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 hepatoxicity
- 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]

[a]Lee WM. *Hepatology* 2004;40:6-9)
[b]Russo et al. *Liver Transplantation* 2004;10:1018

U.S. Reports of Acute Liver Failure

- The US Acute Liver failure Study Group estimates that there are approximately 2000 cases of ALF in the U.S. annually from all causes[a]
- 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[a]
- All other drug (and herbal) causes represent 12-15%
- The more severe the adverse event the more likely it is to be reported

[a]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

Russo et al. *Liver Transplantation* 2004;10:1018

Clinical Features of ALF

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

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

[a]Galan et al, *J Clin Gastroenterol* 2005;39:64; [b]Andrade et al, *Gastroenterology* 2005;129:512; [c]Bjornsson & Olsson *Hepatology* 2005;42:481

Telithromycin Postapproval Safety

- Postapproval safety studies n = 37,142
- US prescriptions n ~ 6 million
- Global exposure n ~ 28 million
- Epidemiologic studies n ~ 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

Causality Assessment in DILI

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

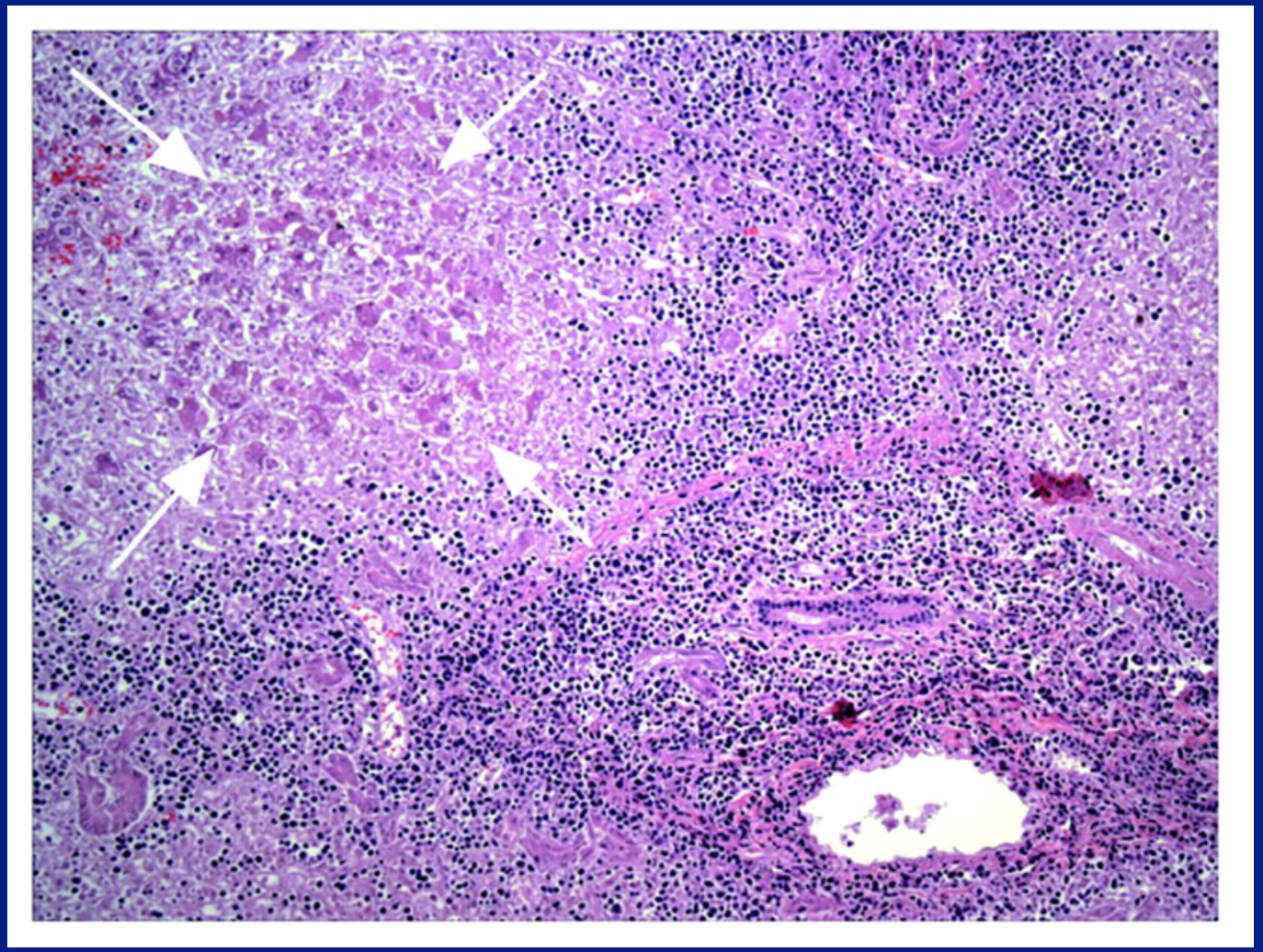
	ALF (US N=12)
Possibly associated with telithromycin (1 OLT; 1 recovered)	**2**
Considered unlikely	**10**
Concomitant medication	
TMP/Sulfa	1
Acetaminophen	1
Other hepatic disease	
Septic shock	1
Ischemic injury	1
Alcoholic cirrhosis	1
Viral (possibly lymphoproliferative)	1
Lacks temporal relationship	1
Insufficient info	2
Case retracted by reporting physician	1

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"

Clay et al, "Severe hepatotoxicity of telithromycin: three case reports and review of the literature" *Annals of Internal Medicine 2006;* 144: 415-420.

Autopsy Findings for Patient 3



Clay, K. D. et. al. Ann Intern Med 2006;144:415-420

Annals of Internal Medicine

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%

Is There a Clinico-Pathological Signature of Telithromycin-Associated Liver Injury? (cont)

- 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
- **Trovafloxacin** 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 antiobiotics in general use