Merrie Mosedale, Ph.D.
Research Investigator, Hamner-UNC Institute for Drug Safety Sciences
The Hamner Institutes for Health Sciences
Research Triangle Park, NC

Click to view Biosketch and Presentation Abstract or page down to review presentation
Personalized DILI Risk Management – The Tolvaptan Initiative

March 19, 2015

Merrie Mosedale, Ph.D.
Hamner-UNC Institute for Drug Safety Sciences
Liver Injury Was Associated with Tolvaptan During Clinical Trials

- $V_2$ receptor antagonist approved for the treatment of hyponatremia
- Promising candidate for the treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD)
- Liver injury observed during clinical trials
  - ~4% develop ALT >3x ULN
  - 3 Hy’s Law cases
- FDA approval not yet received

Time course of liver response for a tolvaptan-treated subject
- Profile suggests final critical event is adaptive immune attack
• Demonstrated HLA risk allele associations (eg. flucloxacillin and lapatinib) have not been clinically useful in risk management
• Unaccounted for susceptibility is at the level of the liver
• Non-HLA risk alleles for DILI have also not been clinically useful
• Likely genetic and non-genetic biomarkers will be required for personalized medicine strategy
Samples with Consent Available from Tolvaptan Clinical Trials

- Genomic DNA
- Plasma and urine
  - Baseline
  - 3 weeks
  - Annually for up to 3 years on drug treatment
- DILI causality assessment by 5 hepatologists

Example of samples from “case”

Opportunity for IDSS to collaborate with Otsuka and other partners to identify a personalized medicine strategy
Objectives

1) Manage the risk of DILI in tolvaptan-treated patients through the identification of genetic and non-genetic risk factors for tolvaptan-induced liver injury

2) Provide a mechanistic understanding of the tolvaptan toxicity in order to further direct discovery efforts and to provide biological plausibility for empirically derived biomarkers
Integrative Approaches Used to Identify Personalized Medicine Strategy

Patients

In Vitro

Cutting Edge Pre-clinical Models

In Silico Modeling

In Silico Modeling
The Collaborative Cross Mouse Population Is a New Genetic Resource for DILI Research

- Success using previous models for translational toxicogenomics
- Rationally designed breeding scheme makes the Collaborative Cross (CC) superior
  - Increased genetic variation
  - Large population
  - Genetically characterized
  - More sensitive to stressors
  - Infinitely reproducible
- Available only through UNC

Evaluating the liver response to tolvaptan in the CC may help to identify sensitive strains → mechanism and risk factors
• Initial events may not involve death of hepatocytes
  – Results in the release of signaling molecules (i.e. exosomes)
• Liver gene expression profiling after an acute high dose exposure can be used to identify early events in the absence of overt toxicity
  – Can also inform mechanism and identify relevant biomarkers
• Combining mouse population models and toxicogenomics can be a very powerful tool to study mechanisms and identify risk factors
45 CC Strains Treated Using Paired Study Design and Single Dose Regimen

- 8 Male mice/strain, $N=4$ per treatment

- One dose of vehicle (HPMC) or tolvaptan (100 mg/kg) i.g.
  - HED and AUC for 100 mg/kg dose in mouse is only 2-5 times the dose and AUC in clinical studies

- Endpoints:
  - Drug concentration
  - Plasma clinical chemistry
  - miR-122
  - Histopathology
  - Gene expression profiling in liver
  - QTL Mapping
Three Strains Have Significant ALT Elevations in Response to Tolvaptan

- Single dose of tolvaptan was well tolerated across all strains

Mean+SEM

\[ p=0.0045 \text{ for treatment, Two-way ANOVA} \]

\[ *p<0.05, **p<0.001 \text{ between tolvaptan and vehicle-treated animals, Bonferroni Post Test} \]
Global Gene Expression Profiling in the Liver Suggests Potential Mechanisms

1) Mitochondrial dysfunction

2) Altered bile acid homeostasis

3) Loss of immune tolerance

May be a biomarker in serum
QTL Mapping with ALT Fold Change Identifies Significant Genetic Associations

- Focus on chromosome 14
- Narrowed down genes in QTL interval to 6 high priority candidates
  - Includes genes with biological relevance: apoptosis and innate immune response
Conclusions

- Tolvaptan-induced liver response was observed in 3 CC strains
  - Animal models for additional mechanistic experiments
- Toxicogenomics work identified treatment-induced adverse outcome pathways across all strains and specific to sensitive strains
- QTL mapping identified genetic associations with susceptibility
- All discovered with single dose comparable to human exposure

Candidate genetic and non genetic biomarkers have been identified
- Will guide hypothesis-based approach to biomarker discovery in samples collected from clinical studies
Data from CC Study Are Integrated with Findings from Other Efforts

- Transitioning from explaining problems to solving them
- All studies and analyses can be completed in a little as 6 months
Many Collaborators Involved in Tolvaptan Research Initiative

The Hamner-UNC Institute for Drug Safety Sciences
Director: Paul Watkins

Project Leaders
Biomarkers: Rachel Church
Cellular Imaging: Joe Trask
DILIsym: Lisl Shoda
Human Genetics: Tom Urban
Mouse Models: Merrie Mosedale
NMR Metabolomics: Jeff Macdonald
Hepatocyte Models: Ed LeCluyse

Collaborative Cross Study
Robert Corty Will Valdar
Scott Eaddy Tim Wiltshire
Darla Miller Yuying Xie
Fernando Pardo Manuel de Villena

Otsuka
Bill Brock
Sharin Roth

UNC
Kim Brouwer

Qualyst
Ken Brouwer

University of Florida
David Ostrov

University of Liverpool
Dan Antoine
Dean Naisbitt
Kevin Park
Munir Pirmohamed
THANK YOU!

QUESTIONS?