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

Treatment emergent ALT	Bilirubin	Symptoms	Action
ALT ≥5x ULN	Normal Gilbert's syndrome or hemolysis: No change in baseline total bilirubin	None	Blood tests should be repeated in 2-5 days Follow-up for symptoms
ALT ≥8x ULN	Normal or elevated	None or present	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
ALT ≥3x ULN	Total bilirubin ≥2x baseline Gilbert's syndrome or hemolysis: direct bilirubin >2x baseline if baseline >0.5 mg/dL	None or present	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
ALT ≥5x ULN	Normal or elevated	Present	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

Monitoring and interrupting study drug for Hepatocellular DILI signals Elevated Baseline ALT

Treatment emergent ALT	Bilirubin	Symptoms [3]	Action
ALT ≥3x baseline or ≥300 U/L (whichever occurs first)	Normal Gilbert's syndrome or hemolysis: No change in baseline total bilirubin	None	Blood tests should be repeated in 2-5 days Follow-up for symptoms
ALT ≥5x baseline or ≥500 U/L (whichever occurs first)	Normal or elevated	None or present	Interrupt study drug. Blood tests should be repeated within 2-5 days Initiate close monitoring and workup for competing etiologies. Restarted only if another etiology is identified and liver abnormalities return to baseline. Cannot be restart if decompensation
ALT ≥2x baseline or ≥300 U/L (whichever occurs first)	Total bilirubin≥2x baseline Gilbert's syndrome or hemolysis: direct bilirubin >2x baseline if baseline >0.5 mg/dL	None or present	Interrupt study drug. BW should be repeated within 2-5 days Initiate close monitoring and workup for competing etiologies. Restart only if another etiology is identified and LFTs return to baseline. Cannot Restart if decompensation occurs
ALT ≥2x baseline or ≥300 U/L (whichever occurs first)	Normal or elevated	Present	Interrupt study drug. Repeat blood tests in 2-5 days Initiate close monitoring/workup for competing etiologies. Restart only if another etiology is identified and LFTs return to baseline. Cannot restart if decompensation occurs.

Monitoring and interrupting study drug for Cholestatic DILI signals

Treatment emergent Alkaline phosphatase (ALP)	Bilirubin	Symptoms [2]	Action
ALP ≥2x baseline without alternative explanation	Normal or Gilbert's syndrome or hemolysis: No change in baseline total bilirubin	None	Repeat Blood tests in 7-10 days [3] Follow-up for symptoms
ALP ≥2x baseline without alternative explanation	Total bilirubin ≥2x baseline or Gilbert's syndrome or hemolysis: direct bilirubin >2x baseline if baseline >0.5 mg/dL	None or present	Interrupt study drug. Blood tests should be repeated within 7-10 days Initiate close monitoring and workup for competing etiologies. Restart only if another etiology is identified and LFTs return to baseline. Cannot restart if decompensation occurred.
ALP ≥2x baseline without alternative explanation	Normal or elevated	Present	Interrupt study drug. Repeat blood tests in 7-10 days Initiate close monitoring and workup for competing etiologies. Restart only if another etiology is identified and LFTs return to baseline. Cannot restart if decompensation occurred.
ALP ≥3x baseline without alternative explanation	Normal or elevated	None or present	Interrupt study drug. Repeat LFTs within 7-10 days Initiate close monitoring and workup for competing etiologies. Restart only if another etiology is identified