Laboratory investigation that identified the cause of thromboembolic events in patients receiving immunoglobulin treatments

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(10 minute presentation followed by Q &A)

Disclaimer

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

Immune Globulin, Intravenous (Human) (IGIV)

- Manufactured from pooled plasma of >1,000 donors (typically 7,000 – 60,000 donors)
- Licensed indications (est. 40 - 50% of supply)
  - Immune deficiencies, ITP, Kawasaki syndrome, CIDP (chronic inflammatory demyelinating polyneuropathy)
- Non-licensed uses (est. 50 - 60% of supply)
  - Various neurological, blood, rheumatic, skin, and other diseases
- Doses: 400 - 800 mg/kg for replacement therapy; 1 - 2 g/kg for other diseases
- Cost: > $50/gram; $1,400 – $7,000 per infusion

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, pulmonary embolism, etc.
- Precautionary labeling recommended by FDA for IGIV products since October, 2003[2]
- Causes uncertain, theories include
  - Coagulation factor contaminants (e.g., FXI, FXIa and PKA)
  - Hyperviscosity
  - Vasospasm

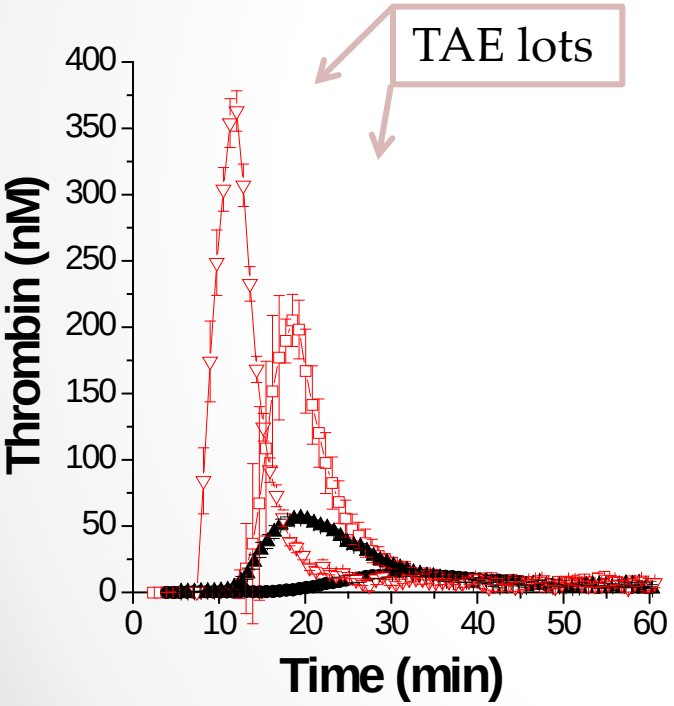
1. Woodruff *et al,* Lancet 2(8500): 217-18, 1986
2. http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm093491.htm

However, lot-associated clusters are uncommon

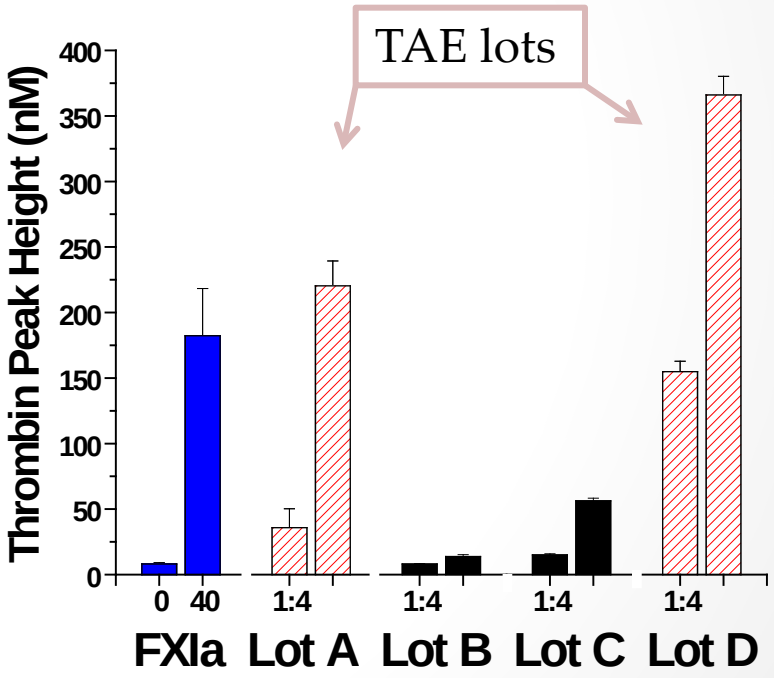
- May 2010 , Manufacturer reported 3 cases for 2 lots
  - Patient 1 (CVA)
  - Patient 2 (CVA)
  - Patient 3 (MI) + second patient with MI reported later
- Release of TAE-associated lots was put "on hold"
- Biochemical investigation did not find abnormalities
- At this time, FDA requested lots from manufacturers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

Research testing at FDA (1):
TAE lots promote thrombin generation (TG)

TG assay - Raw data



TG assay - Analysis (*n*=2)



Assay described in Shibeko *et al*. Blood. 2012 Jul 26;120(4):891-9.

Research testing at FDA (2):
Videomicroscopy of clot growth

- Clotting of plasma in 12x30x1mm microchambers
- Each video experiment is 1 hour long
- Spatial scale: 1mm

TAE lot

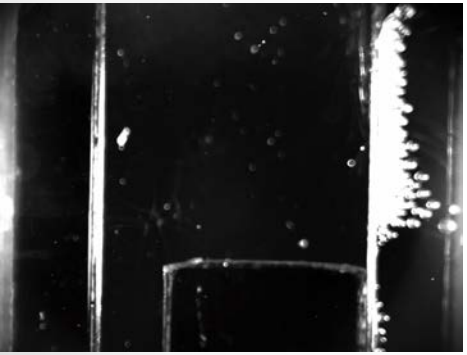
TAE lot

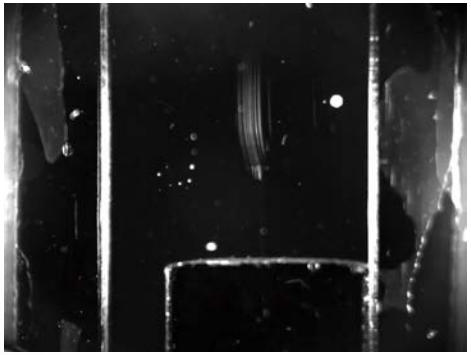
Lot A

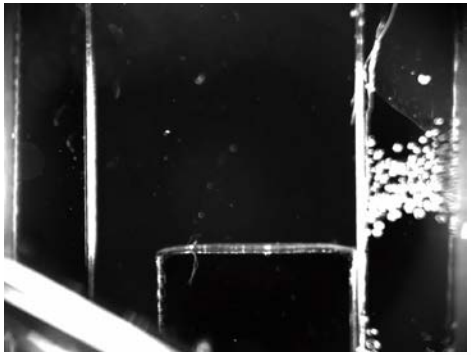
Lot B

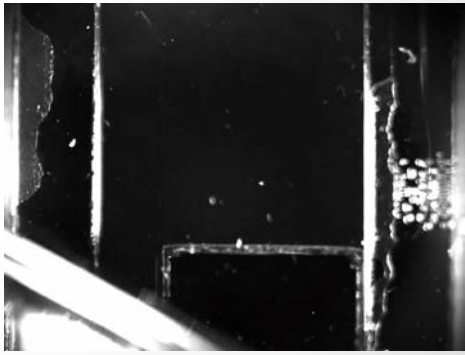
Lot C

Lot D





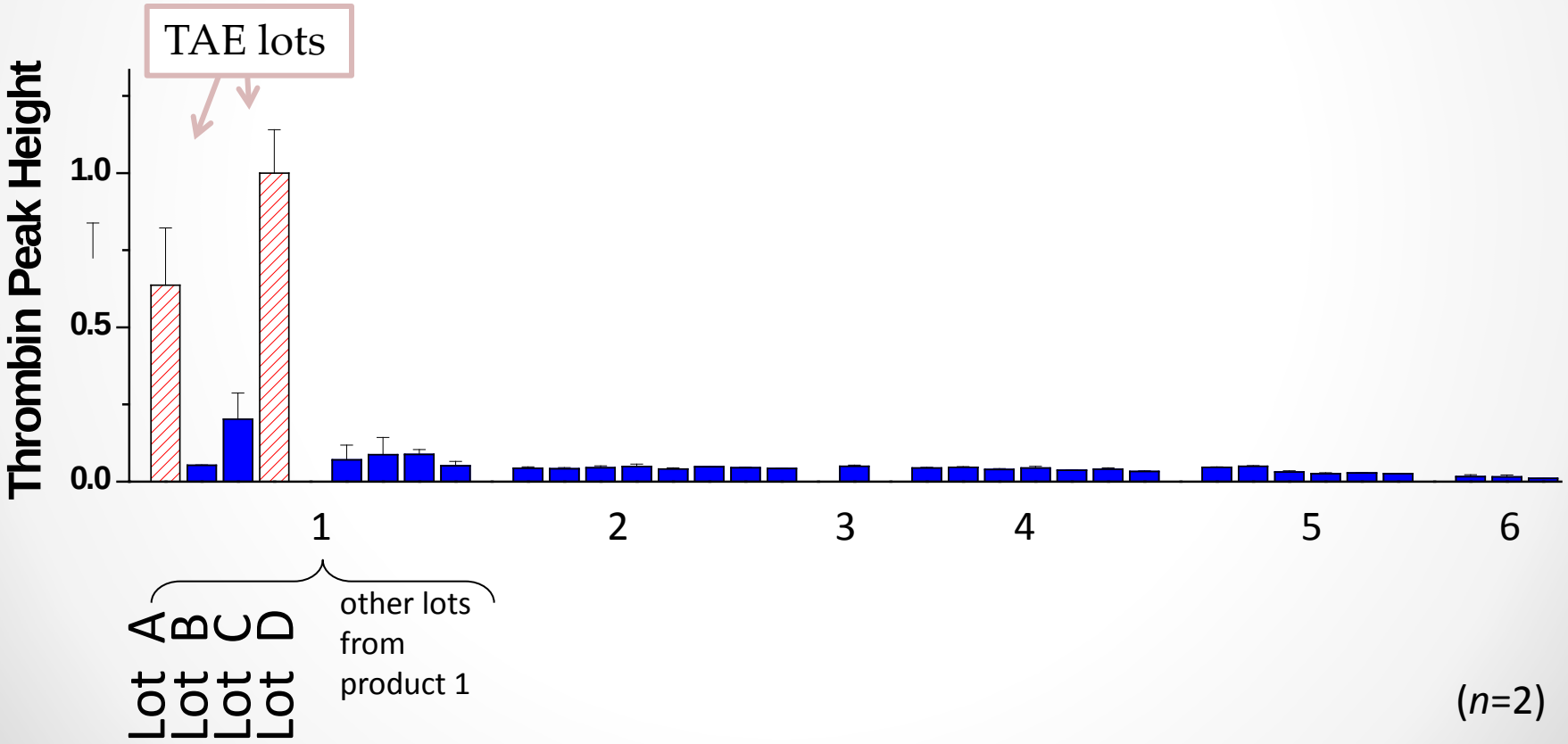




Assay described in Ovanesov *et al*. Biochim Biophys Acta. 2002 Aug 15;1572(1):45-57.

Research 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)



Events leading to product withdrawal in 2010

- August 6 — FDA's results and protocols sent to the company
- August — Company confirmed the results and established lot testing using similar assays
- 20 August — 31 lots withdrawn from the US market
- August/Sept — Many more international reports of thrombotic events ("stimulated" reporting possible)
- 15-24 Sept — PEI suspended license
  EMA recommended suspension
- 24 Sept — All US, EU, Australia lots withdrawn

FDA biochemical root-cause investigation (1):

1. Inhibitors of FXIa block procoagulant activity of lots

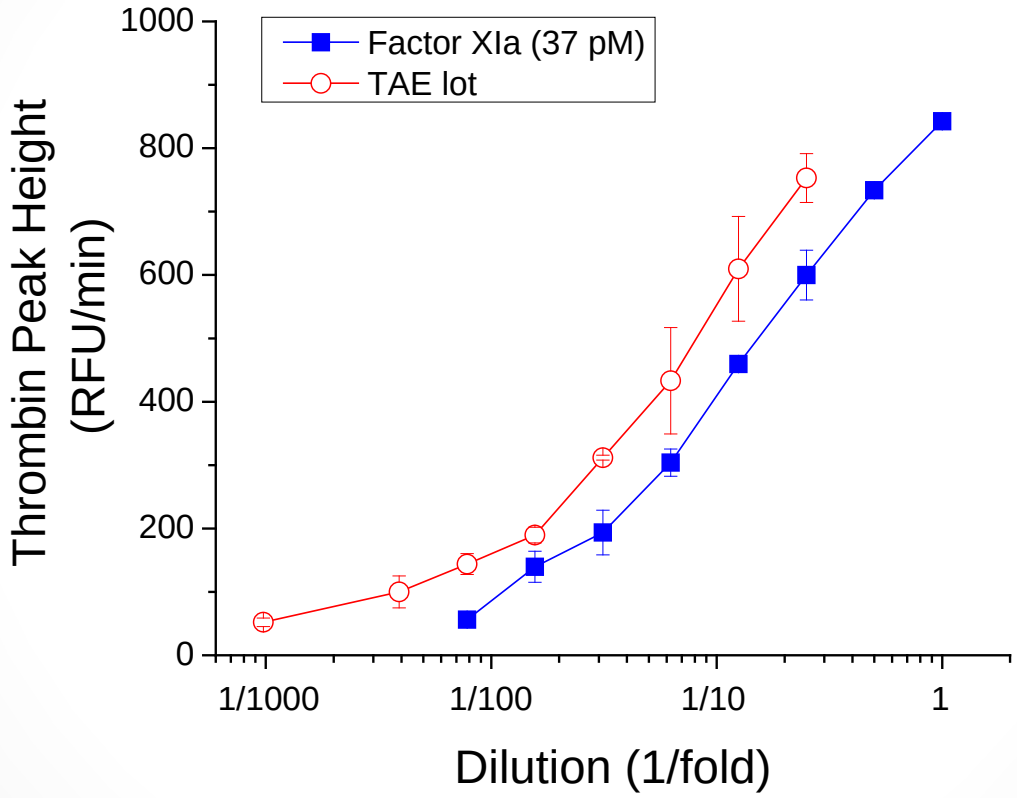
Inhibitor of: / Inhibitor:	CTI	KalliStop	C1-Inh	α1AT	α2AP	α-FXIa ab
FXIa			+	+	+	+
kallikrein		+	+	+		
FXIIa	+	+	+	+	-/+	
Inhibits TAE lot?	No	No	Yes	Yes	Yes	Yes

2. Deficiency of factors downstream to FXI block procoagulant activity of lots A and D

Deficiency:	control	XII (-)	PK (-)	XI (-)	VII (-)	PAI1 (-)	IX (-)	VIII (-)	X (-)	V (-)
Inhibits TAE lot?	No	No	No	No	No	No	Yes	Yes	Yes	Yes

Upstream to FXIa ← → **Downstream to FXIa**

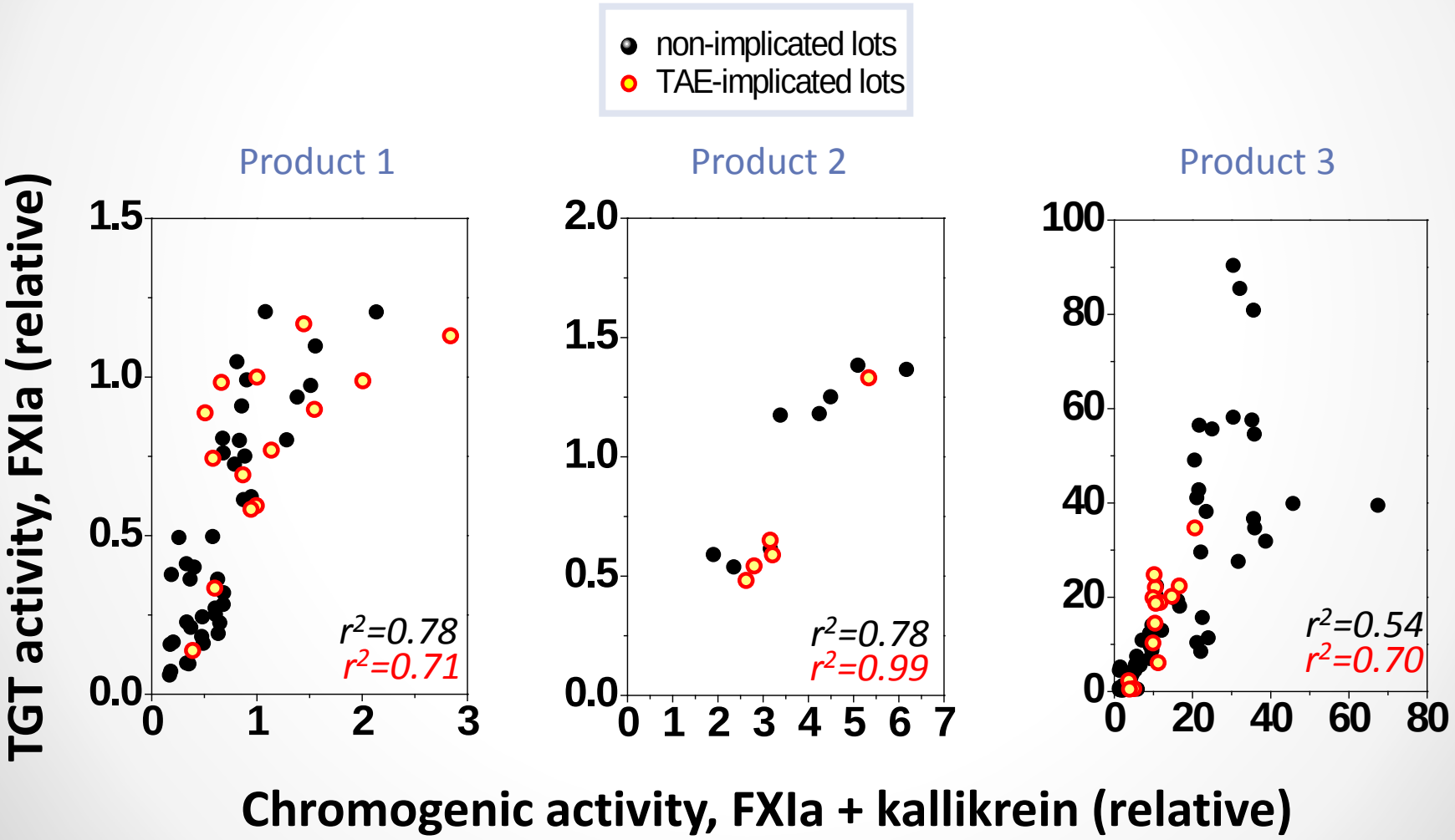
FDA biochemical root-cause investigation (2):
Parallelism of responses to FXIa and TAE lot



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-associated products



Summary of activities 2011-2012

- Investigation extended to all Ig products: IGIV, IGIM, IGSC, 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 (2010, updated in 2011 and 2012)
- Assay transfers: on-site training and consultations
- Participation in and support of international thrombogenicity assay harmonization studies (EMA-NIBSC-FDA), including
  - 1st international reference reagent for Activated Blood Coagulation Factor XI (FXIa), Human, NIBSC 11/236

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