NOVEL TREATMENT OPTIONS FOR HAEMOPHILIA

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HAEMOPHILIA is a deficiency of clotting factor resulting in inadequate haemostasis and bleeding. Treatment requires replacement of the deficient factor.
Degrees of Severity in Hemophilia

Normal

Factor VIII or IX activity
60 - 200%

Mild
5 - 25%

Moderate
1 - 5%

Severe
< 1%
## Clinical presentation in severe haemophilia

<table>
<thead>
<tr>
<th>Neonatal period</th>
<th>Symptomatic CNS bleed rare</th>
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<tbody>
<tr>
<td></td>
<td>Prolonged bleeding post</td>
</tr>
<tr>
<td></td>
<td>circumcision</td>
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<tr>
<td>3 – 4 months</td>
<td>Palpable subcutaneous</td>
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<tr>
<td></td>
<td>ecchymoses</td>
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<tr>
<td>12 months (onset of walking)</td>
<td>More extensive haematomas</td>
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<tr>
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<td>Oral mucosal membrane bleeding</td>
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<tr>
<td>2 years</td>
<td>Large soft tissue and periarticular</td>
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<tr>
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<td>haemorrhages</td>
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<tr>
<td>3 -4 years</td>
<td>Bleeding into muscles and joints.</td>
</tr>
<tr>
<td></td>
<td>Knees, elbows, ankles most</td>
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<tr>
<td></td>
<td>common</td>
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</table>
Hemophilia is a Life-Long Disorder
COMPLICATIONS

• BLEED RELATED
  • MUSCULOSKELETAL
    Inadequately treated bleeds into muscles and joints results in deformity and crippling CNS bleeds

• TREATMENT RELATED
  • INHIBITORS
  • TRANSFUSION TRANSMITTED INFECTIONS
ACUTE JOINT BLEEDS

--Pain+++ 
– warm/ hot 
– swelling 
_ limited ROM 
– respond to factor
INFLAMMATORY RESPONSE TO BLOOD IN JOINTS

Angiogenesis
- Vascular endothelial GF
- Basic fibroblastic GF
- Matrix metalloproteinase-9
- TNF-α
- Cycloxygenase-2

Inflammatory Cytokines
- Interlukin 1-β
- Interlukin 6
- TNF-α

Proto-oncogene
- c-myc and mdm2 expression

Management of the acute haemorrhagic episode  
At home or in hospital

1. **IMMEDIATE REPLACEMENT OF DEFICIENT FACTOR**
   - IV infusion of the deficient FACTOR to a level adequate to stop haemorrhage

2. **PAIN RELIEF**
   - infusion of deficient factor
   - avoid drugs with aspirin – deleterious effect on platelet function may result in increased bleeding

3. **SURGICAL INTERVENTION** – rarely necessary

4. **PHYSICAL THERAPY**
ANNUAL BLEED RATE/YR

- Joint
- Other

ON-DEMA

PROPHY
OUTCOMES OF PROPHYLAXIS IN CHILDREN

• Early start of prophylaxis reduces musculoskeletal/haemophilic arthropathy
• Treatment of choice in severe haemophilia
• Convert severe haemophilia to moderate haemophilia
• Decrease annual bleed rate
• Prevent or reduce arthropathy
• Improve quality of life, decrease school absence
Example of Factor Survival Rate

**Factor VIII**
- Infusion
- 8 hours: 50%
- 16 hours: 25%
- 24 hours: 12.5%
- 32 hours: 6.5%
- 32 hours: <1%

**Factor IX**
- Infusion
- 16 hours: 50%
- 32 hours: 25%
- 48 hours: 12.5%
- 72 hours: 6.5%
- 72 hours: <1%
Novel products:

Development based on recombinant technology:
- Can we improve on nature?

Products under development include:
- Biosimilars
- Long-acting factor VIII and IX
- Porcine factor VIII
- Activated factor VII analogues
- Anti-TFPI antibodies
- Transgenic factor VIII & IX manufactured using animals

Success not guaranteed: several failures/problems encountered already:
- Need for vigilance for unexpected problems
NOVEL FACTORS

Alternative drug delivery – oral, subcutaneous, inhalant.

Redesign of therapeutic proteins to prolong half-life and reduce the frequency of concentrate administration.

PEGylation

Fusion with immunoglobulins/ albumin – rFviii/Fix fused to Fc region of IgG prevents catabolism in Lysosome.

rFVIIIFc – mean T1/2 – 19 hrs (cf 9 hrs)
rFIXFc - mean T1/2 – 82 hrs (cf 19hrs)
Summary profiles comparing N9-GP to previous FIX – normalised to 50 U/kg
“Pharming”: using transgenic animals to manufacture recombinant human therapeutic proteins (e.g. coagulation factors, antithrombin, α2-antitrypsin)
Merry Christmas for Patients with Hemophilia B

Katherine P. Ponder, M.D.

Hemophilia B (also known as Christmas disease) is due to deficiency of coagulation factor IX (FIX). In this issue of the Journal, Nathwani et al. report the first unequivocal evidence of successful gene therapy for hemophilia B—a major advance in this field. This success for hemophilia may translate into gene therapy for other blood protein deficiencies.

FIX concentrates were first used in the late 1960s to treat patients with hemophilia B, and their routine use for bleeding episodes increased the median lifespan to 63 years. Although enthusiasm for protein therapy was temporarily dampened by the HIV epidemic in the early 1980s, improved methods for producing FIX have increased its safety. Recently, implementation of
Summary

10 Patients

Follow up 1 a 4.5 years

Sustained FIX Expression 3-5% in all pts.

4 of 7 no prophylaxis; no spontaneous bleeds; significant improvement in QOL

Transaminitis in patients on higher vector doses controlled with steroids ? To give at time of vector infusion in future.
Hurdles - Glenn Pierce

Past - immunogenicity of gene product - none seen in humans; liver toxicity seen, controlled; no risk of sexual transmission

Present - high quality AAV, sufficient protein expression; long term safety; no standardized assays to measure vectors and anti-AAV antibodies

Future - new vector that can target 100% of population; scale up production of vectors; gene editing to fix the defect with stem cells
FVIII GENE THERAPY

Packaging of FVIII in AAV vectors successful

Therapeutic levels of FVIII Achieved

Gene therapy trial started now
Inhibitors in Haemophilia

INHIBITORS are antibodies that may develop and render the replacement factor ineffective.

Inhibitor development is the most serious and challenging complication of haemophilia treatment with higher levels of morbidity, mortality and poorer quality of life than patients without inhibitors.
INHIBITOR INCIDENCE

Frequency 20-30% in severe FVIII deficiency
(Frequency 3-4% in severe FIX deficiency)
65% of all inhibitors occur in first 20 exposures to administered FVIII
95% of all inhibitors occur in first 50 exposures

Low Responder Inhibitor: < 5 BU
High Responder Inhibitor: > 5 BU
Risk factors for Inhibitors

Modified from J. Astermark, Haemophilia (2006), 12 (Suppl. 3), 52-60
• **Type of Factor Gene mutations**
  
  High risk mutations (assoc with no circulating antigen)
  - null mutations
  - large deletions
  - inversions
  - nonsense mutations
  - Family history of Inhibitors

  The lower frequency of inhibitors in mild/moderate haemophilia FVIII is thought to be related to the type mutation (causative point mutations vs null mutation).
• Polymorphisms

Polymorphic genes encoding for cytokines and immune regulatory factors

**TNF-alpha**
- Pro-inflammatory and immunomodulatory properties
- Polymorphisms in promoter region
- Linked to *autoimmune diseases* eg SLE, IBD

**Interleukin-10**
- Anti-inflammatory cytokine
- Also promotes antibody production of B-lymphocytes as seen in patients with *autoimmune disease* (SLE, myaesthenia gravis)
MHC – Class I and II alleles

MHC plays a central role in the immune system and includes the HLA class I and II

HLA class I, alleles A3, B7, C7 and
HLA class II alleles DQA0102, DQB0602
and DR15 increased risk of inhibitors

HLA C2, DQA0103, DQB0603 and DR13 have been shown to have a protective effect against inhibitor development
Risk factors for Inhibitors

Modified from J. Astermark, Haemophilia (2006), 12 (Suppl. 3), 52-60
BASIC CONCEPT OF IMMUNE TOLERANCE FOR ERADICATING THE INHIBITOR

• Continuous exposure to the antigen will eventually result in loss of the antibody, tolerance to the product and restore normal factor pharmacokinetics.

• Break through bleeds require treatment with by-passing agents (Novoseven rFVIIa; FEIBA)

• ITI can be prohibitively expensive
How can we reduce/prevent risk of inhibitors?

• Non modifiable (Patient genetics)

  vs

Modifiable (treatment/environmental)

• Identify high risk patients (family history/high risk gene mutation/intensive factor treatment at first exposure)

• Advocate early prophylaxis in childhood to induce peripheral anergy and tolerance of FVIII specific T lymphocytes

• Be aware of danger signals
Cost benefit

TREATMENT OF INHIBITOR
- Bleeding episode – By passing agents (rFVIIa; Feiba; cost R50000/bleed); conservative
- Eradication of inhibitor – immune tolerance
- High Dose FVIII(100u/kg) 20000u
- Low Dose FVIII(50u/kg) 10000u
- Cost R50000-R100000
- QOL

PREVENTION OF INHIBITOR
- Low Dose prophylaxis
- Weekly treatment (300u) to 20-30 exposures
- Avoid first treatment during bleeding episode, infection, vaccination or surgery.
- Cost R15000-R30000 (25-50 exposures)
- QOL
Bispecific anti-IXa/X antibody:

- FVIII is essentially the inert scaffold on which FIXa and FX assemble to generate Xa on surface of platelets
- Bispecific monoclonal (hBS23) antibody holds FIXa and FX in spatially correct alignment, mimicking cofactor function of FVIII and leading to generation of Xa
- Not affected by presence of inhibitors
- Clinical trials are in progress
Basic Laboratory Evaluation

Full Blood count, differential and platelet count

Partial thromboplastin time (PTT)

Prothrombin time (PI or INR)
THANK YOU FOR YOUR ATTENTION !!

THANK YOU TO THE PAED HAEM ONC TEAM

Sr Bongi Mbele – Haemophilia Nurse Coordinator

NHLS Coag lab staff

Kabelo – Clinic admin, Pt Registry
Signs and Symptoms

- Bleeding from umbilical cord, mouth, gums, or after circumcision.
- Characteristic bruising of lower extremities, joint and soft tissue and muscle bleeds, or bleeding after surgery, venipuncture, trauma or dental work.
- Late signs: Severe crippling in older children with severe deformities of limbs and joints.