in the context of understanding fundamental hepatology, translational applications, and the challenges associated with the clinical qualification of novel DILI biomarkers.

Disclosure of Interest: None declared.

IMMUNOLOGICAL ASPECTS OF DRUG HYPERSENSITIVITY—FROM MOLECULE TO MAN

K. Park*

Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom

Summary: Drug-induced liver injury (DILI) accounted for >50% of cases of acute liver failure and 15% of patients undergoing liver transplantation between 1990 and 2002. One of the biggest fears is unpredictable idiosyncratic drug-induced liver injury (IDILI), which is a major contributor to the failure of a drug to process through development and is a major cause of withdrawal and black box warnings. Due to the low concordance of the hepatotoxicity of drugs in animals and humans, a fundamental understanding of the mechanistic basis from novel human-relevant in vitro models and biomarkers is critical for the development of effective strategies to prevent and predict DILI.

Hepatocellular activation of drugs has been widely implicated in immune-mediated DILI with concomitant activation of the adaptive immune system. Consistent with this hypothesis, a number of HLA alleles that are associated with DILI have been identified. Studies with patient PBMC and PBMC from drug-naive donors carrying HLA risk alleles have shown that drugs form specific associations with HLA risk alleles generating T-cell antigens and hence provide the immunogenetic basis for the reaction. The identification of HLA alleles as predisposing factors for IDILI suggests that the adaptive immune system also participates in reactions targeting the liver. Furthermore, the release of damage-associated molecular pattern molecules (DAMPs), such as high mobility group box-1, may serve to activate cells of the innate immune system. Certain mediators produced by innate immune cells may cause liver injury, but other factors are actually important to promote tissue repair and regeneration. However, to fully define cause and effect (bioactivation vs liver failure), an integrated approach based on clinical studies, in vitro experiments, and animal models will be required, underpinned by appropriate bioanalysis. We have been able to characterize covalent protein adducts in man formed by reactive drug metabolites (nevirapine, diclofenac) using techniques developed for β-lactam antibiotics that associate with various types of drug hypersensitivity. We have also developed in vitro models to look at the interplay between, genetic, chemical, and immunologic factors using cells from both hypersensitive and drug-naive individuals. Such techniques and concepts should enable us to elucidate various mechanistic pathways and thus define both chemical and biological variables that underpin this rare but serious form of DILI.

Disclosure of Interest: None declared.

NOVEL CLINICAL TRIAL DESIGNS FOR ASSESSING THE EFFICACY OF DRUGS

M. Parmar*

MRC Clinical Trials Unit, London, United Kingdom

Summary: There is a pressing need for faster and more efficient evaluation of new cancer agents to improve outcomes. Although many of the new targeted agents have proved disappointing, there is large range of new agents from varying classes that need to be evaluated alongside a need to evaluate biomarkers to identify more responsive patient subgroups effectively. The current evidence on biomarkers that predict the response to a therapy in oncology has often arisen from post hoc retrospective analyses of Phase III trial data. More recent trials are exploring novel ways to identify potential biomarkers of response much earlier in the drug development process, albeit in a more exploratory fashion. We suggest a new approach to trial design, which links novel treatment evaluation with the concurrent evaluation of a biomarker within a confirmatory Phase II–III trial setting.

We describe such an approach used in a new protocol in advanced colorectal cancer called FOCUS4. The protocol will ultimately answer 3 research questions for a number of treatments and biomarkers: (1) After a period of standard first-line chemotherapy, do targeted novel therapies provide strong signal of activity in different biomarker-defined populations? (2) If so, do these definitively improve outcomes? (3) Is evidence of activity restricted only to the biomarker-defined groups?

Disclosure of Interest: None declared.

THE FUTURE OF MODELING AND SIMULATION APPROACHES IN DRUG DEVELOPMENT

M. Pfister*

Quantitative Solutions Inc, Bridgewater, New Jersey

Summary: High development cost, low development success, cost-disciplined health care policies, and intense competition demand an efficient drug development process. New compounds need to bring value to patients by being safe, efficacious, and cost-effective compared with existing treatment options.

The goal of pharmacometrics/quantitative clinical pharmacology (also called Modeling and Simulation) is to optimize therapies for adult and pediatric patients through integration, innovation, and impact.[1]

- Quantitatively integrate multisource data and clinical, biological, statistical, and mathematical concepts
- Collaborate and innovate across disciplines, enhancing scientific understanding and knowledge
- Impact and enhance key decisions in drug research and development

Pharmacometric approaches, including model-based meta-analyses, allow for integration and utilization of biomarker, efficacy, and safety data and:

- Provide a quantitative framework for comparative efficacy/safety assessments of drugs
- Create opportunities to test assumptions through "virtual" experiments and optimized clinical trials
- Facilitate research and development of new therapies for adults and pediatrics

A sustained collaborative effort between academia, biotech/pharma, hospitals and scientific societies involved in research, development, and use of medicines is required to bring pharmacometrics/quantitative clinical pharmacology to its full potential.

Reference

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PHARMACOLOGY OF CHOCOLATE

C. Pichard*

Clinical Nutrition Geneva University Hospital, Geneva, Switzerland

Summary: Rationale: Chocolate is a popular food. Its consumption is largely associated with pleasure. Beliefs on its positive impact on health, physical, and mental strengths have been well established for