Personalized hemophilia treatment

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Evolution of Hemophilia Therapies:

- **Early 1900s**: Fresh blood can be transfused to patients, but life expectancy is limited to 13 years.
- **1950s**: Plasma becomes available with limited amount of factor protein.
- **1970s to 1980s**: Factor concentrates are available, but infection poses serious health hazard e.g., hepatitis C and HIV.
- **1990s**: First non plasma derived factor products become available using recombinant DNA technology.
- **2014**: The first extended half-life products enter the market.
- **Expected 2022**: Multiple clinical programs are in development for hemophilia gene therapy, potentially to "cure" hemophilia with one injection.
Future Therapies

• Nonfactor replacement therapies for hemophilia
  • Anti-tissue factor pathway inhibitor [Anti-TFPI]; OW/SC
  • RNA interference agent against antithrombin; OW/SC

• Gene Therapy

Gene therapy has the potential to lessen disease severity from a severe phenotype to a moderate or mild phenotype through continuous production of factor VIII or IX after one administration of a gene vector, especially since a small rise in circulating coagulant proteins to at least 1% of normal levels can substantially ameliorate the bleeding phenotype.

Anti-tissue factor pathway inhibitor [Anti-TFPI];
Anti-tissue factor pathway inhibitor [Anti-TFPI];

Intrinsic (Contact) Pathway

Collagen/glass

FXIIa

FXa

Tissue Factor

Extrinsic (TF) Pathway

TFPI

Tissue Factor Pathway Inhibitor

Common Pathway

Activated Protein C (APC)

Thrombin (IIa)

Fibrin (I) clot (soft)

Fibrin (I) clot (X-linked)

APC PATHWAY

TFPI PATHWAY
RNA interference agent against antithrombin
Gene Therapy

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What Is Gene Therapy?

• Gene therapy is:\(^1\,^2\):
  – A strategy used to replace or repair a dysfunctional gene
  – Most applicable to diseases caused by a single gene mutation
  – An approach to improve symptoms or potentially cure a disease
  – Administered *ex vivo or in vivo*, depending on the vector

• The vector (vehicle based on the capsid of a nonreplicating virus) delivers the desired gene to a particular “target”\(^3\)

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Gene therapy aims to give a gene that works correctly to a person who needs it.
Gene Therapy

- A cell contains genetic material within its nucleus made up of genes in chromosomes.
- These genes provide instructions to the cell and help it make proteins (like clotting factor).
- When genes are missing or incorrect, it is difficult for the cell to work correctly.
Background

• Proper factor VIII dosage requirement for hemophilia patients varies significantly due to multifactorial influence including individual pharmacokinetics (PK), age, blood group, gender, type of factor used and type of test.

• Therefore PK has to be performed for each patient according to each clotting factor and has to be repeated at certain intervals.
Pharmacokinetics and dose requirements of factor VIII over the age range 3–74 years

A population analysis based on 50 patients with long-term prophylactic treatment for haemophilia A

Sven Björkman · Anna Folkesson · Siv Jönsson

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Population based PK model

Fig. 1 The FVIII:C data \( (n = 714) \) used for building the population pharmacokinetic model. The *inset* shows individually predicted FVIII:C levels (IPRED)
FVIII clearance obtained from 100 (10-65 y, 10 samples) and 52 children (1-5 y, 4 samples)

Figure 1. Observed FVIII levels (n = 2035) plotted against time after the infusion.
Fig. 3  

a The clearance (CL) of plasma-derived FVIII, normalised for total body weight, as a function of age. 

b The elimination half-life of FVIII as a function of age. Eta (η) shrinkage was 0.04 and 0.10 respectively for the estimates of inter-individual variability of clearance and volume of the central compartment.
Fig. 4 Required dose of FVIII (a in units/kg bodyweight, b in units) to maintain a minimum level of 0.01 U/mL during continuous prophylaxis with administration every 2 days. Solid squares Model predictions (based on age and weight) for all patients (both datasets) and all occasions, solid diamonds “true” dose requirements (based on estimated individual pharmacokinetic parameter values) for all patients and occasions in the model-building data set, open diamonds “true” dose requirements for all patients and occasions in the clinical data set. In a, 5 patients (16 occasions) with true dose requirements >100 U/kg are above the scale, and in b, 11 patients (32 occasions) with true dose requirements >2,000 U.
Influences of ABO blood group, age and gender on plasma coagulation factor VIII, fibrinogen, von Willebrand factor and ADAMTS13 levels in a Chinese population

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Effect of blood groups on FVIII & VWF
O vs non- O (A,B,AB)
Population pharmacokinetics of recombinant factor VIII: the relationships of pharmacokinetics to age and body weight

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Comparison of the pharmacokinetics (PK) of a coagulation factor between groups of patients can be biased by differences in study protocols, in particular between blood sampling schedules. This could affect clinical dose tailoring, especially in children. The aim of this study was to describe the relationships of the PK of factor VIII (FVIII) with age and body weight by a population PK model. The potential to reduce blood sampling was also explored. A model was built for FVIII PK from 236 infusions of recombinant FVIII in 152 patients (1-65 years of age) with severe hemophilia A. The PK of FVIII over the entire age range was well described by a 2-compartment model and a previously reported problem, resulting from differences in blood sampling, to compare findings from children and adults was practically abolished. The decline in FVIII clearance and increase in half-life with age could be described as continuous functions. Retrospective reduction of blood sampling from 11 to 5 samples made no important difference to the estimates of PK parameters. The obtained findings can be used as a basis for PK-based dose tailoring of FVIII in clinical practice, in all age groups, with minimal blood sampling. (Blood. 2012;119(2):612-618)
Effect of **age** on FVIII:C

![Graph showing the effect of age on FVIII:C](image)
Effect of age on VWF: Ag

$r = 0.410, n = 121, p = 0.0003$
Effect of age on ADAMTS13

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F \quad r = -0.306, \quad n=121, \quad p=0.0006
\]
Effect of age on: FVIII:C, VWF: Ag, VWF:CBA, VWF:Rcof, and ADAMTS13
Effect of age on clearance and T1/2 of FVIII

Figure 4. Individually estimated pharmacokinetictic parameter values. FVIII as functions of age. (A) Clearance and (B) terminal half-life. The trend curves are for the typical person (with ideal BMI) at each year of age.
Effect of age on clearance and T1/2 of FVIII
Effect of weight & BMI on in-vivo recovery of FVIII

Impact of being underweight or overweight on factor VIII dosing in hemophilia A patients

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Variation of FVIII T ½ (H)

Data are from different studies with different patients cohorts
Pharmacokinetic blood sampling

• Adults: (11 samples) at zero, 15 min, 30 min, 1 hour, 3, 6, 9 hours, 24, 28, 32 hours, 48 hours
• Children: (5 samples) 30 min., 1, 9 hours, 24 hours, 48 hours

New Methods !!!
New methods with less (2) blood samples

• Many methods are being developed as a software that requires only 2 blood samples within 48 hours after infusion.
• Each method is specific for each product
Variation of FIX T $\frac{1}{2}$ (H)

Data are from different studies with different patients cohorts

Frequency Impact?

EHLs every 7-10 days

SHLs once weekly data !!!
Effect of laboratory tests

• Pre-analytical,
• Test performance,
• Type of test: PTT or chromogenic
• Specific tests
In summary

- Factor VIII & IX recovery, clearance and half-life are influenced by many factors including blood group, age, body weight, ethnicity, type of factor and type of testing.
- Population model PK is not suitable for individual patients,
- PK has to be performed for each patient individually, for each clotting factor concentrate and to be repeated at least once every 10 years, so that, adequate, cost effective dose and frequency can be calculated accurately for each patient.