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Hemophilia Inhibitor Research Study

- **Pilot**
  - Determine the feasibility for national inhibitor surveillance
    - Centralized inhibitor testing
    - Centralized genotyping
    - Prospective collection of product exposure data

- **Phase II**
  - ARM 1 (continuation of pilot)
    - Increase the database on product exposure data
    - Develop nationwide mutation database - CHAMP
  - ARM II
    - Increase genetic data on patients with a history of an inhibitor
      - CHAMP
      - Immune response gene testing
Study Progress

- 17 Hemophilia treatment centers
- Patient Enrollment
  - ARM 1: 1167 patients
  - ARM 2: 11 patients
- 2,679 inhibitor tests performed
- Databases
  - Product Exposure
    - ~100,000 infusion logs collected
  - Genotyping
    - 137 patients with a history of an inhibitor
    - 1041 patients with no inhibitor
Genotyping Results

- **F8 Gene**
  - 248 unique mutations were found.
  - 95 (38%) were not reported in HAMSTeRS or publications.
  - Mutations were identified in 96% of patients.

- **F9 Gene**
  - 62 unique mutations were found.
  - 11 (18%) were not reported in the Haemophilia B Mutation Database.
  - Mutations were identified in 99% of patients.
Race/Ethnicity Differences in Inhibitor Frequency in Severe Hemophilia A

<table>
<thead>
<tr>
<th></th>
<th>White Non-Hispanic</th>
<th>Black Non-Hispanic</th>
<th>Hispanic</th>
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<tbody>
<tr>
<td>n</td>
<td>321</td>
<td>35</td>
<td>32</td>
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<tr>
<td>Inhibitors</td>
<td>63 19.6%</td>
<td>13 37.1%</td>
<td>15 46.9%</td>
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$P=0.0003$
Race/Ethnicity Differences in Inhibitor Frequency

- Increased inhibitor frequencies in Black and Hispanic patients do not appear to be caused by differences in $F8$ mutations present.

- In White patients, $F8$ haplotype mismatch with treatment products is not a factor in inhibitor formation.

- In Black and Hispanic patients, preliminary data suggest that product mismatch does not play a role in higher inhibitor frequencies.

- Study of the immune response may reveal the source of this difference.
Inhibitor Method Validation

- A modified Nijmegen-Bethesda assay was adopted
- A heating step was added to remove infused and endogenous factor VIII
- Effectiveness was confirmed by absence of FVIII activity and antigen in heated specimens
- CV of positive control was 10.3%; negative was 9.8%
- Split sample comparison showed that shipment on cold packs was equivalent to frozen specimens
- Cut-offs were established by comparing results on patients with negative and positive history of inhibitor
Change in Inhibitor Titer after Heating Plasma to 56°C for 30 min & Centrifuging

• 1 of 159 negative inhibitor history and 5 of 30 positive inhibitor history patients went from negative to positive after heating.
• Correlation of results on heated and unheated inhibitor positive specimens was 0.94 (p=0.0001)

a. Negative History

b. Positive History
FVIII Inhibitor Titers

a. Enrollment n=674

b. All Specimens n=1317

Threshold for a positive inhibitor was set at ≥0.5 NBU for factor VIII
Threshold for a positive inhibitor was set at >0.2 NBU for factor IX
The U.S. inhibitor study conducted by CDC has genotyped over 1,000 hemophilia patients.

To aid in analysis and reporting, the CDC Hemophilia A Mutation Project (CHAMP) was established.

First activity of CHAMP was a comprehensive mutation list.

Mutations were collected from:
- HAMSTeRS
- From publications identified by systematic literature review

Each mutation was reviewed and uniquely identified using:
- HGVS nomenclature for cDNA and predicted protein changes
- Traditional nomenclature based on the mature processed protein
Mutations Listed in CHAMP

- Missense: 1091
- Frameshift: 469
- Nonsense: 251
- Splice Site: 154
- Large Str Change: 116
- Small Str Change: 46
- Promoter: 4
- Synonymous: 11
CHAMP Mutation List

- Simple look-up table to identify reported mutations and to assign unique identifiers for accurate reporting
- Excel database format which can be downloaded from the CDC website and searched
- Available at http://www.cdc.gov/hemophiliamutations
- Currently includes 2,142 mutations and will be updated quarterly from submissions and literature reports
- Two additional databases are planned
  - Mutations reported in the U.S.
  - A population-based database of mutation and inhibitor data from defined geographic regions worldwide
Study Findings

- Centralized inhibitor testing feasible
- Prospective data collection of product exposure and genotyping cost-prohibitive on a national level
- Pilot study recommendations for national inhibitor surveillance
  - Routine monitoring of all hemophilia patients for inhibitors in a centralized laboratory
  - Case surveillance for incident cases
    - Retrospective data collected on product exposure & surgical/outpatient procedures from 1 year prior to detection
National Inhibitor Surveillance

- Currently there is no national surveillance for inhibitors in the U.S.

- Reporting of inhibitors by clinicians to the FDA MedWatch system appears to be inconsistent

- Monitoring of inhibitors should focus on:
  - Trends in occurrence over time
  - Demographic and geographic sub-populations
  - Clusters or “outbreaks” of inhibitors
UDC Inhibitor Case Surveillance

- For each new inhibitor case identified as part of the UDC centralized inhibitor testing
  - Sites would collect retrospective data on product exposure & surgical/outpatient procedures from one year prior to the positive titer – as part of the blood safety program

- Many more incident cases could be identified by monitoring all UDC participants

- Genotyping of incident cases important but funding may be an issue
Advantages

- The data collection is more focused and requires less time-intensive work at the HTCs
- The risk factors and their interactions can potentially be determined in a shorter time period
- This surveillance system would collect data comparable to the European Union hemophilia adverse events reporting system
  - Could facilitate future international data comparison on inhibitors – not currently possible
  - Could potentially allow for future international collaboration on inhibitor research sub-studies
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Study Principle Investigators

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