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Biosketch

Michael W. Fried, MD is Professor of Medicine and Director of Hepatology at the University of North Carolina (UNC) at Chapel Hill. Dr. Fried completed his internship and residency in internal medicine at the State University of New York (SUNY) Health Science Center at Syracuse, where he also completed a fellowship in gastroenterology.

From 1990 to 1993, while serving as Medical Staff Fellow in the Liver Diseases Section at the National Institutes of Health (NIH) in Bethesda, Maryland, Dr. Fried performed clinical and laboratory studies of viral hepatitis. During his tenure at UNC, he has been the principal investigator on numerous clinical trials of antiviral agents for hepatitis B and hepatitis C. Dr. Fried has been awarded continuous NIH extramural funding for over 15 years as principal investigator on NIH cooperative clinical trials and he currently serves as the co-chair of the Hepatitis B Research Network (NIDDK). He was also the recipient of an NIH career development award, which allowed him to provide mentorship to junior investigators in hepatitis research. Most recently, Dr. Fried is co-principal investigator of the HCV-TARGET international network studying the real-world outcomes of HCV therapies.

Dr. Fried is the primary author or co-author on over 150 original publications, reviews, and book chapters concentrated in the field of viral hepatitis. He was inducted into the American Society of Clinical Investigation (ASCI), an honor society for clinical investigators. Dr. Fried serves on the Governing Board of the American Association for the Study of Liver Diseases (AASLD) and will assume the role of President of AASLD in 2019.

Abstract: Acute Hepatotoxicity in HCV Infected Cirrhotic Patients Treated with Direct-Acting Antiviral Agents (DAAs)

Direct-acting antiviral agents have transformed the treatment for hepatitis C in patients with cirrhosis. Several phase III trials have demonstrated high rates of efficacy with low rates of adverse events or premature discontinuations in patients with advanced liver disease (1-7). Furthermore, the safety and effectiveness of these agents in longitudinal observational cohorts of patients treated in routine clinical practice were generally similar to those seen in controlled trials. Thus, the incidence of acute hepatototoxicity in patients with cirrhosis is low although subpopulations of cirrhotic patients and certain direct-acting antiviral agents may pose greater risk.

Drug-induced liver injury (DILI) must be carefully differentiated from progression of underlying liver disease or causes of acute on chronic liver disease frequently seen in patients with cirrhosis (8). The implications of DILI in patients with cirrhosis vary with the severity of liver disease. Patients with well-compensated cirrhosis, recognized as the absence of complications of portal hypertension and intact synthetic function, are likely to tolerate an episode of hepatotoxicity provided it is recognized in a timely manner and appropriate management instituted. In contrast, patients with decompensated cirrhosis and very limited hepatic reserve may be at greater risk for hepatic decompensation and serious deterioration of clinical status.

Drug-induced liver injury or hepatic decompensation has been reported with all classes of direct-acting antiviral agents (protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors) although the frequency of events and the quality of evidence for hepatotoxicity substantially vary (8-12). Furthermore, identifying the single responsible agent within a combination of two or three classes of DAAs may be challenging. Members of the protease inhibitor class, compared to

other classes of HCV therapies, appear to have the greatest potential for hepatotoxicity among patients with decompensated cirrhosis. Postmarketing reports of hepatic decompensation and hepatic failure have led to recommendations against the use of protease inhibitor containing regimens in patients with Child's-Pugh B or C cirrhosis (13). The mechanism underlying these events may be related to alterations in hepatic metabolism and elevated systemic exposures associated with impaired hepatic function (14, 15).

Direct-acting antiviral therapies are highly effective and safe for patients with well compensated, Child's-Pugh cirrhosis. Treatment with DAAs for patients with decompensated cirrhosis requires careful selection of appropriate regimens and increased monitoring for changes in clinical status.