



The IQ-DILI Initiative

Arie Regev, MD
Global Patient Safety
Eli Lilly

Background

- Early prediction, diagnosis and assessment of DILI continue to present major challenges to the drug industry during drug development and post marketing
- Hepatic safety concerns remain a major cause for aborted development of new drugs
- Notable gaps exist in current regulatory guidance on detecting and monitoring DILI in clinical trials
- There had been no industry-led effort focusing on clinical aspects of DILI, which are not sufficiently covered by existing guidance

FOREWORD

The Clinical Liver Safety Assessment Best Practices Workshop: Rationale, Goals, Accomplishments and the Future

**Paul B. Watkins · Michael Merz · Mark I. Avigan ·
Neil Kaplowitz · Arie Regev · John R. Senior**

- ❑ 2011: calls from FDA and industry to address gaps in current guidance, and share hepatic safety data across industry
- ❑ 2012: workshop organized by IMI and the Hamner Institute to address gaps in current guidance and initiate alignment on liver safety assessment. Calls for sharing of hepatic safety data.

The IQ Consortium

- The IQ Consortium (the International Consortium for Innovation and Quality in Pharmaceutical Development), composed of over 40 companies, is a leading science-focused organization with a mission to advance science and technology to augment the capability of member companies to bring transformational solutions that benefit patients, regulators and the broader R&D community.
- The IQ Consortium had been primarily focusing on CMC (Chemistry, Manufacturing, and Controls), and preclinical to early clinical trial topics (e.g. preclinical safety, drug metabolism, clinical pharmacology); however, it has an interest in expanding into clinical space.

In June 2016, the IQ Board endorsed the establishment of an IQ initiative on clinical aspects of DILI; “The IQ DILI Initiative”

Priority Topics



Advantages of Housing the Industry DILI Initiative within IQ

- An already established cross-pharma governance structure
- Over 40 pharmaceutical and biotechnology companies may become participants and provide broad industry input
- Opportunities to collaborate with other IQ Leadership Groups with overlapping interests (DruSafe, Drug Metabolism, Clinical Pharmacology)
- Company-vetted and approved membership and data-sharing agreements already in place
- An advanced database solution available to support consortium data-sharing projects
- Scientific, project management, legal and administrative support provided by the Secretariat



Objectives and Deliverables

Gaps in Best Practices and Current Guidances

Patients with pre-existing liver diseases

Hepatitis B, C, metastatic liver disease, alcoholic liver disease, nonalcoholic steatohepatitis

Special populations

Pediatric, geriatric, oncology, immunosuppressed

Non-hepatocellular DILI

Cholestatic injury, steatohepatitis, hepatic vascular injury

Specific drug groups

Immunosuppressives, anti-virals, chemotherapy, cancer immunotherapy

Drug re-challenge

Is re-challenge with a drug implicated in DILI too dangerous? If not, criteria to define a positive re-challenge test

Biomarkers

Are there promising biomarkers for predicting idiosyncratic DILI that should be routinely incorporated into clinical protocols? Should prospective blood samples be banked for further study in subjects with liver signals?

Examples of Key Topics (I)

- Monitoring, assessment and management of DILI in clinical trials in patients with pre-existing chronic liver disease such as NAFLD/NASH, HBV/HCV
 - Inclusion/exclusion criteria?
 - Stopping rules?
 - Use of Hy's law?
 - Use of eDISH?
 - Causality assessment?
- Monitoring diagnosis and management of DILI in patients with preexisting liver failure
- Adjustments in monitoring and assessment of DILI during clinical trials, based on nonclinical toxicology findings
- Assessment and management of immune mediated liver injury due to immunotherapy (e.g. checkpoint inhibitors)

Examples of Key Topics (II)

- Monitoring, assessment and management of DILI in clinical trials in patients with pre-existing chronic liver disease such as NAFLD/NASH, HBV/HCV
 - Inclusion/exclusion criteria?
 - Stopping rules?
 - Use of Hy's law?
 - Use of eDISH?
 - Causality assessment?
- Monitoring diagnosis and management of DILI in patients with preexisting liver failure
- Adjustments in monitoring and assessment of DILI during clinical trials, based on nonclinical toxicology findings
- Assessment and management of immune mediated liver injury due to immunotherapy (e.g. checkpoint inhibitors)

Use of Hy's Law in Patients with Pre-existing Chronic Liver Disease or Oncology Patients

Hy's Law Criteria*

- ALT/AST \geq 3X ULN
- Total bilirubin \geq 2X ULN
- No cholestasis
- No other cause of liver injury



Questions:

- Can the current definition of Hy's law be used in oncology patients (with/without metastasis)?
- Patients with pre-existing chronic liver disease?
- Should a different definition be used?

* as defined in FDA Guidance 2009

Examples of Key Topics (IV)

- Monitoring, assessment and management of DILI in clinical trials in patients with pre-existing chronic liver disease such as NAFLD/NASH, HBV/HCV
 - Inclusion/exclusion criteria?
 - Stopping rules?
 - Use of Hy's law?
 - Use of eDISH?
 - Causality assessment?
- Monitoring diagnosis and management of DILI in patients with preexisting liver failure
- Adjustments in monitoring and assessment of DILI during clinical trials, based on nonclinical toxicology findings
- Assessment and management of immune mediated liver injury due to immunotherapy (e.g. checkpoint inhibitors)

Causality Assessment for Suspected DILI During Drug Development

Questions:

- Expert opinion versus standardized methods (e.g. RUCAM)?
- Can RUCAM be used at all during drug development, prior to being revised?
- Who should perform causality assessment during drug development? (who is an “expert”?)
- Causality assessment in specific populations/ drugs:
 - Pre-existing liver failure
 - Immunotherapy
 - New anti-HBV drugs
- What is the correct definition of “positive rechallenge” for the purpose of causality assessment?

Working Groups as Initial Focus

1. **Abnormal Baselines**: Monitoring and assessment of potential DILI in patients with abnormal hepatic biochemical tests at baseline
2. **Causality Assessment**: Causality assessment in all patterns of DILI (hepatocellular, cholestatic, hepatic steatosis, vascular) and best practices for drug re-challenge
3. **Immunotherapy**: Immune-mediated liver injury due to immunotherapy, such as checkpoint inhibitors
4. **Biomarkers**: Development of strategies to investigate potential emerging biomarkers for the assessment of DILI
5. **Nonclinical Translation**: Adjustments in monitoring and assessment of DILI during clinical trials based on nonclinical toxicology findings
6. **Post-marketing Pharmacovigilance**: Post-marketing pharmacovigilance programs, Risk Evaluation and Mitigation Strategies (REMS) for DILI

Working Group Activities and Plans

- Near-term:
 - Literature search to gather publically-available information
 - Surveys to gather companies' current practices
 - Surveys have been distributed to all IQ member companies (42) to receive broad input
 - Scanning the landscape and developing strategies to collaborate with organizations addressing similar topics
 - Developing white papers summarizing current data in the literature, current industry practices, and proposed best practices for monitoring, diagnosing, managing, and preventing DILI in clinical trials and in post-marketing
- Long-term:
 - Data sharing to substantiate best practice recommendations

Collaboration with Other Stakeholders

- IQ-DILI proactively communicates and coordinates with other regulatory, academic and industry DILI collaborations to:
 - Ensure synergies and maximize value of clinical data
 - Prevent redundant effort
 - Leverage expertise and perspectives of these academic, regulatory and industry experts in such critical areas as nonclinical testing, new biomarkers, in-silico and in-vitro models, causality assessment, phenotypes of DILI in clinical practice, and monitoring and managing DILI in clinical trials and in post-marketing surveillance activities
- Communication with: C-Path-PSTC, TransCelerate, IMI-TransBioline, Liver Forum, HBV Forum, CIOMS

Thank you!