DILIsym™, a Mechanistic Model of Drug-Induced Liver Injury, Supports the Interpretation of Elevated Liver Transaminase Levels in a Healthy Volunteer Pooled Safety Population for an Orphan Drug Designed for a Life-Threatening Situation

Brett A. Howell, Lisl K.M. Shoda, Jeffrey L. Woodhead, Yuching Yang, Scott Q. Siler, Paul B. Watkins

The Hamner - UNC Institute for Drug Safety Sciences, The Hamner Institutes for Health Sciences, Research Triangle Park, NC 27709

Abstract

Background: Compound A is in development for a life-threatening situation. The "Animal Rule" applies to efficacy, but not to safety assessment, which must be determined in humans. In a pooled safety population involving 150 healthy adult volunteers (NHV), marked elevations of serum liver enzymes were observed in some subjects, suggesting possible liver injury.

Methods: The ALT sub-model within the larger DILIsym™ model was utilized. Key parameters were adjusted to generate simulation results consistent with the data obtained in the human volunteers treated with Compound A.

Results: The predicted percentage of functional hepatocytes lost for the maximum observed ALT level was 3.5%, with a predicted range of 2.5% to 4.5% when simulated human variability, or SimPops™, was included.

Conclusions: The simulations and associated analyses suggest that no subject in the clinical trial likely experienced more than a modest loss of hepatocytes, and that the levels lost were much lower than levels reportedly leading to serious health risks in other scenarios.

Introduction

The DILIsym™ Model

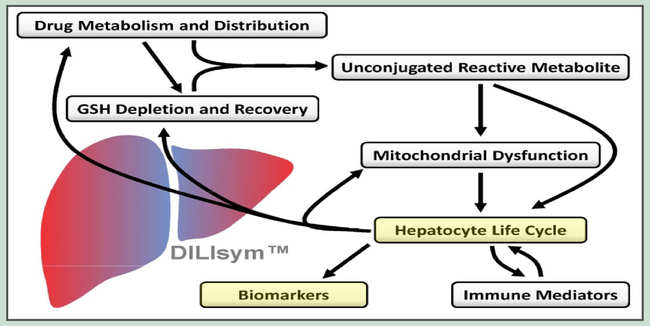
- DILIsym™ is a mechanistic, multi-scale, mathematical model being developed through the DILI-sim Initiative to assist in the safety characterization of compounds in development
- The initial focus is on in vitro to in vivo preclinical and in vivo preclinical to first in human clinical translation [1-3]
- Simulated humans, dogs, rats, and mice are included, with differences in biochemical variability amongst populations captured in SimPops™
- The primary goals for the model include understanding how in vitro toxicity assay results translate to pre-clinical animal models, the relevance of pre-clinical results for humans, and how biomarker results translate to patient safety

Compound A Project

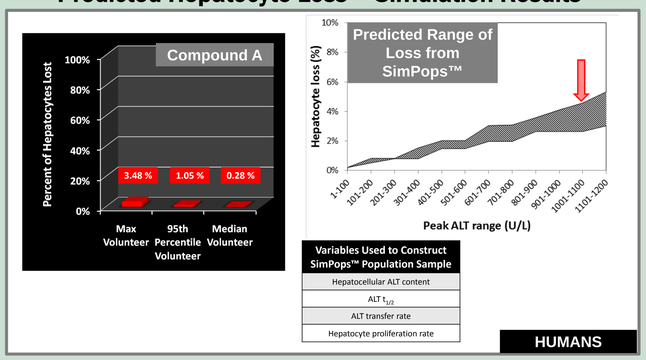
- Safety assessment for Compound A in 150 healthy adult volunteers (NHV) revealed marked elevations of serum aminotransferases
- The DILIsym™ model was employed to help interpret the severity of the injury observed in the healthy volunteer population
- The analysis was purely retrospective, with the goal of providing some insight into the level of potential hepatocyte loss experienced by the subjects
- Predictions of future liver outcomes with Compound A were outside the scope of the project

DILIsym™ ALT Model Design, Healthy Volunteer Data, and Simulation Results

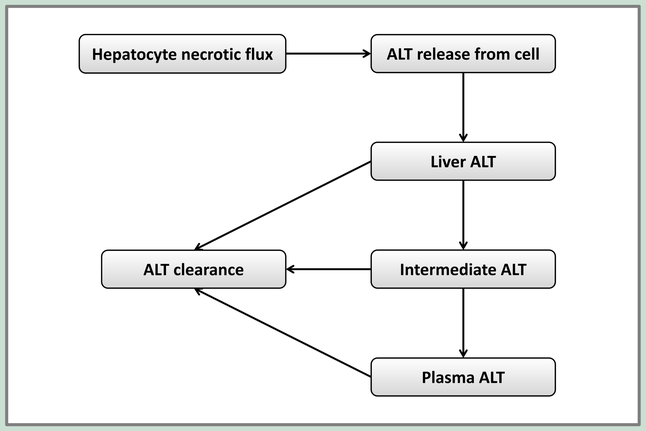
DILIsym™ - Hepatocyte Connection to ALT



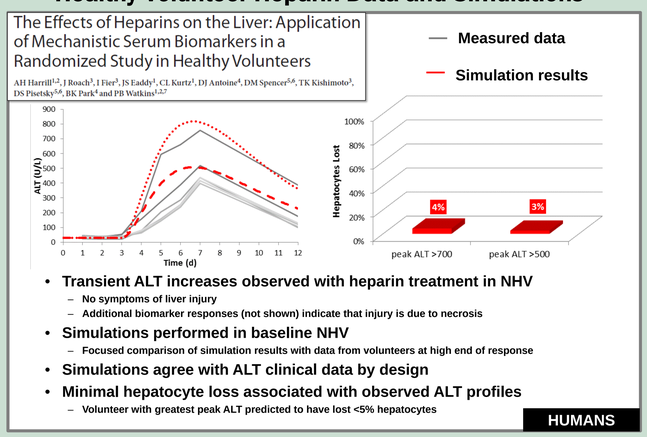
Predicted Hepatocyte Loss – Simulation Results



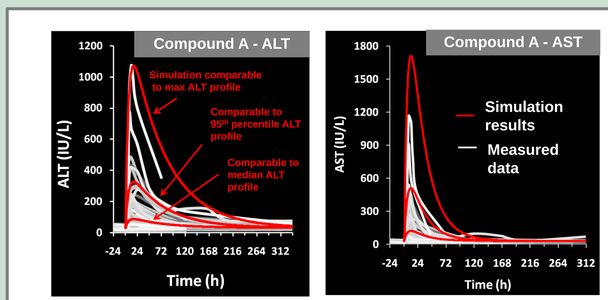
DILIsym™ ALT Sub-model



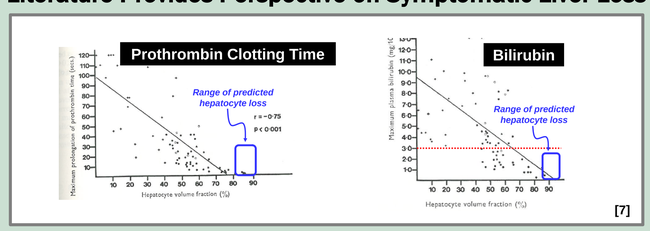
Healthy Volunteer Heparin Data and Simulations



Healthy Volunteer ALT/AST Data and Simulations



Literature Provides Perspective on Symptomatic Liver Loss



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Methods

- Simulation results were compared with clinical data collected from NHV participating in a clinical trial for Compound A
- ALT/AST levels were used in conjunction with the DILIsym™ model to infer the associated hepatocyte loss and time required for regeneration of the liver (to 99% of initial values)
- Analyses of the Compound A clinical data revealed a time to peak ALT (Tmax) that was substantially more rapid than observed with other single dose drug-induced liver injury [4]
- The ALT and AST sub-models within the DILIsym™ model were adjusted to generate simulated Tmax comparable to those observed (8-24 h) after a single dose of Compound A by modifying the transfer rate of ALT from liver to the circulation
- A simulated sample population (SimPops™) was generated following general procedures described previously [1,2] to compare with the clinical data by varying the following parameters:
  - Half-life of circulating ALT [5]
  - Hepatocellular ALT content [6]
  - Rate of transfer of ALT from liver to blood [7]
  - Hepatocellular proliferation rate [7]

Key Findings

- The predicted percentages of functional hepatocytes lost for the maximum, 95th percentile, and median observed ALT levels were around 3.5% (2.5%-4.5%), 1%, and 0.3% of viable hepatocytes
- Virtually all hepatocyte loss was predicted to occur within the first 24 h following dosing, with a median hepatocyte replenishment time of three weeks (to 99% of original hepatocyte levels)
- The predicted levels of hepatocyte loss were lower than levels reportedly leading to serious health risks in other scenarios, based on:
  - A similar level of hepatocyte loss predicted from clinical heparin data in NHV [8]; heparins have not induced clinically important liver injury in many years of use [9]
  - Loss of ~10% of hepatocytes to an injury event is tolerated without an increase in bilirubin or prothrombin time [7]
  - Loss of 20% of liver volume in living donors undergoing excision of the left lateral segment of the liver is generally considered safe [10]

Acknowledgements

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