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Biosketch

Daniel Suzman is a medical officer focused on genitourinary malignancies in the Office of Hematology/Oncology Products at the FDA. He received his MD from the University of Maryland and completed his residency in internal medicine at University of California, San Francisco and fellowship in medical oncology at Johns Hopkins. His research interests include biomarker development, risk stratification of biochemically-recurrent prostate cancer, and non-hormonal therapeutic approaches.

Abstract: Monoclonal Antibody-induced DILI - A Regulatory Perspective

Conventional approaches employed in clinical trials to detect the potential of a drug to cause serious hepatotoxicity are frequently based around Hy's Law of concomitantly elevated transaminases and bilirubin. However, these approaches are predominantly on data from small molecule drugs with some element of hepatic metabolism and elimination. In recent years, monoclonal antibodies have been developed into mainstream therapies with the greatest number of these being approved for oncology indications. The incidence and mechanism of hepatotoxicity associated with these drugs is poorly understood, as the absorption, distribution, metabolism and elimination differs from that of small molecules. Among the 41 monoclonal antibodies and antibody-drug conjugates approved by the FDA, 16 (39%) have been associated with hepatotoxicity. Putative mechanisms of hepatotoxicity among these antibodies include reactivation of hepatitis B and immune-mediated hepatitis, however the mechanism is obscure for the majority. Antibodies and drugs may generate synergistic hepatotoxicity, as was seen in the combination use of ipilimumab and the small molecule BRAF inhibitor, vemurafenib. Thus, conventional approaches to evaluate drug-induced liver injury including Hy's Law may not apply to monoclonal antibodies and further evaluation may be needed before this extrapolation is made. Additionally, Hy's Law may be difficult to apply in oncology patients who may be heavily pre-treated and have liver metastases, liver cancer, multiple comorbidities, and multiple concomitant medications. Better predictive biomarkers and understanding of the pathophysiology in monoclonal antibody-induced liver injury should be explored. Within oncology, criteria for liver dysfunction beyond Hy's Law should be considered.