a novel solution for causality assessment in idiosyncratic drug-induced liver injury

5th Munich Biomarker Conference

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Munich 2015-12-01
Drug-induced liver injury (DILI)

DILI is the major cause for acute liver failure leading to death or requiring liver transplantation\(^1,2\)

DILI is a frequent cause for regulatory actions on drugs and project terminations\(^3\)

Ref.:
3) Stevens JL and Baker TK, 2009 Drug Discovery Today; Volume 14, Numbers 3/4 February
DILI: Mechanisms

Idiosyncratic Toxicity (Patient)
„iDILI“

Intrinsic Toxicity (drug)

- CCL₄
- Paracetamol (APAP)
- Diclofenac
- Phenytoin
- Flucloxacillin

Dose-dependent
Short latency (days)
Predictable by animal / in vitro testing

Affects only susceptibles (1 in 10,000)
Long latency (weeks to months)
No clear dose-relationship
No animal / in vitro model
Idiosyncratic Drug-induced Liver Injury (iDILI) is a challenge

- **for Patients**
  - Liver Failure leading to Death or requiring Transplantation
  - Non-Approval of innovative Drugs

- **for Drug Developers**
  - Failure in Late Stage Development or Postmarketing
  - Investment Losses

- **for Regulators**
  - Risk of incorrect non-approval
  - Risk for patients

Current main problem:
DILI is still a diagnosis of exclusion
MetaHeps®: First *in vitro* Test to Diagnose or Exclude iDILI in Individual Patients
The generation of hepatocyte-like cells for individual drug response

**Peripheral Monocytes**
- Derived from a small blood sample
- Standardized protocol
- Proprietary culture conditions
- Serum-free culture
- No genetic modifications

**MetaHeps®**
- Metabolism (CYP450, UGT)
- Synthesis (Urea, Factor VII)
- Toxicity (metabolism-dependent / -independent)
- Donor specific characteristics

10 days
Proprietary Generation Process

United States Patent no. 8,858,934, issued October 2014
European Patent 11 743 234.4 issued June 2015
Pilot study in patients with acute liver injury

**Study aim:**
- Investigation of potential individual toxicity response of MetaHeps® from iDILI patients in comparison to MetaHeps® from patients with acute liver injury of other origin.

**Methods:**
- Patients treated with at least one drug and acute liver injury according to (1):
  - $\text{ALT} \geq 5\times \text{ULN}$ or $\text{AP} \geq 2\times \text{ULN}$ or $\text{ALT} \geq 3\times \text{ULN}$ and $\text{Bili} \geq 2\times \text{ULN}$
- Diagnostic Workup: laboratory testing, imaging, histology (where available), RUCAM*, drug signature (e.g. LiverTox website (2))
- MetaHeps® generation, toxicity testing, data analysis

ClinicalTrials.gov Identifier: NCT02353455

Ref.:

*RUCAM: Roussell Uclaf Causality Assessment Method
Identification of causative DRUG by MetaHeps®

MetaHeps® Testing with the causative drug is positive in 29 of 31 iDILI patients. The test yields no false positive results in 23 patients with other liver diseases (non DILI).

Testing comedications in iDILI patients with MetaHeps®, only 4 of 84 comedications show positive results.

Ref.:
1) Benesic A, Leitl A, Gerbes AL; Gut 2015
2) Benesic A and Gerbes AL; XV FDA DILI Conference 2015
Results: all drugs in total population
Test results compared to causality likelihood

- RUCAM yields a relevant proportion of false results for drugs with intermediate causality likelihood
- MetaHeps® testing shows stable results independent on causality likelihood

Ref:
1) Benesic A, Leitl A, Gerbes AL; Gut 2015
2) Benesic A and Gerbes AL; XV FDA DILI Conference 2015
Specificity of MetaHeps® testing example: diclofenac

- MetaHeps® testing positive in 4 diclofenac iDILI cases

- MetaHeps® test negative in healthy donors, iDILI patients with another drug as cause and non DILI patients, respectively

Ref.:
1) Benesic A, Leitl A, Gerbes AL; Gut 2015
2) Benesic A and Gerbes AL; XV FDA DILI Conference 2015
Summary

- Our data suggest that monocytes can acquire some hepatocyte properties reflecting donor specific characteristics.
- In our pilot study MetaHeps® testing showed high accuracy in identification of iDILI patients and causative drugs, respectively.
- MetaHeps® testing can help to clarify cases of iDILI suspicion.

Outlook

- Ongoing research further characterises the model using Omics-technologies.
- Enlargement of dataset from independent cohorts.
- Further analyses from MetaHeps® and patient samples to identify novel biomarkers.