

CLINICAL NETWORKS AND CONSORTIA IN DRUG-INDUCED LIVER INJURY (DILI): AN OPPORTUNITY FOR ADVANCING SAFETY SCIENCE

M. Isabel Lucena^{1,2}

¹Head, Department of Clinical Pharmacology, Instituto de Investigación Biomédica de Málaga (IBIMA), Hospital Universitario Virgen de la Victoria, Universidad de Málaga, Málaga, Spain; and ²Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain

The IUPHAR Clinical Division is contributing at the 12th Conference of the European Association for Clinical Pharmacology and Therapeutics (EACPT) to be held in Madrid, 27 to 30 June 2015, sponsoring a symposium along with the EACPT titled “Clinical Networks and Consortia in Drug-Induced Liver Injury (DILI): an opportunity for advancing Safety Science.

Over the past decade several concerted efforts have facilitate an unprecedented grow in clinical and translational research in DILI, which have certainly contributed to highlight the relevance of this safety concern among all stakeholders.

In this session we will update some of the most important steps set forward and the challenges that still remain. We will discuss the prospective networking initiatives that allow collecting well-vetted DILI cases which have provided new insights in clinical phenotypes and severity. The systematic collection of biological samples has enabled to perform pharmacogenetic and mechanistic approaches, providing the rationale for future studies. The discovery, qualification, and validation of new mechanistic and liver specific biomarkers have become an unmet need that can now be dealt through the joined collaborative efforts of the respective hepatotoxicity working groups of the European IMI SAFE-T Consortium and the Predictive Safety Testing Consortium (PSTC) in the US.

Finally, the role of health regulatory agencies to address the major risk of DILI for new compounds to reduce drug attrition, improve safety assessment through risk minimization plans, support conditional approval of new chemical entities with toxicity potential and to move towards truly safety personalized medicine will be also addressed.

PHARMACOVIGILANCE AND RISK MANAGEMENT: HOW TO DETECT, EVALUATE AND MINIMIZE THE RISKS: A EUROPEAN POINT OF VIEW

H. Le Louet

*Head of Pharmacovigilance Federation at Paris University
Hospitals (APHP), Pharmacovigilance Risk Assessment
Committee Member (PRAC/EMA)*

In the seventies, use of thalidomide led to one of the most prominent disasters in the history of drug development. This catastrophe initiated a change of paradigm in the world with regard to drug safety. Quickly after, a global system called pharmacovigilance was implemented in different parts of the world. Pharmacovigilance concerns the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem (WHO 2002).

The pharmacovigilance system is mainly based on spontaneous reporting signal detection and methods for causality assessment. But the only use of spontaneous reporting may lead to extreme regulatory decisions with product withdrawal (today the DILI are one of the main cause of drug withdrawals), delay, or refusal of marketing.

There is no efficient or risky drug for the whole population. Therefore, the concept of global drug risk management with implementation of risk management plan appeared in the early 2000 and is mandatory for all new drugs in Europe since July 2012. The goal is to define an early (preapproval) and proactive approach in order to ensure that the benefit always outweigh the risks during all the lifecycle of the drug and to better target the drug in subpopulation with a high benefit risk balance.

Several approaches mainly from European Medicines Agency (EMA) and US Food and Drug Administration (FDA) have been developed in the frame of ICH recommendations. This presentation will focus on EMA plan.

JOINT EFFORTS FOR THE DEVELOPMENT AND QUALIFICATION OF BIOMARKERS IN DILI. WHERE DO WE STAND NOW?

M. Merz

Discovery and Investigative Safety, Novartis Institutes for BioMedical Research, Werk Klybeck, Bassell, Project Coordinator IMI SAFE-T

Timely detection and in-depth assessment of drug-induced liver injury (DILI), in particular of idiosyncratic forms, is still one of the big safety challenges for clinical drug development. What is needed urgently is a set of biomarkers of hepatic function more sensitive than bilirubin and of hepatocellular injury more specific than ALT and AST. As idiosyncratic DILI by nature is a rare, but serious event, large prospective studies across different patient populations and healthy volunteers are required for clinical qualification of new markers. The IMI SAFE-T (Safer And Faster Evidence-based Translation) consortium has undertaken this effort in close collaboration with Critical Path Institute's Predictive Safety Testing Consortium (PSTC). The talk will present an overview on SAFE-T's objectives and qualification program, discuss results of the program for a set of new DILI biomarkers, share lessons learned from collaborating in a large public-private partnership, and provide an outlook on planned future activities.

CLINICAL DILI NETWORKS AND CONSORTIA: WHAT LESSONS HAVE WE LEARNT?

R.J. Andrade

*Head, Department of Medicine and Gastroenterology Service,
Instituto de Investigación Biomédica de Málaga (IBIMA),
Hospital Universitario Virgen de la Victoria, Universidad de
Málaga, Málaga, Spain; and Centro de Investigación Biomédica
en Red de Enfermedades Hepáticas y Digestivas (CIBERehd),
Madrid, Spain*

Drug-induced liver injury (DILI) is a rare but potentially severe adverse event concerning mostly patients but also pharmaceutical industry, clinicians, and regulatory authorities. The necessity of concerted efforts to obtain reliable information on DILI causal agents, phenotypes, and risk factors has stimulated groups in USA and Europe to develop large DILI prospective registries. The Spanish DILI Registry (www.spanishdili.uma.es) and the Drug-Induced Liver Injury Network (<http://dilin.duke.edu>) are collaborative multicenter networks with large databases and biosample collections of prospectively recorded DILI cases in Spain and the US, respectively, and subsequently important resources for hepatotoxicity studies. The Spanish DILI Registry has recently initiated a new branch into South America, the Spanish-Latin American DILI Network (SLATINDILI; www.slatindili.uma.es), and into Europe, leading the EuroProDILI Registry fostered by the European Association for the Study of the Liver. In this presentation I will discuss on how DILI registries have expanded our knowledge on this fascinating yet challenging and complex disease.

THE DILI-SIM INITIATIVE. INTEGRATED SYSTEMS PHARMACOLOGY MODELING TO EXPLAIN AND PREDICT DRUG HEPATOTOXICITY

P. Watkins

The Hammer Institute, USA

Drugs-induced liver injury (DILI) can occur through a variety of adverse outcome pathways. Understanding and predicting the effects of multiple toxicity pathways as a function of time and exposure are difficult without systematic organization. Quantitative systems modeling can combine multiple drug effects to address this challenge. The DILIsim Initiative is a public-private partnership involving scientists from 14 major pharmaceutical companies and the FDA; it is now entering its fourth year. In addition to financial support, companies provide often unpublished data and perform in kind research to fill gaps in knowledge. The software produced by the initiative, DILIsym®, is a highly specified, mechanistic, hepatic model that utilizes extensive kinetic information among interrelated biological processes to explore the hepatotoxic underpinnings via simulations. Mechanisms currently included in the model are oxidative stress, mitochondrial dysfunction, bile acid transporter inhibition, and lipotoxicity. The Dilisym® software was originally developed to explain and predict interspecies differences in dose dependent hepatotoxicity to help inform first in man dosing. However, the modeling effort has expanded to improve interpretation of traditional and mechanistic serum biomarkers including miR122, CK18 and its caspase-cleaved fragment, and HMGB1. It is now possible to utilize DILIsym® to predict the range of percent hepatocyte loss through necrosis or apoptosis from measurements of these biomarkers in serial serum samples archived from clinical trials. By varying parameters within Dilisym®, it is possible to create simulated patient populations that mimic selected clinic populations in terms of susceptibility to DILI. This approach successfully recently predicted the latency and incidence of serum ALT elevations that were observed in the clinical trials of troglitazone (*ClinPharmacolTher.* 96(5):589–598, 2014). Systems modeling tools such as DILIsym® will increasingly be used to support decision making throughout the life cycle of new drug candidates.