

Hepatic Safety Experience

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Hepatic Safety Experience

- Preapproval summary
- Postapproval experience
 - 1-year
 - 2-year
- Conclusions

Hepatic: Preapproval Experience

- In vitro:
 - slightly less covalent binding to human liver microsomal proteins than clarithromycin or azithromycin
 - significant inhibition of mitochondrial β -oxidation like clarithromycin and azithromycin
- Preclinical toxicity:
 - hepatic effects in rat, dog, monkey comparable to macrolides (based upon literature)

Hepatic: Preapproval Experience

- Clinical studies:
 - no difference in clinical hepatic events vs comparators (2.7% vs 2.8%)
 - no difference in hepatic enzyme changes
 - serious events in 0.1% TEL vs 0.05% comparator
 - no dose adjustment with hepatic impairment
- Ex-US Postmarketing:
 - no TEL-related severe hepatotoxicity (ALF, transplant, death)

Hepatic: United States Prescribing Information (USPI) at Time of Approval

- **Precautions:**

- *Hepatic dysfunction, including increased liver enzymes and hepatitis, with or without jaundice*
- *Use caution in patients with a history of hepatitis/jaundice associated with KETEK.*

Hepatic: Postapproval Experience

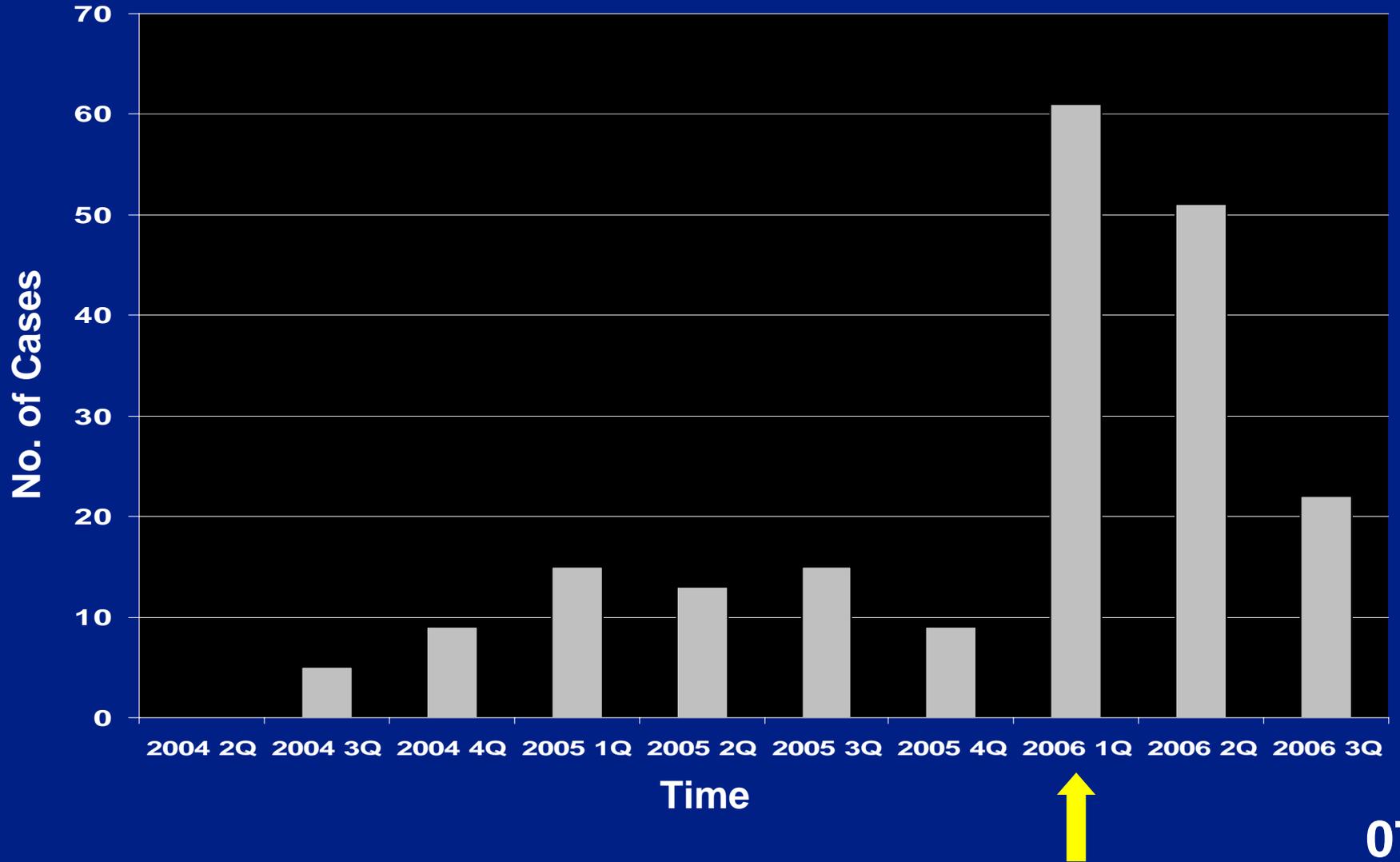
- April 2005: 3 reports from the same N.C. hospital
 - 51 F with subacute ALF requiring transplant
 - 26 M with hepatitis, coded after endoscopy for GI bleeding (fatal)
 - 46 M with reversible hepatocellular injury with jaundice
- Prior to this, 4 reports ALF worldwide (exposure: 17 million)
 - 75 M with acute Hepatitis A and Q fever
 - 78 F with circulatory collapse and septic shock
 - 82 M with cardiac failure (EF 20%) and ischemic liver injury
 - 46 M with epidermoid lung CA and septic shock

Spontaneous Hepatic Reporting Rates: FDA FOI Data 1st year After Launch (May 2005)

	Exposure (x 10 ⁶) *	All Hepatic Events (per 10 ⁶ exposures)	Critical Hepatic Events (per 10 ⁶ exposures)
AZI	1.0	12.7	0
LEV	1.4	4.2	0.7
CLA	2.2	16.9	1.3
TEL	1.95	15.4	1.5
GAT	1.8	7.6	1.6
MOX	0.9	35.1	3.5

* Exposure data from IMS

Spontaneous Hepatic Reporting Trends in United States



sanofi-aventis Hepatic Definitions (2006)

Acute Severe Liver Injury: Hepatic SAE with:

- *Hepatocellular jaundice:*
(ALT > 3x ULN; direct bili > 3 mg/dL; absence of AP ↑)

OR

- Any hepatic SAE *requiring hospitalization*

Acute Liver Failure

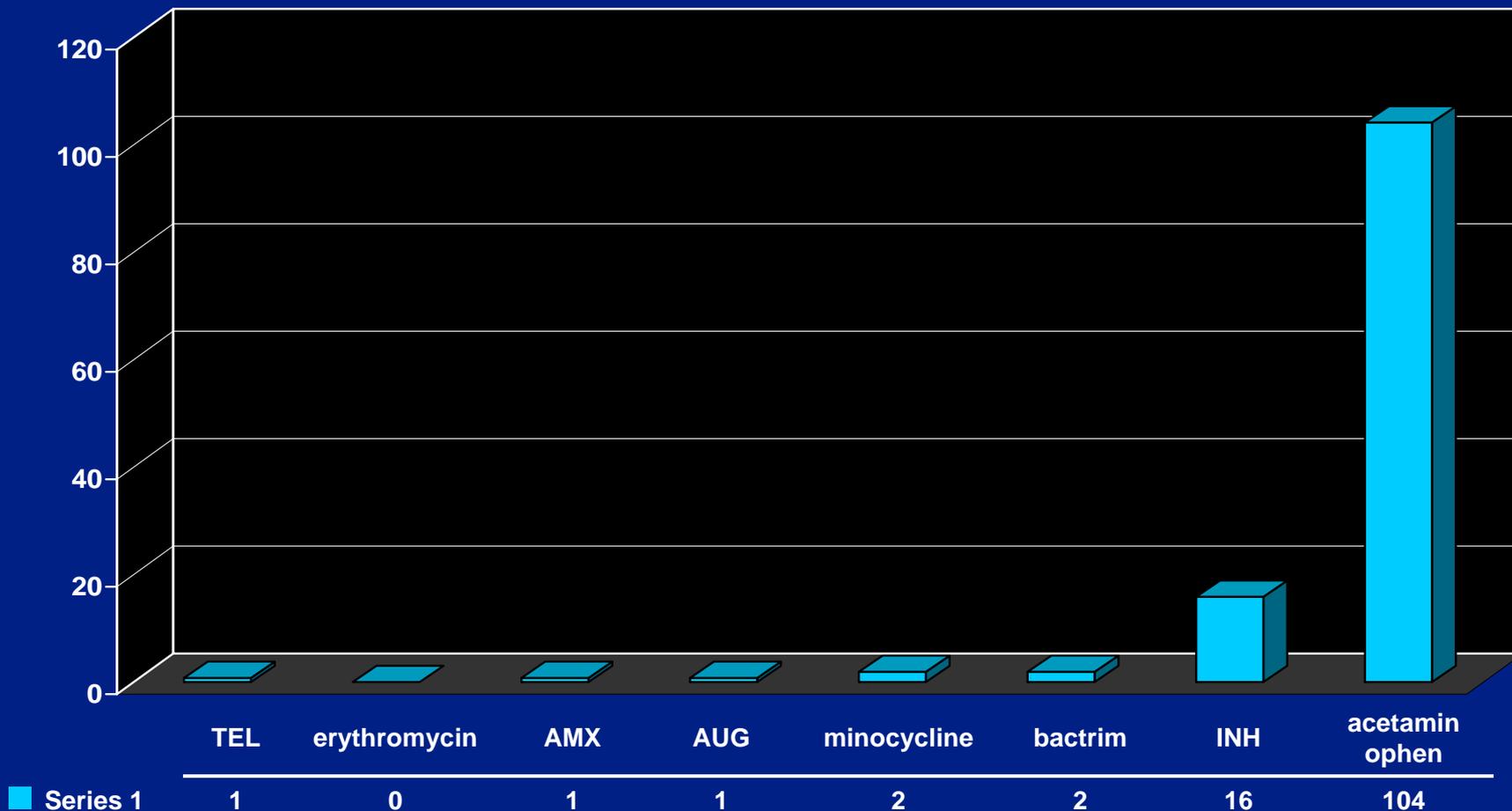
- Acute onset of severe liver injury
- *Encephalopathy or coagulopathy*
- *No underlying liver disease*

Spontaneous Hepatic Reporting Rates: Cumulative Internal Data (Sep 2006)

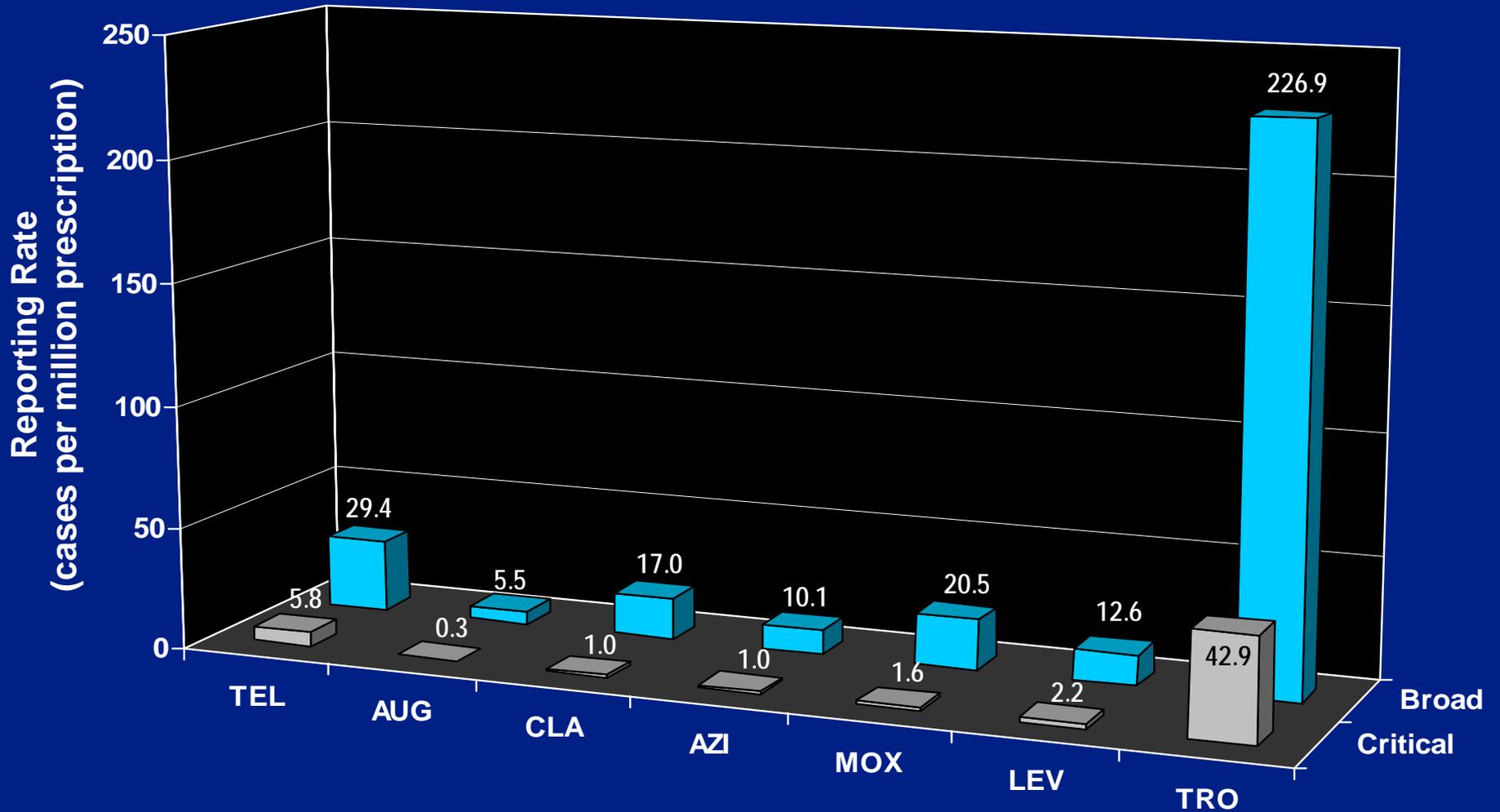
	Global		U.S.	
	No. of Reports	Reporting Rate (per 10 ⁶ exposures)	No of Reports	Reporting rate (per 10 ⁶ exposures)
All Hepatic Reports	443	15.8	212	36.7
ASLI	134	4.9	57	9.9
ALF	16	0.6	12	2.1

United Network for Organ Sharing: Liver Transplant Data

UNOS Liver Transplant Data 2004-2006



Spontaneous Hepatic Reporting Rates: FDA FOI Data 2 Years After Launch (Mar 2006)



Conclusions:

Characterization of Hepatic Events

- Hepatic effects well-characterized through intensive pharmacovigilance practices and further investigated through pharmacoepidemiologic studies
- Generally reversible hepatocellular or mixed injury comparable to other RTI antibiotics
 - rare spontaneous reports of ASLI or ALF
- Hepatic risks communicated through labeling modifications and HCP notifications

Hepatic: Revised USPI*

- **CONTRAINDICATIONS:**

- *patients with history of hepatitis and/or jaundice assoc with KETEK*

- **WARNINGS:**

- *reports of acute hepatic failure/severe liver injury, in some cases fatal*
 - *includes fulminant hepatitis & hepatic necrosis leading to liver transplant observed during or immediately after Rx*
 - *in some cases, injury progressed rapidly after a few doses*
- *monitor for signs/symptoms of hepatitis*
- *if signs/symptoms D/C and seek medical evaluation*

* June 2006