Can Study Protocols Protect Patients with Liver Diseases from Serious DILI?

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NIH NIDDK: Member of DILIN DSMB and Executive Committee of LTCDS

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Identification of drugs or biologics with potential to cause serious, life-threatening DILI requires causality assessment and comprehensive testing for alternative etiologies in each suspected case\(^1\).

Since idiosyncratic DILI is rare, prediction of the risk of serious DILI post-marketing relies on identification of cases of interest meeting Hy’s Law criteria during phase II-III clinical trials\(^2\).

Subjects with pre-existing, chronic liver diseases (CLDs), with or without cirrhosis, are challenging because current FDA guidance is based largely on criteria for studies that exclude subjects with abnormal liver tests \(^3\).

CLDs do not increase overall susceptibility for DILI, but multiple exceptions suggest that additional examples will be identified in future clinical trials \(^2\). DILI in subjects with CLD is worrisome because subjects with reduced hepatic functional reserve are less likely to recover and more likely to die\(^2,3\).

The probability of subjects with CLDs enrolling in clinical trials is increasing, especially in therapeutic trials targeting components of the metabolic syndrome (enriched for NAFLD), antimicrobials, specific CLDs, complications of cirrhosis and hepatocellular carcinoma.

\(^1\)Avigan MI. Semin Liver Dis 2014; 34: 215-26
\(^3\)Chalasonai N, et al Gastroenterology 2015; 148: 1340-52
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Key Questions:
1. What is the probability of enrolling patients with CLDs, including cirrhotics, in drug development trials?
2. What are the risks of serious DILI and hepatic decompensation in subjects with CLDs?
3. How do protocols currently protect subjects with CLDs, including cirrhotics, from serious DILI?
4. What improvements in protocols can provide greater protection from serious DILI in patients with CLD, including cirrhotics?
   a. Assessment pre-enrollment
   b. Monitoring on treatment
   c. Functional assessment of suspected DILI and stopping rules
Etiologic Spectrum of Chronic Liver Diseases with Risk of Progression to Cirrhosis

- Alcoholic
- Viral Hepatitis
- NAFLD
- Genetic
- Autoimmune
- Drug-Induced
- Pediatric
Probability of Enrolling Americans with CLDs with or without Cirrhosis in Clinical Drug Trials

General Drug Development

- Obesity
- Hyperlipidemia
- Hypertension
- Gout

General Population
- 25-35% Expected to have CLDs
- 5-7% Gilbert

Selected Population
- ≥50% with NAFLD (Steatosis/NASH) + Other CLDs
- 5-7% Gilbert

Drug Development
Drugs for specific CLDs
- HBV±HDV, HCV±HIV, HEV
- NAFLD/NASH
- AIH, PBC, PSC
- Genetic

Drugs for Cirrhosis/Complications
- Cirrhosis
- PVHTN
- Varices
- HE
- HCC
- Antifibrotics

Certainty of Enrolling Americans with CLDs with or without Cirrhosis in Clinical Drug Trials
- 100% CLDs
- 5-7% Gilbert
- Compensated Cirrhotic Stage
- Decompensated
- 100%
Cirrhosis: Global Prevalence per 100,000 Persons

Alcohol is cause of 47.9% cirrhosis*

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Risk of DILI in Subjects with CLDs? Increased Susceptibility?

History/PE
Liver Tests

Normal

CLD Possible*

Abnormal

CLD Present

No Inherent Increased Risk

Some Specific Exceptions

*CLDs with potential for Liver Tests WNL: HBV, HCV, NAFLD, AIH, PBC, PSC, burned out cirrhosis (e.g. ETOH, HBV)

Gupta NK, Lewis JH Aliment Pharmacol Ther 2008; 28: 1021-41
Increased Risk of DILI in CLDs?
Disease-Specific and Non-Specific Susceptibility

**Chronic Viral Hepatitis**
- HAART: HCV-HIV
- Anti-TB Rx:
  - HBV
  - HCV ± HIV
  - UGT1A1*27/*28

**NAFLD**
(OR 3.95; 95% CI 1.4-11.5)
- Antihypertensive
- Anti-Platelet agents
- Antimicrobials
- OTC: NSAIDs, PPI, APAP

**Unspecified CLDs**
- Anti-TB Rx:
  - UGT1A1*27/*28
- Azole Antifungals
- Azithromycin
- Tacrolimus

Increased Risk of Serious DILI in CLD
NIDDK DILIN

N= 1257

N= 1091 Causality Assessment

N= 899 Definite, Highly Likely, Probable

N= 89 (10%) CLD

Significantly Higher Mortality
16% vs. 5.2%, p<0.001

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Identification of Study Subjects with CLDs

Current Inclusion and Exclusion Criteria

History/PE
- Lab Tests:
  - CBC, Plts
  - Electrolytes, BUN, creat
  - T (± D) Bili
  - ALP
  - ALT/AST
  - T. Protein/Alb
  - PT INR
  - ± Imaging
  - ± Liver Bx or Non-Invas Test

Liver Tests
- WNL

CLD “Absent” but Possible*

Abnormal Liver Tests

Exclude Acute Liver Disease

CLD Present

Test for Etiology

Assess for Cirrhosis

*CLDs with potential for Liver Tests WNL: HBV, HCV, NAFLD, AIH, PBC, PSC, burned out cirrhosis (e.g. ETOH, HBV)
# Identification of Study Subjects with Cirrhosis

Non-Invasive Detection Methods

<table>
<thead>
<tr>
<th>Test</th>
<th>Parameters</th>
<th>Imaging Methods</th>
</tr>
</thead>
</table>
| FibroTest / FibroSure | Bili, GGT, g-globulin, haptoglobin, α2 M, apolipoprotein | Transient Elastography:  
  - Fibroscan (FDA-approved)  
  - Ultrasonic elastography |
| FibroSpect            | Hyaluronic acid, TIMP-1, α2 M                   | Magnetic Resonance Elastography (MRE)  
  FDA-approved  
  No CPT Billing Code |
| ELF                   | HA, Procollagen III amino terminal peptide (PIIINP), TIMP1 |                                                                                  |
| HepaScore             | Hyaluronic acid, GGT, α2 M                      |                                                                                  |
| Forns                 | GGT, cholesterol, platelets, age                |                                                                                  |
| APRI                  | AST /ULN X 100 / platelets (10⁹/ L)             |                                                                                  |
| SHASTA; (HIV/HCV)     | AST, HA, albumin                                |                                                                                  |
| FIB-4                 | AST, ALT, platelets, age                        |                                                                                  |

Most accurate differentiating F0-1 from F4 cirrhosis
Hy’s Law
Derivation and Current Definition

“Drug-induced hepatocellular jaundice is a serious entity. The mortality rate ranges from 10% to 50%.”


Hy’s Law as defined by FDA1:

- ALT or AST >3 X ULN (good sensitivity; poor specificity)
- Total bilirubin >2 X ULN (improved specificity)
- No “initial findings of cholestasis (elevated ALP)
- No alternative cause of liver test abnormalities

NIDDK DILIN2:

- ALT >3X ULN
- Total bilirubin >2X ULN
- ALP <2X ULN

Caveats:

- Not a Law but a clinically useful tool!
- Calls for urgent assessment and adjudication
- 2 Case Rule: Finding 2 Hy’s Law cases in a clinical trial is highly predictive of ALF3

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2Fontana RJ, et al Gastroenterology 2014; 147: 96-52
3Avigan MI. Semin Liver Dis 2014; 34: 215-26
Identification of DILI in Subjects with CLDs
Importance of eDISH and Kinetic Analyses

eDISH:

Kinetics:

## Serious DILI in Subjects with or without CLDs

### Stopping Rules for Aminotransferases Alone or in Combination with Elevated Bilirubin or PT INR

<table>
<thead>
<tr>
<th>Baseline ALT or AST</th>
<th>Stop if post-randomization values are:</th>
</tr>
</thead>
</table>
| Patients with normal ALT or AST | >8X ULN  
| | >5X ULN in 2 consecutive visits  
| | >3x ULN & (TBL >2xULN or PT INR >1.5)  
| | Any of the above |
| All patients (Regardless of baseline ALT, AST) | >8 ULN  
| | >5X ULN in 2 consecutive visits  
| | >3x ULN & (TBL >2xULN or PT INR >1.5)  
| | Any of the above |

TBL, total bilirubin

## Biochemical Stopping Rules

### Subjects with Decompensated Cirrhosis

<table>
<thead>
<tr>
<th>Baseline ALT or AST</th>
<th>Stop if post randomization values are:</th>
<th>Patients Meeting Rule (GPB)</th>
<th>Patients Meeting Rule (Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with normal ALT or AST</td>
<td>&gt;8 ULN</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;5X ULN in 2 consecutive visits</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt;3xULN &amp; (TBL &gt;2xULN or PT INR &gt;1.5)</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Any of the above</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>All patients (Regardless of baseline ALT, AST)</td>
<td></td>
<td>N=90</td>
<td>N=88</td>
</tr>
<tr>
<td></td>
<td>&gt;8 ULN</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;5X ULN in 2 consecutive visits</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&gt;3xULN &amp; (TBL &gt;2xULN or PT INR &gt;1.5)</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Any of the above</td>
<td>21</td>
<td>14</td>
</tr>
</tbody>
</table>

TBL, total bilirubin

Confounding Variation of Liver Biochemical Results in Decompensated Cirrhosis

Baseline Biochemical Tests:

<table>
<thead>
<tr>
<th>Biochemical Test</th>
<th>Normal (%)</th>
<th>Abnormal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>58</td>
<td>42</td>
</tr>
<tr>
<td>AST</td>
<td>29</td>
<td>71</td>
</tr>
<tr>
<td>T Bili</td>
<td>33</td>
<td>67</td>
</tr>
<tr>
<td>PT INR</td>
<td>38</td>
<td>62</td>
</tr>
</tbody>
</table>

Baseline MELD (SD):
- Range: 5-26
- Mean: PL, 12.3 (3.8); GPB, 12.3 (3.7)

Baseline CTP Class (%):
- A (37)
- B (46)
- C (16)

eDISH Plots:

### Serious DILI in Subjects with or without CLDs

#### Grading of Liver Enzymes and Total Bilirubin

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>&gt;ULN-3xULN</td>
<td>&gt;3-5X ULN</td>
<td>&gt;5X-20X ULN</td>
<td>&gt;20X ULN</td>
</tr>
<tr>
<td>AST</td>
<td>&gt;ULN-3xULN</td>
<td>&gt;3-5X ULN</td>
<td>&gt;5X-20X ULN</td>
<td>&gt;20X ULN</td>
</tr>
<tr>
<td>Alkaline Phosphatase (ALP)</td>
<td>&gt;ULN-2.5x ULN</td>
<td>&gt;2.5-5X ULN</td>
<td>&gt;5X-20X ULN</td>
<td>&gt;20X ULN</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>&gt;ULN-1.5x ULN</td>
<td>&gt;2.5-3X ULN</td>
<td>&gt;3-10X ULN</td>
<td>&gt;10X ULN</td>
</tr>
</tbody>
</table>

CTCAE v4.03 June 14, 2010; http://evs.nci.nih.gov/ftp1/CTCAE/About.html
## Variability of “Stopping Rules” in Current CLD Trials

<table>
<thead>
<tr>
<th>Disease</th>
<th>Sponsor</th>
<th>F4?</th>
<th>Evaluation and Stopping Rules</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>Abbvie DAAs</td>
<td>Yes</td>
<td>Post-baseline ALT &gt;5X ULN AND &gt;2X baseline: comprehensive evaluation DC: ALT ≥20 X ULN w/o alternative etiology; Increasing Direct bili or PT INR</td>
</tr>
<tr>
<td></td>
<td>Gilead DAAs</td>
<td>Yes</td>
<td>ALT and/or AST &gt; ULN and &gt;5X Day 1 or Nadir; ALT &gt;15X ULN; Hy’s Law</td>
</tr>
<tr>
<td></td>
<td>Merck DAAs</td>
<td>Yes</td>
<td>ALT or AST &gt;500 IU/L; ALT or AST &gt;3X baseline (&gt;110 IU/L) + T bili &gt;2X ULN; and/or PT INR &gt;1.5 X baseline; ALT or AST &gt;3X nadir (&gt;100 IU/L) with new eosinophilia (.5%); Onset of moderate/severe TEAEs, including N/V, RUQ pain or tenderness</td>
</tr>
<tr>
<td>PBC</td>
<td>Intercept OCA</td>
<td>Yes</td>
<td>ALT and/or AST &gt;3X ULN and 2X baseline OR 2 consecutive tests of T bili &gt;ULN and &gt;2X baseline in absence of biliary obstruction</td>
</tr>
<tr>
<td></td>
<td>NGM FGF19</td>
<td>Yes</td>
<td>ALT and T bili &gt;2X baseline; ALT &gt;2X baseline may be observed with repeat PT INR</td>
</tr>
<tr>
<td>PSC</td>
<td>Intercept OCA</td>
<td>Yes</td>
<td>ALT and/or AST &gt;3X ULN and 2X baseline OR 2 consecutive tests of T bili &gt;ULN and &gt;2X baseline in absence of biliary obstruction</td>
</tr>
<tr>
<td></td>
<td>NGM FGF19</td>
<td>Yes</td>
<td>ALT and T bili &gt;2X baseline; ALT &gt;2X baseline may be observed with repeat PT INR</td>
</tr>
<tr>
<td>Gilead Simtuzumab</td>
<td>Yes</td>
<td>2X baseline ALP, ALT, AST, ggt, T bili with level TEAE grade 3</td>
<td></td>
</tr>
<tr>
<td>NASH</td>
<td>BMS PEG-FGF21</td>
<td>No</td>
<td>ALT 2x baseline and &gt;5X ULN + either T bili &gt;2x ULN or PT INR &gt;2;</td>
</tr>
<tr>
<td></td>
<td>Immuron Anti-LPS</td>
<td>No</td>
<td>TEAEs grade 3 if related; DC for grade 4</td>
</tr>
<tr>
<td></td>
<td>Gilead Simtuzumab</td>
<td>No</td>
<td>ALT or AST &gt;2X baseline→repeat H&amp;P, labs; ALT &gt;3X ULN or T bili→repeat H&amp;P, labs; Hy’s Law and/or PT INR &gt;1.5;</td>
</tr>
<tr>
<td></td>
<td>Intercept OCA</td>
<td>No</td>
<td>ALT or AST &gt;8X ULN; ALT or AST &gt;5X ULN for &gt;2 weeks; ALT or AST &gt;3X ULN with new onset fatigue, N/V, RUQ pain/tenderness, fever, rash and/or eosinophilia (&gt;5%); Hy’s Law</td>
</tr>
<tr>
<td></td>
<td>Genfit PPARα/δ</td>
<td>No</td>
<td>Normal Baseline ALT/AST: &lt;3X ULN, monitor; &gt;3X-&lt;5X ULN, monitor; &gt;5X ULN D/C; Abnormal Baseline ALT/AST: &lt;3X, monitor; &gt;3X baseline &amp; &lt;10X ULN, closer monitoring; &gt;5X baseline or &gt;10 X ULN, D/C; Hy’s Law; ALT or AST &gt;3X baseline or ULN + PT INR &gt;1.5</td>
</tr>
</tbody>
</table>
### Assessment of DILI Severity

**DILIN Severity Index Score**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild</td>
<td>(\uparrow) ALT/AST or ALP; T Bili &lt;2.5; INR &lt;1.5</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>(\uparrow) ALT/AST or ALP; T Bili &gt;2.5 or INR (\geq) 1.5</td>
</tr>
<tr>
<td>3</td>
<td>Moderate Hospitalized*</td>
<td>(\uparrow) ALT/AST or ALP; T Bili &gt;2.5 or INR (\geq) 1.5 and hospitalized or admission prolonged</td>
</tr>
<tr>
<td>4</td>
<td>Severe*</td>
<td>(\uparrow) ALT/AST or ALP; T Bili (\geq) 2.5 and 1 of following: decompensation (INR (\geq) 1.5, ascites, HE) or other organ failure associated with DILI event</td>
</tr>
<tr>
<td>5</td>
<td>Fatal*</td>
<td>Death or OLT due to DILI</td>
</tr>
</tbody>
</table>

*SAE in Clinical Trials
DILI Severity and Outcome
Acute Liver Failure vs. Acute on Chronic Liver Failure

Acute DILI

Adaptation

Resolve Off Drug

Acute Liver Failure

Cerebral Edema

Acute on Chronic Liver Failure

Multi-Organ Failure

Sepsis

OLT

Death
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1. What is the probability of enrolling patients with CLDs, including cirrhotics, in drug development trials?
2. What are the risks of serious DILI and hepatic decompensation in subjects with CLDs?
3. How do protocols currently protect subjects with CLDs, including cirrhotics, from serious DILI?
4. What improvements in protocols can provide greater protection from serious DILI in patients with CLD, including cirrhotics?
   a. Assessment pre-enrollment
   b. Monitoring on treatment
   c. Functional assessments
   d. Stopping rules
Identification of Study Subjects with CLDs
Expand Testing to Enhance Exclusion or Inclusion

History/PE
- CBC, Plts, retics
- Electrolytes, BUN, creat
- T and D Bili
- ALP/ggt
- ALT/AST/CPK
- T. Protein/Alb
- PT INR
- UGT1A1, OATP, BSEP
- Imaging
- Non-Invasive Testing for Stg 3-4
- QLFTs for Stg 3-4
- ± Liver Bx

Liver Tests
- WNL

Specific Liver Disease

Abnormal Liver Tests

CLD “Absent” but ↑ing Probability*

CLD Present

Test for Etiology

Non-Invasive Testing for Cirrhosis

*NB! Additional testing required to exclude: HBV, HCV, NAFLD, AIH, PBC, PSC, burned out cirrhosis (e.g. ETOH, HBV, AIH), EBV, CMV, SOS, Wilson disease
Risk of Decompensation of Cirrhosis
Gold Standard Fasting HVPG ≥ 10 mm Hg

Cirrhosis

PVHTN

Compensated HVPG < 10

Decompensated HVPG ≥ 10

Hepatic Venous Pressure Gradient (HVPG) = Wedged HV Pressure – Free HV Pressure
Cumulative Proportion of Patients Transitioning from Compensated to Decompensated Cirrhosis

Classification of Study Subjects with Cirrhosis
Surrogate Measures of Hepatic Functional Reserve

Cirrhosis

Mildly Decompensated
- CTP 7-9
- D’Amico Stages 3-4
- ↓ Hepatic Function

Compensated
- CTP 5-6
- D’Amico Stages 1-2
- Preserved Hepatic Function

Severely Decompensated
- CTP 10-15
- D’Amico Stages 4-5
- ↓↓ Hepatic Function

HCC surveillance
Quantitative Liver Function Testing
Non-Disease Specific Assessments of Function

HEPATIQ
- FDA approved
- $^{99m}$Tc-Liver-Spleen Scan
- Software analysis calculates Perfused Hepatic Mass (PHM)

HepQuant
- Not FDA approved
- Analyses of oral and/or iv cholate clearance
- Calculation of Disease Severity Index (DSI) or STAT score

Excalenz
- Not FDA approved
- $^{13}$C-Methacetin breath test of $^{13}$C-M to APAP
- Generates PK/PD of $^{13}$CO$_2$
Stopping Rules Using Functional Monitoring for Severe DILI in CLD with or without Cirrhosis

- Serial Symptom Assessment
- Frequent, Serial Liver Tests + PT INR
- Serial eDISH Plotting of ALT and T Bili
- Serial Assessment ALT Stopping Rules

Any Signal of Interest for DILI

Stable Function: Consider Protocols for Observation

Hepatic Functional Reserve
- QLFTs
- Biomarkers of Function

Worsening Function: Discontinue Drug
Concern About DILI in CLD with or without Cirrhosis: A Call to Clinical Action

- Serial Symptom Assessment
- Frequent, Serial Liver Tests + PT INR
- Serial eDISH Plotting of ALT and T Bili and Kinetics
- Serial Assessment ALT Stopping Rules

Any Signal of Interest for DILI

Urgent Need for:
1. Repeat history and PE
2. Repeat testing to verify
3. Comprehensive testing for etiologies other than DILI
4. Calculate MELD/Na, CTP
5. Repeat QLFTs to detect change in hepatic function
6. More frequent F/U visits, liver tests and QLFTs
7. Adherence to stopping rules
Future Investigative Opportunities in DILI Host Factors and Drug Properties

- Genetics
  - Polymorphisms
  - Proteomics
  - Metabolomics

- Hepatic Function Testing

- Epidemiology of CLDs in Trials

- Biomarkers
  - DILI
  - DILI Severity

- DILI Pathogenetic Mechanism(s)

- Host-Drug Transporters Metabolism

- Microbiome Drug Metabolism

- PK/PD for Hepatic Dosing
  - Stages 0-3
  - Cirrhosis
Enrollment of patients with CLDs, with and without cirrhosis, in trials of drug development is increasing due to the rising prevalence of CLDs and cirrhosis:
- general drug development
- disease-specific therapies for all major classes of CLDs
- cirrhosis (antifibrotics) and complications of PVHTN and HCC

In general, CLDs do not increase susceptibility for DILI, but exceptions exist, and more are likely to be discovered.

Subjects with CLDs and low hepatic functional reserves have increased risks of serious DILI and death.

Currently, study protocols provide protection for subjects with CLD from serious DILI by alerting investigators to the need for urgent, comprehensive evaluation of cases meeting Hy’s Law or other criteria and/or exhibiting evidence of decompensated cirrhosis.

Future study protocols should provide additional protection for subjects with CLD by direct quantitative testing of hepatic functional reserve at baseline and during any suspected DILI event, applying biomarkers of DILI and its severity, testing for polymorphisms of UGT1A1, OATP and BSEP to aid in interpretation of abnormal bilirubin and cholestasis and utilizing advanced imaging techniques with the goal of producing better evidence-based stopping rules for patients with CLDs.