Rare Coagulation Disorders: The Way Forward

ATHN Data Summit 2008
July 31, 2008
Presenter: Donna Di Michele, M.D.
The Need

• Patients with rare coagulation disorders (RCDs) need safe and effective therapies and deserve excellent long term health outcomes
  – Many RCD patients still have no treatment options other than non-virally attenuated plasma products or non-specific PCC’s
  – RCD patients may not have access to new product trials

• Industry sponsors and investigators need special incentives to develop products for and conduct trials on rare disease populations
Objectives

• Prioritize rare coagulation disorder-related initiatives for ATHN

• Explore the clinical need and current evidence base of support for RCD product development

• Begin to formulate a work plan for RCD data collection that ensures coordination among national and international efforts with the 3 primary goals of:
  — Developing an evidence base for the clinical care of RCD patients
  — Promoting and supporting RCD product development
  — Stimulate clinical and basic research in this field
# Rare Bleeding Disorders

<table>
<thead>
<tr>
<th>Clotting Protein Disorders</th>
<th>Platelet Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>Glanzmann</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>Thrombasthenia</td>
</tr>
<tr>
<td>Factor V</td>
<td>Bernard Soulier Syndrome</td>
</tr>
<tr>
<td>Factor VII</td>
<td>Storage Pool Disease</td>
</tr>
<tr>
<td>Factor X</td>
<td></td>
</tr>
<tr>
<td>Factor XI</td>
<td></td>
</tr>
<tr>
<td>Factor XIII</td>
<td></td>
</tr>
<tr>
<td>Combined Factors V &amp; VIII</td>
<td>Connective Tissue Diseases</td>
</tr>
<tr>
<td>Combined Factors II, VII, IX, X</td>
<td></td>
</tr>
<tr>
<td>PAI – 1 Deficiency</td>
<td>Collagen Defects</td>
</tr>
</tbody>
</table>
Rare Clotting Protein Disorders Prevalence

Rare Bleeding Disorders (Deficiencies of Factors II, VII, X, V, XIII, Fibrinogen & Dysfibrinogenemia)

Prevalence – 1 in 500,000 to 1 in 1,000,000 (~ 0.0002%)

<table>
<thead>
<tr>
<th>Registry</th>
<th>Prevalence Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iranian Registry (RIBD)</td>
<td>0.3 – 6.6%</td>
</tr>
<tr>
<td>UK Registry (HCDO)</td>
<td>0.02 – 3.3%</td>
</tr>
<tr>
<td>Italian Registry (AICE)</td>
<td>0.2 – 1.3%</td>
</tr>
</tbody>
</table>

Source: D DiMichele
## Clinical Manifestations

<table>
<thead>
<tr>
<th></th>
<th>FVIII</th>
<th>Fibrinogen</th>
<th>FII</th>
<th>FV</th>
<th>FVII</th>
<th>FV+FVIII</th>
<th>FX</th>
<th>FXI</th>
<th>FXIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nose bleeding</td>
<td>15%</td>
<td>70%</td>
<td>60%</td>
<td>57%</td>
<td>64%</td>
<td>77%</td>
<td>72%</td>
<td>34%</td>
<td>32%</td>
</tr>
<tr>
<td>Uterine bleeding</td>
<td>0%</td>
<td>50%</td>
<td>75%</td>
<td>50%</td>
<td>60%</td>
<td>58%</td>
<td>50%</td>
<td>8%</td>
<td>35%</td>
</tr>
<tr>
<td>Haematuria</td>
<td>25%</td>
<td>0%</td>
<td>7%</td>
<td>6%</td>
<td>10%</td>
<td>0%</td>
<td>25%</td>
<td>3%</td>
<td>10%</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>13%</td>
<td>0%</td>
<td>15%</td>
<td>6%</td>
<td>14%</td>
<td>7%</td>
<td>38%</td>
<td>0%</td>
<td>10%</td>
</tr>
<tr>
<td>Joint bleeding</td>
<td>75%</td>
<td>50%</td>
<td>38%</td>
<td>26%</td>
<td>21%</td>
<td>25%</td>
<td>69%</td>
<td>29%</td>
<td>55%</td>
</tr>
<tr>
<td>Muscle bleeding</td>
<td>81%</td>
<td>0%</td>
<td>38%</td>
<td>29%</td>
<td>12%</td>
<td>7%</td>
<td>66%</td>
<td>32%</td>
<td>58%</td>
</tr>
<tr>
<td>CNS bleeding</td>
<td>16%</td>
<td>5%</td>
<td>7%</td>
<td>6%</td>
<td>17%</td>
<td>4%</td>
<td>9%</td>
<td>0%</td>
<td>25%</td>
</tr>
<tr>
<td>Cord bleeding</td>
<td>0%</td>
<td>75%</td>
<td>15%</td>
<td>3%</td>
<td>0%</td>
<td>22%</td>
<td>28%</td>
<td>73%</td>
<td></td>
</tr>
<tr>
<td>Post-partum, -operation bleeding</td>
<td>90%</td>
<td>40%</td>
<td>23%</td>
<td>43%</td>
<td>55%</td>
<td>63%</td>
<td>63%</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>Oral cavity bleeding</td>
<td>70%</td>
<td>70%</td>
<td>46%</td>
<td>57%</td>
<td>66%</td>
<td>51%</td>
<td>20%</td>
<td>55%</td>
<td>48%</td>
</tr>
</tbody>
</table>
## Summary of Factor Replacement

<table>
<thead>
<tr>
<th>Factor Deficiency</th>
<th>FFP</th>
<th>Platelets</th>
<th>Cryo</th>
<th>Plasma Concentrate</th>
<th>Prothrombin Complex</th>
<th>Recombinant Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X (study only)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Factor V</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor VII</td>
<td>X</td>
<td></td>
<td>X (not US)</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Factor X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Factor XI</td>
<td>X</td>
<td></td>
<td>X (not US)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor XIII</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X (study only)</td>
<td></td>
<td>X (study only)</td>
</tr>
</tbody>
</table>

Source: D DiMichele
NA Rare Bleeding Disorder Registry

Treatment Related Complications

- Allergic reactions: 26%
- CVAD – related: 14%
- Inhibitor development: 3%
- Viral seropositivity:
  - Hepatitis A: 15%
  - Hepatitis C: 25%
  - HIV: 1%
Collagen Defects
ATHN’s Strategic Opportunities

• Gain and engage ATHN Affiliates re: database
• Build community trust
• Expand local capacity by funding and training data managers
• Establish regional data management structure
• Define and establish the core dataset: rare coagulation disorders
Need for Standardized Data

• Demonstrate service delivery.
• Better understand the epidemiology, clinical presentation, genetics and natural history of the disorders;
• Facilitate the development of standards of care;
• Support advocacy for drug development;
• Identify population subsets for special study;
• Identify subjects eligible for clinical trials of new products;
• Aid in post-marketing surveillance;
• Analyze clinical outcomes;
• Identify care providers with patients to facilitate communication & networking;
ATHN Initiatives:

Present and Future
ATHN Roles and Activities: Coagulation Disorder Resource Room

• Planned link from ATHN to NHF, WFH and NATT web sites to help disseminate peer-reviewed information to providers, researchers and patients
  – Spearheaded by Amy Shapiro MD
  – 17 manuscripts (e.g., clinical manifestations, treatments, diagnostic testing, etc.)
  – Publication date Sept. – Nov. 2008
  – All manuscripts in final stages of review & revisions
U.S. Rare Bleeding and Clotting Disorder Database Pilot Project

• ATHN funded by Baxter for next 2 years
• Uses the infrastructure funded by Novo Nordisk
• The purpose is to support the development and testing of standardized data collection and supporting components for rare coagulation factor deficiencies that is compatible with the ATHN infrastructure.
• Conference call held May 08 to discuss plans
• Members of MASAC RDB subcommittee included
# Staging Rare Disorder Data Collection

<table>
<thead>
<tr>
<th>Stage</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How many patients?</td>
<td>Identify patients with rare disorders</td>
</tr>
<tr>
<td>2. Who’s served?</td>
<td>Gather what’s needed for HDS report</td>
</tr>
<tr>
<td>3. What if disaster strikes?</td>
<td>Other info for the emergency preparedness flash drive</td>
</tr>
<tr>
<td>4. Where is public health at risk?</td>
<td>(UDC specific measures in development)</td>
</tr>
<tr>
<td>5. What outcomes?</td>
<td>Specific disease management templates and research</td>
</tr>
</tbody>
</table>
Synchronize with CDC

• Enter data into Lab Tracker today
• Encourage sites to start enrolling rare coagulation disorder patients in UDC
• Encourage CDC Coordinating Committee to include in the Data Sharing Agreement under development, the ability to share data with ATHN to facilitate study coordination and site recruitment through ATHN
ATHN Roles and Activities: Stewardship of A Secure National Database

- Present platform: Lab Tracker
- Conversion to web based system
- Server housed at CDC

Patient Types Entered into Lab Tracker

(Based on 61 users of the 78 responding HTCs)
Three Components to the Grant

• Rare coagulation deficiency standardized data collection
  – Review existing data collection efforts;
  – Identify data elements for rare disorders;
  – Validate applicability of existing data fields in Lab Tracker (web)
  – Integrate changes to Lab Tracker (web) data dictionary and data collection templates

• National system for patient identifier

• Portal for development of data collection forms
RBD UDC Working Group

• Collaboration of the Lab Tracker (web) development to ultimately capture and report data to RDB UDC working group
  – Formed July 2007; Multi-disciplinary
  – Work on data collection forms started in August 2007 (demographics; diagnosis; bleeding manifestations; treatment; complications)
  – Coordination with the CC and CDC grant research priorities (Diane Nugent, Chair)
Desire to Collaborate and Harmonize

- HDS Reporting
- UDC Women Study, Rare Bleeding Disorder Group
- Rare Bleeding Disorder Resource Room
- EN-RBD approach
- ISTH RBD Working Group
- World Federation of Hemophilia efforts
- Others
Help Companies Coordinate Studies

• ATHN should begin to build capacity to help companies coordinate studies in the U.S.
  – Refer to experts to frame studies
  – Identification of study sites
  – Active tracking of site interest
  – Data to help define data points
  – Outcomes data to determine that the product is working
  – Aid in post-marketing surveillance
New Product Development: Underway but Challenging

• Fibrinogen concentrate (Haemocomplettan; CSL- Behring)
• FXIII concentrate (Fibrogammin ( CSL- B); rFXIII (NovoNordisk)
• FXI concentrate (HemEleven; LFB)
• FX concentrate (BPL)
• FV concentrate (Kedrion)
• Possibly, plasminogen

Source: D. DiMichele