Challenges in the Diagnosis and Management of Hemophilia

Nigel Key, MB ChB FRCP
Disclosures for Nigel Key

In compliance with COI policy, ISTH requires the following disclosures to the session audience:

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Presentation includes discussion of the following off-label use of a drug or medical device:
None
Outline

- Factor VIII Assays
  - One-stage vs. chromogenic

- When Phenotype and Factor Levels Don’t Agree
  - Severe hemophilia A
  - Non-severe hemophilia A

- Prophylaxis and ‘Personalized Medicine’
  - Pharmacokinetic heterogeneity
  - Monitoring replacement therapy

- Inhibitors and Novel Therapies
  - SIPPET study
  - Disruptive technologies, e.g. Emicizumab
One-Stage FVIII Assay

Reference plasma
100% of all factors

Substrate plasma
0% FVIII, 100% all others

Patient plasma
? FVIII
One-Stage FVIII Assay

Reference + Substrate

1:10 1:20 1:40 1:80 1:160

Patient + Substrate

1:10 1:20 1:40 1:80 1:160

aPTT

aPTT

ISTh
One-Stage FVIII Assay

Graph showing the relationship between aPTT (s) and Concentration % with a reference point indicated.
Chromogenic FVIII Assay

Intrinsic pathway

Extrinsic pathway

XII → XI → IX → VIII → Xa → V → Thrombin → Fibrin → Clot

VII
Chromogenic FVIII Assay: Add Reagent Cocktail → Generate Factor Xa
Add Chromogenic Substrate to Measure Generated Factor Xa
Why Should the Clinician Care about Which FVIII Assay is Used?

- Maintaining target trough levels in the 1-5% range depends on accurate assessment of factor activity in plasma

  - Assay details are increasingly important:

    - aPTT-based one-stage assays use various activators
      - Silica
      - Ellagic acid
      - Kaolin….

    - Chromogenic assays
      - At least 3 on the market – variable method/reagents
Why Should the Clinician Care about Which FVIII Assay is Used?

- Maintaining target trough levels in the 1-5% range depends on accurate assessment of factor activity in plasma

- Assay details are increasingly important:
  - aPTT-based one-stage assays use various activators
    - Silica → greatly over-estimates activity of Novo8-GP product
    - Ellagic acid
    - Kaolin….
  - Chromogenic assays
    - At least 3 on the market – variable method/reagents
Know Your Product!

AFSTYLA®️, Antihemophilic Factor (Recombinant), Single Chain For Intravenous Injection, Powder and Solvent for Injection Initial U.S. Approval: 2016

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions, including anaphylaxis, are possible. Should symptoms occur, immediately discontinue AFSTYLA and administer appropriate treatment. (5.1)
- Development of Factor VIII neutralizing antibodies (inhibitors) can occur. If expected plasma Factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, perform an assay that measures Factor VIII inhibitor concentration. (5.2)
- If the one-stage clotting assay is used, multiply the result by a conversion factor of 2 to determine the patient’s Factor VIII activity level. (5.3)
‘Mild Bleeding Phenotype’:  
- ≤ 2 bleeding episodes/year  
- median lifelong concentrate consumption < 500 IU/kg

‘Severe Bleeding Phenotype’:  
- > 25 bleeding episodes/year  
- median lifelong concentrate consumption > 2000 IU/kg
Thrombin Generation Testing

- Peak Thrombin
- Inactivation phase
- Lag Phase

Thrombin Generation Curve:
- Y-axis: Thrombin
- X-axis: Time
Severe hemophilia with mild bleeding phenotype: molecular characterization and global coagulation profile

E. SANTAGOSTINO, M. E. MANCUSO, A. TRIPODI, V. CHANTARANGKUL, M. CLERICI, I. GARAGIOLA
and P. M. MANNUCCI

Fig. 1. Endogenous thrombin potential (ETP) measured in platelet-rich plasma (PRP) in 22 cases (mild bleeders) and 50 controls included in the study. Each box plot represents interquartile range with median value (black line in the middle) and 95% confidence intervals.
Variability in Clinical Phenotype of Severe Hemophilia: Age at First Joint Bleed

- In a study of 171 patients (2,166 patient-years of follow-up), those who experienced their first joint bleed later needed less treatment and developed less arthropathy.

- Onset of joint bleeding was inversely related to treatment requirement and may serve as an indicator of clinical phenotype.

‘Discrepant’ Mild Hemophilia A

- In mild & moderate hemophilia A:
  - At least a two-fold discrepancy between one-stage and chromogenic assay in up to 40% of cases, most of which are below normal limits of FVIII for both assays, but
    - A subset that shows normal one stage and aPTT, but reduced activity by two-stage testing (5-10% of mild hemophilia A patients)
      - **Bleeding symptoms are usually in accord with the two-stage/chromogenic assay result**
    - Opposite has also been described to occur (reduced one-stage, and normal chromogenic)
      - **At least some of these cases are not associated with a bleeding disorder** (investigated with incidental prolonged aPTT)
Western Denmark Study

- 109 patients with mild hemophilia A
  - 92 patients/53 unrelated families

- Baseline FVIII levels measured by both assays

Poulsen, AL. *Haemophilia*. 2009
Chromogenic/1-Stage Assay Ratios

Fig. 2. Ratio FVIII:C chrom/FVIII:C one-stage intervals in 92 patients with mild haemophilia A.

Poulsen, AL. *Haemophilia*. 2009
# Prophylaxis in Hemophilia; ISTH Definitions

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<th>Factor replacement therapy</th>
<th>Definition</th>
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<td><strong>Episodic (“on demand” treatment)</strong></td>
<td>Treatment given at the time of clinically evident bleeding</td>
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<td><strong>Continuous prophylaxis</strong></td>
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<tr>
<td>• Primary prophylaxis</td>
<td>Regular continuous* treatment started in the absence of documented osteochondral joint disease, determined by physical examination and/or imaging studies, and before the second clinical evident large joint bleed** and age 3 years</td>
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<td>• Secondary prophylaxis</td>
<td>Regular continuous* treatment started after 2 or more bleeds into large joints** and <strong>before</strong> the onset of joint disease documented by physical examination and/or imaging studies</td>
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<td>• Tertiary prophylaxis</td>
<td>Regular continuous* treatment started <strong>after</strong> the onset of joint disease documented by physical examination and plain radiographs of the affected joints</td>
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PK Parameters Determining Bleeding Frequency in Hemophilia

- **Adequate hemostasis range**
  - May help prevent activity-related bleeds
- **Area under the curve**
  - May help prevent subclinical bleeding
- **Trough**
  - Determines spontaneous bleeding risk

Annual Number of Joint Bleeds According to Baseline FVIII Level

Factor Dosing: Comparison of FVIII Half-Life for (Non Inhibitor) Patients on 5th and 95th Percentiles

Individual Variation of rFVIII-Fc Half Life

Eloctate Pharmacokinetics

Data courtesy of Stacy E. Croteau, MD, MMS.
Plasma VWF Level is Critical in Determining Inter-Individual PK Variability

Determinants of Breakthrough Bleeding Frequency on 3x per Week FVIII Prophylaxis

• Annualized bleeding rate (ABR) significantly correlated with VWF:Ag (p=0.038) and with age (p = 0.021)

• AUC and $T_{1/2}$ increased with increased VWF:Ag (p<0.001)

Lalezari S. *Haemophilia* 2014:19;e15
Determinants of Breakthrough Bleeding Frequency on 3x Per Week FVIII Prophylaxis

Linear regression line: Intercept = 5.650773, slope = 0.063847

Spearman
$r = 0.8200$
$P < 0.0001$

Pearson
$r = 0.6993$
$P < 0.0001$

Lalezari S. Haemophilia 2014:19;e15
Factor Level and Bleed Risk

Prophylaxis Model: FVIII dosing to prevent spontaneous bleeds

Activity Increases Risk

Inactive or No Expected Collisions

Chance of Significant Collisions

Significant Collisions are Inevitable

Survey of Inhibitors in Plasma Product Exposed Toddlers (SIPPET) Study

- Study of inhibitor formation rates

- Screening
  - Age < 6y
  - Plasma FVIII activity < 1%
  - No previous FVIII concentrate treatment (‘PUPs’)
  - Blood component exposure < 5 times

- Randomized for FVIII replacement

SIPPET Results

High titer (peak > 5 BU/ml)
- pdFVIII: 18.6%
- rFVIII: 28.4%
- HR: 1.69

New and Emerging Treatments

- Concentrates
  - Extended half-life products
  - Alternative products (Disruptive technologies)

- Gene therapy
  - Biomarin, Freeline Therapeutics, Baxalta, UniQure, Spark Therapeutics, Dimension, Biogen, Sangamo, LogicBio Therapeutics

- Gene editing
  - CRISPR-Cas9/Cpf1 editing of embryos or iPS cells
  - Zinc finger nucleases (Sangamo)
Antibody Analog of Factor VIII (FVIII): ACE910/Emicizumab

Emicizumab Pilot Efficacy Study

- 18 Japanese patients with severe hemophilia A
- N = 6 per cohort group
- Cohorts: 0.3, 1.0, or 3.0 mg/kg
- Weekly sc dosing for 12 weeks
- Results
  - Dose-dependent PK
  - APTT remained short
  - FXIa-triggered thrombin generation detected at all assessments
  - No serious adverse events

Emicizumab Impact on ABR

Conclusions

- In hemophilia A, there are exceptions to the generally reliable relationship between baseline FVIII level and clinical phenotype, both for severe and non-severe disease.

- Consider measuring both 1-stage and chromogenic FVIII levels in non-severe patients on at least one occasion.

- FVIII half-life is quite variable in patients without recognized inhibitors, and it partly driven by vW factor levels.

- The variable half-life of FVIII, along with the inter-individual variability of patient activity levels argues for ‘personalized’ prophylaxis.