Hy's Law & Drug-Induced Liver Injury (DILI) - Part I

Dr. Sumit Verma MD, DNB - Director and President, Operations Management, CSPV

Drug-Induced Liver Injury Occurrence

- Most frequent cause of acute liver failure in North America and Europe.
- No definite causative agent has been attributed in several cases. Underlying mechanisms are still unclear and hence is difficult to predict during drug development.
- May mimic almost any known type of liver disease.
- Rare yet potentially life-threatening.
- Key reason for drugs to fail to achieve marketing authorization, frequent cause for post-authorization restrictions and product withdrawals.

- Monitoring of standard serum liver tests to detect milder liver injury is the main approach to anticipate a possible DILI risk in Clinical Trials.
- Evaluation of each potential DILI case in clinical trials requires a systematic collection of adequate diagnostic datasets and a rigorous assessment for causality, performed by clinical experts in this area.
- The evaluation of DILI is critical because most drugs that cause severe DILI do so infrequently and usual drug development databases with up to a few thousand subjects exposed to a new drug will not reveal any cases.
- Such databases, on the other hand, may show evidence or signals of a drug's potential for severe DILI, if clinical and laboratory data are properly assessed for evidence of lesser injury, that may not be severe but could predict the ability to cause more severe injuries.

Hy's Law cases have the following three components:

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo.
- Among trial subjects showing such AT elevations, often with ATs much greater than 3 x ULN, one or more also show elevation of serum TBL to >2 x ULN, without initial findings of cholestasis (elevated serum ALP).
- No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

This observation formed a basis for the development of the e-DISH plot by the U.S. FDA.

- Translation of Zimmerman's observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury.
- Recognition of the importance of altered liver function, in addition to liver injury, began with Zimmerman's observation that drug-induced hepatocellular injury (i.e., aminotransferase elevation) accompanied by jaundice had a poor prognosis, with a 10 to 50 percent mortality from acute liver failure (in pre-transplantation days).
- Finding one Hy's Law case in the clinical trial database is worrisome; finding two is considered highly predictive that the drug has the potential to cause severe DILI when given to a larger population.
- USFDA has been using Hy's law rigorously to screen out potentially hepatotoxic drugs for almost 20 years, and "since 1997 did not have to withdraw a single drug approved after 1997 because of post-marketing hepatotoxicity".*

*

1.EASL Clinical Practice Guidelines: Drug-induced liver injury. J Hepatol (2019), https://doi.org/10.1016/j.jhep.2019.02.014
2.EVOLUTION OF THE FOOD AND DRUG ADMINISTRATION APPROACH TO LIVER SAFETY ASSESSMENT FOR NEW DRUGS: CURRENT STATUS AND CHALLENGES. JOHN R. SENIOR. DRUG SAF (2014) 37 (SUPPL 1):S9–S17

Any potential Hy's Law case should be:

- Handled as a serious unexpected adverse event associated with the use of the drug.
- Reported to the FDA/Regulators promptly (i.e., even before all other possible causes of liver injury have been excluded).
- Reporting should include all available information, especially that needed for evaluating the severity and likelihood that the drug caused the reaction, and,
- Should initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

Time Lag:

- Combined elevation of ALT or AST and TBL may not be concurrent elevation.
- Typically, ALT or AST elevation are followed by bilirubin elevation (delay of up to 4 weeks).

Time course of elevations - ALP elevations:

- "Pure" hepatocellular injury initially may show secondary ALP elevations due to intrahepatic cholestasis.
- Hence, cases with increased ALT or AST and TBL, associated with increased ALP, cannot automatically be discarded as not matching Hy's law criteria.
- Additionally, ALP values >2 x ULN were not found to decrease the risk of ALF in patients fulfilling Hy's law in the Spanish DILI registry.

R Ratio and ALP:

- Both ALP activity and the R ratio should be considered in the exclusion of cholestatic or mixed type injury.

Direct vs Indirect Bilirubin:

- Hepatocellular dysfunction is indicated by increased direct, i.e. conjugated bilirubin only.
- Conditions such as hemolysis, or drug-related enzyme inhibition may lead to increase in indirect, i.e., unconjugated bilirubin.
- Hence, fractionated bilirubin should be assessed since cases with predominantly unconjugated mild hyperbilirubinemia would not qualify as potential Hy's law cases.

Conclusion:

1. DILI is a key concern for regulators, drug developers, and physicians, and is difficult to predict during drug development process.
2. As severe DILI is generally rare, finding a single case may require treatment of thousands of people from varied patient populations.
3. The clinical trials present an exclusive opportunity to detect hepatotoxicity and cases of potential DILI with a study drug prior to its use in general population.

4. Monitoring the liver test abnormalities is useful for assessing trends over time and to analyze imbalance between study drug and placebo/comparator groups.
5. Due to the limited number of subjects in a clinical trial, monitoring the standard serum liver tests to detect milder liver injury can be considered a predominant approach to \ predict the risk of possible DILI in clinical trials.
6. Considering that there may be varied mechanisms of DILI and different clinicopathological phenotypes, a systematic collection of adequate diagnostic datasets along with a focused causality assessment performed by clinical experts is required fo evaluation of each potential case of DILI in clinical trials.

Selected References

1. EASL Clinical Practice Guidelines: Drug-induced liver injury. J Hepatol (2019), https://doi.org/10.1016/j.jhep.2019.02.014
2. Evolution of the Food and Drug Administration Approach to Liver Safety Assessment for New Drugs: Current Status and Challenges. John R. Senior. Drug Saf (2014) 37 (Suppl 1):S9–S17
3. Drug-induced liver injury (DILI): Current status and future directions for drug development and the post-market setting. A consensus by a CIOMS Working Group. Geneva, Switzerland: CIOMS, 2020
4. Guidance for Industry Drug Induced Liver Injury: Premarketing Clinical Evaluation. U S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER). July 2009. Drug Safety
5. EASL Clinical Practice Guidelines: Drug-induced liver injury. Journal of Hepatology 2019, Vol. 70, Issue 6, P1222–1261.
6. Evolution of the Food and Drug Administration Approach to Liver Safety Assessment for New Drugs: Current Status and Challenges. Drug Saf (2014) 37 (Suppl 1):S9–S17
7. Guidance for Industry (Draft). Sponsor Responsibilities - Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies. FDA June 2021.

Author

Dr. Sumit Verma

Director and President,
Operations Management, CSPV
Soterius, Inc.

Dr. Sumit Verma is a medical graduate with specialization in anesthesiology and has more than 15 years of experience in the pharmaceutical industry, clinical medicine, clinical research, and pharmacovigilance. He has built teams that have consistently delivered and exceeded customer expectations across pharmacovigilance domains such as case processing, signal management, risk management, aggregate reports, and clinical safety. He has co-authored two books – one on pharmacovigilance and another on pharmacology.

Our Services

Soterius offers full suite of Pharmacovigilance, Medical Affairs and Regulatory services.

- Clinical Safety Services
  - Case Processing, DSUR Authoring, Medical Monitoring, Medical Reviews, CSR Narratives Authoring, etc
- Post-marketed Pharmacovigilance Services
  - Case Processing, Aggregate Report Authoring, Risk Management Plan (RMP) & Risk Minimization, Global and Local Literature, etc
- Medical Affairs and Medical Writing
- Innovation & Technology Solutions in Pharmacovigilance and Medical Affairs

Like This Blog?

Share on LinkedIn

Share on Facebook

Share on Twitter/X

Share on Email

Disclaimer

The scenario described in this post is entirely hypothetical. It is not based on real-world patient data or individual case safety reports. All pharmacological mechanisms and regulatory references are cited to support discussion only. This post is intended to facilitate dialogue on signal detection and does not imply new safety findings, labeling recommendations, clinical guidance or clinical relevance.

Any content presented herewith should only be considered for general informational purposes and should not be considered as specific to the requirements of any particular organisation or for any specific purpose. Soterius, including its authors, presenters, and any affiliated individuals, does not make any representations or warranties about the completeness, reliability, appropriateness, relevance, or accuracy of the content presented here.

Please consult your physician/Health Care Provider for any matters related to health. No one should act on this information without specific professional advise.

connect@soterius.com

www.soterius.com