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

This session will start at 7pm SGT

Speakers and Panellists

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Report of CIOMS DILI Working Group

Mark I Avigan, MD CM: Session Chair
Associate Director for Critical Path Initiatives
Office of Pharmacovigilance & Epidemiology
Center for Drug Evaluation & Research
U.S. Food and Drug Administration

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.

CIOMS Working Group on Drug-Induced Liver Injury (DILI)

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Mark AVIGAN	U.S. Food and Drug Administration (FDA)
Amel BENKRITLY*	Sanofi
Einar S. BJÖRNSSON	National University Hospital of Iceland
Michele BORTOLINI	Roche
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Jia-bo WANG*	Fifth Medical Center of Chinese PLA General Hospital, China
Hui-Talia ZHANG	Bayer

*** = Participated in fewer than three meetings.**

Consensus report of the CIOMS DILI Working Group

Available on the CIOMS website at:

- https://cioms.ch/publications/product/drug-induced-liver-injury/

Speakers: CIOMS Report on DILI

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??

Professor Hervé LE LOUET, MD, PhD
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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

DILI Working Group

Several initiatives from academic, regulators, industry and patient organisations that need to be coordinated to avoid redundancies, improve dissemination and widen the audience

CIOMS DILI WORKING GROUP

Arie Regev,
MD, FAASLD
Global Patient Safety
Eli-Lilly

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 1. General categories of DILI

(Modified from: [Hoofnagle & Björnsson. N Engl J Med 2019;381:264-273])

	Direct (intrinsic)	Indirect	Idiosyncratic
Dose-related	Yes	No (generally)	No (with some exceptions)
Latency	Short (few days)	Typically delayed (weeks to months)	Variable (days to months), may occur after treatment discontinuation
Rate of occurrence	High	Intermediate	Low
Predictable	Yes	Occasionally	No
Implicated drugs (examples)	Acetaminophen, nicotinic acid, aspirin, cocaine, many cancer chemotherapies, fialuridine, amiodarone, methotrexate (intravenous), plants containing pyrrolizidine alkaloids	High-dose corticosteroids; some antineoplastic agents: immune checkpoint inhibitors, protein kinase inhibitors, monoclonal antibodies (*e.g.*anti-TNF, anti-CD20), daclizumab	Isoniazid, amoxicillin-clavulanate, macrolide antibiotics, fluoroquinolones, statins, flucloxacillin, diclofenac; certain herbal and dietary supplements (HDS), *e.g.* green tea extract, *Polygonum multiflorum*
Pathologic mechanisms	Liver damage occurs if parent drug or metabolite concentrations in liver cells exceed a toxic threshold	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)	Adaptive immune response to a parent drug or drug metabolite may contribute. Mitochondrial damage and hepatic steatosis may also be observed

DILI Phenotypes

DILI Phenotypes

Acute hepatitis (resembling viral-hepatitis)	isoniazid, ketoconazole, ximelagatran
Cholestatic or mixed hepatitis	amoxicillin-clavulanate, macrolides
Acute hepatic necrosis	acetaminophen, IV amiodarone
Hypersensitivity syndrome (DRESS*)	phenytoin, carbamazepine
Chronic steatosis/ steatohepatitis	methotrexate, tamoxifen, irinotecan
Acute fatty liver with metabolic acidosis	stavudine, tetracycline, sodium valproate
Drug-induced autoimmune hepatitis	minocycline, nitrofurantoin
Sinusoidal obstruction syndrome	cyclophosphamide, azathioprine
Nodular regenerative hyperplasia	azathioprine, HAART, bleomycin
Immune-mediated liver injury	ipilimumab, pembrolizumab, nivolumab

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

*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

Aithal et al. Clin Pharmacol Ther 2011;89:806-15.
Regev et al. Aliment Pharmacol Ther. 2019;49:702–713.

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

1. Chalasani & Regev. Gastroenterology. 2016;151:1046-51.
2. Regev et al. Aliment Pharmacol Ther. 2019;49:702–713.
3. Palmer et al. Aliment Pharmacol Ther. 2020;51:90–109

DILI Detection and Risk Assessment in Clinical Trials

Nonclinical Assays/ Studies: Assessment of Idiosyncratic DILI Risk (?)

Drug-Specific In Vitro/ Toxicology Predictors	Predictive value	
Formation of reactive metabolites	High[1]	Low[2,3]
Inhibition of drug transporters (BSEP, MRPs)	High[4,5]	Low[3,6]
Mitochondrial toxicity	High[4]	Low[3]
ROS/ATP*	High[7]	Low[3]
Animal toxicology studies	High[11]	Low[12]
BDDCS**	High[3,6]	Low[8]
Rule of 2 (daily dose + lipophilicity)	High[4]	Low[3]
Rule of 2 + reactive metabolites	High[5]	Low[3]

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

1. Thompson et al. Chem Res Toxicol 2016;29:505
2. Park et al. 2011;10:292–306
3. Chan & Benet. Chem Res Toxicol 2017;30:1017
4. Aleo et al Hepatology 2014;60:1015
5. Aleo et al. Chem Res Toxicol 2017;30:1219
6. Chan & Benet. Toxicological Science 2017;1
7. Zhang et al. Chem Biol Interact 2016;255:3
8. Vuppalanchi et al. Clin Gastroenterol Hepatol. 2014;12:1550
9. Chen et al. Hepatology 2013;58:388
10. Chen et al. Hepatology 2016;64:931
11. Olson et al. Regul Toxicol Pharmacol 2000;32:56
12. Tamaki et al. J Toxicol Sci. 2013;38:581

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

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

DukeNUS Medical School

CIOMS

CoRE Centre of Regulatory Excellence @ Duke-NUS Medical School

Raúl J Andrade
Professor of Medicine

Liver Safety Biomarkers

Herbal and Dietary Supplement Hepatotoxicity

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Director: Spanish and Spanish/Latin-American DILI Networks

CIOMS DILI: Liver Safety Biomarkers

- **FDA Context of use** [1]
  - Description of **how, when** and **why** a biomarker is to be used in a drug development program or clinical trial

- **EMA Context of use** [2]
  - "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)

CIOMS DILI: Liver Safety Biomarkers

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

CIOMS DILI: Liver Safety Biomarkers

Biomarker	Application (COU)	Comments
Total cytokeratin-18 *	Early diagnosis Prognosis	Hepatocyte necrosis
ccCytokeratin-18	Early diagnosis	Hepatocyte apoptosis
miR122	Early diagnosis	Hepatocyte specific Not DILI specific (?)
Total HMGB1	Early diagnosis	Wide tissue expression
Glutamate dehydrogenase (GLDH)	Early diagnosis	Mitochondrial matrix ? Pericentral hepatocytes
Sorbitol dehydrogenase (SDH)	Early diagnosis	Hepatocyte necrosis
Macrophage colony stimulating factor receptor 1 (MCSFR1) **	Prognosis	Macrophage cytokine receptor
Osteopontin *	Prognosis	Wide tissue expression ? Inflam vs regeneration

* 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) (1) Hepatology 2019; 69: 760
  - MCSFR AUC= 0.77 Osteopontin AUC= 0.86
  - INR AUC = 0.92 Total Bili AUC = 0.82

- DILI mortality risk calculator (2) (2) Gastroenterology 2019; 157: 1245
  - Charlson co-morbidity index > 2 + MELD + albumin
    - AUC = 0.89

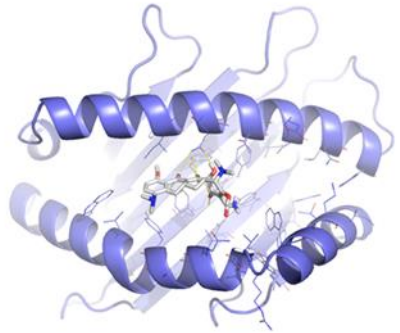
MELD < 19	CCI 0-2 N=207	CCI > 2 N=30
6 mon mortality (%)	2.4 %	20%
MELD > 19	CCI 0-2 (n=45)	CCI > 2 (n=23)
6 mon mortality (%)	13.3%	39.1%

CIOMS DILI: Liver Safety Biomarkers

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

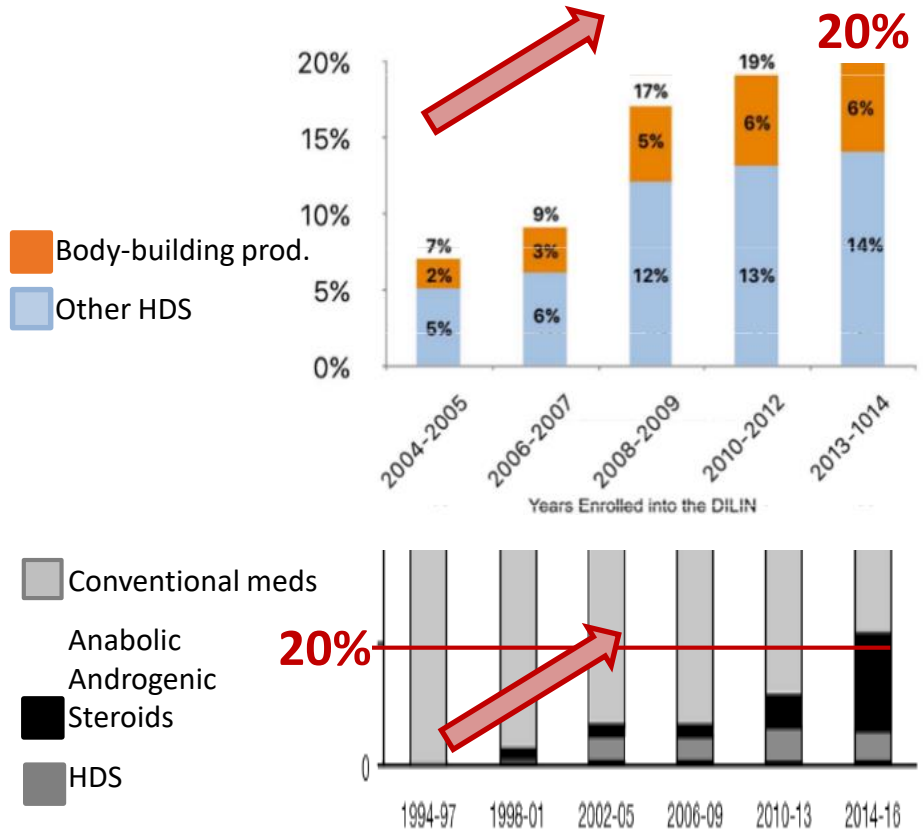
(Daly Nature Gen 2009: 41: 816)

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

CIOMS DILI: Herbal & Dietary Supplements (HDS)

- **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



1. Nut Bus J 2015: 67; Navarro Hepatology 2017; 65: 363
2. Medina-Cáliz et al, Clin Gastroenterol Hepatol 2018

CIOMS DILI: HDS Hepatotoxicity

HDS liver injury in DILIN

	Body Building N=45	Non-body building N=85 *
Age	31	47
% Male	100%	35%
Latency (days)	43	30
% Hospitalized	71%	68%
% Liver Transplant	0%	13%
% Death	0%	4%

* 58% multi-ingredient nutritional supplements

(DILIN Hepatology 2014: 60)

CIOMS DILI: HDS product labelling

Category	Samples with Labels n	**Inaccurate Labels n (%) ***
General Health	53	**26 (49%)**
Bodybuilding	46	**37 (80%)**
Weight Loss	36	**26 (72%)**
GI Symptoms	22	**9 (41%)**
Energy Boosters	5	**3 (60%)**
Sexual Enhancers	4	**4 (100%)**
Misc or Unknown	106	**35 (33%)**
TOTAL	272	**140 (51%)**

***(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

Best practices in post-market DILI risk assessment, risk minimization and communication

Walter Straus, MD, MPH, FACP:
On Behalf of the Working Group
AVP and Chair, Organ-Specific Safety Boards,
Merck Research Laboratories, United States
MSD

Background: Risk Assessment for DILI

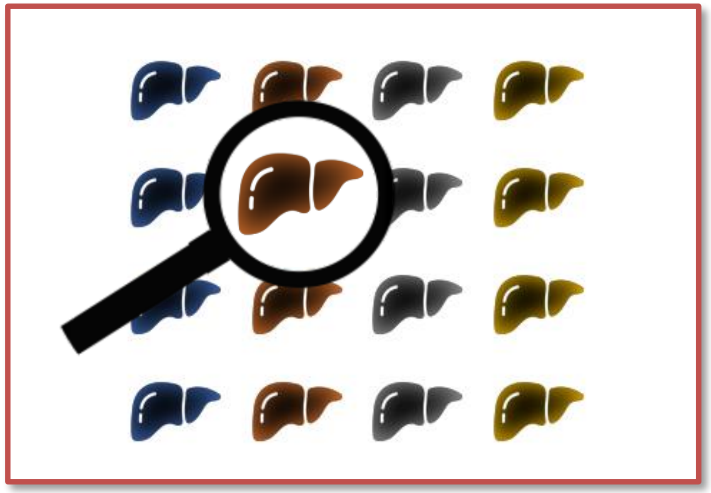
Challenges

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)



Solutions

Working groups

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

*CIOMS Working Group VIII, Practical Aspects of Signal Detection in Pharmacovigilance (1987).
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.

Passive Surveillance

- Voluntary Spontaneous reporting systems
- Common in much of world, but:
  - Limited by under-reporting
  - Higher AE reporting rates in countries with mandatory reporting requirements
  - Additionally, such reports often are incomplete and missing key data needed to support causality assessment (e.g. concomitant medications and co-morbidities)

* Major sources of data

Active Surveillance

- Prospective monitoring, typically involved standardized data collection, e.g. pharmacoepidemiologic study
- 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).
  - Application of new technologies, e.g. data mining, natural language processing

Risk Assessment Recommendations

- 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

	Spanish DILI Registry	ALFGS	DILIN	Japanese DILI registry	LATINDILIN	Pro-Euro DILI Net	DILI-P
	National Spain	National US	National US	National Japan	International	International	National China
Initiation	1994	1998	2003	2010	2010	2014	2016
Causality assessment tool	RUCAM	None	Expert opinion; RUCAM	RUCAM and modified RUCAM	RUCAM	RUCAM	Expert opinion; RUCAM
Case enrollment*	946	2626	1257	307	280	44	6663
Biological specimens	Yes	Yes	Yes	Yes	Yes	Yes	Yes

* 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

DILI risk management and communication

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

EU SmPC	US PI
Contraindications	
None pertaining to hepatic disorders	None pertaining to hepatic disorders
Warnings and Precautions	
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 reoccurred 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.	Clinically significant liver injury has been reported in patients treated with natalizumab in the postmarketing setting. Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, occurred as early as six days after the first dose; signs of liver injury have also been reported for the first time after multiple doses. **In some patients, liver injury recurred upon rechallenge, providing evidence that natalizumab caused the injury.** The combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients. Natalizumab should be discontinued in patients with jaundice or other evidence of significant liver injury (e.g., laboratory evidence).
Undesirable effects	
Spontaneous cases of serious liver injuries, increased liver enzymes, hyperbilirubinaemia have been reported during the post marketing phase. **No data from clinical trials disclosed.**	Abnormal liver function test **(5% vs. 4% in placebo controls in clinical trials).**
Pharmacokinetics	
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.	Pharmacokinetics of natalizumab in patients with renal or hepatic insufficiency have not been studied. and no change in dosing recommended

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.

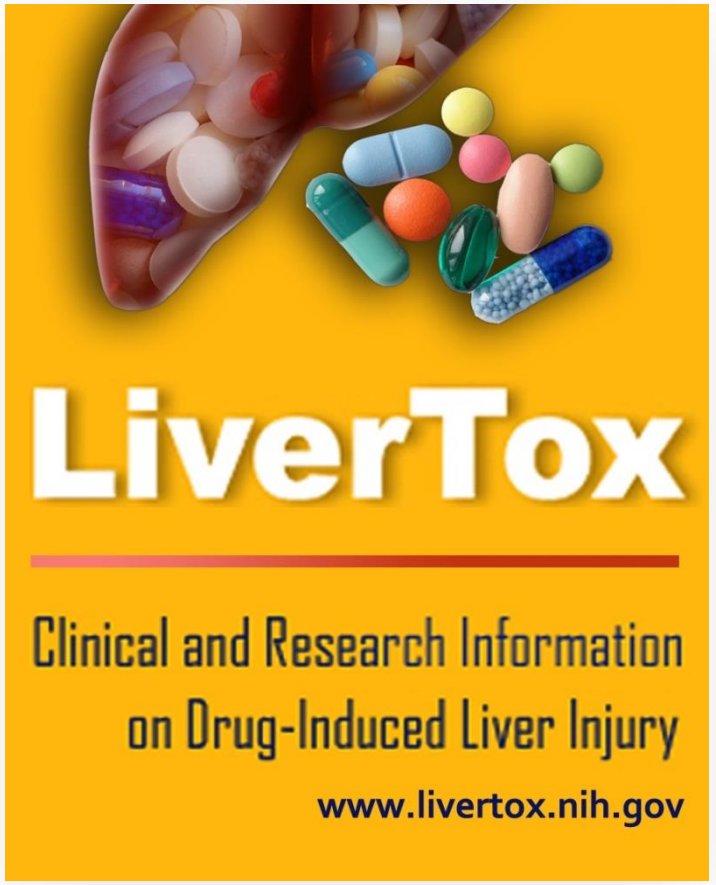
Management would be improved with:

- 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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Summary and Key Takeaways

Thank you for attending the Webinar!

We appreciate your feedback!

https://tinyurl.com/DILIzoom

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