Thrombotic adverse events and procoagulant impurities in immune globulin products

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Disclaimer

- My comments are an informal communication and represent my own best judgment. These comments do not bind or obligate FDA.
Plasma-derived products

• Plasma is a complex biological fluid rich in proteins, carbohydrates and lipids

• Examples of plasma-derived products:
  o S/D treated plasma
  o Coagulation factors
  o Fibrinogen & Thrombin products for topical use
  o Albumin
  o Immune Globulin, Intravenous

• Co-purification of plasma protein impurities that resulted in adverse events is well documented
Clinical significance of plasma-derived impurities

• Some impurities are inert or even beneficial, e.g., as stabilizers

• Other impurities impact safety and may be linked to Serious Adverse Events, e.g.,
  o Hypotension
  o Thrombosis
  o Bleeding
  o Allergic reactions

• When a new link can be established, tangible measures to improve the safety are implemented
Control of impurities

• The control of the levels of impurities of concern may be achieved by
  o changing the manufacturing process to remove the impurities
  o monitoring the quality of the product using relevant lot release assays

• Harmonization and development of international reference standards will help to maximize the scope of influence of these efforts
Transmission of Viral Contaminants in Plasma-derived Products

- In late 1970s - early 1980s around 6,000 to 10,000 hemophiliacs in the United States were infected with HIV\(^1\)
- 80-100% infected with Hepatitis C\(^2\)
- Leading cause of mortality among older hemophiliacs
- **Root-cause:** Co-precipitation of Hepatitis C and HIV from infected plasma pools\(^2\)
- **CAPA:** Introduction of viral inactivation steps and mandatory donor screening

**Literature**

1) And the Band Played On, Randy Shilts, 1987, St Martin's Press
Plasma-derived impurities: Bleeding

- Up to 76 cases of acquired FV deficiency known by 2009\(^1\)
- Mortality rate 8%
- **Root-cause:** bovine FVa light chain fragments in topical bovine thrombin\(^2\)
- **CAPA:** Improved purification process\(^2\)

**Literature**

Plasma-derived impurities: Hypotension

- Hypotensive reactions in recipients of a Plasma Protein Fraction (PPF) product
- Implicated product withdrawn from market in 1977\(^1\)
- **Root-cause**: PKA impurity linked to a fractionation step
- **CAPA**: PKA lot release assay for PPF, immune globulin and albumin products

**Literature**

Thrombotic Adverse Events (TAE) and Immune Globulin Products

- First literature report in 1986\(^1\)
- ~30 TAEs/year or 18% of Serious AEs reported to FDA (spontaneous reporting, 1999-2005)
- Serious events - myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism
- Precautionary labeling recommended by FDA for IGIV products since October 2003\(^2\)

- Causes uncertain, theories included
  - Coagulation factor impurities (e.g., FXI, FXIa and PKA)
  - Hyper-viscosity
  - Vasospasm

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May 2010, a manufacturer reported 3 cases for 2 lots
  - Patient 1 (CVA)
  - Patient 2 (CVA)
  - Patient 3 (MI) + second patient with MI reported later
- Release of TAE-implicated lots was put “on hold”
- Biochemical investigation did not find abnormalities
- At this time, FDA requested lots from manufacturers for research testing
- 4 samples, TAE-implicated and control lots, blinded:
  1. **Lot A** – TAE implicated (2 strokes)
  2. **Lot B** – control lot
  3. **Lot C** – non-TAE (headaches and aseptic meningitis)
  4. **Lot D** – TAE implicated (MI during infusion x 2)
Investigational testing at FDA (1): TAE lots promote thrombin generation (TG)

TG assay - Raw data

TAE lots

TG assay - Analysis (n=2)

TAE lots

Investigational testing at FDA (3): 6 products from different manufacturers

Note: additional IG products with procoagulant activity have been identified since the time of this experiment (August 2010)
### FDA biochemical root-cause investigation (1):

1. **FXIa inhibitors block procoagulant activity in TAE-implicated lots**

<table>
<thead>
<tr>
<th>Inhibitor of:</th>
<th>Inhibitor:</th>
<th>CTI</th>
<th>KalliStop</th>
<th>C1-Inh</th>
<th>α1AT</th>
<th>α2AP</th>
<th>α-FXIa ab</th>
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</thead>
<tbody>
<tr>
<td>FXIa</td>
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<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>KalliKrein</td>
<td></td>
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<tr>
<td>FXIIa</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
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<td>-/+</td>
</tr>
</tbody>
</table>

| Inhibits TAE lot? | No | No | Yes | Yes | Yes | Yes |

**2. Deficiencies in coagulation factors downstream to FXI block procoagulant activity of lots A and D**

<table>
<thead>
<tr>
<th>Deficiency:</th>
<th>control</th>
<th>XII (-)</th>
<th>PK (-)</th>
<th>XI (-)</th>
<th>VII (-)</th>
<th>PAI1 (-)</th>
<th>IX (-)</th>
<th>VIII (-)</th>
<th>X (-)</th>
<th>V (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibits TAE lot?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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</tr>
</tbody>
</table>

*Upstream to FXIa*

*Downstream to FXIa*
FDA biochemical root-cause investigation (2): Parallelism of responses to FXIa and TAE lot

Similar results were obtained when FXIa was spiked into five different IGIV products.
FDA biochemical root-cause investigation (3): Correlation between TG and FXIa activity assays in three TAE-implicated products

Chromogenic activity, FXIa + kallikrein (relative)
Regulatory Actions: Product Recalls

URGENT: Voluntary Market Withdrawal - September 23, 2010
Octagam [Immune Globulin Intravenous (Human)] 5% Liquid Preparation
DATE MARKET WITHDRAWAL INITIATED:
September 23, 2010

URGENT VOLUNTARY PRODUCT RECALL
Omr-IgG-am™ 5% IV, Registration Number 127543069800 - ALL LOTS
November 7, 2010

May 29, 2012

Please be advised that Cangene Corporation is issuing a voluntary DRUG RECALL of the following finished product lots associated with one bulk lot of the following product:

Product Name/Description:
Hepatitis B Immune Globulin (Human) (HepaGam B) (> 312 IU/mL)

Reference:
2. www.omrix.com/IVIG%20HepB%20Combined%20Voluntary%20Recall%20Dr%20Doctor%20FINAL.pdf
Regulatory Actions: Safety Updates

Important Safety Information: Risk of Thrombotic Adverse Events with Subcutaneous or Inappropriate Intravenous Use of Vivaglobin (Immune Globulin Subcutaneous)
Date: March 11, 2011

IMPORTANT SAFETY INFORMATION: Potential Risk of Thrombotic Events with Use of GamaSTAN® S/D (Immune Globulin (Human))
March 23, 2012

Subject: Theoretical Risk of Thrombotic Events with Intravenous HepaGam B® (Hepatitis B Immune Globulin (Human) Injection) and Related Labeling Update
June 11, 2012

References:
Additional evidence on FXIa thrombogenicity

- FXI(a) known to co-purify with Igs\(^1\)
- FXI(a)-mediated activity found in IG/IGIVs\(^2,3\)
- FXIa found in thrombogenic FXI concentrates\(^4\)
  - Early FXI concentrates were extremely thrombogenic.
  - Administration of pure FXIa activated coagulation in vivo\(^5\).
  - New generation of FXI products, which are formulated with inhibitors\(^6\), are safer.
- Circulating FXIa found in thrombotic patients\(^7\)

Why we didn’t find FXIa impurity earlier

- **Deficient hypotheses:**
  1. It was believed that TAEs happened to sick patients, i.e., TAEs were often considered as unrelated to product.
  2. Differences in thrombogenicities of FXI and FXIa were not recognized.
- **FXIa assays were not sensitive nor calibrated:**
  No FXIa activity standard.
- **Most important:** TAE lots were not available for analysis.
Reference: J. Dodt (PEI, Germany). Workshop on Risk Mitigation Strategies to Address Procoagulant Activity in Immunoglobulin Products, May 17-18, Rockville, MD, USA
Wessler stasis test

TEE associated batches.

Reference: Roemisch et al. WebmedCentral IMMUNOTHERAPY 2011;2(6):WMC002002
Summary of activities 2011-2012

• Investigation extended to all Ig products: IG IV, IG IM, IG SC, hyperimmune products: Rho(D), HBIG, etc.

• FDA/PPTA/NHLBI Workshop (May 2011): Risk Mitigation Strategies to Address Procoagulant Activity in Immune Globulin Products

• CBER assay protocols shared with industry and regulators (Sept. 2010, updated in 2011 and 2012)

• Assay transfers: on-site training and consultations

• International thrombogenicity assay harmonization studies (EMA-NIBSC-FDA) including
  • 1st international reference reagent for Activated Blood Coagulation Factor XI (FXIa), Human, NIBSC 11/236
Looking into the future

- Recent serious adverse events that led to the voluntary withdrawal of thrombogenic products from the market highlight
  - the benefits of characterization of implicated lots, and
  - the importance of collaborations between industry and regulatory agencies
to assure the safety of plasma-derived therapeutics.
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