

New classification of drug induced liver injury (DILI) in AASLD guidance: What is next?

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Drug-induced liver injury (DILI) can be defined as an injury to the liver or biliary system caused by medications, herbal or dietary supplements. By using the R value, calculated as the alanine aminotransferase (ALT) to alkaline phosphatase (ALP) ratio, the pattern of injury is classified as hepatocellular, cholestatic, and mixed. Previously, DILI was classified as direct (dose-dependent, intrinsic, and predictable) or idiosyncratic (largely dose-independent and unpredictable). In the last AASLD guidance, a third mechanism, called indirect DILI, was added to this classification. In this type of DILI, the biological action of drugs, by affecting the host immune system, causes a secondary form of liver injury.^[1]

The molecular mechanisms responsible for DILI include mitochondrial dysfunction, reactive oxygen species (ROS) generation, endoplasmic reticulum stress, increased apoptosis and necrosis, bile duct injuries, and finally cell death by apoptosis or necrosis.^[2,3] In direct or intrinsic DILI, three mechanisms account for the majority of cases: mitochondrial dysfunction, oxidative stress, and alterations in bile acid homeostasis. Mitochondrial dysfunction causes a reduced level of ATP and a decline in cell function, and finally cell death. ROS are byproducts of normal metabolism, but when the regulation mechanisms that control the cellular levels of ROS break down, oxidative stress occurs, resulting in damage to key cellular components and cell death. Additionally, if drugs reduce hepatic bile acid efflux by inhibiting the bile salt export protein (BSEP), this results in the accumulation of toxic bile acids inside the cell, which can lead to hepatocyte death. These three mechanisms are often interlinked and work together to cause toxicity.^[4,5] Acetaminophen toxicity is a prototypical example of intrinsic DILI. A reactive intermediate of the drug, N-acetyl-p-benzoquinone imine (NAPQI), produced by cytochrome P450 (CYP) metabolism, is detoxified by conjugation with glutathione (GSH) under normal conditions. Overproduction of this metabolite depletes mitochondrial GSH, reducing the ability to neutralize ROS and causing mitochondrial injury. Besides prolonged fasting and chronic alcohol use, there is some evidence that host immunity might be involved in acetaminophen toxicity.

Polymorphisms in genes encoding the enzymes and other differences in innate immunity in drug metabolism can be responsible for the interindividual difference in susceptibility to toxicity and also in the outcome following the onset of liver injury.^[5]

The underlying mechanism of idiosyncratic DILI is not clear but is believed to be multifactorial, including environmental, chemical, and pharmacological factors.^[6] The hypotheses that describe the pathogenesis involve mostly the adaptive immune system.^[2] The adaptive immune response, a critical process in acute injuries, is stimulated by the activated immune system, released damage-associated molecular patterns (DAMPs), and reactive metabolites from antigen-presenting cells or drug-protein complexes. This includes CD4+ and CD8+ T-cell responses and B cell-mediated humoral reactions, resulting in hepatocyte damage.^[7] In most cases, liver injury is delayed and develops suddenly after months of exposure without symptoms. This latency of injuries is accepted as a sign of the role of the adaptive immune system in idiosyncratic DILI.^[8]

Although acute and immune-mediated DILI demonstrate distinct underlying causes, they both share molecular mechanisms resulting in hepatic injury. In both types, inflammation plays a key role. In direct injury, the immune response is the result of toxic metabolites overwhelming hepatic cells, while in immune-mediated DILI, immune mechanisms might mistakenly identify drug-altered hepatic cells as foreign. Also, proinflammatory cytokines release and endoplasmic reticulum stress can be seen in both types of DILI. Despite these similarities in pathogenesis, acute DILI is associated with recent exposure and may resolve quickly upon discontinuation, whereas immune-mediated DILI might be chronic, requiring immunosuppressive treatment.^[3]

The third mechanism, named indirect DILI, is described as a secondary form of liver injury. It is similar to idiosyncratic DILI because of dose independency and long latency. In this type of injury, the main problem is the effect of the drug on the host immune system. Immune-mediated hepatitis observed with immune checkpoint inhibitors and reactivation of hepatitis B virus (HBV) infection can be given as examples.^[1] In an infected patient with HBV, it is shown that HBV DNA, cccDNA, and/or replicating DNA can persist in the liver for decades after apparent recovery from HBV infection. Adaptive T and B cells are responsible for the outcome. T cells eliminate infected cells by a cytopathic effect or suppress viral replication by cytokine-mediated pathways. On the other hand, B cells limit the spread of HBV infection via neutralizing antibodies. But if the immune control mechanisms are suppressed, reactivation occurs with "latent" HBV cccDNA or low-level replicating HBV that escape targeting by the HBV-specific immune cells. Especially molecularly targeted therapies, used for altering the disease process, increase the risk of HBV reactivation.^[9] The main effect of immune

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checkpoint inhibitors (ICI) is to increase immune activity against tumor cells by the activation of T cells. But at the same time, they may reduce immune tolerance to self antigens, causing immune-mediated tissue damage.^[10] Drug-induced autoimmune hepatitis is a form of DILI, which is defined as patients presenting with acute DILI with serological and/or histological markers of idiopathic autoimmune hepatitis. From the pathological perspective, in the liver biopsy of patients with ICI-induced DILI, one of the most reported patterns is lobular hepatitis indistinguishable from autoimmune hepatitis.^[11] Because of these findings, some authors describe ICI-associated DILI as idiosyncratic liver injury with autoimmune features.^[12] As new drugs and herbal supplements are discovered in clinical practice, different mechanisms of DILI may be described, and new classes will be added in the future.

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