Detection and Assessment of Drug Induced Liver Injury (DILI) in NASH Clinical Trials. Key Questions and Future Challenges.

Arie Regev, MD
Global Patient Safety
Eli Lilly and Company

Outline

- Background
- Risk of DILI in NASH patients
- Current Regulatory Guidelines
- Hy's law and NASH patients
- eDISH for NASH databases
- ALT/AST Exclusion Criteria
- Hepatic stopping rules
- Summary

Drug-Induced Liver Injury (DILI) Background (I)

- The most frequent cause of drug withdrawal in 50 years
  (troglitazone, benoxaprofen, bromfenac, ticruynafen, ximelagatran, etc.)
- A frequent cause for limiting drug use
  (isoniazid, labetalol, trovafloxacin, felbamat, nefazodone,etc.)
- The leading cause of acute liver failure (ALF) in the US and EU
- Exceeds all other ALF causes combined

DILI Background (II)

- Most significant DILI events in the clinic are idiosyncratic
- Presently there are no diagnostic or predictive DILI biomarkers
- ALT is a sensitive but nonspecific marker for hepatocellular DILI
- Animal studies generally do not predict idiosyncratic DILI
- DILI may be predicted by careful data collection and analysis in early phases of clinical development

Risk of DILI in NASH patients

Are NASH patients susceptible to DILI?

Risk of DILI in NASH Patients

- Still a matter of debate due to scarce and mixed evidence.
- Generally, it is believed that chronic liver disease does not predispose to DILI[1-4]
- "*The often cited warning that drugs known to produce hepatic injury should not be given to patients with liver disease has little foundation in fact*"

  Hyman Zimmerman

- Advanced pre-existing liver disease may lead to worse outcome when DILI occurs.

1. Zimmerman H. Hepatotoxicity: 2nd ed. Philadelphia, 1999.
2. Lewis JH. Expert Opin Drug Saf 2002;1:159–172.
3. Russo MW and Watkins PB. Gastroenterology 2004;126:1477–1480.
4. FDA Guidance for Industry 2009

Current Guidelines

What do current guidelines teach us about DILI in NASH clinical trials?

Current DILI Guidelines

- Presently, most drug makers rely on regulatory guidlines[1,2] and published position papers[3-5].
- Most published guidelines address comprehensively clinical trials enrolling patients with normal livers.
- However, they typically do not cover issues pertaining to patients with pre-existing liver diseases such as NASH.
- As a result, approaches and practices of assessment of liver safety vary greatly between drug makers.

1. FDA. 2009. DILI: premarketing clinical evaluation. Guidance for industry.
2. Health Canada. 2012. Guidance document: pre-market evaluation of hepatotoxicity
3. Aithal et al. Clin Pharmacol Ther. 2011;89(6):806–15
4. Regev et al. Drug Saf;2014:37 (Suppl 1):S47–S56
5. Avigan et al. Drug Saf;2014:37 (Suppl 1):S19–S31

Guidance for Industry

Drug-Induced Liver Injury: Premarketing Clinical Evaluation

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2009
Drug Safety

Hy’s Law and NASH patients

Should Hy’s law be applied to NASH patients?

Hy's Law Criteria*

- ALT/AST ≥ 3X ULN
- Total bilirubin ≥ 2X ULN
- No initial cholestasis
  (alkaline phosphatase < 2X ULN)
- No other cause of liver injury

Hyman Zimmerman
1914-1999

*as defined by FDA Guidance for Industry 2009

Hy's Law and DILI Prediction

- Hy's Law cases carry >10% risk of live transplant or death
- Two Hy's Law cases in a clinical trial of 1,000 subjects
  - → risk of liver transplant or death: **>2:10,000**
  - → risk post marketing: **>200 per million**
- Unacceptable risk for almost all drugs

ALT & AST Values in NASH

- ALT values in NASH clinical trials:
  - 76 ± 43[1]
  - 52 ± 39[2]
  - 81 ± 48[3]
  - 61 (38 to 85)[4]
- ALT values> 3x ULN are possible
- AST values typically lower than ALT

1. Ekstedt et al. Hepatology 2006;44:865-873
2. Hyysalo et al. J Hepatol 2014;60:839–846
3. Sanyal et al. N Engl J Med. 2010;362:1675–1685
4. Angulo et al. Gastroenterology;2013;145:782–789

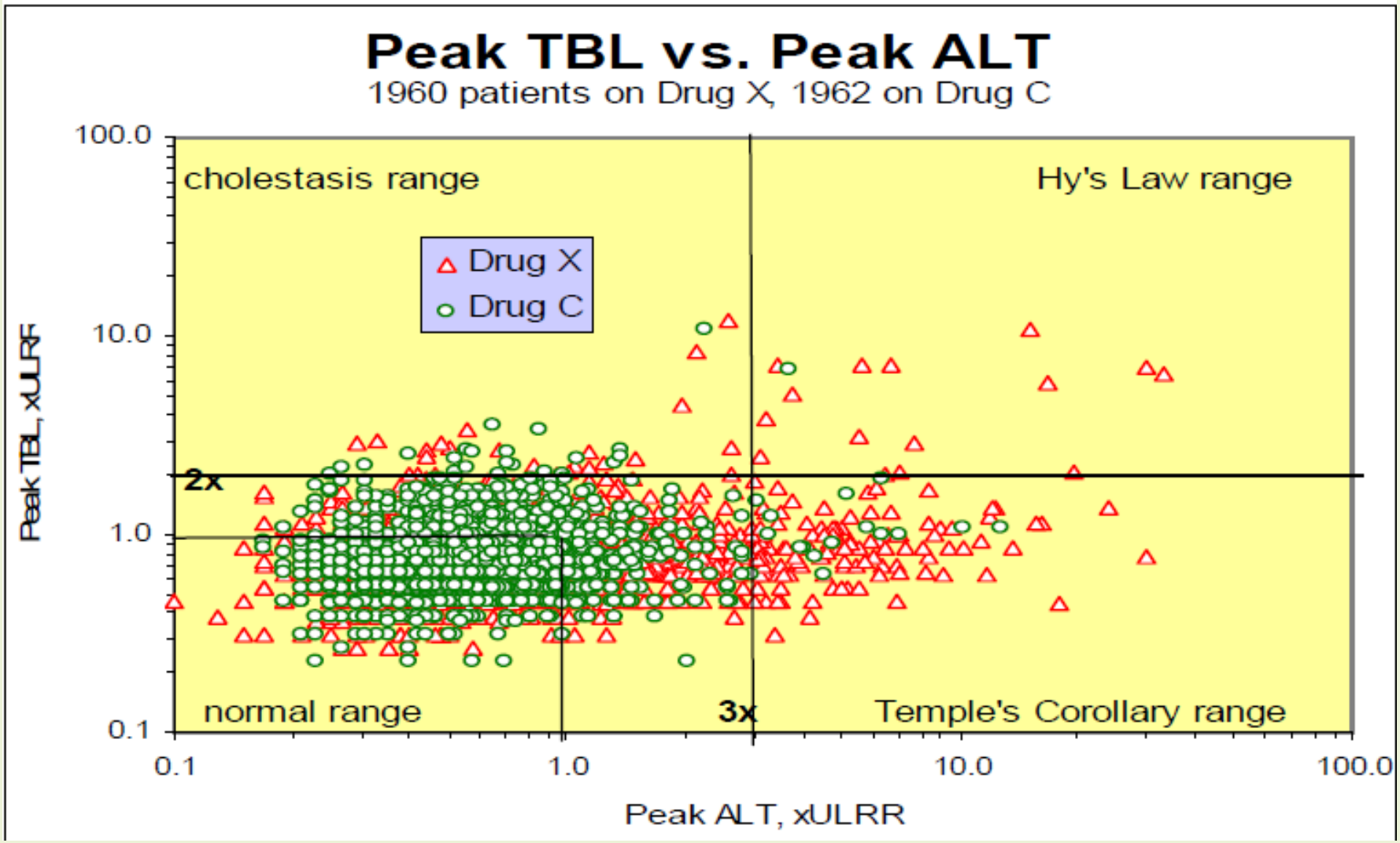
Hy's Law and NASH patients

- Can Hy's law be applied to NASH patients with baseline ALT> 3x ULN?
- Per definition, a case that has another cause for elevated ALT would not meet the full definition of HY's law.

eDISH for NASH Databases

Can eDISH be applied to NASH databases?

eDISH Plot (Evaluate Drug Induced Severe Hepatotoxicity)



ALT/AST Exclusion Criteria

Which ALT/AST level should be an exclusion criterion?

ALT/ AST Exclusion Criteria in NASH Clinical Trials

- "If the drug is intended to be prescribed or marketed to such patients after approval, they should be studied during controlled trials."[1]
- ALT> 200 U/L is uncommon in NASH patients.
- Inclusion of patients with high ALT levels may lead to potential difficulties:
  - Increased likelihood of underlying liver disease other than NASH
  - Difficulties in detection and monitoring of potential DILI

1. FDA Guidance for Industry. July 2009

Hepatic Stopping Rules

When should the study drug be discontinued?

Hepatic Stopping Rules

Discontinuation of treatment should be considered if: [1]

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN **and** (TBL >2xULN **or** INR >1.5)
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

- Discontinuing the drug too early will interfere with understanding the drug's hepatic safety profile, and will potentially increase the risk post-marketing.

1. FDA Guidance for Industry. 2009

Hepatic Stopping Rules

- Suggested stopping rules for NASH patients in previous position papers:[1]
  - ALT/AST>3x baseline or >500 U/L
  - New onset jaundice (total bilirubin ≥ 3 mg/dl)
  - Increase in ALT/AST < 3x baseline, associated with symptoms
- Difficult to apply in patients with low normal ALT/AST values
- May need to be adjusted based on individual baseline values or best pre-event values.

1. Sanyal et al. Hepatology. 2011; 54: 344–353

Summary

- There is no clear evidence of increased risk of DILI in NASH patients, however patients with advanced NASH may have worse outcome when DILI occurs.
- Current regulatory guidelines do not address specific questions related to detection assessment and monitoring of DILI in NASH patients.
- Hy's law and eDISH may be difficult to apply to all NASH patients, especially those with baseline ALT>3x ULN.
- ALT/AST exclusion criteria may have important implications in NASH studies, and need to be pre-determined.
- Hepatic stopping rules may need to be adjusted based on baseline (or best pre-event) ALT/AST levels.
- Studies of large cross-pharma databases will enable better understanding and improved approaches for detection and assessment of DILI in NASH clinical trials.

Thank you!