Other Safety Events of Interest

Barbara Rullo, MD

Global Pharmacovigilance & Epidemiology

Other Safety Events of Interest

- Visual
- Syncope
- Exacerbation of Myasthenia Gravis
- Conclusions

Visual

Visual: Preapproval Experience

IOVE - analysis of all relevant data in 2003:

- Receptor studies: Minimal binding at muscarinic 1 and 2
- Preclinical toxicity studies: no relevant changes
- Clinical studies:
  - two Phase I studies (2400 mg): severe etiologies excluded
  - Phase III studies: ~1% of subjects

Visual: Preapproval Experience

IOVE - analysis of all data in 2003:

- Postmarketing (N = 207):
  - analyzed like clinical trial data
  - rare cases of more severe disturbances
  - two reports of vision loss (unconfirmed)
- German Postmarketing Observational Survey
- Comparative FDA FOI analysis for events impacting driving
- Literature review of visual events for marketed products

Visual: Preapproval Experience

Event:	Blurred vision
Onset:	1-2 hrs after 1-2nd dose
Duration:	3-6 hrs
Risk:	Females and < 40 y
Impact on activity:	44% of visual complaints No MVA
Exam findings:	No consistent findings
Outcome:	Reversible; no sequelae

Visual: USPI at Time of Approval

PRECAUTIONS:

- *Visual disturbances: slowing the ability to accommodate / release accommodation*
  - *including blurred vision, difficulty focusing and diplopia*
  - *caution about potential effects on driving a vehicle, operating machinery or engaging in other potentially hazardous activity*

Visual: Postapproval Commitment

- US approval letter requirement
- Surveillance period: 15-May-04 to 01-Feb-06
- Ongoing clinical case monitoring
  - data collection with standardized questionnaire
  - emphasis on case follow-up
- Descriptive analysis performed
- Submitted to FDA: October 2006

Visual: Preapproval vs Postapproval Experience

	Preapproval	Postapproval
Event:	Blurred vision	Blurred vision
Onset:	1-2 hrs after 1-2nd dose	1-3 hrs after 1-2nd dose
Duration:	3-6 hrs	3-7 hrs
Risk:	Females and < 40 y	Females and < 40 y
Impact on activity:	44% of complaints reading No MVA	44% of complaints reading 2 MVAs
Exam findings:	No consistent findings	No consistent findings ↓ visual acuity
Outcome:	Reversible; no sequelae	Reversible; no sequelae

Visual: Postapproval Experience

Preclinical:

- Electroretinography study in cynomologus monkeys
  - to evaluate potential effects on retinal adaptive processes
  - no changes during light and dark adaptation (rod and cone functions) up to 500 mg/kg (single dose)

Conclusions: Characterization of Visual Events

- Visual effects investigated thoroughly through preclinical/ Phase I studies and postmarketing commitment study
- Consistent after 28 million exposures:
  - infrequent event: 1° blurred vision/ difficulty focusing
  - rare reports of transient loss of vision
  - mechanism unknown: No permanent sequelae
- Launch label appropriately describes risk and driving precautions

Syncope

Syncope: Preapproval Experience

- Phase I studies
  - infrequently reported
    - primarily at supratherapeutic dose
    - secondary vasovagal response
- Phase III studies
  - rare event (0.1%); similar for TEL and comparators
- Postmarketing reports
  - rare reports; none suggestive of drug-induced malignant arrhythmia
- Syncope not described in USPI at approval

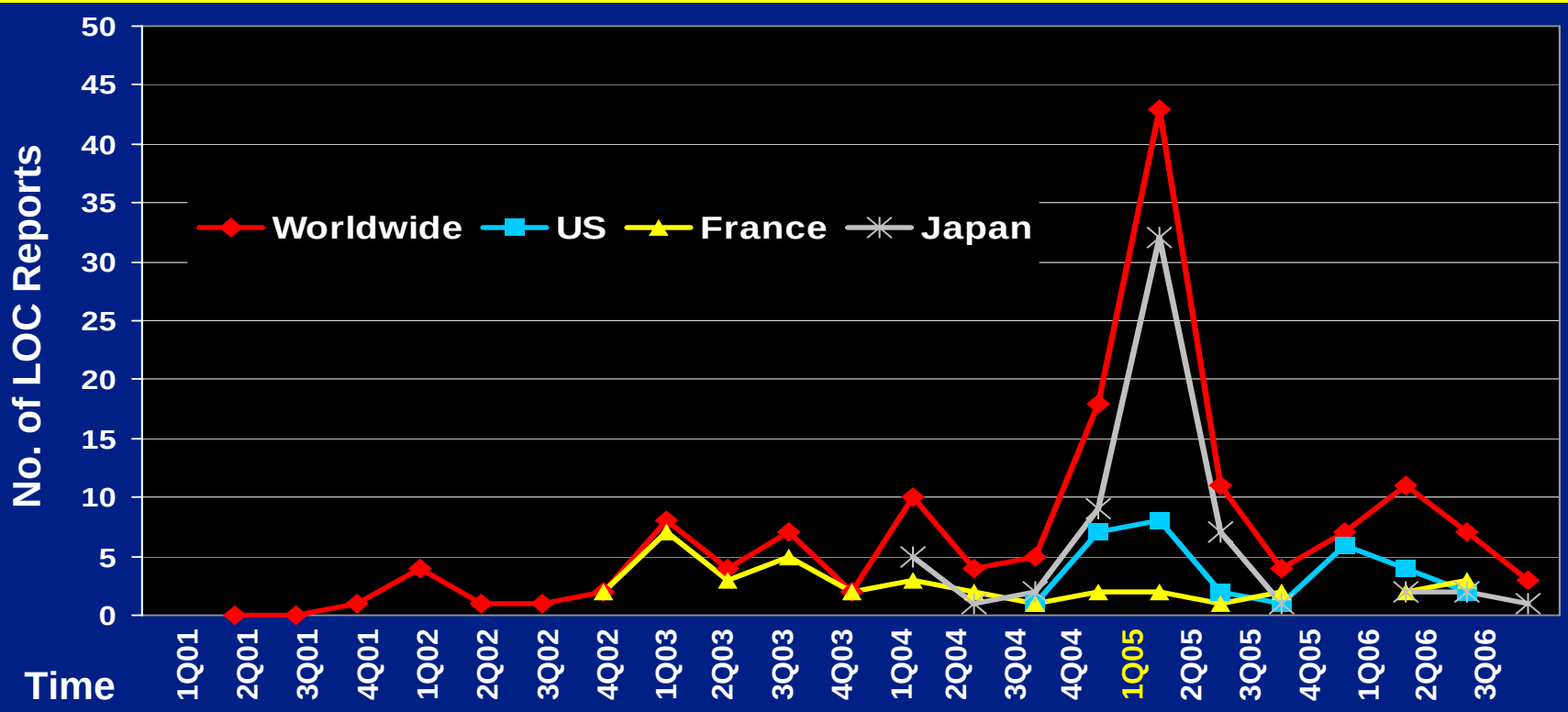
Syncope: Postapproval Experience

- Increased reports of syncope early 2004
- Cluster of reports received from Japan (approved Oct 2003)
  - six reports of syncope in 6 months (Jan-Jul 2004)
  - two reports of associated MVA

Syncope: Postapproval Experience

- Preclinical Study:
  - to assess effects on orthostatic response
  - postural tilt test in dogs
    - iv infusion of TEL (2.4 and 15 mg/kg)
    - heart rate, blood pressure, carotid flow
    - compared with CLA, AZI and LEV
    - Prazosin given as reference
  - no direct effect by TEL or comparators on orthostatic response

Spontaneous Reporting Rate Trends for Syncope (Sep 2006)



Ex US Preapproval	US	Ex US Cumulative	Japan Cumulative	Global
4.0	5.4	3.2	20.1	5.5

per 10^6 exposures

Conclusions: Characterization of Syncopal Events

- Syncopal events identified through safety surveillance and further evaluated through preclinical study
- Heterogeneous reports
  - 1/3 to 1/2 with secondary vasovagal phenomenon
  - complication of another primary event (e.g. anaphylaxis, seizures)
- Postmarketing label updates describe risk and driving precautions

Exacerbation of Myasthenia Gravis

Exacerbation of Myasthenia Gravis: Preapproval Experience

- Receptor studies: physiologic mechanism for weakness not identified
- Clinical studies: No reports
- Postmarketing: 4 spontaneous reports received in 2002
  - comparative FDA FOI data analysis
  - reviewed with external expert
    - occurred within few hours of first dose
    - generally resolved with D/C of TEL

Exacerbation of Myasthenia Gravis: Preapproval Experience

- MG exacerbation added to warnings/precautions in 2003
  - *Dear HealthCare Professional* letter issued in Europe
- Included in US launch label in 2004
  - communicated to Myasthenia Gravis Foundation of America

Spontaneous Reporting Rates for Exacerbation of MG: Internal Data (Sep 2006)

	All MG Reports		Fatal MG Reports	
	No. of Reports	Reporting Rate (per 10^6 exposures)	No of Reports	Reporting rate (per 10^6 exposures)
Ex US Preapproval	19	3.2	1	0.1
Ex US Cumulative	31	1.4	4	0.2
US	29	5.0	3	0.5
Global	60	2.1	7	0.3

Exacerbation of Myasthenia Gravis: Revised USPI*

- Changed from:
  - *not recommended* unless no other alternative

    to
  - *should not be used* … unless no other alternative
- Changed from:
  - Reports include rapid onset, *life-threatening* respiratory failure

    to
  - Reports include *death and life-threatening* acute respiratory failure with rapid onset

*June 2006

Conclusion: Characterization of Exacerbation of MG

- Risk of exacerbation of myasthenia gravis detected early in postapproval European surveillance and updated following postapproval US surveillance
- Rapid onset, frequently severe, rapid resolution with D/C
- Originally in US launch label - warning strengthened and shared with professional organizations:
  - Myasthenia Gravis Foundation of America
  - National Organization for Rare Disorders
  - Muscular Dystrophy Association

Post US Approval Safety Experience

- sanofi-aventis team: continuity of global surveillance
- Intensified pharmacovigilance initiatives and pharmacoepidemiologic activities
- Partnered with external thought leaders
- Exposure of 28 million globally
  - MG, visual, hepatic, syncope risk further defined
- Actions taken to communicate information to manage risks
- Balance of net risks similar to other marketed antibiotics for RTI