IQ DILI Consensus Guidelines PSC

Best Practices For Detection, Assessment and Management Of Suspected Acute Drug Induced Liver Injury Occurring During Clinical Trials In Adults With Chronic Cholestatic Liver Disease

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IQ DILI Initiative

• **IQ**: International Consortium for Innovation and Quality in Pharmaceutical Development
  – Not-for-profit organization addressing scientific and technical aspects of drug development
  – 38 pharmaceutical and biotechnology companies.

• **IQ-DILI Initiative**
  – June 2016
  – 17 IQ DILI member companies
  – Purpose: reach consensus and propose best practices on topics related to DILI

• **Consensus Guidelines PSC**: best practices for detection, assessment and management of suspected DILI occurring during clinical trials in adults with chronic cholestatic liver disease
  – Extensive literature review
  – Industry members
  – Academics
  – Regulatory

• **Disclosure**: Recommendations do not imply a regulatory guidance or mandate.
Key Challenges Faced in Detecting, Assessing, and Managing DILI Occurring During Clinical Trials in PSC

- The natural course of PSC includes liver test fluctuations and episodes of cholangitis which may mimic DILI biochemically, making detection and assignment of causality challenging.

- Standard liver biochemical monitoring and stopping rules utilized for patients with normal livers or those with parenchymal CLD may not be applicable.

- The optimal approach of applying Hy’s Law in clinical trials in PSC patients is still a matter of debate. Patients without underlying liver disease, (1) ALT ≥3x ULN; (2) TBL ≥2x ULN; (3) no initial finding of cholestasis (elevated ALP); and (4) no competing etiology to explain these liver elevations.

- Establishing liver biochemical test monitoring stopping rules based solely on multiples of ULN may result in inconsistent and/or incorrect evaluation of the hepatotoxicity of the candidate drug.

- Cholestatic DILI may be indistinguishable from progression of PSC both clinically as well as histologically.

- Unknown if PSC patients have an increased susceptibility to DILI or worse outcomes when DILI occurs, compared with those with normal livers or patients with hepatocellular liver disease.

- Scarce literature

- No regulatory guidelines or society position papers that address monitoring and stopping criteria.
Hepatic Eligibility Criteria Consensus Recommendations

1. ALP >10x ULN should be set as the upper limit for exclusion
2. Two ALP and ALT should be obtained at least >2 weeks apart during the screening - If values vary widely (e.g., >30%), enrollment should be postponed
3. Ave 2 consecutive screening + baseline measurement should determine baseline ALP and ALT
4. Absolute values should be reported and analyzed along with multiples ULN
5. GGT and and/or ALP fractionation should be done prior to study start
6. Patients with baseline elevations in TBL should be excluded unless Gilberts or hemolysis
7. Aminotransferases > 5x ULN
8. ANA and ASMA should be established at baseline. Overlap syndrome should be excluded.
9. IgG levels should be tested at screening and IgG4-associated PSC should be excluded.
Monitoring & Stopping Rules

Should be based on:
1. Multiples of baseline
2. Nadir values of ALP and ALT
3. Baseline values of TB and or DB
4. Liver-related or immunologic-related symptoms
   • If cases of suspected DILI occur in a clinical trial with no alternative cause an unblinded safety assessment should be performed by an external panel of experts, and a temporary pause of the trial should be considered.
   • An episode of DILI resulting in hepatic decompensation should trigger permanent drug discontinuation.
   • Blood tests should be repeated within 2-5 days if hepatocellular DILI is suspected, and 7-10 days if cholestatic DILI is suspected. However, the specific interval between the tests should also be based on the patient’s clinical condition.
Additional Considerations

- Nadir Values
- Gilberts Disease
- Persistent isolated DBL elevations
- Cholestatic DILI
- Fat Soluble Vitamin Deficiency
- HBV reactivation
- Ursodeoxycholic Acid
- PK and pill counts
- Decompensated Cirrhotics
## Algorithm for Monitoring and Interrupting study drug for Hepatocellular DILI signals with Normal Baseline ALT

<table>
<thead>
<tr>
<th>Treatment emergent ALT</th>
<th>Bilirubin</th>
<th>Symptoms</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALT ≥5x ULN</strong></td>
<td>Normal</td>
<td>None</td>
<td>Blood tests should be repeated in 2-5 days Follow-up for symptoms</td>
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<tr>
<td></td>
<td>Gilbert’s syndrome or hemolysis: No change in baseline total bilirubin</td>
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<td></td>
</tr>
<tr>
<td><strong>ALT ≥8x ULN</strong></td>
<td>Normal or elevated</td>
<td>None or present</td>
<td>Interrupt study drug. Repeat BW within 2-5 days Initiate close monitoring and workup for competing etiologies. Restart only if another etiology is identified and ATs return to baseline Cannot restart if decompensation</td>
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<td><strong>ALT ≥3x ULN</strong></td>
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# Monitoring and interrupting study drug for Hepatocellular DILI signals

## Elevated Baseline ALT

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<td>ALT ≥3x baseline or ≥300 U/L (whichever occurs first)</td>
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