Industry Clinical Perspective on DILI and CIVM Application

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Historical perspective

- Hy Zimmerman MD, lecturing on the mechanisms of DILI (c. 1970)

Lewis et al. AASLD, 2020
Current challenges posed by DILI in drug development

- A major cause of **early termination** of drug development (1)

- A frequent cause for **regulatory action** and limiting drug use

- Most cases are **idiosyncratic** and therefore **difficult** or **impossible to predict**

- **Lack of biomarkers** for risk assessment, diagnosis, and outcome prediction

- **Limited translatability** of nonclinical findings

(1) Guengerich F. *Drug Metab Pharmacokinet.* 2010
Objectives

• Industry perspective on human DILI

• Highlight impact of CIVM on IND submission
Patient A.

- Presented with ALT 3 x ULN, Phase 1 SAD
Patient B.

- Presented with elevated ALT, fever and rash, Phase 3
Patient C.

- Presented with elevated ALT and ANA(+), post-approval
### Phenotypes of human DILI

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Image</th>
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<tbody>
<tr>
<td>Acute hepatic necrosis</td>
<td><img src="https://example.com/image1.png" alt="Image" /></td>
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<tr>
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<td><img src="https://example.com/image2.png" alt="Image" /></td>
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<tr>
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<td><img src="https://example.com/image3.png" alt="Image" /></td>
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<tr>
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<tr>
<td>Hypersensitivity syndrome with liver involvement (DRESS)</td>
<td><img src="https://example.com/image5.png" alt="Image" /></td>
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<tr>
<td>Severe cutaneous adverse reactions (SJS/TEN)</td>
<td><img src="https://example.com/image6.png" alt="Image" /></td>
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<td>Drug-induced autoimmune hepatitis</td>
<td><img src="https://example.com/image7.png" alt="Image" /></td>
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<td>Hepatic steatosis (macrosteatosis)</td>
<td><img src="https://example.com/image8.png" alt="Image" /></td>
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<td>Acute fatty liver (microsteatosis)</td>
<td><img src="https://example.com/image9.png" alt="Image" /></td>
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<tr>
<td>Sinusoidal obstruction syndrome</td>
<td><img src="https://example.com/image10.png" alt="Image" /></td>
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<tr>
<td>Nodular regenerative hyperplasia</td>
<td><img src="https://example.com/image11.png" alt="Image" /></td>
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<tr>
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**Phenotypes**

- **Acute hepatic necrosis**
- **Acute hepatitis**
- **Bland cholestasis/Mixed cholestatic hepatitis**
- **Vanishing bile duct syndrome**
- **Hypersensitivity syndrome with liver involvement (DRESS)**
- **Severe cutaneous adverse reactions (SJS/TEN)**
- **Drug-induced autoimmune hepatitis**
- **Hepatic steatosis (macrosteatosis)**
- **Acute fatty liver (microsteatosis)**
- **Sinusoidal obstruction syndrome**
- **Nodular regenerative hyperplasia**
- **Neoplasia**
- **Secondary sclerosing cholangitis**
- **Granulomatous hepatitis**
- **Peliosis hepatis**
Multiple facets of human DILI

• 3 major categories (direct, idiosyncratic, indirect)

• 11+ potential mechanisms (1)

• 15+ phenotypes (2)

• 3 biochemical patterns (hepatocellular, cholestatic, mixed)

• 4+ routine diagnostic biomarkers (ALT, AST, alkaline phosphatase, bilirubin)

(1) Hoofnagle et al. NEJM, 2019
(2) CIOMS Working Group, 2020
CIVM and categories of DILI

- CIVM is well-suited to detect direct hepatotoxicity
  - Lead optimization (i.e., candidate selection)
  - Due diligence (collaborations, acquisitions)
  - Preclinical
  - Phase 1

- CIVM can fill a key unmet need with idiosyncratic hepatotoxicity
  - Limitations with animal models
  - Low frequency of severe DILI in development programs/registrational trials
  - Opportunity to screen (e.g., human donor genotypic variability)
  - Drug-drug interactions

- CIVM and indirect hepatotoxicity may be considered ‘future direction’
CIVM and potential mechanisms of DILI

- Various mechanisms have been proposed
  - Formation of reactive metabolites
  - Hapten formation
  - Danger signals hypothesis
  - Bile Salt Export Pump (BSEP) inhibition
  - Drug transporter/metabolizing enzymes modulation
  - Mitochondrial toxicity
  - Oxidative stress
  - Modulating adaptive/innate immune reactions
  - Biliary epithelial injury
  - Histone acetylation
  - Autoimmunity
  - Immune-mediated toxicity

Luedde T et al. Gastroenterology 2014;147:765-83
Can CIVM expand breadth of diagnostic biomarkers?

- **Glycochenodeoxycholic acid** (GCDCA) as a surrogate biomarker of **cholestasis**
- **Urea** synthesis as surrogate biomarker of **mitochondrial function**
- **miR122, GLDH** and **cytokines** as biomarkers of **hepatocyte damage**
- **Autoantibodies** and **Th17** as biomarkers of **autoimmunity**
- **DAMPs** and **macrophage phenotypes** as biomarkers of **immune stimulation**
How can CIVM impact IND submission

• As part of a nonclinical toxicology package

• Inform ‘pre-test probability’ of DILI

• Support rationale for conducting/not-conducting Phase 1 liver safety study

• Impact design of Phase 2/3 studies (e.g., screening labs; frequency of surveillance exclusion criteria; discontinuation rules)

• Is there a role for CIVM and prediction of adaptation (for development programs with imbalance of cases in Temple’s quadrant but not Hy’s quadrant)
A hepatologist sees hepatology everywhere