Future prospects for the treatment of haemophilia

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Topics to be covered:

- Extended half-life FVIII & IX products
- Novel products (not coagulation factors):
  - Concizumab
  - Emicizumab
  - Fitusiran
- Gene therapy
Longer-acting products:

• Half-life of FVIII & IX can be extended by:
  – Pegylation, fusion to IgG or albumin or modification of amino acid sequence

• Significant advantages of these products:
  – Less frequent infusions
  – Higher trough levels feasible
  – Less need for venous access devices
  – Facilitates earlier prophylaxis and compliance

• Clinical benefit is particularly evident for longer-acting novel FIX products:
  – 5x increase in half-life vs 1.5 x increase for FVIII
Pharmacokinetics of N9-GP:


\[ T_{\frac{1}{2}} \, 93 \text{ hours (5 times longer than conventional plasma-derived and recombinant FIX)} \]
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 to higher baseline levels of 3 or 5% would be a step in the right direction”
- “The research challenges of the last decade may soon be replaced by advocacy challenges”
Practical considerations (1):

• Consensus need on target trough levels: 3-5% ?
• Limited data available indicate that T½ in paediatric patients is significantly shorter than quoted headline figure derived in adults
• Data from PUP studies required to determine immunogenicity of these new products
• Not feasible to compare conventional and longer-acting products in usual “cents/unit” way
• Adoption of novel products is likely to drive the use of chromogenic assays in laboratories
Assay problems with EHL products:

• “For some extended half-life FVIII and FIX products, some one stage assays are entirely unsuitable for monitoring purposes.”

• “For most products and assay reagents, chromogenic FVIII or FIX assays can be safely used with conventional plasma standards.”

• “If one stage assays are used then they should be performed using carefully selected reagents/methods which have been shown to recover activity close to the labelled potency of the specific product being monitored.”
Practical considerations (2):

- Hand held “point of care” devices for coagulation factor assay would also be very useful
  - Particularly useful in less affluent countries without access to sophisticated laboratory equipment
  - Patients could monitor their treatment at home
  - Could be product specific or generic

- Consensus on global assays of haemostasis (e.g. thrombin generation, thromboelastography) also needed for clinical monitoring:
  - Treatment with emicizumab; concizumab; fitusiran
  - Patients with inhibitors undergoing surgery
Practical considerations (3):

• Focus has hitherto been on trough levels but peak levels will also require consideration:
  – People who are very active or who play sports may need high peaks at these times
  – Time spent at low levels more relevant to people with low levels of activity

• Once weekly infusions of FIX feasible

• Data from FVIII studies suggest at least twice weekly dosing will be required

• Compliance with therapy will be important:
  – Consequences of missing a dose of long-acting product could potentially be more significant
Factor VIII:

How will new products be adopted in clinical practice?

**Obvious clinical benefit:**
- Young children
- Patients on regular prophylaxis
- Poor venous access
- Reluctance to self-infuse/needle phobia
- Active lifestyle requiring high target trough levels

**No compelling advantage:**
- On demand therapy
- Record of poor treatment compliance
- Mild haemophilia
- Surgery
- Immune tolerance

Limitations of coagulation factor concentrates:

- Need for intravenous infusion
- Limited duration of action (even extended half-life FVIII and FIX products)
- May be immunogenic and provoke inhibitors
- Will not be clinically effective in presence of inhibitory antibodies
- Only work in one specific condition: not of general benefit in all bleeding disorders
Emicizumab:

• FVIII is essentially the inert scaffold on which FIXa and FX assemble to generate Xa on surface of platelets

• Emicizumab is bispecific monoclonal which 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

• Xa generation equivalent to factor VIII levels of 1-10 % can be achieved \textit{in vitro}
Emicizumab:

Figure 1 A bispecific antibody therapy to restore cofactor activity in the intrinsic tenase complex in hemophilia A. In the normal physiological intrinsic tenase complex (left), FVIIIa functions as a scaffold for the optimal alignment of the serine protease FIXa and its substrate, FX. FIXa and FX bind the procoagulant phospholipid surface (activated platelets in normal hemostasis) in a calcium-dependent manner via their N-terminal Gla domains, whereas FVIIIa binds in a calcium-independent manner through its C-terminal C1 and C2 domains. In hemophilia A, FVIIIa is either absent, reduced in amount or functionally defective. Kitazawa et al. have now generated a bispecific antibody that binds FIXa and FX, which continue to mediate phospholipid interactions through their Gla domains (right).

Phase 3 studies of emicizumab:

- **HAVEN 1**: weekly prophylaxis in adolescents and adults aged 12 years and older with haemophilia A and factor VIII inhibitors.
- **HAVEN 2**: weekly prophylaxis in children under the age of 12 years with haemophilia A and factor VIII inhibitors.
- **HAVEN 3**: prophylaxis with emicizumab administered once a week or every other week, in patients aged 12 years and over with haemophilia A without inhibitors to factor VIII.
- **HAVEN 4**: prophylaxis every four weeks in patients aged 12 years and older with haemophilia A with or without inhibitors to factor VIII.
Emicizumab for prophylaxis:

• Results of Phase 3 HAVEN 1 study
• 109 patients from 43 centres in 14 countries
• All had history of high titre inhibitors (≥5BU)
• Median age 28 years (range: 12-75)
• Randomly assigned to emicizumab prophylaxis (group A) or no prophylaxis (group B)
• Prophylaxis regime: 3.0 mg/kg for 4 weeks, followed by 1.5 mg/kg weekly thereafter
• Followed up for at least 24 weeks
Emicizumab for prophylaxis:

- The annualized bleeding rate was 2.9 events among participants who were randomly assigned to emicizumab prophylaxis versus 23.3 events among those assigned to no prophylaxis
  - Significant difference of 87% in favour of emicizumab prophylaxis (P<0.001)
- A total of 22 participants in group A (63%) had no bleeding events, as compared with 1 participant (6%) in group B
- Now licensed (Hemlibra®, Roche) by FDA and EMA for prophylactic treatment of children and adults with haemophilia A and inhibitors
Figure 1. Annualized Bleeding Rate in Trial Groups A, B, and C.

The annualized bleeding rate was calculated with the use of a negative binomial-regression model. Participants in groups A and B had previously received episodic treatment with bypassing agents; participants in group C had previously received prophylaxis with bypassing agents. Group D was not included in the current analysis owing to the short follow-up at the time of data cutoff.
Impact of emicizumab:

• Will be widely adopted for prophylaxis in adults and children with persistent inhibitors and bleeds:
  – Once weekly s/c injection effective and convenient
• Of no use in haemophilia B with inhibitors
• Data from HAVEN 1 study highlighted risk of thrombosis with repeated high doses of FEIBA
  – “Black box” warning mandated by FDA
  – NovoSeven likely to be preferred option for treatment of breakthrough bleeds
• Not intended for sole use in setting of surgery
The role of TFPI:

Blocking of Tissue Factor Pathway Inhibitor (TFPI) may facilitate haemostasis initiated by FVIIa/TF
TFPI inhibition: concizumab

- Concizumab (mAb 2021) is a humanized monoclonal antibody against TFPI with high affinity for the Kunitz-2 domain, the binding site of Fxa
  - Grown in serum-free CHO cells
- Concizumab blocks TFPI inhibition of TF–FVIIa, resulting in increased FXa and thrombin generation \textit{in vitro}
- Could concizumab be useful as adjunctive or prophylactic treatment in patients with haemophilia A and B, with or without inhibitors?
Concizumab:

- Liquid formulation in pen designed for s/c injection
- No safety concerns identified in Phase 1 study in 28 normal volunteers and 24 haemophilic subjects
  
  - No serious adverse events, such as antibody formation
  - One case of superficial thrombophlebitis

- Concizumab induces increased thrombin generation in plasma from haemophilia patients (and healthy subjects) measured by the thrombin generation assay
  

- A multicentre, blinded, phase Ib multiple-dose study (explorer 3) in patients with haemophilia A has recently been completed: results are awaited
Fig. 1. Thrombin generation parameters of individual plasma samples from patients with severe haemophilia B (a, d, g), and severe haemophilia A with (b, e, h) and without inhibitors (c, f, i) in the ex vivo spiking study. Thrombin generation was measured in platelet-poor plasma from 18 patients spiked with increasing concentrations of concizumab. These panels show results for blood drawn in the absence of corn trypsin inhibitor: (a–c) peak thrombin (nM); (d–f) endogenous thrombin potential (ETP; nM min); (g–i) lag time (min).
Targeting antithrombin:

- Fitusiran [ALN-AT3] (Alnylam/Sanofi) reduces antithrombin synthesis by targeted RNA interference
- Once monthly subcutaneous injection
- Dose dependent knockdown of antithrombin by up to 86%
- Significant improvement in thrombin generation and whole blood clotting
  - Reduction in bleeding frequency in haemophilia
Fitusiran:

- Phase 1 dose-escalation study: 4 normal volunteers and 25 patients with severe or moderate haemophilia A or B without inhibitors
- Participants with haemophilia received three injections of fitusiran:
  - Administered either once weekly (at a dose of 0.015, 0.045, or 0.075 mg/kg) or once monthly (at a dose of 0.225, 0.45, 0.9, or 1.8 mg/kg or a fixed dose of 80 mg).
- Study objectives: assess the pharmacokinetics and pharmacodynamics and safety of fitusiran
- Dose dependent reduction in antihrombin levels of 70-89% from baseline
- No thromboembolic events
Figure 3. Relationship between Antithrombin Level and Thrombin Generation.

Shown are paired antithrombin levels and peak values for thrombin generation in all the participants with hemophilia A or B and in healthy volunteers for whom data were available. The dashed line shows the median baseline values for the participants with hemophilia A or B. Antithrombin levels were determined relative to a standard human plasma reagent with a defined antithrombin activity level calibrated against a World Health Organization reference.
Update on fitusiran clinical trial:

- Patient with haemophilia A without inhibitors enrolled in phase 2 study died
  - Cause of death identified as cerebral venous thrombosis only after patient died
- Prior to death, patient treated himself with three doses of factor VIII for apparent right hip bleed after exercise
- When patient developed severe headache, was diagnosed as subarachnoid haemorrhage and treated intensively with more factor VIII
- Clinical trial suspended in September 2017
  - Company now plans to restart clinical trial after reaching agreement with FDA on changes to protocol
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
Fig. 3 AAV vector uptake, in-cell processing and initiation of the immune response. Fenestrated endothelium of hepatic sinusoids allows the AAV vector to freely reach the hepatocyte. Once reaching the target cell, the vector binds an extracellular receptor and co-receptor specific to the capsid motifs. After an uptake by endocytosis, the vector is trafficked in the cytoplasm in early then late endosome. Acidification of the endosome modifies the capsid conformation. After endosomal escape, the AAV vector enters the nucleus via the nuclear pore complex. Capsid uncoating and release of the proviral DNA precede the synthesis of the 2nd strand of DNA. The viral genome then persists either as a non-integrated single- or double-stranded epismome (99%) or (small percentage) integrates into the host genome (1%). Expression of the transgene is followed by synthesis of the protein of interest. Cell-mediated immune responses are initiated by the degradation of capsid or the transgene product (protein) in the proteasome and presentation at the surface of the transduced cell via the major histocompatibility complex I. CD8+ T cells recognise the antigen at the cell surface and initiate the immune cascade. Neutralising antibodies bind to the vector in the bloodstream and impair or prevent successful transduction of the organ target. MHC1: major histocompatibility complex I.
Gene therapy for haemophilia B:

• Update on UCL/St Jude study:
  – 12 subjects now treated with AAV8 vector
  – FIX level in first six who received highest dose $2 \times 10^{12}$ vg/kg was $5.1 \pm 1.7\%$ after at least 3 years of follow up

• Spark Therapeutic/Pfizer SPK-9001 study:
  – Novel engineered AAV vector containing gain-of-function $F9$ Padua (R338L) variant
  – Mean FIX activity level for 10 patients after a single i/v infusion of vector was $33.7\pm18.5\%$ (range: 14 – 81%)
  – Range of follow up: 28 to 78 weeks
  – Mean ABR reduced: 0.4 after treatment (11.1 before)
  – Two patients had a transient elevation in liver enzymes
Gene therapy for haemophilia A:

- Biomarin BMN270 uses 5.2 kb SQ linker codon-optimized FVIII expression cassette packaged in AAV5 vector
- Participants were enrolled sequentially into one of three dose cohorts (low dose [6×10^{12} vg/kg; one participant], intermediate dose [2×10^{13} vg/kg; one participant], and high dose [6×10^{13} vg/kg; seven participants]) and were followed up for 52 weeks
- In the high-dose cohort, the factor VIII activity level was > 5 IU/dl between weeks 2 and 9 after gene transfer in all seven participants
  - The level in six participants increased to a normal value (>50 IU/dl) that was maintained at 1 year after receipt of the dose
Figure 2. Factor VIII Activity Levels in the High-Dose Cohort.

Factor VIII values are from the one-stage assay performed by a central laboratory (Esoterix), with normal values of 50 to 150 IU per deciliter (shaded area). Data were available for all seven participants in the high-dose cohort, except that data were not available for Participant 7 at week 32. The plot is based on the median values of factor VIII activity within 4-week windows for each participant. The horizontal line within each box indicates the median value among the participants. The lower and upper boundaries of the box represent the 25th and 75th percentiles, respectively. The ends of the whisker lines represent the minimum and maximum values within 1.5 times the interquartile range from the lower and upper box boundaries. Mean values are indicated by diamonds. Factor VIII activity levels below the limit of quantitation were imputed as being 0.5 IU per deciliter. Factor VIII activity levels within a 72-hour period since the last consumption of factor VIII were excluded. Data points beyond the range (i.e., 1.5 times the interquartile range from the lower and upper box boundaries) were considered to be outliers and are marked with an x.
Gene therapy for haemophilia A:

- In the high-dose cohort, the median ABR decreased from 16 events before the study to 1 event after gene transfer
- Factor VIII use for participant-reported bleeding ceased in all the participants in this cohort by week 22
- The primary adverse event was an elevation in the serum alanine aminotransferase level
- No neutralizing antibodies to FVIII detected
Unresolved issues in gene therapy:

• Duration of effect remains unclear
  – Immune responses precludes repeated treatment
• High prevalence of innate immunity to AAV
  – ≈50% against AAV8 (up to 80% reported in China)
• Unpredictability of transaminitis
• AAV vector integration into genome may occur rarely, introducing potential risk of oncogenesis
• Cost likely to be high, despite expectations:
  – Cost of “Glybera” developed by uniQure for lipoprotein lipase deficiency was around €1M
Principal conclusions:

• Novel products with extended half-lives have the potential to dramatically improve lives of patients:
  – Benefit is particularly evident for novel FIX products
  – Consensus on target trough levels is required

• Emicizumab likely to transform outlook for patients with haemophilia A with inhibitors

• Adoption of new products will drive changes in laboratory practice

• Cure by gene therapy has become a realistic goal