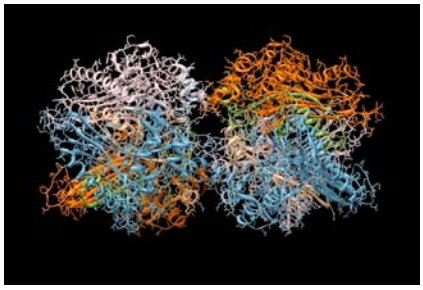
Advancing Regulatory Science

Evidence for a Link between an Immune Globulin Product and Thrombosis

A retrospective study using a health insurance claims database found for the first time a possible association between a subcutaneous immune globulin product (Vivaglobin®) and thrombotic events



Immune Globulin

"Immune Globulins and Thrombotic Adverse Events as Recorded in a Large Administrative Database in 2008-2010"

Transfusion

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Gregory W. Daniel,[1] Mikhail Menis,[2] Gayathri Sridhar,[1] Dorothy Scott,[2] Anna E. Wallace,[1] Mikhail V. Ovanesov,[2] Basil Golding,[2] Steven A. Anderson,[2] Jay Epstein,[2] David Martin,[2] Robert Ball,[2] Hector S. Izurieta[2]

[1]HealthCore Inc., Alexandria, VA; [2]Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, Rockville, MD

What are Immune Globulins (IG)?

IG products contain antibodies removed from the plasma of donated blood. These products have a variety of uses, such as protecting the recipient against a specific disease (e.g., hepatitis) or reducing the severity of a particular disease. They can also treat people who have an inherited immune deficiency or replace antibodies in patients being treated for cancer. IG products can be administered subcutaneously (SC), intravenously (IV), or intramuscularly (IM).

Thrombotic Events: Rare but Potentially Fatal Adverse Effects of IGs

- IG products are generally safe and effective; however, potentially serious systemic renal, hematologic, thrombotic, and allergic reactions occasionally occur.
- Thrombotic events (TEs) that occur after administration of IG products are often serious and potentially fatal.
- TEs are likely to occur during, or within 24 hours after, administration of IG.

Retrospective Statistical Study of Individuals Exposed to IG Products

The Office of Biostatistics and Epidemiology performed a retrospective claims-based cohort study of individuals exposed to intravenous or subcutaneous IG products. The main goals of the study were to:

- **Assess** the occurrence of TEs on the same day as administration of any of a variety of US-licensed IG products
- **Investigate** potential risk factors (e.g., age, gender, TE history)

Source of information: Healthcore's Integrated Research Database (HIRD™), a large, private, longitudinal healthcare database.

Same-Day TE Rates for IG Products Overall and by Age, Sex, Location of TE, and Specific Products

- **Overall rate of TE**
  122 out of 11,785 (1%) of individuals had TEs recorded on same day as IG administration

- **TE rate per 1000 individuals by IG Products**
  6.1-20.5/1000 persons exposed to one of the IG products had TEs recorded on same day as IG administration, depending on product.

Product	# Persons	TEs	Cases/1000 persons exposed
Gammagard Liquid	2,699	20	7.4
Octagam	675	11	16.3
Flebogamma	723	8	11.1
Gamunex	2,032	24	11.8
Privigen	492	4	8.1
Lyophilized product	1,788	28	15.7
Vivaglobin	440	9	20.5
Multiple products	2,936	18	6.1

- **TE rates per 1000 individuals by age and sex**
  - < 15 years of age: **3.6** females: **6.9** males: **1.5**
  - 15-44 years of age: **5.0** females: **5.9** males: **3.7**
  - 45-64 years of age: **11.9** females: **11.3** males: **12.6**
  - 65 and over: **15.5** females: **13.8** males: **17.0**

- **TE locations among the 122 same-day events**
  - Arterial: **35 (28.7%)**
  - Venous: **84 (68.9%)**
  - Both: **3 (2.5%)**

Risk Factors according to Product and Patient Characteristics

- **Product risk factors**
  - **Vivaglobin** was the only product that had a statistically significant increased same-day TE risk compared to Gammagard Liquid, the product against which all tested products were compared.
  - **Octagam**, **Gamunex**, and **lyophilized product** appeared to have a higher but not statistically significant risk of same-day TEs as compared to Gammagard Liquid product.

- **Patient characteristic risk factors**
  - Older age (>/= 45 years)
  - Prior TEs
  - Hypercoagulable state (abnormal tendency to form blood clots)
  - Gender
    - Females had a statistically significant increased TE risk on the same day as IG exposure for **Vivaglobin**, **lyophilized product**, and **Gamunex** compared to Gammagard Liquid.
    - Males had a statistically significant increased TE risk on same day as IG exposure only with **Vivaglobin** compared to Gammagard Liquid.

What Do These Findings Mean?

1. **Support** TE preventive clinical recommendations and recent warnings of elevated TE risk with specific products (e.g., Vivaglobin, Octagam)
2. **Suggest** that risk-benefit should be weighed before IG products are given to patients ages 45 and over with hypercoagulable state or history of thrombotic events
3. **Suggest** need to further evaluate possible role of manufacturing processes and activated factor XI in the observed elevations of recorded TEs with some IG products (including subcutaneous products)
4. **Suggest** need to investigate thrombogenicity testing prior to lot release as an option that might improve safety of IG products

Looking to the Future: Factors Needing Further Evaluation

These findings suggest that observed differences in TE occurrences with products might be due to various factors that warrant further evaluation, such as dosage, administration rates, and product manufacturing processes. FDA held a workshop in May 2011 to discuss these issues.