What are the goals of treatment?
A Haematologist’s perspective

Professor Cedric HERMANS
MD PhD FRCP (Edin, Lon)
Haemostasis and Thrombosis Unit
Haemophilia Clinic
Division of Haematology
Cliniques Universitaires Saint-Luc
Catholic University of Louvain
1200 Brussels, Belgium
cedric.hermans@uclouvain.be
# Speaker disclosures

<table>
<thead>
<tr>
<th>Category</th>
<th>Conflicts of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shareholder</td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td>Grant / Research Support</td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td>Consultant</td>
<td>Pfizer, Bayer, Shire, Novo Nordisk, CSL Behring, Octapharma, Sobi, LFB, CAF-CDF, OctaPharma</td>
</tr>
<tr>
<td>Employee</td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td>Paid Instructor</td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td>Speaker bureau</td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td>Other</td>
<td>No relevant conflicts of interest to declare</td>
</tr>
</tbody>
</table>
THE MOST FAMOUS HAEMOPHILIA PATIENT
Tsarévitch Alexis (1904-1918)

4 year-old

8 year-old

10 year-old
HAEMOPHILIA TODAY : NOT LONGER A ROYAL DISEASE BUT A DISEASE THAT CAN BE TREATED

This young boy with severe haemophilia can now be treated safely and have a normal life.
HAEMOPHILIA

Blood Coagulation Defect

Debilitating Arthropathy
Bleeding complications in patients with haemophilia

Intra-Cranial

Ilio-psoas Muscle

Hip
Factor Level (%)

- >150%
- 50–150%
- 25–49%
- 6–24%
- 1–5%
- <1%

Phenotype
Annual bleeding rate (ABR) without Replacement

- Severe
  - >150%
  - 50–150%
  - 25–49%
  - 6–24%
  - 1–5%
  - <1%
- Mild
  - 0–1
- Moderate
  - 1–5
- 52
The Most Affected Joints in Haemophilia

- 90% of bleeding episodes affect MSK system
- Up to 80% in ankles, knees and elbows
- 10% of hematomas
- Begin by age 2
Why do patients with haemophilia bleed in their joints? Haemotological reason

• Nonvital tissues express low levels of TF.

• These tissues appear to rely more on the intrinsic pathway of coagulation to maintain hemostasis.

• This may explain why hemophilia A and B patients exhibit spontaneous hemorrhages into skeletal muscle and joints.
Why do patients with haemophilia bleed in their joints? Anatomical reason

Elbows, knees and ankles are the most susceptible to acute haemarthrosis

« hinge joint » ➔ synovium gets stuck in the joint

Shoulders and hips are less susceptible to acute haemarthrosis
Consequence of hemarthrosis: Inflammation and hypertrophy of the Synovium

Source: S. Lobet

Source: Novo Nordisk

Interleukin-1
Interleukin-6
TNF-alpha
Musculoskeletal bleeding episodes in patients with haemophilia

<table>
<thead>
<tr>
<th>Features</th>
<th>Location</th>
<th>Reason</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Joint</td>
<td>Spontaneous</td>
<td>Clinically patent</td>
</tr>
<tr>
<td></td>
<td>Muscle</td>
<td>Induced (trauma, physical activity)</td>
<td>Suclinal</td>
</tr>
</tbody>
</table>

**Clinically** patent
Symptomatic

Clinical haemarthrosis
Large amount of blood
Clinically patent

Subclinical haemarthrosis
Small amount of blood
Clinically silent

Asymptomatic
Treatment of haemophilia

Replacement or substitutive therapy by regular intravenous infusions of exogenous clotting factor F8 or F9 to correct clotting factor deficiency in order to treat or prevent bleeding episodes.

Injection of missing Factor VIII or IX
Treatment of haemarthrosis should not be delayed.
WITH A JOINT BLEED, TIME LOST IS JOINT AND CARTILAGE LOST

Visit our Website: http://www.hemophilie-ucl.be and discover our computer-generated movie on blood coagulation and haemophilia
The benefits of early treatment: a well-known concept in various therapeutic areas

<table>
<thead>
<tr>
<th>CARDIOLOGY</th>
<th>Acute myocardial infarction</th>
<th>Saves cardiac muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEUROLOGY</td>
<td>Acute ischemic stroke</td>
<td>Saves neurones</td>
</tr>
<tr>
<td>HAEMOPHILIA</td>
<td>Acute haemarthrosis</td>
<td>Saves cartilage</td>
</tr>
</tbody>
</table>
Requirements for early treatment of bleeding episodes in patients with haemophilia

PATIENT
- Education
- Good understanding
- Rapid recognition
- Good venous access

TREATMENT
- Replacement or Bypassing
- Haemostatic efficacy
- Convenience of use

HEALTH CARE SYSTEM
- Home-treatment
- Education
Better than early treatment, PREVENTION of haemarthrosis is the optimal option
Ideal treatment of Severe Haemophilia: Prevention of bleeding episodes by regular infusions

Regular self-administration of F8 or F9 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 haemarthrosis than patients with severe disease (<1%)

- The rationale for prophylaxis is to maintain FVIII / FIX >1% in order to prevent spontaneous bleeding episodes, especially haemarthrosis
Prophylactic Treatment of Haemophilia A: Basic Principles

- Regular infusions of FVIII concentrates aim to convert severe into moderate
- No consensus on optimal prophylaxis regimen
- Considering a recovery of 2, and a half-life of 9-13 hours for currently available FVIII concentrates, 2-3 infusions per week are needed
Choices of Treatment Regimens and Different Ages at Which They Are Implemented

How should prophylaxis be started in 2017?

- To all boys with severe haemophilia A/B
- Around the age of one year
- At a low dose, i.e. usually 25 U/kg
- Frequency of every 2\textsuperscript{nd} day/trough guided
- Avoiding “immunological danger signals” first 20 ED
- As “prophylaxis” during first 20 ED instead of “on demand”
# Data Supporting Prophylaxis: Retrospective and Prospective Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Outcome</th>
<th>Prophylaxis</th>
<th>On-Demand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liesner et al. 1996¹</td>
<td>All bleeds/year (median)</td>
<td>1.5</td>
<td>14.7</td>
</tr>
<tr>
<td>Szucs et al. 1998²</td>
<td>Joint bleeds/6 mos (mean)</td>
<td>3.1</td>
<td>8.8</td>
</tr>
<tr>
<td>Yee et al. 2002³</td>
<td>Joint bleeds/year (median)</td>
<td>0.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Panicker et al. 2003⁴</td>
<td>Major bleeds/year (mean)</td>
<td>1.9</td>
<td>15.5</td>
</tr>
<tr>
<td>Feldman et al. 2006⁵ (Interim results: prophylaxis only)</td>
<td>Joint bleeds/year (mean)</td>
<td>1.2</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A = not available.

### Prophylaxis Reduces 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</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=33)</td>
<td>(n=32)</td>
</tr>
<tr>
<td><strong>Total Bleeds/year</strong></td>
<td>18</td>
<td>1.9 (90% less)</td>
</tr>
<tr>
<td><strong>Joint Bleeds/year</strong></td>
<td>5</td>
<td>0.5 (90% less)</td>
</tr>
</tbody>
</table>

PK of FVIII and the risk of haemarthrosis

Peak / time spent in reduced bleeding risk zone: Important to prevent activity related and traumatic bleeds

Trough Important to prevent spontaneous break through bleeds

AUC Important to prevent subclinical bleeds, maximizing the window of protection

Collins PW: Plenary lecture „Personalized Prophylaxis“ WFH congress July, 10 2012
RISKS OF STOPPING PROPHYLAXIS IN ADULTS

• Haemophiliacs do not lose the risk of joint bleeding at the age of 18

• Switching to “on-demand” will lead to haemarthroses – how many before haemophilic arthropathy develops ?

• Risk of losing the benefits of the financial and human resource invested in childhood
• Introducing prophylaxis in adulthood is effective in reducing joint bleeding and improving joint function
## Number of Bleeds on Secondary Prophylaxis

<table>
<thead>
<tr>
<th>Median (interquartile range) number of bleeds per patient</th>
<th>On-demand treatment*</th>
<th>Prophylactic treatment†</th>
<th>P value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Joint bleeds</strong></td>
<td>Months 1–6 (n = 20)</td>
<td>Months 7–13 (n = 19)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>15.0 (11–26)</td>
<td>0 (0–3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All bleeds</strong></td>
<td>20.5 (14–37)</td>
<td>0 (0–3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Spontaneous bleeds</strong></td>
<td>13.5 (7–29)</td>
<td>0 (0–1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Trauma bleeds</strong></td>
<td>2.5 (0–9)</td>
<td>0 (0)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Median observation period was 192 days. †Median observation period was 177 days. ‡Wilcoxon test.

Collins et al JTH 2009 8, 83-89
Patients receiving prophylaxis had 15.2 times fewer bleeds

Note: Median treatment duration at time of data analysis was 1.4 years; data shown are for all nondiscontinued patients who completed at least 1 study year.

*On demand vs prophylaxis; adjusted for stratification variables (presence/absence of target joints and number of previous BEs).

Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens.

- Current prophylactic regimens, although very effective, do not completely prevent joint disease in a long-term perspective.

- Joint arthropathy in primary prophylaxis develops over many years, sometimes over a decade or even longer time periods.

- The ankle joints are the first and most severely affected joints in those patients and thus may serve in outcome assessment as an indicator of early joint arthropathy when followed by ultrasound or magnetic resonance imaging.

Patients with Different Lifestyle and Activity Level may need Different FVIII Trough Levels

- >3% ?
- 1% ?
- 10% ?
Individualized prophylaxis should be

- Based on FVIII PK parameters
- Based on bleed pattern
- (presence of target joints/joint damage)
- Tailored to activity level (sports)
- Tailored to personal circumstances
- Based on all available information
- Efficient

Standard prophylaxis not optimal for everybody

Patient with an average half-life (25 IU/kg every other day)

Patient with a short half-life (25 IU/kg every other day)

Time spent with FVIII plasma levels <1%

Increased risk for break through bleeds
**PHARMACOKINETIC DOSING**

A new ambition in haemophilia therapy

Not only an issue of treatment availability and intensity

Only achievable with major collaboration of the patient and his family
### Aiming for zero bleeds

**Patient–doctor relationship**

<table>
<thead>
<tr>
<th></th>
<th>4 or more</th>
<th>3</th>
<th>0–2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</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>

**Lifetime joint bleeds**

**Joint scores**

**Joint health**

**Patient impact**

Which FVIII Trough Levels are needed for Zero Joint Bleeds?

Correlation of endogenous FVIII level and annual number of joint bleeds

INTEGRATION OF REAL WORLD-DATA COLLECTION, TAILORED CARE AND PATIENT EMPOWERMENT

Personalized Medicine
1. PK profiling
2. Bleeding risk profiling
   1. Bleeding phenotype
   2. Target joints
   3. Joint status
   4. Work and sport activity
   5. Lifestyle
   6. Compliance
3. Bleeding recognition

Patient Empowerment
1. Disease and treatment understanding (adherence) / psychological support
2. Shared treatment and goals decision making (GAS)
3. Life-style and activity adjustment
4. Promotion of self-management

Real-World Data Collection
Treatment tracking
(recording of bleeding episodes and factor consumption)
Outcome tracking

Patient-centric prophylaxis

Haematological treatment of hemophilia

<table>
<thead>
<tr>
<th>TODAY</th>
<th>TOMORROW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compensation of defective production of FVIII or FIX</td>
<td>&quot;Cure&quot;</td>
</tr>
<tr>
<td>Factor replacement therapy with plasma-derived or recombinant concentrates</td>
<td>Gene therapy</td>
</tr>
<tr>
<td>Non-factor replacement / Disruptive therapy</td>
<td>Endogenous production of natural/unmodified FVIII or FIX</td>
</tr>
</tbody>
</table>
Inflammation is key to hemophilic arthropathy

Alok Srivastava  CHRISTIAN MEDICAL COLLEGE, VELLORE

Could IL-1 blockers prevent blood-induced joint damage in hemophilia?

• It would be ideal if there were oral drugs which could be taken soon after a joint bleed for a short period of time during the period associated with damaging inflammatory responses along with CFC replacement to prevent further bleeding.

• This could be particularly significant for the vast majority of patients in the world who do not have access to prophylaxis with CFC.

Haemarthrosis and targeted biological therapies

Antibodies to block TNF-a / IL-1

antiangiogenesis drugs
Impact of innovation on haemophilia care

- More efficient treatments
- Persistent control of FVIII or FIX deficiency
  - Cure of the disease
  - No BLEEDS
- More time and resources for assessing and following non-bleeding consequences of haemophilia
The goal / ambition of the haematological treatment of haemophilia should be a complete abolition of all bleeding episodes and a full preservation of the musculo-skeletal system. This is now achievable with current treatment options in a large proportion but not all patients with severe haemophilia. The focus should be on patients with an Annual Bleeding Rate (ABR) > 0. In these patients, different strategies should be implemented to better control their disease.
Thank you for your attention