
- Nursing
- Psychosocial Support
- Physical Therapy
- Home Training
- School/Work Training
- Clinical and Patient Goals

IMPLEMENTATION / INTERVENTIONS
Coordination of Care:
- Medication/Supplies
- Lifestyle/Service Items
- Education & Support
- Pain Management
- Adherence Monitoring
- On-site coordination of care

EVALUATION / REASSESSMENT / OUTCOMES
Desired vs. Actual
- Clinical
- Humanistic
- Economic

OUTCOMES ANALYSIS & REPORTING
Continuous monitoring of outcomes with goal of improving overall health. Ongoing communication between the HTC care team and patient is critical.

Targeted education, adherence coaching, and side effect management improve clinical outcomes
CASE STUDY: COST SAVINGS ANALYSIS

HTC provides clinical care to patient with hemophilia but patient’s insurance requires patient to utilize a national PBM or specialty pharmacy provider listed in their network to obtain drug.

Quoted charges obtained from insurance company as of April 10, 2014.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Price</th>
<th>Unit Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xyntha Solofuse</td>
<td>$45,980</td>
<td>$1.51/unit</td>
</tr>
<tr>
<td></td>
<td>$36,845</td>
<td>$1.21/unit</td>
</tr>
<tr>
<td></td>
<td>$29,841</td>
<td>$0.98/unit</td>
</tr>
</tbody>
</table>

ANNUAL SAVINGS recognized by insurance company by contracting with HTC specialty pharmacy versus national PBM

$193,668
COST MANAGEMENT

THE HTC COMMITMENT:
Effectively manage the complications of hemophilia while monitoring adherence to drug treatment and decreasing total cost of care.
COST MANAGEMENT

APPROPRIATE DOSING & ASSAY MANAGEMENT:

HTC physicians prescribe drug utilizing manufacturer prescribing information balancing the assay size and number of vials needed to achieve prescribed dosing and to maximize patient therapy compliance. **Collaboration between the clinical team and pharmacy at the HTC is crucial to achieving this goal.**
What will 340B look like for novel strategies?

• Monthly SubQ medication not sold by the unit?
• Gene therapy administration and supervision?
• What happens when an emicizumab patient needs a dose of regular factor also?
  – Nobody will know how to infuse any longer
  – Will every patient essentially be “mild”
• How shall HTCs work best with Medicaid and other payors for the optimal and most efficient care of patients?
CONCLUSION: BIG CHANGES AHEAD?

• Usage patterns for extended half-life factors
  – Distinguishing factor IX and Factor VIII deficiencies
• Gene therapy starts to make a clinical impact
  – Exactly when? 2018-2020?
  – At what cost by what model?
• Alternative therapies
  – Possible dramatic change inhibitor management 2018
  – Alternatives come to non-inhibitor care? 2021-2022?
• (Not to mention uncertainty of new administration 2017-)
THANK YOU!

Questions?
Discussion?