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Biosketch

Mark Avigan obtained his B.Sc. (1972) and M.D. C.M. degrees (1977) from McGill University in Montreal, Canada. He completed residency training in Internal Medicine at the VA Medical Center/Georgetown University in Washington DC. Subsequently, he completed a clinical GI/Hepatology/Nutrition fellowship. Dr. Avigan served as a staff fellow in the Liver Unit of the National Institute of Arthritis Diabetes, and Digestive and Kidney Diseases where he participated in studies of viral hepatitis and in the evaluation of new therapeutics for the treatment of these conditions. He later moved to NCI where he pursued studies in molecular and cellular mechanisms governing the dysfunctional expression of oncogenes during carcinogenesis. In 1990 Dr. Avigan joined the faculty at the School of Medicine at Georgetown University. As an assistant and later associate professor he attended patients on the GI/Liver service at the Georgetown University Medical Center and served as a mentor of graduate students in the Department of Pathology and clinical fellows in the GI clinical program. He was the principal investigator of NIH funded R-29 and R0-1 grants to elucidate basic mechanisms in the transcriptional and post-transcriptional regulation of pathways critical for cellular growth and differentiation.

After joining the Center for Drug Evaluation of the Food and Drug Administration in 1999 as a Medical Officer in the Division of Gastrointestinal and Coagulation Drug Products, he developed a strong interest in drug-induced liver injury and the impact of pharmacogenomic analysis on evaluation of risk associated with drug treatment. Between 2003 and 2011 he served as Director of the Division of Drug Risk Evaluation, and then Pharmacovigilance I, in the Office of Surveillance and Epidemiology (OSE). With an interest to develop mechanistic as well as population-based perspectives in drug safety, Dr. Avigan is Associate Director for Critical Path Initiatives in the Office of Pharmacovigilance and Epidemiology and a member of CDER's Drug Safety Oversight Board. He has authored or co-authored over 120 scientific publications, book chapters and professional meeting abstracts.

Abstract: Challenges in developing a DILI guidance for patients with chronic liver disease

The current FDA guidance for the pre-marketing evaluation of DILI1 provides a useful framework to evaluate and manage hepatotoxicity in the clinical trials of patients without significant underlying hepatic abnormalities. However, modification or elaboration of the guidance is needed to address study subjects with pre-existing chronic liver disease. An updated guidance might establish granular scientifically-based criteria relevant to patient populations with different liver diseases and/or cirrhosis in the following study protocol domains: 1) Clinical expertise and study site lab testing systems that are required for the optimal recognition and management of DILI; 2) Categories and levels of severity of pre-existing liver abnormalities that warrant enrollment in clinical trials; 3) Methods for DILI detection; 4) Methods for close observation of cases of acute liver injury & confirmation of DILI; 5) Definitions of changing liver findings that would prompt discontinuation, interruption, or dose-adjustment of study drug(s); 6) Methods & graphic tools that facilitate the reliable & efficient analysis of DILI risk in a treatment population.

With this goal in mind, the reliable assessment of DILI in clinical trial subjects with pre-existing chronic liver disease faces significant challenges. Among these, different liver diseases are connected to distinct clinical, pathological and lab test signatures that impact baseline levels of serum liver aminotransferases (AT) and bilirubin before the initiation of treatment with study drug(s). Even though fold increases over baseline levels of these indicators are often used to characterize acute on chronic liver injury, there are a number of reasons why they may not reflect the proportionate contribution of acute drug-induced hepatocellular injury with respect to the actual background levels of chronic organ damage. First, different underlying liver diseases are marked by different clinical and lab test profiles and rates of progression. Depending on the hepatic disease and whether it is marked by episodes of heightened necrosis or apoptosis, the baseline liver test measurements may be expected to fluctuate or remain stable in time-separated serum samples. Second, drug-induced changes of bilirubin levels, INR and other indicators of liver function may not be linear as severe liver injury progresses to liver failure. Therefore, episodes of acute DILI in study subjects with a baseline of underlying liver abnormalities may be difficult to discern. On one end of a spectrum of chronic liver disease, patients with baseline elevations of serum AT and normal liver function may show further increases of AT with DILI that are sometimes accompanied by worsening liver function; at the other extreme, patients with baseline abnormal liver function reflecting advanced cirrhosis, may have further acute deterioration of liver function that in some cases is accompanied by negligible or only small additional rises of AT. Third, cholestatic forms of drug-induced injury in patients with underlying severe liver disease may be difficult to distinguish from hepatocellular forms based on serum enzyme and bilirubin changes alone. Fourth, worsening liver tests may reflect loss of treatment effects intended to reverse the underlying disease, rather than drug-induced toxicity. For example, in Type C hepatitis responders to anti-viral drugs would be expected to show normalization of AT levels. Thus, new onset elevations of AT during treatment with study drugs may reflect the emergence of viral resistance rather than drug toxicity. In addition, if liver cells are the intended targets for pharmacological action in a chronic liver disease, there may be a reduction of drug efficacy due to pathologically altered hepatic drug processing steps including diminished or altered first-pass drug uptake, hepatocellular bio-activation, metabolism and/or transport of drugs that are cleared by the liver. Finally, phase I, II and III enzyme activities responsible for the activation or clearance of a drug may be changed.

1. FDA Guidance for Industry; Drug-induced liver injury: premarketing clinical evaluation (2009); http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf