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Biosketch

Dr. Arun Sanyal is a Professor of Medicine, Physiology and Molecular Pathology at Virginia Commonwealth University School of Medicine in Richmond, Virginia. He has over 25 years of experience as a hepatologist and has served as the secretary and president of the American Association for Study of Liver Diseases, founding member of the Hepatology board of the American Board of Internal Medicine, chair of the NIH hepatobiliary pathophysiology study section and member of the council of the NIH. He has been continuously funded by the NIH for over 25 years.

Dr. Sanyal's research spans two major areas: (1) cirrhosis and its complications, and (2) alcoholic- and nonalcoholic steatohepatitis (NASH). His work informs several recommendations in national practice guidelines related to the management of variceal hemorrhage, ascites, hepatorenal syndrome, hepatic encephalopathy and nonalcoholic steatohepatitis. His work in these areas extends from basic molecular discovery to development of animal models, preclinical evaluation, first in humans to pivotal human trials and then development of practice guidelines and health care delivery and population based outcomes. He has been continuously funded since 1995. Recently, he has helped establish and chair the "Liver Forum" which brings FDA, European Medical Agency, Academia, NIH and industry stakeholders in NASH and hepatic fibrosis together to accelerate therapeutic development in these areas.

Abstract: Can we test liver function to assess treatment effects and course of NASH?

Nonalcoholic steatohepatitis (NASH) is a common chronic liver disease that can progress to cirrhosis and is also a risk factor for hepatocellular cancer. The adverse outcomes associated with NASH and lack of approved therapies is driving large-scale ongoing efforts to develop effective therapeutics for NASH. A key challenge in this process is the assessment of treatment effects, especially adverse effects, on the liver. Liver function tests (LFTs) is a loosely defined term in routine clinical practice that includes measures of both liver injury and liver function. The serum AST, ALT and Alkaline phosphatase (AP) are widely used to ascertain the presence of liver injury and its type i.e. parenchymal (mainly AST and ALT elevation) or cholestatic (mainly AP elevation). In clinical practice, an elevated AST and ALT often brings the presence of underlying chronic liver disease including NASH. However, what constitutes a normal ALT for purposes of clinical research versus practice continues to be debated. An ALT > 19 IU/l for women and 31 IU/l for men is considered to be abnormal in Western populations. Most clinical laboratories however still report upper limits of normal, based on historical self-identified controls, in the 40-50 IU/l range. The ALT levels are also affected by the methods used to measure ALT. In NASH, while elevated ALT is associated with a greater risk of disease progression than normal ALT (using conventional upper limits of normal), the full spectrum of disease including cirrhosis has been reported with persistently normal ALT. Clinical experience further suggests that, with disease progression to cirrhosis, ALT levels tend to decline. It is also important to note that most subjects with NASH have modest ALT elevation (< 200 IU/l) and that there is no correlation between ALT levels and severity of underlying disease. All of these confound the use of ALT to assess disease severity or progression. Furthermore, in clinical trials, ALT declines in both placebo and active drug exposed subjects for the first 8-12 weeks and separation of the groups is best seen after 12 weeks and peaks at 24 weeks. ALT can also fluctuate during the course of the disease. Ideally having a 6 month trend-line of ALT for an individual subject may allow assessment of whether treatment associated increase in ALT reflects the underlying disease or DILI. For those with normal baseline ALT, a 5-fold increase in ALT and for those with elevated baseline ALT, a 3-fold

increase or values over 300 IU/l may warrant consideration of DILI. Any increase in conjugated bilirubin above ULN or INR > 1.4 should be considered to represent DILI until proven otherwise and lead to drug discontinuation.