Adverse Event Reports to FDA for Immunoglobulins and TEEs

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Adverse Event Reports for Immunoglobulins

Objective:

- Characterize thromboembolic adverse event (AE) reports for immune globulins (IGs)
- Identify trends in reports across products or other factors
  - TEEs as a proportion of all AEs, by product
  - Demographics
  - Indication for therapy
  - Type and site of event
  - Risk factors
  - Time to onset

Adverse Event Reports for IGs

Method:

- Case series assembled from FDA Adverse Event Reporting System (AERS)
  - At least one AE term in “Embolic and thrombotic events” Standard MedDRA Query (SMQ)
  - Report received by FDA 2006 through 2010
  - Any IG as a suspect product
  - Excluded duplicates and cases with TEE prior to IG

AERS Passive Surveillance Data: Strengths

- National sample
- Provides clinical information (e.g., demographics, medical history, concomitant medications)
- Provides product information, (e.g., date of administration, route, and lot number)
- Complementary to HealthCore data

AERS Passive Surveillance Data: Limitations

- Underreporting
- Not medically confirmed, nor verified by FDA
- Missing data
- Stimulated reporting (publicity, regulatory action, labeling changes)
- Potentially biased reporting (time to onset)
- Unable to assess causality

Case Series Results

- 209 unique TEE reports, all Igs

FDA Received Year	n
2006	46
2007	25
2008	24
2009	46
2010	68

TEEs as a Proportion of all IG AEs, 2006 - 2010

- 7.3% (209/2857) of all AEs for IG products are TEEs
- All products with substantial distribution had at least 1 TEE AE report
- By product, TEEs range from 4.0% to 25.8% of all AE reports
- Most products are less than 5.0%

Demographics in TEE Reports for IGs

- Average age 54.1 years; median 58.6 years
  - Range: 82 days to 88 years
  - Reported for 191 cases
- Gender 86 females/111males
  - F/M ratio: 0.8:1
  - Reported for 197 cases
- Weight: avg 78.3 kg (median 80kg)
  - Min. 6 kg; Max 136.4 kg
  - Reported for 81 patients

Indication for Therapy in IG TEE Reports

Indication	n = 209	%
Neurologic	65	31.1%
Primary ID	34	16.3%
Miscellaneous	29	13.9%
Secondary ID	23	11.0%
ITP	22	10.5%
Rheumatologic	13	6.2%
ID NOS	3	1.4%
Kawasaki Dz	2	1.0%
Unknown	18	8.6%

Type of Event

- Arterial events more common than venous events
- Some patients had both arterial and venous events

Type of event	n	%
Arterial	122	58.3
Venous	76	36.4%
Both	6	2.9%
Type not specified	5	2.4%

Risk Factors for Arterial Events

- Risk factors known for 83 of 128 patients
- Most common were male gender, hypertension, hyperlipidemia, and coronary disease
- Average of 2.7 risk factors/patient

Risk Factors for Arterial Events

Risk Factor	n = 128	%
Male gender	63	49.2%
Hypertension	39	30. 5%
Hyperlipidemia	26	20.3%
Coronary disease	24	18.8%
Diabetes	13	10.2%
Hypercoagulable state	10	7.8%
Smoking	10	7.8%
Previous stroke	8	6.3%
None (specifically stated)	2	1.6%
Unknown/ no info.	45	35.2%

Risk Factors for Venous Events

- Risk factors known for 50 of 82 patients
- Most common were use of oral contraceptives (OCPs), previous DVT, or in-dwelling catheter

Risk Factors for Venous Events

Risk Factor	n = 82	%
Oral contraceptive	7	8.5%
Previous DVT	7	8.5%
In-dwelling catheter	6	7.3%
Myeloproliferative d/o	5	6.1%
Immobility	4	4.9%
None (specifically stated)	1	1.2%
Previous PE	0	0.0%
Unknown/no info.	32	39.0%

Site of Event

- For arterial events, stroke and MI most common
- For venous events, DVT and PE most common

Art. Event	n	%
Stroke	60	46.9%
MI	33	25.8%
Other	16	12.5%
TIA	14	10.9%
Multi. Sites	5	3.9%

Ven. Event	n	%
DVT	36	43.9%
PE	25	30.5%
Other	11	13.4%
Multi. Sites	10	12.2%

Time to Onset

- Arterial events occurred most commonly during infusion or in first 24 hours after infusion.
  - 61.4% occurred during or within 24 hours
  - Timing known for 101 of 128 events
- Venous events occurred most commonly ≥2 days after infusion
  - 74.6% occurred ≥2 days after infusion
  - Timing known for 59 of 82 events

Time to Onset

Arterial events n=128

Time to Onset	n
During	28
<24 hours	34
Next day	11
2-5 days	14
>5 days	14
Unknown	27

Venous events n=82

Time to Onset	n
During	4
<24 hours	8
Next day	3
2-5 days	13
>5 days	31
Unknown	23

Summary

- TEE reporting present across IG product class
- For most IG products, reports for TEEs represent <5.0% of reports for all AE types
- Arterial events more common than venous events
- Patients with arterial events commonly have multiple risk factors
- Arterial events have shorter time to onset

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Reserve Slides

Analysis of “Same Day” Events Demographics

- 72 cases occurred during or within 24 hours of infusion
  - Slightly older (avg 58.8 vs. 54.1 years)
  - More frequently male (63.2% vs. 56.3%)
  - Weight minimally different (avg 79.5 vs. 78.3kg)

- Mostly arterial (83.8%), including 23 strokes, 19 MIs, 8 TIAs

Same Day Events – Risk Factors

Risk Factor	Same Day (%)	All TEEs (%)
Male	63.2%	56.3%
Hypertension	50.0%	43.0%
Hyperlipidemia	29.2%	26.7%
CAD	27.1%	22.7%
Diabetes	22.9%	14.8%
Unknown	33.3%	38.8%

Same Day Events – Site

Site	Same Day (%)	All TEEs (%)
Stroke	31.9%	28.7%
MI	26.4%	15.8%
TIA	11.1%	6.7%
DVT	9.7%	17.2%
PE	5.6%	12.0%

Same Day Events - Indication

Indication	Same day (%)	All TEEs (%)
Neurologic	26.4%	31.1%
Other	18.1%	13.9%
Primary ID	15.3%	16.3%
Secondary ID	12.5%	11.0%
ITP	9.7%	10.5%
Rheumatologic	9.7%	6.2%
ID NOS	1.4%	1.4%
Unknown	6.9%	8.6%