Hepatic Safety Experience

Barbara Rullo, MD

Global Pharmacovigilance & Epidemiology
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 \( \beta \)-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)
• 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)

<table>
<thead>
<tr>
<th>Exposure (x 10^6)</th>
<th>All Hepatic Events (per 10^6 exposures)</th>
<th>Critical Hepatic Events (per 10^6 exposures)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZI 1.0</td>
<td>12.7</td>
<td>0</td>
</tr>
<tr>
<td>LEV 1.4</td>
<td>4.2</td>
<td>0.7</td>
</tr>
<tr>
<td>CLA 2.2</td>
<td>16.9</td>
<td>1.3</td>
</tr>
<tr>
<td>TEL 1.95</td>
<td>15.4</td>
<td>1.5</td>
</tr>
<tr>
<td>GAT 1.8</td>
<td>7.6</td>
<td>1.6</td>
</tr>
<tr>
<td>MOX 0.9</td>
<td>35.1</td>
<td>3.5</td>
</tr>
</tbody>
</table>

* Exposure data from IMS
Spontaneous Hepatic Reporting Trends in United States
Acute Severe Liver Injury: Hepatic SAE with:

- **Hepatocellular jaundice:**
  \( \text{ALT} > 3\times \text{ULN}; \text{direct bili} > 3 \text{ mg/dL}; \text{absence of AP} \uparrow \) 

  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)

<table>
<thead>
<tr>
<th></th>
<th>Global</th>
<th>U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Reports</td>
<td>Reporting Rate (per 10^6 exposures)</td>
</tr>
<tr>
<td>All Hepatic Reports</td>
<td>443</td>
<td>15.8</td>
</tr>
<tr>
<td>ASLI</td>
<td>134</td>
<td>4.9</td>
</tr>
<tr>
<td>ALF</td>
<td>16</td>
<td>0.6</td>
</tr>
</tbody>
</table>
United Network for Organ Sharing: Liver Transplant Data

UNOS Liver Transplant Data 2004-2006

<table>
<thead>
<tr>
<th>Medication</th>
<th>Series 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEL</td>
<td>1</td>
</tr>
<tr>
<td>erythromycin</td>
<td>0</td>
</tr>
<tr>
<td>AMX</td>
<td>1</td>
</tr>
<tr>
<td>AUG</td>
<td>1</td>
</tr>
<tr>
<td>minocycline</td>
<td>2</td>
</tr>
<tr>
<td>bactrim</td>
<td>2</td>
</tr>
<tr>
<td>INH</td>
<td>16</td>
</tr>
<tr>
<td>acetaminophen</td>
<td>104</td>
</tr>
</tbody>
</table>
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
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