

Robert J. Fontana, MD
Professor of Internal Medicine
Medical Director of Liver Transplantation
University of Michigan, Ann Arbor, M
rfontana@med.umich.edu



Biosketch

Dr. Fontana is a translational investigator with research interests in drug induced liver injury and acute liver failure. Dr. Fontana completed his gastroenterology/ hepatology training at the University of Michigan and has been on the faculty since 1995. He is currently a Professor of Medicine and Medical Director of Liver Transplantation. He is a principal investigator at one of the 6 Drug Induced Liver Injury Network (DILIN) clinical sites and also serves as Co-chair of the DILIN Steering committee. He has helped lead efforts to carefully phenotype patients with DILI as well as determine the likelihood of early adverse outcomes and chronicity with prolonged follow-up in the DILIN prospective study. Dr. Fontana is also the current Chair of the AASLD Hepatotoxicity Special Interest Group. He has also been an active member of the US Acute Liver Failure Study Group as a site principal investigator and lead investigator on the long-term outcomes protocol since 1998.

Abstract: Recognition and Management of DILI in Patients with NASH

As the number of drugs being tested for patients with NAFLD/ NASH increases, the importance of having robust and clinically meaningful endpoints (i.e. ALT, histology, HVPG, non-invasive assessment of steatosis) is of growing interest. Similarly, the importance of monitoring for potential worsening of underlying NASH and untoward drug-induced hepatotoxicity with the myriad of clinical phenotypes it can lead to is apparent. Fortunately, most NAFLD/ NASH patients in clinical trials should have an available pre-treatment liver biopsy for review in the event of an hepatic adverse event. Furthermore, placebo-controlled studies can be designed with frequent monitoring of hepatic function using various modalities and with predetermined stopping rules. However, this circumstance further emphasizes the growing need to develop sensitive and specific diagnostic biomarkers for idiosyncratic DILI.

The natural history of untreated NASH is characterized by fluctuating serum aminotransferase levels as well as variable rates of fibrosis progression in individual patients (1). Hepatic steatosis increases the risk of idiosyncratic DILI in various animal models presumably due to enhanced oxidative stress or altered CYP/ transporter expression resulting in aberrant drug pharmacokinetics and/or pharmacodynamics but confirmatory human data is lacking. Although more common competing causes of acute and chronic liver injury must first be excluded via serological testing (Hep A, B, C, E, ANA, SmAb), structural imaging (Ultrasound, CT/MRI), and history (alcohol, ischemia), new onset or worsening laboratory abnormalities in NASH patients with suspected DILI could be due to an exacerbation of the underlying liver disease. As a result, many experts have suggested a higher laboratory threshold for DILI in patients with known chronic liver disease (i.e. a serum AST/ ALT > 3 X the pretreatment baseline or an absolute value > 5 X ULN or 300 IU/ml, a serum alk phos > 2 x baseline or 3X ULN, or total bilirubin > 2.5) but a consensus on these criteria is not established (2).

Nearly 50% of patients with suspected DILI undergo a liver biopsy to help exclude more common causes of liver injury and also to confirm the presence of histological features suggestive of DILI (e.g. granulomas, necrosis, mixed injury patterns) (3). However, the diagnostic and prognostic value of liver biopsy in patients with suspected DILI and underlying NASH or viral hepatitis remains uncertain. Furthermore, several drugs can lead to a clinical phenotype of hepatic steatosis as their manifestation of DILI (4). For example, amiodarone can cause progressive steatohepatitis and tamoxifen can lead to reversible hepatic steatosis/ NASH in 5% to 10% of patients receiving prolonged treatment (5,6).

Furthermore, some patients with valproate hepatotoxicity may present with microvesicular steatosis +/- lactic acidosis due to presumed impairment of mitochondrial B-oxidation while some patients on longstanding antiretroviral therapy may also develop progressive NASH over time(7). The issue of DILI diagnosis is further complicated by the observation that some patients with baseline hepatic steatosis/ NASH are at increased risk of developing DILI with progressive fibrosis from specific agents such as methotrexate (8). In addition, several studies have demonstrated that diabetic patients who have a high prevalence of underlying NAFLD (50 -60%) are over-represented in DILI registries and may be at increased risk for fatal outcomes (9).

The management of suspected DILI in NASH patients is to immediately discontinue the suspect agent and carefully monitor the patient for worsening hepatic function. Corticosteroids are frequently used in DILI patients with severe hypersensitivity features but there are no data demonstrating their efficacy or safety in patients with NASH. A recent analysis from the DILIN Prospective registry study demonstrated that the 89 subjects with pre-existing HCV, NAFLD/ NASH were at increased risk of adverse hepatic outcomes and liver related death presumably due to impaired hepatic regeneration and reserve compared to the patients without pre-existing liver disease (16% vs 5.2%) (10). Further studies of laboratory parameters, liver histology, non-invasive estimates of fibrosis and steatosis severity, and metabolic parameters are clearly warranted for patients with underlying liver disease receiving investigational agents.