Council for International Organizations of Medical Sciences

Third meeting of the CIOMS Working Group on Drug-Induced Liver Injury (DILI)

8-9 May 2018, Reykjavík, Iceland

Minutes (web)

Introductory session

During the opening ceremony a video on the venue, Hannesarholt House Iceland, was presented showing the heritage and culture in remembrance of Iceland's first Prime Minister, Hannes Hafstein.

This was followed by a brief presentation of recent important developments and cooperation with other initiatives in DILI:

IMI2 TransBioLine

The new IMI consortium TransBioLine has been selected as the winning consortium for stage 2 of Call 13 in early May. TransBioLine will focus on qualification of new safety biomarkers for drug induced liver, kidney, vascular, pancreas, and CNS injury. For liver, kidney, and vascular markers, the consortium is aiming at completing full regulatory qualification initiated by IMI SAFE-T, but also expanding application of the new markers to clinical practice. A strong focus will also be on evaluation of miRNA profiles for diagnosis of disease, so-called "liquid biopsies".

CA 17-112 Prospective European Drug-Induced Liver Injury Network (PRO-EURO-DILI-NET)

This initiative is a COST (Cooperation in Science & Technology) Action led by Raúl J Andrade and Guruprasad Aithal. It was approved by the European Commission on 13 April 2018. A brief description was provided about what this COST Action is about, its mission and strategy, policies and tools. The objectives of the PRO-EURO-DILI-NET Cost Action are to create a unique, co-operative, interdisciplinary European-based DILI network of stakeholders to co-ordinate efforts in DILI, to facilitate bidirectional exchange of discovered knowledge and generated hypotheses among different disciplines, and to promote clinically impactful knowledge discovery and its translation into clinical practice. The Action will involve 51 partners derived from 16 COST countries, 6 of them are Inclusiveness Target Countries, and 5

International Partners. There are contributions from CIOMS DILI WG members and potential synergies with CIOMS DILI.

Working Group Report

Professor Le Louet, after having reviewed the draft chapters delivered by the subgroups, raised two points for discussion, i.e. comprehensiveness and core audience.

- **Core audience:** It was agreed that the white paper should be addressing all key stakeholders: regulators, industry and practising physicians. Thus, it will need to have a broad scope in order to be useful to agencies, clinicians, pharmaceutical industry.
- **Comprehensiveness** is not a disadvantage. It may be useful to have a core document comprising essential points and satellites focusing on more dynamic content, as the field of DILI is a moving target and other initiatives keep coming up.

The Working Group agreed that the CIOMS DILI eCRF will be a great accomplishment, filling a crucial gap, as there is no specific hepatic standard CRF available yet, and current approaches to capture relevant data are very diverse. Formal guidance is needed as to what information to gather in order to determine DILI phenotype and properly assess causality.

Reports from the subgroups

Group 1: Principles in Detection, Characterization and Risk Assessment of DILI in Clinical Trials and Post Marketing

The group is making good progress in writing the specific parts assigned. There is a wide range of topics to be covered. The guidance needs to be very specific and highlight available evidence.

The group is working on a hepatic safety CRF for significant liver injury cases. It is more tailored to the regulator. There is also a need for an adequate narrative, ideally with patient profiles displayed graphically over time.

Another challenge is to highlight what is important across different stakeholders.

Group 2: Liver Safety Biomarkers: Recommended strategies for pre-marketing and post-marketing studies and efforts

A short overview was provided of the status of the individual sections: biomarker definitions, performance characteristics, ethical considerations, standard and new liver safety biomarkers, and post-marketing pharmacovigilance.

Good progress has been made on most sections. The section on standard safety biomarkers is still to be written, the post-marketing section is currently available as an outline. Two additional Working Group members agreed to contribute to the work of Group 2.

Group 3: DILI risk stratification, minimization, and communication

The group is looking at a quantitative DILI risk assessment with specific agents. Risk stratification and management has been discussed and work advanced. The sections are to be harmonized and compiled.

Risk minimization programs need to be realistic and assess the impact of pharmacovigilance requirements in place.

It is considered important to provide recommendations that are amenable to evaluation.

Biologics and immune checkpoint inhibitors should be considered.

Discussion points from subgroup breakouts

Group 1

The area encompasses a wide range of topics.

Areas decided not to be addressed systematically:

- Principles of herbal and dietary medicines
- Management and treatment (will be taken over by subgroup 3)
- RUCAM vs Expert Opinion. RUCAM is not yet ready for causality assessment in clinical development.

Documents will be shared on the dedicated website for the CIOMS DILI WG.

As for causality assessment, it was agreed that RUCAM needs revision and improvement. As is, it is useful as a check list to ensure all key data domains are covered when assessing causality in individual cases.

Group 2

The section has been revised and condensed. In particular, the overlapping post-marketing part will be shortened significantly.

- Summary of sections and discussion points:

Sections	Discussion points
1. Biomarker definitions a. Definition of different types of biomarkers b. Contexts of use	• Target audience: including practitioners/standard clinicians, not only investigators involved in drug development/consultants • Should we include translational markers as well? • Reduce section on biomarker definitions to safety biomarkers? Just refer to FDA definitions? • Keep marker types that are relevant for DILI, replace examples by ones that are relevant for DILI (Hy's law, MELD, King's College, composite markers in general).
2. Biomarker performance characteristics	• ROC plot: add plot of frequency distributions to explain • Add section on which characteristics are most relevant for DILI
3. Current standard liver safety biomarkers a. Overview b. Shortcomings	• Text on DILI diagnosis: in group 1 section • Make sure group 1 is not covering standard markers already • Specify biomarker gaps that new markers need to address • Proper baseline definition. Should we follow Chalasani/Regev

Sections	Discussion points
	paper on patients with baseline abnormalities? • Should we just have a simple approach for toxicity management? For example, close observation needed if ALT > 3 x ULN, for patients with bsl > 2 x ULN if > 5 x ULN? • Include recommendation on central and local labs: record data including reference ranges, units, store in clinical trial database, flag in dataset. • CTCAE: used in isolation it is inadequate for DILI monitoring. Has value in signal detection but not in risk stratification • Monitoring schemes: use GSK approach on evidence based liver chemistry monitoring • Include sentence on limitations of monitoring • Liver metastases: don't differentiate between 3 x and 5 x ULN as inclusion criterion. Patients may have micrometastases, so even without liver metastases in the records, they may already have liver abnormalities! • Summarize shortcomings of standard markers in a table
4. New biomarkers a. Requirements b. Current exploratory liver safety biomarkers c. Soluble markers d. Genetic markers e. Biomarker discovery vs qualification f. Recommendations on application and exploration of new liver safety biomarkers	• Specify which makers have been assessed in APAP overdose only, and which in idiosyncratic DILI • Safe harbour conditions? Always discuss with agencies before using new markers? • Serial sampling when possible along with liver chemistry monitoring • At this stage: only recommend use for individual case adjudication (ICF). Prerequisite for broader application: full qualification. • Have core chapter static, and dynamic appendices. Follow NICE process indicating date of review and update on website.
5. Ethical issues and considerations a. Background b. Critical areas c. Possible reason for REC concern d. Justification e. Actions to mitigate harm f. Conclusion	
6. Postmarketing pharmacovigilance a. Challenges with liver signal detection and assessment in a postmarketing setting b. Current efforts by regulatory agencies in US,	• Refer to group 3 for weaknesses of PV system • Two objectives: 1. How do we maximize output from single case reporting? 2. How do we optimize aggregate information from DILI cases/signals? • Provide guidance on which data to collect related to biomarkers • Generic recommendations: ○ Collect standard liver biomarkers including RR and units.

Sections	Discussion points
Europe and Asia?	○ For drugs that have DILI in the label collect baseline samples. • Three use cases to optimize DILI reporting with respect to biomarker data: 1. All ("average prescriber"): Use group 1 CRF as starting point, cut down to biomarker related data items most relevant for PV; standardized follow-up form? 2. If drug is part of a prescription event monitoring system: provide links to system 3. If prescribing overproportional number of hepatotoxic drugs: refer to registries, provide references and links • Recommend list of DILI compounds by regulatory agencies? ○ Something similar to WHO list of drugs of special interest? ○ Can we refer to LTKB as reference for DILI compounds?

Group 3

The group will take care of the following topics:

- DILI management and therapy
- Severity definitions
- Non-genetic risk factors
- Detection and management of ant-Tbc, HIV, and chemotherapeutic drugs

Plenary discussion on report

The WG will make sure to avoid overlaps, and, even more important, contradictions across the chapters. Management of DILI will be taken care of by subgroup 3 instead of subgroup 1.

Questions around DILI therapy, rechallenge etc. to be aligned across subgroups 1 and 3.

Stick to available robust evidence and align with existing guidance, e.g. the recently finished EASL Clinical Practice Guideline on DILI.

Liver biopsy as a biomarker to be discussed in subgroup 2.

Standard biomarkers to be covered by subgroup 2.

Postmarketing safety assessment, discussed in subgroup 2, may overlap with subgroup 3.

The goal will be to compile a first draft across all three chapters as soon as possible to facilitate exclusion of overlaps and duplications and address any potential contradictions (to be taken care of by editorial group).

The CIOMS paper should encourage also non-expert clinicians to report suspected DILI cases.

Place and date of next meeting

The next meeting will take place in Aix-en-Provence, France, on 27-28 November 2018.

Participants

CIOMS	Hervé **Le Louet**	APHP, CIOMS President
	Lembit **Rägo**	CIOMS Secretary-General
WHO	Shanthi **Pal**	Safety and Vigilance (SAV) team
Regulators	Mark **Avigan**	U.S. FDA
	Elmer **Schabel**	EMA, BfArM Germany
	Uzu **Shinobu**	PMDA Japan
	Monica **Soares**	ANVISA Brazil
	James **Southern**	SAHPRA / Medicines Control Council South Africa
	Hajime **Takikawa**	Teikyo University, consultant of MHLW, Japan
	Mari **Thörn**	MPA Sweden
Academia	Guruprasad **Aithal**	University of Nottingham, United Kingdom
	Raul **Andrade**	University of Málaga, Spain
	Einar **Björnsson**	National University of Iceland
	Maribel **Lucena**	International Union of Basic and Clinical Pharmacology (IUPHAR)
	Michael **Merz**	University Hospital Zurich, Switzerland
Industry	Stewart **Geary**	Eisai
	Gerd **Kullak-Ublick**	Novartis
	John **Marcinak**	Takeda
	Manfred **Oster**	Sanofi
	Arie **Regev**	Eli Lilly
	Walter **Straus**	MSD
	Javier **Waksman**	Fibrogen
	Hui-Talia **Zhang**	Bayer
Consortia	John-Michael **Sauer**	C-Path Predictive Safety Testing Consortium

Apologies

Regulators	Haibo **Song**	CFDA China
Academia	Robert **Fontana**	University of Michigan
Industry	Michele **Bortolini**	Hoffmann La Roche
