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REVIEW

Drug-Induced Liver Injury

Michael D. Leise, MD; John J. Poterucha, MD; and Jayant A. Talwalkar, MD

Abstract

Drug hepatoxicity can be nonidiosyncratic (predictable), as in the case of acetaminophen, or idiosyncratic (unpredictable). This review article focuses primarily on idiosyncratic drug-induced liver injury (DILI). New epidemiologic data suggest that approximately 20 new cases of DILI per 100,000 persons occur each year. Idiosyncratic DILI accounts for 11% of the cases of acute liver failure in the United States. Risk factors for DILI include medication dose, drug lipophilicity, and extent of hepatic metabolism. There is mixed evidence to support the role of host factors such as age, sex, and chronic liver disease in the development of DILI. For specific drugs, a genetic predisposition appears to be a risk factor for DILI. Suspected cases of idiosyncratic DILI should be categorized as hepatitic, cholestatic, or mixed on the basis of the degree/ratio of abnormalities in the alanine aminotransferase and alkaline phosphatase. A careful evaluation for other causes of liver disease should be performed, though a liver biopsy is rarely needed. There is evidence that some patients with DILI may actually have hepatitis E and this diagnosis should be considered. Amoxicillin/clavulanate isoniazid, and nonsteroidal anti-inflammatory drugs are among the most common causes of DILI. Drug discontinuation or dechallenge should lead to an improvement in liver biochemistries in most patients, though a bilirubin value of more than 3 g/dL is associated with mortality of at least 10%. New biomarkers for DILI using proteomics and micro RNA appear promising but require further study. New studies on drugs with potential for causing DILI are reviewed herein, including tumor necrosis factor-alpha antagonists, fluoroquinolones, tyrosine kinase inhibitors, statins, and supplements. PubMed was used with search terms of drug induced liver injury OR DILI with filter settings of "English language" and "humans" and custom date range of "January 1, 2000." The authors also manually searched bibliographies from key references and included seminal references before the year 2000.

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From the Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN.

The true incidence of drug-induced liver injury (DILI) is difficult to discern because of an unknown denominator of individuals receiving a drug, lack of a simple objective test for the diagnosis of DILI, lack of consensus on what liver test abnormalities constitute DILI, difficulty in attribution of causation to a single drug in those on many medicines, and lack of systematic reporting. Multiple studies have attempted to address the epidemiology of DILI, which are summarized in Table 1.[1-6] It is important to note that the main cause of DILI in 4 of the 6 studies was amoxicillin/clavulanate and that isoniazid and nonsteroidal anti-inflammatory drugs were also one of the top 3 culprits across studies.

A recent study by Bjornsson et al[5] helped to define the incidence of idiosyncratic DILI by prospectively examining a population-based cohort in Iceland. Overall prescription medication consumption in this population was documented through linkage to nationwide pharmaceutical databases for outpatient prescriptions and inpatient medication use. This is the most recent population-based study (2013) on DILI, with the only other population-based study coming from France (2002).[1] In Iceland, 96 cases of DILI were identified between 2010 and 2011, and the crude annual incidence was 19.1 (95% CI, 1.54-23.3) cases per 100,000 inhabitants. This incidence is higher than that in the French study, which reported an annual incidence of 13.9 cases per 100,000 inhabitants. It is notable that the French study used a lower liver test threshold to define DILI cases, included acetaminophen cases, and did not examine inpatients. In the United States, the Drug Induced Liver Injury Network (DILIN) reported on 300 idiosyncratic DILI cases on which information was collected prospectively by the National Institute of Health at 5 academic medical centers.[3] In these 300 cases, the mean age was 48 years, 60% were women, and the largest 2 categories were antimicrobial agents and central nervous system (CNS) agents. Eight percent of the patients died,

ARTICLE HIGHLIGHTS

- In the most recent and well-executed population-based study, the crude annual incidence of drug-induced liver injury was 19.1 (95% CI, 1.54-23.3) cases per 100,000 persons.
- The most common drug causing drug-induced liver injury is amoxicillin/clavulanate.
- The most common class of drug responsible for acute liver failure from drug-induced liver injury is antibiotic medications, with isoniazid, sulfur antibiotics (trimethoprim-sulfamethoxazole), and nitrofurantoin being the most common individual drugs.
- Hepatitis E can masquerade as a drug-induced liver injury in 3% to 13% of the cases.
- Drug-induced autoimmunelike hepatitis responds to steroids and generally does not recur after a steroid taper.
- Drug-induced liver injury with predominant elevations in aminotransferase levels (hepatocellular pattern) in those who develop jaundice has a mortality of approximately 10% (Hy's law).
- N-Acetylcysteine should be considered for patients with non-acetaminophen drug-induced acute liver failure, because it has been shown to improve transplant-free mortality in a randomized controlled trial.

and 2% required liver transplantation (LTx). Interestingly, 14% had continued liver test abnormalities at 6 months, regarded as "long-term DILI" in this study. Although this ongoing study provided data for US cases of DILI, it did not define the incidence of the condition. DILI also contributes significantly to the burden of acute liver failure (ALF) in the United States. In a prospective study of ALF in the United States (n=308), 13% of the ALF cases were thought to be caused by idiosyncratic DILI while 39% of the ALF cases were due to acetaminophen toxicity.[7] Between 1990 and 2002, 270 patients underwent LTx in the United States for drug hepatoxicity (49% from acetaminophen toxicity and 51% were idiosyncratic). More recent estimates suggest that idiosyncratic DILI is responsible for 11% of all cases of ALF in the United States. The most common agent in a US registry was isoniazid, followed by sulfur antibiotics (trimethoprim-sulfamethoxazole), nitrofurantoin, antifungals, antiepilepsy (especially phenytoin), and complementary-alternative medications (11%). Transplant-free, 3-week survival for this group is poor (27%).[8]

CLASSIFICATION

DILI is a broad term applied to any injury to the liver by a prescribed medication, over-the-counter medication, herb, or dietary supplement manifesting as a spectrum from asymptomatic liver test elevations to ALF. Epidemiologic studies and prospective registries use different, arbitrary liver biochemical thresholds to define what constitutes DILI. The first step in describing DILI is to differentiate idiosyncratic (unpredictable) DILI from intrinsic (predictable) DILI. The most common example of a drug causing predictable DILI is acetaminophen. This type of drug injury has a short latency period, is dose related, and is the most common form of DILI observed. On the contrary, idiosyncratic DILI is unpredictable, has longer/variable latency, and is less common. Examples of idiosyncratic DILI include those related to amoxicillin/clavulanate, nonsteroidal anti-inflammatory drugs, and isoniazid.

The second distinction to make is in regard to the pattern of drug injury. DILI can be categorized as hepatitic (hepatocellular injury), cholestatic, or mixed on the basis of liver biochemical parameters. Common examples of each pattern are given in Table 1. Formulas defined by the Council for International Organizations of Medical Sciences and modified by the Food and Drug Administration (FDA) determine the R ratio, which is a ratio of the alanine aminotransferase (ALT) to the alkaline phosphatase relative to their respective upper limits of normal (ULN).[9] The R ratio for hepatitic DILI is more than 5, for cholestatic DILI is less than 2, and for mixed DILI is between 2 and 5. The formulas are as follows: (1) Hepatitic DILI: ALT $\geq$3ULN and (ALT/ULN)/(alkaline phosphatase/ULN) $\geq$5; (2) Cholestatic DILI: alkaline phosphatase $\geq$2ULN and (ALT/ULN)/(alkaline phosphatase/ULN) $\leq$2; (3) Mixed DILI: ALT >3ULN and alkaline phosphatase >2ULN and (ALT/ULN)/(alkaline phosphatase/ULN) between 2 and 5. These formulas can be applied in practice to narrow down the differential diagnosis in patients in whom DILI is plausible yet multiple possible offending agents exist. Although many medications responsible for DILI produce stereotypical

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