Telithromycin and the Liver: Putting Benefit vs Risk into Clinical Perspective

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Overview

- Clinical development program
- Drug induced liver disease in the US
- Postmarketing hepatic safety
- Causality assessment of acute liver failure cases
- The “Annals cases”
- Clinical signature of telithromycin hepatotoxicity
- Conclusions
Telithromycin and the Liver

• Preclinical studies identified the liver as a potential target organ
• Extensive focus on hepatotoxicity in all phases of development
  – Phase I studies: asymptomatic elevations in ALT/AST
  – Well tolerated in patients with mild hepatic impairment
  – Phase III studies
    • ALT > 3x ULN 1.6% vs 1.7% comparators
    • AST > 3x ULN 1.2% vs 1.3%
    • Bilirubin > 2x ULN 0.2% vs 0.2%
    • No Hy’s Law cases
    • 5 serious hepatic AEs
      – 3 considered possible, all recovered
      – 1 (Finnish case) deemed autoimmune
Drugs and the Liver

• Drug induced liver injury (DILI) is common (up to 9% of all drug-related AEs)

• Hy’s Law predicts a case fatality or need for transplant in > 10% in hepatocellular jaundice due to drug

• Drugs cause more than half of all acute liver failure (ALF) cases in the US annually (n=2000 total)a
  – Acetaminophen >> other drugs

• Drugs are responsible for 15% of all emergency liver transplants in the US (acetaminophen in about 50%)b

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aLee WM. *Hepatology* 2004;40:6-9)
bRusso et al. *Liver Transplantation* 2004;10:1018
The US Acute Liver failure Study Group estimates that there are approximately 2000 cases of ALF in the U.S. annually from all causes. Latest figures indicate 40-50% of cases are due to acetaminophen (intentional or inadvertent overdose) causing 56,000 ER visits, 2600 hospitalizations and an estimated 458 deaths due to ALF annually. All other drug (and herbal) causes represent 12-15%. The more severe the adverse event the more likely it is to be reported.

Lee WM. Hepatology 2004;40:6-9)
U.S. Reports of Acute Liver Failure Requiring Emergency Liver Transplant 1990-2002

- Causes reported by UNOS database of 51,741 transplants:
- 2291 OLTs done for acute liver failure of any cause
- 357 cases (15%) were UNOS status 1 (from “acute hepatic necrosis due to drugs”)  
- Annual incidence of 8-20% over the study period
- 270 had an identifiable drug:
  - APAP in 46%
  - APAP + another agent in 3%
  - non-APAP drugs in 51%
- 41 cases were in children (<18yr); APAP in 15, VPA in 8, PTU in 4

Clinical Features of ALF

<table>
<thead>
<tr>
<th>Feature</th>
<th>Acetaminophen</th>
<th>other drugs</th>
<th>all other causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age yr</td>
<td>36</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>% Women</td>
<td>79</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>Mean ALT IU/L</td>
<td>4310</td>
<td>574</td>
<td>1060</td>
</tr>
<tr>
<td>Mean AST IU/L</td>
<td>4333</td>
<td>636</td>
<td>1003</td>
</tr>
<tr>
<td>Mean bili mg%</td>
<td>4.3</td>
<td>20.2</td>
<td>12.6</td>
</tr>
<tr>
<td>Mean INR</td>
<td>2.8</td>
<td>2.4</td>
<td>2.7</td>
</tr>
<tr>
<td>% Transplanted</td>
<td>6</td>
<td>53</td>
<td>36</td>
</tr>
</tbody>
</table>

USALFSG 2002
Acetaminophen ALF: “The Elephant in the Room”

• Given the known risks of acetaminophen to cause intentional and unintentional ODs
  – leading cause of suicide in the UK
  – single leading cause of acute drug-induced fulminant hepatic failure in US, Europe
  – single leading cause of liver transplant due to drugs

• How should the risk of any other drug causing rare, unpredictable acute liver failure be judged?
Drug Classes Causing DILI

- Antimicrobial agents top the list!
  - 44% of all hepatotoxic drug reactions\(^a\)
  - 32%\(^b\)
  - 27%\(^c\)

- Amoxicillin-clavulanate
- Flucloxacillin
- TMP-SMX
- Erythromycins
- Other macrolides
- Fluoroquinolones (trovafloxacin)

- INH, rifampin, pyrazinamide, et al
- HAART (nevirapine)
- Sulfonamides
- Nitrofurantoin
- Azoles, terbinafine

Telithromycin Postapproval Safety

- Postapproval safety studies $n = 37,142$
- US prescriptions $n \sim 6$ million
- Global exposure $n \sim 28$ million
- Epidemiologic studies $n \sim 200,000$
- AERS Database
Telithromycin US Postmarketing Experience
15 May 04 – 15 Sep 06

Hepatic adverse events

- 212 total hepatic AE reports
  - 45 acute serious liver injury (ASLI)
  - 12 ALF cases
    - 1 report of liver transplantation after TEL injury
- Revised labeling (June 2006) warns of severe acute liver failure and possible liver transplant
Assigning causality is challenging but critical to establish true benefit/risk of a drug (Hy’s 2nd Law)

- Cases often heavily confounded
- Missing information is frequent
- Liver biopsy rarely done
- Workup for alternative causes often incomplete or not reported
- “Reported term” is often incorrect
ALF Causality Assessment

<table>
<thead>
<tr>
<th>ALF (US N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possibly associated with telithromycin (1 OLT; 1 recovered)</td>
</tr>
<tr>
<td>Considered unlikely</td>
</tr>
<tr>
<td>Concomitant medication</td>
</tr>
<tr>
<td>TMP/Sulfa</td>
</tr>
<tr>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Other hepatic disease</td>
</tr>
<tr>
<td>Septic shock</td>
</tr>
<tr>
<td>Ischemic injury</td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
</tr>
<tr>
<td>Viral (possibly lymphoproliferative)</td>
</tr>
<tr>
<td>Lacks temporal relationship</td>
</tr>
<tr>
<td>Insufficient info</td>
</tr>
<tr>
<td>Case retracted by reporting physician</td>
</tr>
</tbody>
</table>
Published Postmarketing Reports of Liver Injury with Telithromycin: The “Annals Cases”

• **Case 1**
  - 46M, otitis/sinusitis
  - Reversible mixed hepatocellular injury pattern without ALF
  - ALT 948; AST 200; AP 291, bili 3.8mg% on presentation
  - Normal LFT’s at 8 weeks

• **Case 2**
  - 51F, cough/rhinorrhea; no pretreatment LFTs
  - Subacute liver failure requiring transplant despite discontinuing Ketek
  - Shrunken liver on explant (with areas of regeneration)
  - ALT 730; AST 930; AP 188; bili 9.5mg% on presentation
  - positive smooth muscle antibody (autoimmune hepatitis?)

• **Case 3**
  - 26M, sinusitis/bronchitis;
  - ALT 2200; AST 3638; AP 575; bili 13.6mg%; platelets 39K, creatinine 3.9, INR 2.3
  - MSOF; Preliminary autopsy report: massive hepatic necrosis likely immune-mediated; “consider possible hypersensitivity reaction”

Autopsy Findings for Patient 3

Causality Assessment of the “Annals Cases”: New Information

- **Case 3**
  - Complained of weakness, nosebleeds, nausea, hematemesis, right sided “belly pain for 2 months prior to going to the ER (approximately 6 weeks prior to taking telithromycin)
  - Death from MSOF followed cardiopulmonary arrest during endoscopy
  - Moderate amount of bloody and frothy fluid in the lungs
  - Absence of eosinophils in the lymphoplasmacytic hepatic infiltrate makes hypersensitivity reaction due to a drug less likely according to pathologist in **final** autopsy report
  - Massively enlarged liver and spleen, multiple “prominent” mediastinal lymph nodes and suspected viral myocarditis on **final** autopsy
Is There a Clinico-Pathological Signature of Telithromycin-Associated Liver Injury?

• 54 ASLI reports (clinical trials and postmarketing reports) assessed as possibly or probably related:
  – females n=35 / mean age 55 (15-90yr)
  – males n=16 / mean age 42 (18-72yr)
  – hepatocellular injury 76%
  – mixed injury with cholestasis (↑ AP) 24%
  – mean ALT 750; AST 497 IU/L; jaundice in 24%
• Latency reported after single dose to 2 months after telithromycin given (mean is 7-8 days after dosing)
• Some cases describe hypersensitivity features (with a few cases of injury after re-exposure)
• Majority are self-limited reactions
• ALF, subfulminant liver failure appear to be very rare
• No clear host risk factors have emerged (although female gender, underlying liver disease, prior exposure are possible)
“Delayed” Antibiotic DILI

- **Amoxicillin-clavulanate** latency after start of therapy to jaundice averages about 2 weeks (range up to 6-7 weeks); immunoallergy in 2/3
- **Trovaflaxacin** associated with eosinophilia and hypersensitivity (usually short latency)
- **Emycin** (estolate) associated with jaundice in 1-2% with hypersensitivity in 60% +/- intrinsic toxicity starting 5-20 days after start of Tx
- **Telithromycin** latency 7-8 days (possibly more rapid in instances of prior exposure)
Telithromycin and the Liver: Conclusions

- Hepatic adverse events similar to comparators in clinical trials
- Postmarketing acute liver failure very rare (2 cases in 5.8 million exposures assessed as possible)
- No deaths due to acute liver failure in adjudicated cases
- As with other antibiotics, hepatotoxicity can be “delayed”
- Overall hepatic safety appears comparable to other oral antibiotics in general use