CIOMS Consensus report on Drug-Induced Liver Injury (DILI)

This session will start at 7pm SGT

Speakers and Panellists

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Office of Pharmacovigilance & Epidemiology
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Eli Lilly and Company

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Disclaimer

- The views and opinions expressed in the following PowerPoint slides are those of the individual presenters and should not be attributed to any organization, including those with which the presenters are employed or affiliated.

- Any views we will discuss are our own and not an official position of any regulatory organization.
<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>Guruprasad P AITHAL</td>
<td>University of Nottingham, United Kingdom</td>
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<tr>
<td>Raul J ANDRADE</td>
<td>University of Málaga, Biomedical Research Institute of Málaga (IBIMA), Spain</td>
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<td>Mark AVIGAN</td>
<td>U.S. Food and Drug Administration (FDA)</td>
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<td>Amel BENKRITLY*</td>
<td>Sanofi</td>
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<td>Einar S. BJÖRNSSON</td>
<td>National University Hospital of Iceland</td>
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<tr>
<td>Michele BORTOLINI</td>
<td>Roche</td>
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<td>Robert J FONTANA</td>
<td>University of Michigan Medical Centre, U.S.</td>
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<tr>
<td>Stewart GEARY</td>
<td>Eisai</td>
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<td>Alexandre KIAZAND*</td>
<td>Astra Zeneca</td>
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<td>Gerd A KULLAK-UBLICK</td>
<td>Novartis</td>
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<td>RenJi Hospital, Shanghai Jiao Tong University, School of Medicine, China</td>
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<td>John MARCINAK</td>
<td>Takeda (until September 2019, then: AbbVie)</td>
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<td>Michael MERZ</td>
<td>University of Zurich, Switzerland</td>
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<td>Manfred OSTER</td>
<td>Sanofi</td>
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<tr>
<td>Shanthi PAL*</td>
<td>World Health Organization (WHO)</td>
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<td>Xingmin QIU*</td>
<td>Pfizer</td>
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<td>Lembit RÄGO</td>
<td>CIOMS</td>
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<td>Arie REGEV</td>
<td>Eli Lilly</td>
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<td>John Michael SAUER*</td>
<td>Critical Path Institute (C-Path)</td>
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<td>Elmer SCHABEL*</td>
<td>Federal Institute for Drugs and Medical Devices (BfArM), Germany</td>
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<tr>
<td>Monica SOARES</td>
<td>Brazilian Health Regulatory Agency (Anvisa)</td>
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<tr>
<td>Haibo SONG*</td>
<td>China Food and Drug Administration (CFDA)</td>
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<td>James SOUTHERN</td>
<td>South African Health Products Regulatory Authority</td>
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<tr>
<td>Walter STRAUS</td>
<td>Merck</td>
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<tr>
<td>Hajime TAKIKAWA</td>
<td>Teikyo University, Japan</td>
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<tr>
<td>Daisuke TANAKA*</td>
<td>World Health Organization (WHO)</td>
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<td>Mari THÖRN</td>
<td>Swedish Medical Products Agency (SMPA)</td>
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<td>Jean-Marc VIDAL*</td>
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<td>Javier WAKSMAN</td>
<td>FibroGen</td>
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<td>Jia-bo WANG*</td>
<td>Fifth Medical Center of Chinese PLA General Hospital, China</td>
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<tr>
<td>Hui-Talia ZHANG</td>
<td>Bayer</td>
</tr>
</tbody>
</table>

* = Participated in fewer than three meetings.
Consensus report of the CIOMS DILI Working Group

Available on the CIOMS website at:

Herve Le Louët, MD PhD: President CIOMS
• Goals, initiatives & context of the 2020 report

Arie Regev, MD: Chair, GI & Liver Safety Committee, Elli Lilly & Co, USA
• Clinical trials: DILI detection, characterization & assessment

Raúl J Andrade, MD, PhD: Professor of Medicine, University of Málaga, Spain
• Identification & utilization of liver safety biomarkers

Walter Straus, MD: AVP and Chair, Organ-Specific Safety Boards, Merck Res Labs, USA
• Postmarket: DILI risk assessment, minimization & communication

Questions??
What CIOMS is and What it does: The DILI initiative
Council for International Organizations of Medical Sciences

- Founded in 1949 by WHO and UNESCO
- In official relations with WHO
- ICH Observer since 2016

**Mission Statement**

CIOMS mission is to advance public health through guidance on health research including ethics, medical product development and safety
CIOMS in short

Organization located in Geneva:
A – International
B – Nongovernmental
C – Not-for-profit

In official relations with WHO + Associate Partner of UNESCO
For WHO, health authorities, academic organizations, pharmaceutical industry and other concerned stakeholders

An organization of medical science organizations

Forum for discussion and neutral platform to elaborate new ideas in medical product development, pharmacovigilance and research ethics (bioethics)
Current Active International CIOMS Working Groups

- WG on MedDRA Implementation; in cooperation with ICH MedDRA Management Board
- WG on Drug induced Liver Injury (DILI)
- WG on Clinical Research in Resource-limited settings
- WG XI : Patient Involvement in Development and Safe Use of Medicines
- WG XII : Benefit-Risk Balance for Medicinal Products
- WG XIII : Real World Data and Real World Evidence in Regulatory Decision-Making
Several initiatives from academic, regulators, industry and patient organisations that need to be coordinated to avoid redundancies, improve dissemination and widen the audience.
Principles in Detection, Characterization and Risk Assessment of DILI in Clinical Trials

CIOMS Working Group on DILI
Outline

- General Classification of DILI
- DILI Phenotypes
- DILI in Patients with Pre-existing Liver Disease
- DILI Detection
- Risk Assessment in Drug Development
- Summary
General Classification of DILI
# Classification of Drug-Induced Liver Injury

<table>
<thead>
<tr>
<th>Category</th>
<th>Direct (intrinsic)</th>
<th>Indirect</th>
<th>Idiosyncratic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-related</td>
<td>Yes</td>
<td>No (generally)</td>
<td>No (with some exceptions)</td>
</tr>
<tr>
<td>Latency</td>
<td>Short (few days)</td>
<td>Typically delayed (weeks to months)</td>
<td>Variable (days to months), may occur after treatment discontinuation</td>
</tr>
<tr>
<td>Rate of occurrence</td>
<td>High</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td>Predictable</td>
<td>Yes</td>
<td>Occasionally</td>
<td>No</td>
</tr>
<tr>
<td>Implicated drugs (examples)</td>
<td>Acetaminophen, nicotinic acid, aspirin, cocaine, many cancer chemotherapies, ifaluridine, amiodarone, methotrexate (intravenous), plants containing pyrrolizidine alkaloids</td>
<td>High-dose corticosteroids; some antineoplastic agents: immune checkpoint inhibitors, protein kinase inhibitors, monoclonal antibodies (e.g. anti-TNF, anti-CD20), daclizumab</td>
<td>Isoniazid, amoxicillin-clavulanate, macrolide antibiotics, fluoroquinolones, statins, fluocoxacinil, diclofenac; certain herbal and dietary supplements (HDS), e.g. green tea extract, <em>Polygonum multiflorum</em></td>
</tr>
<tr>
<td>Pathologic mechanisms</td>
<td>Liver damage occurs if parent drug or metabolite concentrations in liver cells exceed a toxic threshold</td>
<td>Unintended effects of drug actions on the liver (e.g. increased drug-induced immune autoreactivity or reduced insulin sensitivity may cause immune-mediated hepatitis and fatty liver, respectively)</td>
<td>Adaptive immune response to a parent drug or drug metabolite may contribute. Mitochondrial damage and hepatic steatosis may also be observed</td>
</tr>
</tbody>
</table>
DILI Phenotypes
DILI Phenotypes

- Acute hepatitis (resembling viral-hepatitis)
- Cholestatic or mixed hepatitis
- Acute hepatic necrosis
- Hypersensitivity syndrome (DRESS*)
- Chronic steatosis/steatohepatitis
- Acute fatty liver with metabolic acidosis
- Drug-induced autoimmune hepatitis
- Sinusoidal obstruction syndrome
- Nodular regenerative hyperplasia
- Immune-mediated liver injury

- Different clinical manifestations
- Different biochemical abnormalities
- Different clinical outcomes

Isoniazid, ketoconazole, ximelagatran, amoxicillin-clavulanate, macrolides, acetaminophen, IV amiodarone, phenytoin, carbamazepine, methotrexate, tamoxifen, irinotecan, stavudine, tetracycline, sodium valproate, minocycline, nitrofurantoin, cyclophosphamide, azathioprine, HAART, bleomycin, ipilimumab, pembrolizumab, nivolumab

*Drug reaction with eosinophilia and systemic symptoms
DILI Case Definitions

Laboratory criteria proposed by an international DILI expert working group:

- Any one of the following criteria, is indicative of DILI, once other causes of liver injury have been systematically excluded:
  - ALT ≥ 5x ULN
  - ALT ≥ 3x ULN and total bilirubin ≥ 2x ULN
  - ALP ≥ 2x ULN when the source of increased ALP levels is the liver

- Isolated hyperbilirubinemia is usually not DILI
- Isolated elevation of GGT is insufficient to qualify as DILI

These criteria may not be applicable to patients who have pre-existing liver disease

DILI in Patients with Pre-existing Liver Disease
Identifying DILI in Patients with Pre-existing Liver Disease

- A substantial proportion of clinical trials enroll patients with pre-existing liver diseases such as NAFLD, NASH, hepatitis B/C, alcohol-related liver disease, metastatic liver disease.
- DILI phenotype may be considerably different when superimposed on an underlying liver disease.
- DILI may be difficult to differentiate from a fluctuation in pre-existing disease.
- Detection may be delayed; ALT and AST may be mildly elevated or normal.
- Outcome may be more severe including a higher mortality.
- Pre-existing hepatic impairment may lead to increased exposure and higher risk of dose-dependent hepatotoxicity.

DILI Detection and Risk Assessment in Clinical Trials
Nonclinical Assays/ Studies: 
Assessment of Idiosyncratic DILI Risk (?)

<table>
<thead>
<tr>
<th>Drug-Specific In Vitro/ Toxicology Predictors</th>
<th>Predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formation of reactive metabolites</td>
<td>High(^1)</td>
</tr>
<tr>
<td>Inhibition of drug transporters (BSEP, MRPs)</td>
<td>High(^4,5)</td>
</tr>
<tr>
<td>Mitochondrial toxicity</td>
<td>High(^4)</td>
</tr>
<tr>
<td>ROS/ATP*</td>
<td>High(^7)</td>
</tr>
<tr>
<td>Animal toxicology studies</td>
<td>High(^{11})</td>
</tr>
<tr>
<td>BDDCS**</td>
<td>High(^3,6)</td>
</tr>
<tr>
<td>Rule of 2 (daily dose + lipophilicity)</td>
<td>High(^4)</td>
</tr>
<tr>
<td>Rule of 2 + reactive metabolites</td>
<td>High(^5)</td>
</tr>
</tbody>
</table>

*Ratio of reactive oxygen species to cellular ATP depletion; **Biopharmaceutical Drug Disposition Classification System

4. Aleo et al Hepatology 2014;60:1015
6. Chan & Benet. Toxicological Science 2017;1
Principles of Risk Assessment for Idiosyncratic Hepatocellular DILI During Clinical Development

- Understanding the difference between “benign” ALT elevation and a potential DILI signal:
  - Effective versus ineffective hepatic monitoring
  - “Adaptation” versus liver injury
  - Analysis of extreme values (outliers) rather than mean or median

- Identification of Hy’s law cases and correct use of eDISH plot

- Differentiation between DILI and liver injury due to other causes:
  - Causality assessment

- Adherence to appropriate hepatic discontinuation rules:
  - Avoidance of too early and too late discontinuation
Summary

- DILI is divided into direct, idiosyncratic, and indirect hepatotoxicity
- As novel drugs are being developed, new DILI phenotypes are encountered, and should be looked for
- DILI phenotypes may change in patients with pre-existing liver disease, and diagnosis may be challenging
- Severe liver injury may occur without ALT or AST elevation, which requires careful monitoring in patients with pre-existing liver disease
- Despite extensive research, the value of nonclinical methods for the prediction of idiosyncratic and indirect DILI is still controversial
- The most useful approach for DILI detection and risk assessment is based on comprehensive hepatic data collection, assessment, and interpretation during clinical phases of drug development
CIOMS DILI Working Group

COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES
Associate partner of UNESCO - in official relations with WHO.

THANK YOU!
Liver Safety Biomarkers

Herbal and Dietary Supplement Hepatotoxicity

Raúl J Andrade
Professor of Medicine

Head: Department of Medicine, University of Málaga, Spain
Head: Gastroenterology Service, Virgen de la Victoria University Hospital, Málaga, Spain
Director: Spanish and Spanish/Latin-American DILI Networks
CIOMS DILI: Liver Safety Biomarkers

- **FDA Context of use**
  - Description of **how, when and why** a biomarker is to be used in a drug development program or clinical trial

- **EMA Context of use**
  - “Full, clear and concise description of how novel methodology is to be used and the medicine-related purpose of the use”

1. FDA Biomarker Qualification Program
2. EMA/750178/2017, 5 Dec 2017
CIOMS DILI: Liver Safety Biomarkers

• Diagnostic
  – Presence of disease (HCV RNA)

• Efficacy/pharmacodynamics
  – Biological response (Normal ALT, HCV-RNA clearance)

• Monitoring/safety
  – Baseline and serial tests (ALT)

• Predictive/susceptibility
  – Baseline predictor of efficacy or AE (HLA-B* 57:01)

• Prognostic
  – Likelihood of future event/disease progression (MELD)
There are currently **NO** liver safety biomarkers qualified by regulatory authorities

- Serum ALT (Safety & efficacy)
- Total bilirubin & INR (Hepatic function/ severity)

**Biomarker Discovery** - superior performance to established biomarkers
- Sens, Spec, PPV, NPV (AUROC to compare performance)
  - Specificity > ALT for liver injury
  - Sensitivity > Total bilirubin for severity
  - Accuracy > MELD for prognosis
- Biobanked baseline, serial samples

**Biomarker Qualification**
- Validate in independent datasets
- Analytical standardization, precision, accuracy, reproducibility
<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Application (COU)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cytokeratin-18 *</td>
<td>Early diagnosis, Prognosis</td>
<td>Hepatocyte necrosis</td>
</tr>
<tr>
<td>ccCytokeratin-18</td>
<td>Early diagnosis</td>
<td>Hepatocyte apoptosis</td>
</tr>
<tr>
<td>miR122</td>
<td>Early diagnosis</td>
<td>Hepatocyte specific, Not DILI specific (?)</td>
</tr>
<tr>
<td>Total HMGB1</td>
<td>Early diagnosis</td>
<td>Wide tissue expression</td>
</tr>
<tr>
<td>Glutamate dehydrogenase (GLDH)</td>
<td>Early diagnosis</td>
<td>Mitochondrial matrix, Pericentral hepatocytes</td>
</tr>
<tr>
<td>Sorbitol dehydrogenase (SDH)</td>
<td>Early diagnosis</td>
<td>Hepatocyte necrosis</td>
</tr>
<tr>
<td>Macrophage colony stimulating factor receptor 1 (MCSFR1)**</td>
<td>Prognosis</td>
<td>Macrophage cytokine receptor</td>
</tr>
<tr>
<td>Osteopontin *</td>
<td>Prognosis</td>
<td>Wide tissue expression, Inflam vs regeneration</td>
</tr>
</tbody>
</table>

* 2016 FDA/EMA Letter of support

** (Hepatology 2019 69:760)
CIOMS DILI: Liver Safety Biomarkers

- Prognostic biomarkers in 15 of 133 DILIN pts that died (1)
  - MCSFR  AUC= 0.77
  - Osteopontin  AUC= 0.86
  - INR         AUC = 0.92
  - Total Bili  AUC = 0.82

- DILI mortality risk calculator (2)
  - Charlson co-morbidity index > 2 + MELD + albumin
    - AUC = 0.89

<table>
<thead>
<tr>
<th>MELD &lt; 19</th>
<th>CCI 0-2 N=207</th>
<th>CCI &gt; 2  N=30</th>
</tr>
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<tbody>
<tr>
<td>6 mon mortality (%)</td>
<td>2.4 %</td>
<td>20%</td>
</tr>
<tr>
<td>MELD &gt; 19</td>
<td>CCI 0-2 (n=45)</td>
<td>CCI &gt; 2 (n=23)</td>
</tr>
<tr>
<td>6 mon mortality (%)</td>
<td>13.3%</td>
<td>39.1%</td>
</tr>
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</table>

(1) Hepatology 2019; 69: 760
(2) Gastroenterology 2019; 157: 1245
Predictive DILI Biomarker Discovery
- Need high specificity
  - PPV may be low due to low incidence
- For DILI (other AE), need clear case definition
  - Exclusion of other causes, phenotype & pattern
    - ? Gold standard
- Collect biosamples from ALL patients
  - Specimen collection, handling, & processing
CIOMS DILI: Predictive Biomarkers

• 1 in 10,000 flucloxacillin-treated pts develop jaundice
  – HLA-B *57:01 over-represented in DILI cases
    • 87% vs 13%  Odds Ratio = 36

• Pop controls: HLA-B * 57:01 in 7% Cau
  – High NPV (98.7%)
  – Low PPV (51.3%)

• Test HLA-B *57:01 in 1000 pts to prevent 1 flucloxacillin DILI case
  – Low PPV (990 HLA-B *57:01+ →would not be treated)
  – High NPV (useful confirmatory diagnostic test)

(Daly Nature Gen 2009: 41: 816)
CIOMS DILI: Other Proposed Biomarkers

- **Diagnostic/ prognostic serum biomarkers**
  - Bile acids, GSTa, FABP

- **Diagnostic/ causality biomarkers**
  - Lymphocyte transformation test (MetaHeps)
  - Drug-protein adducts

- **Diagnostic/ prognostic imaging biomarkers**
  - MRI (PDFF, elastography)
  - USN with contrast

- **Predictive/ susceptibility genetic biomarkers**
  - Drug specific SNP’s
• HDS used to enrich diet and improve health/function
  • Vitamins, minerals, amino acids/powders/herbals/botanicals, multi-ingredient nutritional supplements, and other products
    • Regulated as foods (DSHEA 1994)
    • No efficacy or safety testing required
    • Variable manufacturing (Batch variation)

• HDS widely used worldwide (20-90%)
  • “Natural is safer” “More is better”
  • > 80,000 products in 2014

2. Medina-Cáliz et al, Clin Gastroenterol Hepatol 2018
### HDS liver injury in DILIN

<table>
<thead>
<tr>
<th></th>
<th>Body Building N=45</th>
<th>Non-body building N=85 *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31</td>
<td>47</td>
</tr>
<tr>
<td>% Male</td>
<td>100%</td>
<td>35%</td>
</tr>
<tr>
<td>Latency (days)</td>
<td>43</td>
<td>30</td>
</tr>
<tr>
<td>% Hospitalized</td>
<td>71%</td>
<td>68%</td>
</tr>
<tr>
<td>% Liver Transplant</td>
<td>0%</td>
<td>13%</td>
</tr>
<tr>
<td>% Death</td>
<td>0%</td>
<td>4%</td>
</tr>
</tbody>
</table>

* 58% multi-ingredient nutritional supplements

(DILIN Hepatology 2014: 60)
### CIOMS DILI: HDS product labelling

<table>
<thead>
<tr>
<th>Category</th>
<th>Samples with Labels n</th>
<th>Inaccurate Labels n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Health</td>
<td>53</td>
<td>26 (49%)</td>
</tr>
<tr>
<td>Bodybuilding</td>
<td>46</td>
<td>37 (80%)</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>36</td>
<td>26 (72%)</td>
</tr>
<tr>
<td>GI Symptoms</td>
<td>22</td>
<td>9 (41%)</td>
</tr>
<tr>
<td>Energy Boosters</td>
<td>5</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Sexual Enhancers</td>
<td>4</td>
<td>4 (100%)</td>
</tr>
<tr>
<td>Misc or Unknown</td>
<td>106</td>
<td>35 (33%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>272</strong></td>
<td><strong>140 (51%)</strong></td>
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*(Hepatology Com 2019; 3: 792-794)*
CIOMS DILI: HDS Causality Assessment

- Latency
- Dechallenge
- Prior reports of phenotype
  - LiverTox profile (50 HDS products)
- Exclude other causes

- Prospective DILI registries
  - Expert opinion
    - Ingredient analysis
Walter Straus, MD, MPH, FACP:
On Behalf of the Working Group
AVP and Chair, Organ-Specific Safety Boards, Merck Research Laboratories, United States

MSD

Best practices in post-market DILI risk assessment, risk minimization and communication
Background: Risk Assessment for DILI

Challenges

Clinical Trial Setting
DILI is rare, and clinical trials are usually underpowered to detect them prior to licensure

Post Marketing
- DILI information is often identified post-licensure
- However, clinical practice is generally inadequate to identify DILI
  - Less intensive monitoring of patients
  - Providers unfamiliar with identifying hepatotoxicity
  - Lack of deep familiarity with product labels as well as with clinical practice guidelines (example: isoniazid)

Working groups
- Considered key international pharmacovigilance documents*
- Provided recommendations that build on those, incorporate recent development, pertinent to DILI

ICH Technical, Requirements for Pharmaceuticals for Human Use (ICH) E2E guideline on planning pharmacovigilance activities (1989)
**Current Post-Marketing Surveillance systems**

Can provide key insights into susceptibility factors and signal detection for idiosyncratic DILI in the general population, but is incompletely exploited.

<table>
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<th>Passive Surveillance</th>
<th>Active Surveillance</th>
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<tr>
<td>Voluntary Spontaneous reporting systems</td>
<td>Prospective monitoring, typically involved standardized data collection, e.g. pharmacoepidemiologic study</td>
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<td>Common in much of world, but:</td>
<td>Increasing interest in prospective use of electronic data sources (e.g. medical records and administrative claims data) to identify novel risk factors and features of DILI (e.g. drug-drug interactions, time to onset).</td>
</tr>
<tr>
<td>- Limited by under-reporting</td>
<td>- Application of new technologies, e.g. data mining, natural language processing</td>
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<td>- Higher AE reporting rates in countries with mandatory reporting requirements</td>
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<tr>
<td>- Additionally, such reports often are incomplete and missing key data needed to support causality assessment (e.g. concomitant medications and co-morbidities)</td>
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</table>

* Major sources of data
Recommendations

Risk Assessment

- Strong recommendation for signal detection of potentially hepatotoxic drugs and herbal and dietary supplement (HDS) products in the marketplace, using resources such as:
  - FDA's adverse event reporting system (FAERS)
  - WHO's VigiBase
  - Administrative (claims) data, utilizing ICD-10 codes (e.g. much of SENTINEL)

- Collect (at least) minimum common data elements for all DILI case series publications to facilitate interstudy comparisons

- Drugs with validated hepatotoxicity safety signals arising from spontaneous datasets should generally trigger an in-depth investigation, including comparative population based studies to characterize and quantify the post-market DILI risk.
DILI registries

- Organized set of prospectively and systematically collected observational records, incorporating a common minimum data set, on specified outcomes in a population defined by a particular disease, condition or exposure.
  - Registries are of particular value to collect data on rare events

- DILI registries can augment case detection and enhance signal detection in the general population.

- Samples collected by DILI registries can be used to develop new diagnostic and prognostic biomarkers.
## Prospective DILI registries in place at time of report

<table>
<thead>
<tr>
<th></th>
<th>Spanish DILI Registry</th>
<th>ALFGS</th>
<th>DILIN</th>
<th>Japanese DILI registry</th>
<th>LATINDILIN</th>
<th>Pro-Euro DILI Net</th>
<th>DILI-P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initiation</strong></td>
<td>National Spain</td>
<td>National US</td>
<td>National US</td>
<td>National Japan</td>
<td>International</td>
<td>International</td>
<td>National China</td>
</tr>
<tr>
<td><strong>Causality assessment tool</strong></td>
<td>RUCAM</td>
<td>None</td>
<td>Expert opinion; RUCAM</td>
<td>RUCAM and modified RUCAM</td>
<td>RUCAM</td>
<td>RUCAM</td>
<td>Expert opinion; RUCAM</td>
</tr>
<tr>
<td><strong>Case enrollment</strong></td>
<td></td>
<td>946</td>
<td>2626</td>
<td>1257</td>
<td>307</td>
<td>280</td>
<td>44</td>
</tr>
<tr>
<td><strong>Biological specimens</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* See report for references
Risk minimization and communication
Principles

• Risk management is required to mitigate risk of DILI in real world settings
  – Structured and ongoing process to calibrate evolving safety and effectiveness profile, supported by actions to minimize risk and maximize benefit
  – Current focus on proactive signal detection and periodic risk evaluation

• Product label is core document for HCPs on product use, and has legal standing to support proper dissemination of product information
SUMMARY

Risk stratification is used to categorize risk by segmenting a population that may be prescribed a drug according to the expected likelihood of harm (or benefit).

Currently available regulatory recommendations to detect and mitigate DILI risk were developed for the setting of closely monitored clinical studies. They are also typically used in product labelling, but might not suffice in the more heterogeneous setting of real-world use of the products.

Risk mitigation in special patient populations (e.g. those with preexisting liver disease or malignancies) remains an unfulfilled goal despite previous international efforts and clinical society consensus statements on this issue.

Additionally, the information provided in the product labels of drugs marked by similar risk often varies, even among drugs within the same class, as a result of many factors.
Challenges in effective communication of DILI risk in product labeling

• Confusion between liver function and liver injury
  – The severity of liver injury and the degree of impaired liver function are different concepts but are often conflated.
  • Example: serum levels of aminotransferases measure cellular damage, but are often erroneously considered to measure liver function.

• Reliance upon safety terms used in clinical trials, not clinical practice
  – Terms may be used imprecisely: examples include “autoimmune hepatitis” and “steatohepatitis.”
  – There are also international differences in the use of certain liver failure terms: acute, sub acute, acute on chronic, and chronic liver failure
Challenges in effective communication of DILI risk in product labeling

• **Inconsistent product labeling across countries:** Product labeling practices are not uniform, leading to variability even within the same drug class.

  • **Countries differ in:**
    – assessment of a product's benefit risk profile
    – regulatory review division strategies and requirements
    – time lag in adopting new scientific evidence
    – medical treatment practices and guidelines

• Companies often have some latitude to propose their own semantic descriptions to communicate risks and management.
### Example of differences in EU Summary of Product Characteristics (Nov 2019) and the US label (Aug 2019) regarding information on hepatic adverse effects

<table>
<thead>
<tr>
<th>EU SmPC</th>
<th>US PI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contraindications</strong></td>
<td>None pertaining to hepatic disorders</td>
</tr>
<tr>
<td><strong>Warnings and Precautions</strong></td>
<td>Spontaneous serious adverse reactions of liver injury have been reported during the post marketing phase. These liver injuries may occur at any time during treatment, even after the first dose. In some instances, the reaction recurred when natalizumab was reintroduced. Some patients with a past medical history of an abnormal liver test have experienced an exacerbation of abnormal liver test while on natalizumab. Patients should be monitored as appropriate for impaired liver function, and be instructed to contact their physician in case signs and symptoms suggestive of liver injury occur, such as jaundice and vomiting. In cases of significant liver injury natalizumab should be discontinued.</td>
</tr>
<tr>
<td><strong>Undesirable effects</strong></td>
<td>Spontaneous cases of serious liver injuries, increased liver enzymes, hyperbilirubinaemia have been reported during the post marketing phase. <strong>No data from clinical trials disclosed.</strong></td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td>The pharmacokinetics of natalizumab in patients with renal or hepatic insufficiency has not been studied. The mechanism for elimination and results from population pharmacokinetics suggest that dose adjustment would not be necessary in patients with renal or hepatic impairment.</td>
</tr>
</tbody>
</table>
Optimal risk management for DILI requires that:

- Risk factors are well characterized
- The known features of liver injury due to a drug (the "drug's signature") are well described
- Risk monitoring and management are based on reliable measures that can predict the outcome
- The pattern and course of the injury are well defined, accounting for possible variability related to different features of patient groups.

In practice, characterizing DILI risk can be difficult due to inconsistency in nomenclature, uncertainties in pathogenesis, limited data, and low event rates.

Management would be improved with:
- Greater adherence to systematic data collection to characterize DILI
- Additional research to characterize pathogenesis
- Harmonization of reporting and labeling approaches
Risk Management and Communication

RECOMMENDATIONS

• Descriptions in product labels of risk for DILI (e.g., time course, clinical pattern and mechanism of liver injury) and recommendations for liver monitoring should be informed by available product-related data.

• Peer-reviewed publications can often provide a rich source of developing information on risk for DILI that is associated with a suspect marketed drug or class of drugs.

• Regulatory agency websites and the LiverTox® database provide useful additional information for clinicians to guide them in managing hepatotoxicity risk.

• Medical professional societies and practice guidelines generally provide valuable recommendations on the optimal use of potentially hepatotoxic drugs in patients.
Thank you

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https://tinyurl.com/DILIzoom

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