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Biosketch

Christine M. Hunt is board-certified in Internal Medicine and Gastroenterology/Hepatology. She pursued basic and clinical hepatology research on the faculty of Virginia Commonwealth University (1987-1988) and Duke University (1988-1996), examining the effects of aging on drug metabolism and pursuing viral hepatitis research. In 1996, she was recruited to GSK to develop new hepatitis and GI drug therapies; these efforts yielded successful new drug approvals. Dr. Hunt created and chaired the GSK Hepatotoxicity Board, which analyzed liver safety data, risk factors and predictors of drug toxicity, and developed computer algorithms to identify drug-induced liver injury in electronic health records. She developed and executed proactive safety systems for global clinical studies. Dr. Hunt was Vice President, GSK Clinical Safety Systems from 2007-2012 and collaborated globally in academic and regulatory consortia on drug safety, prediction of risk factors, phenotyping, genotyping, and biomarkers. She then left GSK to pursue public health and obtained her Masters in Public Health at the University of North Carolina in 2013. While serving as an Adjunct Associate Professor of Medicine at Duke University, she collaborates on clinical care systems at the VA and globally and consults in hepatology.

Abstract: Rechallenge is Too Dangerous

Drug rechallenge following drug-induced liver injury (DILI) is associated with up to 13% mortality in prospective studies.¹ When compared to the initial liver injury, drug rechallenge injury occurs more rapidly (sometimes within hours),² with accompanying jaundice (64%), allergic/hypersensitivity features (39%), and/or hospitalization (52%).³ Hence, except for critical treatments, drug rechallenge is seldom appropriate.⁴

Rechallenge clinical outcomes vary markedly by drug, from asymptomatic⁵ to fatal⁶ - suggesting that drug-specific factors influence rechallenge injury. DILI results from cumulative oxidative stress, reactive metabolites, immune injury from protein adducts, inflammation, impaired adaptation/regeneration, inhibited/disrupted transporters or drug metabolism, mitochondrial dysfunction, and loss of ion gradients and ATP, resulting in apoptosis, necroptosis, or necrosis.⁷⁻⁹ Of these, drugs inducing hepatocellular vulnerability through mitochondrial impairment (with weeks required to regenerate new mitochondria for cellular energy) or immune injury (i.e. recurring upon re-exposure) may specifically increase the risk of positive rechallenge.¹⁰

Preceding rechallenge, initial DILI may be complicated by chronic liver injury (17%)¹¹ or Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis in up to 5% of patients, accompanied by 36% mortality.¹² Further, drug-induced autoimmune hepatitis may uncommonly afflict those subsequently exposed to a related or unrelated drug after initial DILI.¹³ These data, combined with the sparse, yet concerning, drug rechallenge data, highlight the critical need for drug rechallenge data. This data can be derived from clinical studies of cyclically administered drugs (e.g. oncology agents) or large healthcare databases. Currently, drug rechallenge should generally be avoided, and considered only if the benefit exceeds the risk.