“Management of Hemophilia: Where are we now and what does the future hold?”

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Professor of Pediatrics, UNM
GMA – Hematology, Bayer
Hemophilia

Blood coagulation defect
(Factor VIII or IX < 1 %)

Spontaneous bleeding complications
Debilitating arthropathy
Circumcision: The first hemostatic challenge!

“For it was taught: if she circumcised her first child and he died, and a second one also died, she must not circumcise her third child...”

Talmud, Yevamoth, 64b
Tzipori, Israel
fourth century
Thrombogram™ measurement in platelet-rich plasma: effect of FVIII infusion in hemophilia

Thrombin (nM) vs Time (min)

- Normal control
- FVIII – 45.0%
- FVIII – 32.0%
- FVIII – 7.0%

Hemophiliac before Rx
Evolution of FVIII / FIX concentrates

- **Subfraction I-O**
  - Cryo-precipitates
  - Donor / plasma screening for HBV
  - Plasma fractionation

- **Low purity pdFVIII concentrates**
  - Heat treatment of pdFVIII

- **Intermediate purity concentrates**
  - Heat-treated concentrates widely available
  - Immunoaffinity, S / D, ion exchange

- **High purity concentrates**
  - HIV / HCV screening

- **rFVIII**
  - Modified rFIX and rFVIII
  - rFVIII: Recombinant FVIII; rFIX: Recombinant FIX; pdFVIII: Plasma derived FVIII; HBV: Hepatitis B virus; HCV: Hepatitis C virus; S / D: Solvent detergent; NAT: Nucleic acid testing

Key NS, Negrier C. Lancet 2007;370:439–48
Life expectancy of patients with hemophilia

Hemophilia treatment goals

- To treat/avoid/abolish bleeding complications
- To avoid joint disease
- To avoid side effects
  - Inhibitors
  - Infection
- To achieve the life the patient chooses
Ideal treatment of severe hemophilia: Prevention of bleeding episodes by regular infusions

Regular self-administration of FVIII or FIX concentrate in order to prevent bleeding episodes (20-40 units/kg – 3x/week or 1x/2days)
The concept of prophylaxis

- Patients with moderate hemophilia (FVIII / FIX 2–5%) have much less frequent hemarthrosis than patients with severe disease (<1%).

- The rationale for prophylaxis is to maintain FVIII / FIX >1% in order to prevent spontaneous bleeding episodes, especially hemarthrosis.
Prophylaxis reduces but does not abolish the occurrence of bleedings

Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia

<table>
<thead>
<tr>
<th></th>
<th>On-demand (n=33)</th>
<th>Prophylaxis (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Bleeds/year</td>
<td>18</td>
<td>1.9</td>
</tr>
<tr>
<td>Joint Bleeds/year</td>
<td>5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

(90% less)
Choices of treatment regimens and different ages at which they are implemented

- Prevention of Life-threatening Bleeding
- Reduction of Progression of Arthropathy and Disability
- Enable Normal Activities of Daily Life and Physical Exercise
- Enable Practically Normal Psychosocial Development without Overprotection
- On-demand Treatment
- Short-term Prophylaxis
- Secondary Prophylaxis in Adolescents and Adults
- Late Secondary Prophylaxis
- Early Secondary Prophylaxis
- Primary Prophylaxis

Age (years)

Challenges of replacement therapy in different age categories

Children
- Venous access
- Inhibitors
- Parents

Adolescents
- Compliance
- Adherence
- Self-management

Adults
- Joint disease
- Infection
- Comorbidities
How should prophylaxis be started in 2016?

- To all boys with severe hemophilia A/B
- Around the age of one year
- At a low dose
- Avoiding “immunological danger signals” first 20 ED
- As “prophylaxis” during first 20 ED instead of “on demand”
Aiming for zero bleeds enables patients to live normal lives

<table>
<thead>
<tr>
<th>Lifetime Joint Bleeds</th>
<th>4 or More</th>
<th>3</th>
<th>0-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhEx</td>
<td>3-7</td>
<td>0-2</td>
<td>0</td>
</tr>
<tr>
<td>X-ray</td>
<td>7-12</td>
<td>0-3</td>
<td>0</td>
</tr>
<tr>
<td>MRI</td>
<td>3-8</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Sources: Funk M et al. Haemophilia 2002; 8:98-103
Standard of care 2015

- Prophylaxis is the gold standard of care for children with severe hemophilia
- Increasing numbers of adults are taking advantage of prophylaxis as well
- On-demand treatment with pdF/rF is used for those who are not on prophylaxis
- Uniform, weight based dosing is most often used
- A “one size/dose fits all” policy has dominated hemophilia treatment for decades
  - And has helped to significantly improve the care
Does “one size fits all” work?

… perhaps, it is time to shift our paradigm …
Hemophilia is characterized by phenotypic variability

Environmental factors
- BMI
- First joint bleed
- Treatment

Genetic factors
- Physical activity
- Factor 8/9 genotype

Environmental factors
- BMI
- First joint bleed
- Treatment

Genetic factors
- Physical activity
- Factor 8/9 genotype

Modifiers of severe hemophilia phenotype
- Small del/ins in a stretch
- Nonconserved splice-site mutations
- Missense mutations

Inherited FVIII:C assay discrepancy
- Missence mutations with discrepancy between FVIII:C assays

Co-inherited genetic variables
- FV Leiden/prothrombin 20210
- AT, PROT C, PROT S deficiencies
- Polymorphisms in F7
- Platelets function
- Polymorphisms in inflammatory, immunoregulatory genes
Patient’s hemophilia severity

Patients are different
(even those with severe hemophilia)

Age at first joint bleed

Bleeding predisposition

Their prophylaxis needs may be very different
Severe hemophilia A: A heterogenous disease with phenotypic variation

- 10 to 15% of patients with phenotypically severe hemophilia (<1% clotting factor activity) have relatively mild disease clinically with less frequent spontaneous bleeding.

- Among patients who bleed, the extent of joint damage tends to vary considerably.
Inter-individual variability

There are no “one-size-fits-all” solutions
Needs of hemophilia patients do differ!

Should the treatment be the same for these patients?
FVIII half-life vs. time-to-trough

Adapted from Collins PW et al. Haemophilia 2011;17:2-10
Factor VIII / IX levels and bleeding rates

- Some patients have normal joints despite factor levels below 1%
  - Orthopaedic Outcome Study (1994): approx. 10% of severe patients (FVIII <1%) entered with all six joints normal
- Some patients bleed with factor levels >1%
- Ahlberg (1965) suggested a 3% threshold level to prevent arthropathy
When should a trough level >3 % be targeted?

- For prolonged periods, in patients with
  - Target joint
  - Repeated breakthrough bleeding episodes
  - Concomitant treatment with antithrombotic agents

- Punctually, in patients
  - Before active physical activities

Tailoring treatment
What have we learned about prophylaxis?
A patient tailored approach

- Age of start may be a more important independent predictor of arthropathy regardless of dosing regimen
- Personalized approach should be applied as individual PK response is variable
- Any form of tailoring of prophylaxis needs to take into consideration the economic resources of the country; for many countries very intense prophylaxis regimens are just not possible

Carcao MD, Iorio A. Individualizing Factor Replacement Therapy in Severe Hemophilia. Semin Thromb Hemost. 2015
Strategies to optimize hemophilia therapy by individualizing the prophylactic regimen

Clinical approach
• Clinical bleeding patterns may be significantly different in patients having similar coagulation factor activity
• Base dosing on observed bleeding pattern and clinical response to treatment

Pharmacokinetic approach
• Standard number of 2 to 3 infusions per week to maintain residual plasma FVIII/FIX activity >1 IU/dL
• Dosing and frequency of infusions according to individual PK data

Laboratory markers such as global hemostasis assays
• Significant correlation between the thrombin-generating capacity of patients and their bleeding symptoms
• Thrombin generation measurement may be useful for determining individually tailored prophylactic regimens
Two ways to use PK

- Tailor your dosing to your life-style
- Tailor your life-style (daily activities) to your dosing (PK profile)
Pharmacokinetics – is it difficult?

- Hemophilia A
  - < 30 min prior FVIII infusion
  - 7 time-points post infusion in older kids
    - 30min, 1, 3, 6, 12, 24, 48 hours
  - At least 5 time-points in patients ≤ 6 years old

- Hemophilia B
  - 7 samples over a period of 72 hours

Bayesian pharmacokinetic evaluation

A Bayesian approach takes into account the individual value and the population profile to predict an individual half-life.

... Do you know the average curve of your population!

Join the WAPPS network at: www.wapps-hemo.org
Parameters to be taken into account when deciding how to treat a patient with hemophilia

| Age | Bleeding phenotype
Joint status | Venous Access | Availability of replacement therapy (qualitative and quantitative) | Goals of treatment (prevention - abolition of bleeds, even subclinical) |
| --- | --- | --- | --- | --- |
| Response to replacement therapy (measured or predicted) | Family support – understanding (partner, parents) | Life-style
Physical activities | Expected quality of life | Adherence and compliance to treatment |
| Availability of tailoring approaches | | Optimal target level | | |
The 10 European Principles of Hemophilia Care

1. A central hemophilia organisation with supporting local groups
2. National hemophilia patient registries
3. Comprehensive care centres and hemophilia treatment centres
4. Partnership in the delivery of hemophilia care
5. Safe and effective concentrates at optimum treatment levels
6. Home treatment and delivery
7. Prophylaxis treatment
8. Specialist services and emergency care
9. Management of inhibitors
10. Education and research
Ideally, hemophilia management in 2016 should conciliate evidenced-based individualization of treatment and care, and integration of individual data in multicenter and international prospective databases.
A memorable past: Now it’s time to look to the future

Recombinant era


Whole blood transfusion Plasma Cryoprecipitate α-derived concentrates Viral inactivation KOGENT® KOGENT®

Prophylaxis becomes possible Prophylaxis becomes standard of care

Challenge: taking treatment to the next level Anti-TFPI and gene therapy

BAY 81-8973 BAY 94-9027

Plasma-derived concentrates Viral inactivation

Whole blood transfusion Plasma Cryoprecipitate Viral inactivation KOGENT® KOGENT®

Prophylaxis becomes possible Prophylaxis becomes standard of care

Challenge: taking treatment to the next level Anti-TFPI and gene therapy

BAY 81-8973 BAY 94-9027
Kovaltry: Bayer’s new standard-acting rFVIII

- A new, full-length, unmodified rFVIII product with the **same amino acid sequence** as Kogenate FS/Bayer, but is produced with enhanced manufacturing technologies.

- Manufactured using an **improved cell bank** compared with Kogenate FS/Bayer; the inclusion of the gene for **HSP70**, which inhibits apoptosis, may increase proper folding of the FVIII protein and expression.

- **No human- or animal-derived** materials are added to the cell culture, purification, or formulation processes.

- A new viral filtration step has been added, which uses **20 nm** pore-size viral filter capsules capable of removing even small non-enveloped viruses and potential protein aggregates.

- Has **consistent glycosylation and increased sialylation** relative to Kogenate FS/Bayer.

- Offers **advanced protection** with proven efficacy and dosing as few as 2x weekly.

PK, pharmacokinetic.
Kovaltry: Manufacturing technique advancements

- Improved consistency in glycosylation and expression compared with rFVIII-FS
- Co-expression of human HSP70
  - Enhances viability of expression cell line
    - Inhibits apoptosis
    - May enhance proper folding of the FVIII protein
- Additional level of virus removal
- Nanofiltration step
  - No human or animal raw materials added to cell culture, purification, or formulation processes

References:

HSP70=70 kilodalton heat shock protein
Consistent Gylcosylation
Kovaltry: Glycan structure

- Consistent glycosylation
- High level of branched glycans
- Highly sialylated galactose branches
- Potential reason for decreased FVIII clearance

FVIII=factor VIII

Kovaltry: Improved protein translates into excellent efficacy at high and low dose regimens
LEOPOLD Kids (PTP, ≤12 years old): Mean ABR per Treatment Arm

- The median number of bleeds is 0 for any bleeds in both age groups and all treatment regimens
- No inhibitors were reported in PTPs
Novel treatment regimens with longer-acting FVIII
Novel treatment regimens with longer-acting FVIII

Fewer injections

Higher troughs

Reduction of bleeds
Physical activity
Higher consumption and cost?

Reduced burden for families
Reduced need for CVLs
More acceptable regimens
Less importance of morning injections

Higher FVIII doses might be needed
Longer periods with low level FVIII
Higher adherence?

…

Advantages of long-acting products

• Potential to dramatically improve treatment and overall quality of life of patients:
  • Maintain higher trough levels than 1% level usually aimed for nowadays, offering greater protection against bleeds
  • Less frequent venipuncture and reduced need for venous access devices
  • Facilitate early prophylaxis in children
  • Fewer doses for bleeds in “on demand” patients
  • Facilitate management of surgical patients

• More obvious advantage for long-acting IX:
  • Five fold prolongation of half-life of FIX, by contrast with factor VIII where not even twofold prolongation has been achieved
# Longer-Acting FVIII Technologies

<table>
<thead>
<tr>
<th>Technology</th>
<th>Description</th>
<th>Mechanism of prolonged half-life</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fc fusion</strong>¹</td>
<td>Fusion of the Fc domain of human immuno-globulin G (IgG) to rFVIII</td>
<td>Binding of Fc to FcRn delays lysosomal degradation of the fusion protein and recycles it back into the circulation¹</td>
<td>Efraloctocog alfa (Biogen Idec)</td>
</tr>
<tr>
<td><strong>Single-chain</strong>²</td>
<td>Single-chain rFVIII</td>
<td>Improves FVIII stability by increasing the interaction between the heavy and light chains, and increasing affinity for vWF²</td>
<td>CSL-627 (CSL Behring)</td>
</tr>
<tr>
<td><strong>Polysialylation</strong>³</td>
<td>Conjugation of linear polymers of N-acetylneuraminic acid (sialic acid) to rFVIII</td>
<td>Improves enzymatic stability and decreases renal excretion by increasing molecular mass³</td>
<td>BAX 826 (Baxter)</td>
</tr>
<tr>
<td><strong>PEGylation</strong>⁴</td>
<td>Covalent attachment of long-chained PEG molecules to rFVIII</td>
<td>Improves stability and reduces clearance of rFVIII⁴</td>
<td>Damoctocog alfa pegol (BAY 94-9027; Bayer); N8-GP (Novo Nordisk); BAX 855 (Baxter)</td>
</tr>
</tbody>
</table>

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### PEGylated FVIII Products in Development

<table>
<thead>
<tr>
<th>Product</th>
<th>Recombinant protein</th>
<th>Modification</th>
<th>Cell line</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Damoctocog alfa pegol (BAY 94-9027)</td>
<td>BDD-rFVIII</td>
<td>Site-specific PEGylation&lt;sup&gt;1&lt;/sup&gt; (PEG 60 kDa branched)</td>
<td>BHK</td>
<td>Bayer</td>
</tr>
<tr>
<td></td>
<td>(Ser743-Gln1638)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N8-GP</td>
<td>BDD-rFVIII</td>
<td>Site-specific glycoPEGylation&lt;sup&gt;2&lt;/sup&gt; (PEG 40 kDa branched)</td>
<td>CHO</td>
<td>Novo Nordisk</td>
</tr>
<tr>
<td></td>
<td>(Ser750-Gln1638)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAX 855</td>
<td>FL-rFVIII</td>
<td>Random PEGylation&lt;sup&gt;3&lt;/sup&gt; (PEG 20 kDa)</td>
<td>CHO</td>
<td>Baxter</td>
</tr>
</tbody>
</table>

BDD=B-domain–deleted; BHK=baby hamster kidney; CHO=Chinese hamster ovary; FL=full length

Two weeks after dosing, four patients had received FIX treatment as on-demand or prophylaxis. Four weeks after dosing, nine patients had received FIX treatment. FIX activity values from these patients were excluded from the pharmacokinetic evaluation after two or four weeks depending on the time when they received their FIX treatment.

What is our goal?

- FVIII level of 1% “wholly insufficient”
- Trough level of 15% “ideal” but “unattainable in short term due to cost”
- “Improving patient quality of life should drive treatment decisions, not economics”
- “Moving forward incrementally to higher baseline levels of 3 or 5% would be a step in the right direction”
- Longer-acting products will certainly help achieve this goal but:
  - Will they be affordable?
  - Should we use long-acting products for prophylaxis but use cheaper current products for breakthrough bleeds?

BAY 94-9027 is a site-specific PEGylated B-domain-deleted recombinant FVIII

- BAY 94-9027 has undergone site-specific PEGylation (60 kDa PEG) to increase half-life
- Half-life of BAY 94-9027 is ~19 hours, as demonstrated in a Phase I study¹

PROTECT VIII Study Design

- 134 patients were treated (prophylaxis, n=114; on demand, n=20)
  - 4 prophylaxis patients discontinued during the run-in phase

- 2x/wk, low bleeders 30–40 IU/kg n=11
- 2x/wk, high bleeders 30–40 IU/kg n=13
- Every 7 days 60 IU/kg n=43
- Every 5 days 45–60 IU/kg n=43

Screening

On-demand treatment Individual dosage

Weeks

Boggio et al. Presented at: European Association for Haemophilia and Allied Disorders; February 11–13, 2015; Helsinki, Finland
BAY 94-9027 Prevented Bleeding at Dose Intervals Up to Every 7 Days

- ABR in 2x/wk low bleeder group was comparable to every-5-days group
- All patients randomized to every 5 days (n=43) remained in the treatment arm

*Weeks 0–36 for on-demand arm, weeks 10–36 for other treatment arms
†Includes all bleeds for the entire time patient was in the treatment arm

Reding et al. Presented at: Congress on Controversies in Thrombosis and Hemostasis; October 30–November 1, 2014; Berlin, Germany
Excellent bleeding control continues in long-term extension

Improved bleeding control in extension likely reflects a learning curve and increased comfort in making treatment and dose decisions

Median ABR for all prophylaxis groups: 1.87

ABR in once weekly arm continues to improve from 0.96 to 0.54
Hemophilia gene therapy

- Can we ultimately achieve a *bona fide* cure by gene therapy in patients suffering from hemophilia ‘A’ or ‘B’?  **YES**
Hemophilia gene therapy: Adeno-associated virus (AAV) & lentiviral vectors (LV)

- Mainly episomal
- Anti-AAV T cells
- Limited innate immune response

- Genomic integration
- No anti-LV T cells
- Innate immune response

Clinical gene therapy for hemophilia B

2-6% FIX activity 6/6 high dose subjects

Long-Term Safety and Efficacy of Factor IX Gene Therapy in Hemophilia B

How to further improve efficacy and safety?

Anti-TFPI antibody for prophylactic hemophilia therapy for inhibitor-/ non inhibitor patients (Hem A/B)

High unmet medical need:
- Current prophylactic treatment for hemophilia:
  - Frequent intravenous infusion
  - Low compliance
  - FVIII resulting in 15–30% inhibitor formation

Goal:
- To develop improved prophylactic treatment to reduce frequency of intravenous injections
- Potential for subcutaneous administration

Approach:
- BAY 1093884, human monoclonal antibody blocking the function of TFPI
  - High affinity (KD <50 pM) to compete with TFPI/Xa binding
  - Sequence optimized framework for potential low immunogenicity
In 2014, Bayer entered into a collaboration agreement with Dimension Therapeutics.

Efforts will be focused on developing and making available a novel gene therapy for the treatment of hemophilia A.

Fully synergistic collaboration that combines Bayer’s strength in hemophilia with Dimension’s strength in novel AAV gene therapy treatments.

AAV, adeno-associated virus.
Alternative MoA to FVIII replacement
Aiming to reduce treatment burden

PROTECT VIII study ongoing

Anti-TFPI therapy

Gene therapy

AAV-based gene therapy
First clinical trials expected within 2 years

AAV, adeno-associated virus; MoA, mechanism of action; TFPI, tissue factor pathway inhibitor.
Thank you!