How Can We Break the Logjam for Predictive DILI Biomarkers?

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New IDILI Biomarkers in the Clinic: State of the Art

- Number of new IDILI biomarkers in clinical practice in the last 40 years: 0
- Number of new IDILI biomarkers currently in clinical development: 0
- Number of drugs for which IDILI mechanism is completely understood: 0
- Number of widely accepted animal models for IDILI: 0
- Number of clinicians and basic-research scientists who agree with each other on IDILI biomarkers: Too Low
Potential Barriers for the Development of Predictive IDILI Biomarkers

1. Are we using “clean” well adjudicated DILI cases?
2. Are we differentiating between benign reversible enzyme elevations and clinically significant DILI?
3. Are we adhering to evidence based approach?
4. Do we address relevant clinical questions?
5. Do we differentiate between various types of DILI?
6. Do we know the limitations of animal studies, and in-vitro models?
7. Do preclinical scientists and clinicians communicate and collaborate throughout the biomarker development process?
Are We Using “Clean” Well Adjudicated DILI Cases?

- Real IDILI cases are typically rare
- Non-DILI cases are typically much more common
  - Viral hepatitis in the US >2.5%
  - DILI for most hepatotoxic drugs < 0.00001%
- Causality assessment is complex and limited
- After thorough investigation, other potential causes are still possible
- Enrollment pressure may lead to bias
Alternative Causes of Hepatic Abnormality

- Viral Infection A-E
- Autoimmune hepatitis
- Alcoholic liver disease
- Non alcoholic steatohepatitis (NASH)
- Gallstone disease
- Genetic liver disease (e.g. hemochromatosis, Wilson)
- Acute infection
  - Sepsis
  - Septic shock
- Congestive heart failure
  - Acute myocardial infarction
  - Cardiogenic sock
- Hypotension
- Hypoxemia
Alternative Causes of Liver Injury

Fig. 1. Proportion of ALF cases attributed to acetaminophen in each of the first 6 years of the ALF Study Group: January 1998 to December 2003.

Larson et al, Hepatology 2005;42:1364
Hepatitis E Virus, Underestimated Cause


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Hepatitis E Virus, Underestimated Cause

- HEV seroprevalence in the studied population was 21%
- In US born individuals HEV seroprevalence was 20%
- HEV seroprevalence was highest in the Midwest and West US

Table 1. Prevalence of antibody to hepatitis E virus (anti-HEV) for selected demographic variables among participants (age, ≥6 years) in the Third National Health and Nutrition Examination Survey, 1988–1994.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Samples tested, no. (n = 18,695)</th>
<th>Positive for anti-HEV, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10,124</td>
<td>20.4 (18.3–22.5)</td>
</tr>
<tr>
<td>Male</td>
<td>8571</td>
<td>21.6 (19.3–23.9)</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (reference)</td>
<td>7052</td>
<td>22.1 (19.8–24.4)</td>
</tr>
<tr>
<td>Black</td>
<td>5312</td>
<td>14.5 (13.1–15.9)</td>
</tr>
<tr>
<td>Mexican American</td>
<td>5527</td>
<td>20.3 (18.3–22.3)</td>
</tr>
<tr>
<td>Other</td>
<td>804</td>
<td>20.2 (16.5–23.9)</td>
</tr>
<tr>
<td><strong>Country of birth</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States (reference)</td>
<td>15,051</td>
<td>20.1 (18.1–22.0)</td>
</tr>
<tr>
<td>Mexico</td>
<td>2357</td>
<td>30.9 (28.9–32.9)</td>
</tr>
<tr>
<td>Other</td>
<td>1233</td>
<td>26.2 (22.9–29.5)</td>
</tr>
<tr>
<td><strong>Region of residence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South (reference)</td>
<td>8168</td>
<td>14.7 (12.3–17.0)</td>
</tr>
<tr>
<td>Northeast</td>
<td>2372</td>
<td>20.8 (16.5–25.1)</td>
</tr>
<tr>
<td>Midwest</td>
<td>3655</td>
<td>26.6 (22.4–30.8)</td>
</tr>
<tr>
<td>West</td>
<td>4500</td>
<td>25.0 (20.9–29.1)</td>
</tr>
</tbody>
</table>

Kuniholm et al. JID 2009:200:48-56
Hepatitis E Virus and DILI

The role of hepatitis E virus testing in drug-induced liver injury


SUMMARY

Background
Locally acquired hepatitis E is an emerging infection in developed countries and can be misdiagnosed as drug-induced liver injury.

Hepatitis E Virus and DILI

- 47 patients had criteria for DILI
- 19 of 47 had no serum sample available
- 22 of the 47 were negative for HEV
- 6 of 47 were HEV positive
  - 13% of the 47 DILI patients
  - 21% of the 28 with serum samples

**Conclusion:** “The diagnosis of drug-induced liver injury is not secure without testing for HEV.”

Among 318 patients with suspected DILI
- 50 (16%) tested positive for anti HEV IgG
- 9 (3%) tested positive for anti HEV IgM
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Transient Enzyme Elevation is a Poor Predictor of DILI and May Lead to Erroneous Results

- Patients with transient enzyme elevations often do not have clinically significant DILI
- Most drugs that cause transient enzyme elevation do not cause significant DILI
  - Statins
  - Aspirin
  - Heparin
  - Tacrine
  - Etc.
- Benign transient enzyme elevation is often erroneously called “hepatitis”, “liver dysfunction”, “liver injury”
- Assessing a mix of patients with benign enzyme elevations and patients with DILI may produce misleading results
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FDA-approved drug labeling for the study of drug-induced liver injury

Minjun Chen¹,³, Vikrant Vijay¹,³, Qiang Shi¹, Zhichao Liu¹, Hong Fang² and Weida Tong¹

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² Z-Tech Corporation, an ICF International Company at NCTR, Jefferson, AR, USA
Caveats of using drug labeling

Many inherent defects are associated with drug labeling. Drafting a drug’s label by the drug manufacturer is a complex process involving not only safety concerns but also efficacy, benefit:risk, legal and other considerations. The liver safety profile could therefore be worded differently for drugs with different indications, efficacy and benefit:risk ratios, despite similar hepatic risks. Because the language regarding appropriate wording and the placement of safety-related information is flexible [37], data regarding adverse effects could be disclosed using ambiguous semantic descriptions [45]. Sometimes, the mention of liver injury in the label is based on relatively little objective data and instead reflects the drug manufacturer’s or the regulator’s concern of the possibility of DILI. In
In some cases, liver injury is mentioned in the label to increase physician awareness of the potential risk, because hepatic events were reported in patients taking a related drug and there is concern that they might represent a class effect. For example, lamivudine was issued a BW because it is a synthetic nucleoside analog. It belongs to a subclass of antivirals and some of these have caused severe liver injury. In some cases liver injury is mentioned in the label to acknowledge that such cases were reported to the drug manufacturer or to the regulators. However, these reports do not necessarily imply a causal relationship between the drug and the hepatic event, because they might reflect hepatic events unrelated to the drug. Overall, labeling can sometimes be capricious and inconsistent.
Biliary Ductular Hyperplasia
A Reliable DILI Predictor?

- Although isolated BH is hardly ever discussed in humans, it is a well recognized finding in laboratory animals.
- Relevance and predictive value of isolated biliary hyperplasia in laboratory animals to DILI in humans remain controversial.
- While some experts view IBH as a potential adverse event predicting an increased risk of DILI in humans, others view it as a nonspecific finding of unclear significance.
The Toxicology of HMG–CoA Reductase Inhibitors: Prediction of Human Risk

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²Bristol-Myers Squibb Research Institute, New Brunswick, New Jersey 08903-0191, USA

TABLE 4.—Incidence of hepatic morphologic abnormalities in rats treated with lovastatin and mevalonic acid.

<table>
<thead>
<tr>
<th>Hepatic morphologic abnormality</th>
<th>Control</th>
<th>Mevalonic acid (0.5%, diet)</th>
<th>Lovastatin (200 mpk, bid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal basophilic cellular alteration</td>
<td>1</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Focal eosinophilic cellular alteration</td>
<td>1</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Cellular atypia</td>
<td>3</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>Bile duct hyperplasia</td>
<td>8</td>
<td>7</td>
<td>23</td>
</tr>
</tbody>
</table>

Numbers show number of animals with indicated abnormality; n = 15 from MacDonald J. S. et al. (1988). Am J Cardiol 62, 161–271.
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Blind Men and an Elephant
Blind Men and an Elephant

It’s an elephant

It’s an elephant

It’s an elephant

It’s an elephant
DILI- A Group of Diverse Entities?

- Dose Dependent DILI ≠ Idiosyncratic DILI
- Isoniazid ≠ Amoxicillin-Clavulanate ≠ Methotrexate

Main biomarker- ALT

Main biomarker- AlkP

Main biomarker- ?

- A-C induced Cholestatic injury ≠ A-C induced Hepatocellular inj.?
- Hepatocellular DILI due to drug X in patient A ≠ Hepatocellular DILI due to drug X in patient B?

A-C= Amoxicillin-Clavulanate
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Summary: How Can We Break the Logjam for Predictive DILI Biomarkers?

1. Use of “clean” well adjudicated DILI cases
2. Differentiation between benign reversible enzyme elevations and clinically significant DILI
3. Adherence to evidence based approach
4. Addressing relevant clinical questions
5. Differentiation between various types of DILI
6. Knowledge of the limitations of animal studies, and in-vitro models
7. Communication and collaboration between preclinical scientists and clinicians throughout the biomarker development process
Thank you