

John M. Vierling MD, FACP, FAASLD
Chief, Hepatology
Baylor College of Medicine
vierling@bcm.edu



Biosketch

Dr. Vierling is a tenured Professor of Medicine and Surgery and Chief of Hepatology at the Baylor College of Medicine in Houston, Texas. He is also Director of Advanced Liver Therapies, a clinical research center devoted to the study of liver diseases and Program Director of the Transplant Hepatology Fellowship. He obtained his undergraduate degree in Biology with great distinction and departmental honors from Stanford University and his medical degree from Stanford University School of Medicine. He is ABIM certified in internal medicine, gastroenterology and transplant hepatology. His clinical interests include viral hepatitis, autoimmune liver diseases, liver transplantation, metabolic/genetic diseases and drug-induced liver injury. Basic science and translational research interests span immunologic mechanisms of hepatobiliary injury, viral hepatitis, auto- and allo-immune diseases, liver transplantation, drug-induced liver injury and acute liver failure. He has authored over 250 manuscripts, reviews and chapters on these subjects. His honors include Phi Beta Kappa, Alpha Omega Alpha, Best Doctors in America, Top 1% physician rating by U.S. News and World Report, Who's Who in America, Who's Who in Science and Engineering and Who's Who in Healthcare. He is a former President of the American Association for the Study of Liver Diseases, past Secretary-Treasurer of Digestive Disease Week® and past Chairman of the National Board of Directors of the American Liver Foundation.

Abstract: Can Study Protocols Protect Patients with Liver Disease from Serious DILI?

Background: Identification of investigational drugs or biologics with the potential to cause serious, life-threatening DILI requires integrative assessment of causality using pre- and post-marketing data and comprehensive testing for alternative etiologies in each suspected case¹. Since idiosyncratic DILI is rare, prediction of the risk of serious DILI in the post-marketing population relies on identification of cases of interest that meet Hy's Law criteria during phase II-III trials². Patients with pre-existing liver diseases (PLD) represent a challenging population³. The probability of enrolling adults with chronic PDL in randomized, controlled trials of drugs is increasing, especially for drugs targeting components of the metabolic syndrome associated with NAFLD and antimicrobials. Moreover, the number of clinical therapeutic trials targeting chronic PLDs and their complications also are increasing rapidly.

Risk and Outcomes of DILI with PLD: PLD does not inherently increase the risk of serious DILI, although some exceptions exist for specific drugs². The primary concern about PLD is the risk of reduced hepatic functional reserve that might worsen the severity of DILI, prevent recovery and lead to death^{2,3}. Indeed, the positive predictive value of Hy's Law is 16% for liver-related death and/or transplantation in subjects with DILI and chronic PLD³. Concern about decreased functional reserve is particularly germane for cirrhotics because of their substantial risks for acute on chronic liver failure or progressive decompensation.

Risk Reduction and Profiling of Subjects with PLD: Since drug dose and high hepatic metabolism are correlated with DILI severity⁴, correct dosing for hepatic impairment is essential. Expansion of PK/PD studies in stable cirrhotics with active inflammation and different etiologies (hepatitic vs. cholestatic) could increase the safety of drug dosing in patients with PLD. Ranges of acceptable ALT/AST, total/direct bilirubin (T/DBR), ALP, albumin and PT INR for subjects with PLD that exceed the normal limits should be defined in inclusion and exclusion criteria. Cirrhotics should be classified at baseline using MELD, Child-Turcotte-Pugh (CTP) and clinical severity scores as surrogates for hepatic reserve. The hepatic venous pressure gradient (HVPG) can accurately assess the risk of decompensation; however, its availability is limited. , making development of biomarkers of HVPG a priority. Baseline testing for hepatic functional reserve and disease severity of

PLD (e.g. HEPATIQ™, 13CO2 methacetin breath test, HepQuant™) should be performed. Candidate DILI biomarkers should also be tested. Ongoing studies of genomics, pharmacogenomics, proteomics, and polymorphic alleles of HLA, BSEP, UGT1A1 and OATP should be extended to include subjects with PLD.

Special Considerations for Study Protocols Enrolling Subjects with PLD: All clinical trials should explicitly screen subjects for PLD, determine its etiology and define the presence or absence of advanced fibrosis and cirrhosis³. In cirrhotics, imaging surveillance for hepatocellular carcinoma must be up to date. Hepatic impairment dosing should be used in cirrhotics. Allelic testing for UGT1A1 and OATP can aid in interpretation of indirect and direct hyperbilirubinemia, respectively. All protocols should mandate frequent testing for ALT/AST, T/DBR, ALP, albumin, and PT INR. Elevations from baseline should be scrutinized, and ALT and TBR should be plotted using eDISH, including the kinetics of elevations. Predetermined stopping rules for liver test abnormalities should be defined. For Hy's Law cases, alternative etiologies should be investigated, concurrently with expert adjudication of the probability of DILI. Spontaneous fluctuations in ALT, T/DB, PT INR and creatinine in cirrhosis may confound assessment of DILI⁵. While benign fluctuations of MELD scores frequently occur in cirrhotics, worsening CTP or clinical severity scores are always ominous. Cholestatic abnormalities should be assessed using Hy's Law modification, after confirming the hepatobiliary origin of ALP and excluding biliary obstruction. Hepatic function tests should be repeated whenever DILI is suspected to assess the impact of putative DILI on functional reserve.

Conclusions: Subjects with PLD, including compensated and decompensated cirrhotics, will be enrolled in ever increasing numbers in clinical therapeutic trials for both general medical conditions and liver diseases. Improved study protocols for subjects with PLDs are needed to define the specific risk of DILI in this population and to mitigate its serious consequences.