Review Article

Drug-Induced Liver Injury: A Primer for Cardiologists

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ABSTRACT

Although drug-induced liver injury (DILI) is an uncommon diagnosis, it is an important cause of morbidity and mortality in hepatology practice. A timely diagnosis of DILI is important to stop causative drugs and keeping a high index of suspicion is important. There is no gold standard single test to diagnosed DILI, causality scores help in establishing a diagnosis. DILI presenting as acute liver failure is associated with poor prognosis in natural course. The association of nonalcoholic fatty liver disease with cardiac disease makes it more important to think of DILI in a patient with liver dysfunction. We discuss various aspects of DILI in cardiology context in the current review.

KEYWORDS: *Cardiac medicines, causality, drug-induced liver injury, prognosis, statins*

How to Define Drug-Induced Liver Injury

Drug-induced liver injury (DILI) is defined in the presence of one of the following thresholds:[1]

a. ≥5 upper limit of normal (ULN) elevation in alanine transaminase (ALT)
b. ≥2 ULN elevation in alkaline phosphatase (ALP) in the absence of known bone pathology
c. ≥3 ULN elevation in ALT and simultaneous elevation of total bilirubin >2 ULN.

In patients with abnormal liver function test (LFT) before starting treatment with the implicated drug, ULN is replaced by the mean baseline values before DILI onset and increase should be proportionate to this modified baseline.

There are several limitations of this definition. It excludes isolated hyperbilirubinemia (rise of bilirubin without elevation of liver enzymes), also DILI by certain drugs may happen without significant changes in liver enzymes (e.g., nodular regenerative hyperplasia, liver tumors, methotrexate-associated liver fibrosis, and valproate-associated mitochondrial toxicity).[2]

DILI severity is defined as mild (raised liver enzymes but bilirubin <2 ULN), moderate (raised liver enzymes, bilirubin ≥2 ULN, or symptomatic hepatitis), severe (as moderate + one of INR ≥1.5, ascites/encephalopathy and other organ failures due to DILI), and category 4 (death or transplantation).[2]

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What are Types of Drug-Induced Liver Injury?

DILI can manifest in multiple ways.[1-4] Manifestations of DILI include acute hepatitis, chronic hepatitis, cholestasis (with or without hepatitis, with bile duct injury), drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), drug-induced autoimmune hepatitis, granulomatous hepatitis, secondary sclerosing cholangitis, acute fatty liver and fatty liver disease, nodular regenerative hyperplasia, ductopenic (vanishing bile duct) syndrome, and liver tumors.

Sometimes, DILI is chronic.[5] R ratio is used for classifying DILI as hepatitis or cholestatic. R ratio is calculated as (ALT/ALT ULN)/(ALP/ALP ULN). A DILI is designated as hepatocellular when there is a ≥5-fold rise in ALT or R ratio is ≥5, cholestatic when there is a ≥2-fold rise in ALP alone, or when R ratio is 2 or less, and as mixed when R ratio is between 2 and 5.[2]

How Common is Drug-Induced Liver Injury and What Are Common Etiologies?

Retrospective studies from Europe and North America have shown an incidence of 2–3/100,000 population. Prospective

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population-based studies have shown a higher incidence.[6-8] A meta-analysis found that the most common agents implicated in DILI were different in the east and west. Antituberculosis drugs (26.6%), herbal and alternative medications (25.3%), and antibiotics (15.7%) were common causes of DILI in the east. Antibiotics (34.9%), cardiovascular agents (17.3%), and nonsteroidal anti-inflammatory drugs (12.5%) were common causes of DILI in the west.[9] The Indian Network for Drug-Induced Liver Injury published a prospective multicentric study of 1288 patients with idiosyncratic DILI. Antituberculosis drugs (ATD) (46.4%) was the most common etiology followed by complementary and alternative medicine (13.9%), antiepileptic drugs (8.1%), and antimicrobials (6.5%). Statins were the cause of DILI in 1.4%. DILI was associated with mortality in 12.3% of patients. Importantly, 65% of patients with hepatic encephalopathy, and 16.6% of patients with jaundice died.[10]

DILI is an uncommon diagnosis and different drugs are associated with the different potential of DILI. A nationwide study from Iceland showed that DILI occurred in overall 35,252 patients received as outpatients, and DILI occurred in 1 of 2350 on amoxicillin-clavulanate (43 of 100,000), 1 in 3693 on atorvastatin, (27 of 100,000) 1 of 1369 patients taking nitrofurantoin (73 of 100,000), 1 of 148 patients taking infliximab (675 of 100,000), 1 of 133 patients taking azathioprine (752 of 100,000), and 1 of 9480 on diclofenac (11 of 100,000).[11]

Pathogenesis of Drug-Induced Liver Injury

While some agents have direct (intrinsic) and dose-dependent hepatotoxicity potential, most of DILI are idiosyncratic (unpredictable). Common examples of intrinsic hepatotoxicity are paracetamol, amiodarone, anabolic steroids, antiretroviral drugs, valproic acid, and antimetabolites. Some of these medications cause idiosyncratic DILI also. Direct hepatotoxicity occurs when a known hepatotoxic agent causes death of hepatocytes. The majority of medications implicated in idiosyncratic DILI undergo hepatic metabolism and toxic intermediates are generated. These products are usually inactivated by glutathione or sulfate conjugation. If the presence of excess production (of metabolites) or depletion of the conjugating factors, these toxic intermediates lead to mitochondrial dysfunction, production of reactive oxygen species, and cellular organelle/membrane dysfunction. These events lead to cellular dysfunction and/or death. Sometimes immunity pathways are also involved in the pathogenesis of DILI. Reactive metabolites may bind to cellular proteins, producing neoantigens, or may directly bind to human leukocyte antigen molecules. The neoantigens may lead to activation of the adaptive immune system causing hepatocyte injury in genetically susceptible individuals. A sublethal injury leads to adaptation.[1,3]

Several drugs can lead to different types of DILI. Following patient is at higher risk of developing DILI: higher age, female gender (for autoimmune hepatitis type DILI), African-Americans, chronic alcohol intake, presence of prior liver disease, malnutrition, obesity, or nonalcoholic steatohepatitis. Several HLA genotypes are at a higher risk of developing DILI.[1,3,12]

Diagnosing Drug-Induced Liver Injury

A high index of suspicion is required to diagnose DILI. Diagnosis of DILI is made by exclusion of other causes and by the use of causality assessment scales. Ruling out congestive hepatopathy is important in patients with heart failure. The approach to diagnosis is shown in Figure 1.

There is no gold standard test to diagnose DILI, so these scales should supplement and not substitute clinical judgment. The Council for International Organizations of Medical Sciences scale, also called RUCAM scale is commonly used for the evaluation of causality.[13] This scale consists of seven domains: time to onset of injury after initiation of suspected drug, course after stopping the drug, presence of risk factors (alcohol, pregnancy, and age), concomitant medications, exclusion of other causes, previous information available about hepatotoxicity, and response to unintentional readministration (if any). A readministration to reproduce DILI is not advised. Other available causality assessment scales/processes are the clinical diagnostic scale and structured expert opinion process suggested by the United States Drug-Induced Liver Injury Network and Digestive Disease Week–Japan, Maria, and Victorino.[14-16] Some of the limitations of causality scales include cases with concomitant drugs, arbitrary weightage of factors, and the absence of known literature in the case of new drugs.[17] LiverTox® is a web-based searchable database of information (http://www.livertox.nih.gov/) about DILI.

It should be noted that a liver biopsy is not needed to make a diagnosis of DILI. A biopsy can be done if serology suggests autoimmune hepatitis or in patients with progressive or not improving DILI (to rule out the alternate diagnosis and for prognostic information).

Course and Management of Drug-Induced Liver Injury

DILI generally develops between 5 days and 3 months after initiation of causative medication; however, it may happen at shorter (e.g., DILI associated with hypersensitivity features)

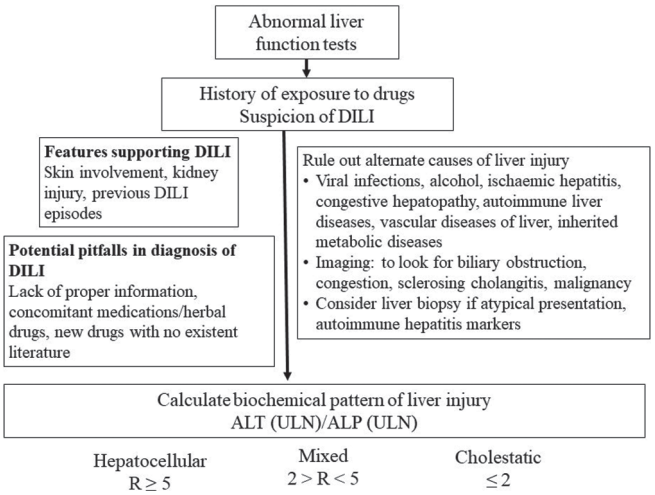

Figure 1: Diagnostic approach to drug-induced liver injury

or longer duration (e.g., antitubercular therapy) also. Recovery after withdrawal of implicating agent takes days to weeks or may take several months. The most important thing is the identification of implicated drug and prompt withdrawal. Improvement may not begin immediately and ongoing worsening may happen, particularly in cases with severe DILI.[1,3,12] Figure 2 describes the management of DILI.

Drug-Induced Liver Injury Reported With Cardiac Medications

Various DILI associated with cardiac medications are shown in Table 1.[12,18-20]

Statin-related DILI needs a detailed mention. Statins are commonly used medications to decrease cholesterol levels. It is important to understand that despite having hundreds or thousands of patients, clinical trials may remain underpowered to detect rare side effects (like DILI) and phase 4 studies (postmarketing studies) may pick up DILI potential of a drug. Statins have been associated with several types of DILI as shown in Table 1. Various prospective studies have shown that 1.9%–5.5% of DILI were due to statins.[11,21,22] Early clinical trials showed asymptomatic elevations of aminotransferases in up to 2% of patients (normally resolved after dose reduction), and clinical apparent injury was very rarely observed.[11,23] High dose is likely a risk factor.[24] The prognosis of statin-related DILI is generally favorable, but mortalities have been observed with atorvastatin and simvastatin.[18]

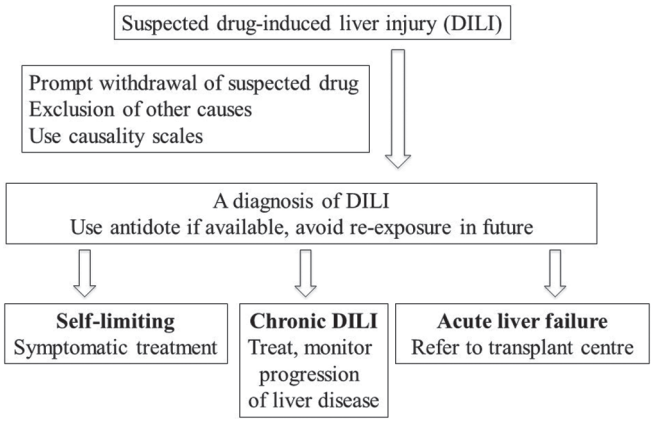

Figure 2: Management of drug-induced liver injury

Table 1: Cardiac medications associated with drug-induced liver injury

Implicated medications	Type of DILI
Hydralazine, amiodarone, diltiazem, disopyramide, methyldopa, procainamide, quinidine	Granulomatous hepatitis
Angiotensinogen-converting enzyme inhibitors	Cholestatic hepatitis
Amiodarone[#]	Steatohepatitis*
Nicotinic acid	Dose-dependent hepatotoxicity
Aspirin (Reye's syndrome in febrile children)	Microvesicular steatosis
Amiodarone, captopril, enalapril, lisinopril, labetalol, statins	Acute liver failure
Statins	Hepatitis, cholestasis, autoimmune hepatitis
Amiodarone	Cirrhosis
Rivaroxaban	Hepatitis, cholestasis, mixed

*Some other drugs also have been implicated. As steatosis is a common diagnosis in the population and is often associated with hypertension, causation may not be there, [#]Both acute and chronic liver injury have been described with amiodarone. DILI=Drug-induced liver injury

It is very difficult to get a reliable estimate of DILI due to most of the drugs, which is true for statins also. In the prospective Iceland study, 2 of 7385 patients on atorvastatin and 1 of 27,845 patients on simvastatin developed DILI, thus statin-related DILI is rare.[11] An analysis of 74,078 individuals from 16 studies showed that odds ratio with statin therapy was 1.18 (95% confidence interval [CI]: 1.01–1.39, $P = 0.04$; $I^2 = 0.0\%$) for liver injury. In a subgroup analysis, fluvastatin was associated with more risk (OR, 3.50; 95% CI: 1.07–11.53, $P = 0.039$), also higher dose (>40 mg/daily) was associated with increased risk (odds ratio, 3.62; 95% CI: 1.52–8.65, $P = 0.004$).[25]

The use of statins is associated with decreased cardiovascular risk,[26] which is a common cause of mortality in patients with NAFLD.[27] Studies have shown that patients with abnormal liver tests at baseline were not at a higher risk of statin-related DILI when compared to those with normal liver tests at baseline.[28] The use of statins in patients with cirrhosis is associated with improved portal hemodynamics, decrease hepatocellular carcinoma risk, and decreased mortality risk.[29,30] Hence, patients with liver disease can be started on statins as the risk of DILI is very low, but awareness of potential of DILI is recommended.

Groups at Higher Risk of Drug-Induced Liver Injury

Although DILI can happen without any risk factor, some groups are at higher risk. Following are the risk factors for DILI and more caution is needed in these groups: age (older age, younger age for valproic acid and Reye's syndrome, associated with aspirin use), obesity, alcohol use, underlying liver disease (chronic viral hepatitis, nonalcoholic fatty liver disease), presence of cirrhosis, presence of cardiovascular disease, and patients with diabetes or hyperlipidemia.[31,32] As patients with cardiovascular disease often have some of these risk factors (obesity, diabetes, hyperlipidemia, and nonalcoholic fatty liver disease), awareness about DILI becomes more important among cardiologists.

Conclusions

DILI is a rare adverse event but is associated with a significant risk of morbidity and mortality (in cases with severe DILI). Awareness about DILI is the most crucial thing in diagnosis and it should be considered in patients with raised LFTs.

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Conflicts of interest

There are no conflicts of interest.

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