REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY

John P. Lynch and David C. Metz, Section Editors

Risk Factors for Idiosyncratic Drug-Induced Liver Injury

NAGA CHALASANI[*,‡] and EINAR BJÖRNSSON[§]

[*]Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana; [‡]Clarian/IU Digestive Diseases Center, Indianapolis, Indiana; and [§]Department of Internal medicine, Section of Gastroenterology and Hepatology, Landspitali University Hospital, Reykjavik, Iceland

Idiosyncratic drug-induced liver injury (DILI) is a rare disorder that is not related directly to dosage and little is known about individuals who are at increased risk. There are no suitable preclinical models for the study of idiosyncratic DILI and its pathogenesis is poorly understood. It is likely to arise from complex interactions among genetic, nongenetic host susceptibility, and environmental factors. Nongenetic risk factors include age, sex, and other diseases (eg, chronic liver disease or human immunodeficiency virus infection). Compound-specific risk factors include daily dose, metabolism characteristics, and propensity for drug interactions. Alcohol consumption has been proposed as a risk factor for DILI from medications, but there is insufficient evidence to support this. Many studies have explored genetic defects that might be involved in pathogenesis and focused on genes involved in drug metabolism and the immune response. Multicenter databases of patients with DILI (the United States Drug Induced Liver Injury Network, DILIGEN, and the Spanish DILI registry) are important tools for clinical and genetic research. A genome-wide association study of flucloxacillin hepatotoxicity has yielded groundbreaking results and many similar studies are underway. Nonetheless, DILI is challenging to investigate because of its rarity, the lack of experimental models, the number of medications that might cause it, and challenges to diagnosis.

Keywords: HLA; Amoxicillin-Clavulanate; Hy's Law; DILI.

The liver metabolizes xenobiotics, so it is not surprising that drug-induced liver injury (DILI) is a potential complication of many drugs. DILI broadly is classified into intrinsic and idiosyncratic types; intrinsic DILI generally is dose-dependent and predictable (eg, acetaminophen toxicity), whereas idiosyncratic DILI is unpredictable and does not depend directly on dose. This review focuses on the idiosyncratic type of DILI, which accounts for the majority of hepatotoxicity associated with medication use. Idiosyncratic DILI is rare even among individuals who are exposed to drugs that are known to be hepatotoxic. It occurs in 1 in 5000 to 1 in 100,000 individuals who take medication; the risk is lower for some drugs.[1,2] The epidemiology of DILI is not well understood; most studies that assessed the risk of liver injury from different medications have been retrospective.[3,4] There are no surveillance mechanisms in place to monitor DILI, so adverse drug reactions, including DILI, are under-reported. Controlled clinical trials provide reliable information about abnormal liver test results that are associated with specific medications, but these generally do not detect rare adverse drug reactions, so most cases of idiosyncratic hepatotoxicity are not detected.[1,2]

To our knowledge, there is only one population-based prospective study that systematically assessed the incidence of DILI.[5] The incidence of DILI in a French population was 13.9 cases per 100,000 inhabitants, a frequency that is 16-fold higher than that estimated from spontaneous reporting methods.[4] Based on this incidence rate, it was estimated that more than 8000 cases of DILI might occur in France each year and lead to approximately 500 deaths.[5] The United States Acute Liver Failure Study Group reported that acetaminophen and idiosyncratic drug reactions combined account for approximately 50% of cases of acute liver failure in the United States.[6] Vuppalanchi et al[7] reported that drug hepatotoxicity accounted for 4% of all cases of new-onset jaundice, but most cases of drug hepatotoxicity (24 patients) were attributable to acetaminophen toxicity and idiosyncratic DILI occurred in only 5 patients (0.7% of total study population). By using several different International

Abbreviations used in this paper: anti-TB, antituberculosis; BSEP, bile salt export pump; DILI, drug-induced liver injury; IL, interleukin; MnSOD, manganese superoxide dismutase; MRP, multidrug resistance protein; NAT2, N-acetyltransferase 2; OR, odds ratio.

© 2010 by the AGA Institute

0016-5085/$36.00
doi:10.1053/j.gastro.2010.04.001

Classification of Diseases 9th revision codes and the names of specific medications (amoxicillin/clavulanate, phenytoin, valproate, and isoniazid), Jinjuvadia et al[8] identified an overall DILI frequency of 1.6% (119 DILI cases of 7395 total patients) using the most sensitive combination of an acute liver injury International Classification of Diseases 9th revision code plus a medical record search of the University of Michigan Health System database. Importantly, 36 of these DILI cases (0.5%) were attributed to acetaminophen overdose, whereas the remaining 83 were caused by other agents (1.1%).[8]

Studies of unselected patients with DILI revealed that their prognosis generally is favorable.[9–11] Hyman Zimmerman,[12] a drug hepatotoxicity researcher, observed that mortality of patients with hepatocellular injury accompanied by jaundice was 10%–50%, depending on the drug involved. This observation, called *Hy's rule*, is used by the United States Food and Drug Administration to assess hepatotoxicity in drug development.[13] Recent studies from Spain, Sweden, and the United States confirmed Zimmerman's observation—mortality among patients with hepatocellular jaundice is approximately 9%–12%.[9–11]

It is virtually impossible to predict an individual's susceptibility to DILI from a specific compound (with the exception of flucloxacillin). Obviously, if an individual already has experienced DILI from a particular drug there is significant risk for recurrence.[14] Genetic susceptibility is one of the most important risk factors for DILI, but the genetic basis of causes of liver injury are poorly understood for most drugs with documented hepatotoxicity.[15–18] Chemical properties of the drug, daily dose, drug metabolism, and other factors such as age, sex, nutritional factors, and underlying disease states might mediate the development of DILI. The pathogenic mechanisms of idiosyncratic DILI have been reviewed extensively[19–21] and are not covered in this review. We summarize our current understanding of nongenetic and genetic risk factors for idiosyncratic DILI in human beings (Table 1).

Table 1. Factors That Cause Predisposition to Idiosyncratic DILI

Nongenetic factors	Genetic variability
Age	Phase 1 enzymes
	CYP 2C8
Sex	CYP 2C9
	CYP 2C19
Daily dose	CYP 2D6
	CYP 2E1
Metabolism profile	Phase 2 and detoxifying enzymes
	NAT2
Drug interactions	GSTM1 and T1
	MnSOD
Alcohol	UGT2B7
Underlying comorbidities (pre-existing liver disease, HIV infection, diabetes)	Drug transporters
	BSEP (ABCB11)
	MRP2 (ABCC2)
	MDR3 (ABCB4)
	Immunologic
	HLA class antigen
	Cytokines (IL-10, IL-4, tumor necrosis factor-α)
	Mitochondrial DNA mutations (POLG)

GST, glutathione S-transferase.

Nongenetic Risk Factors

Age

Age is a risk factor for DILI, but only from specific medications.[1,2] Younger age is a risk factor for certain medications such as valproic acid and for Reye syndrome, associated with aspirin use.[1,2] As age increases, so does the risk of liver injury from compounds such as erythromycin, halothane, isoniazid, nitrofurantoin, and flucloxacillin.[1,2,12] The risk of hepatotoxicity from isoniazid increases significantly with age.[1,8] In a large study of patients in a US tuberculosis clinic, the age-specific incidence of isoniazid hepatotoxicity was 4.4 per 1000 patients age 25–34 years, whereas it increased to 20.83 per 1000 patients age 50 years and older.[22] Increasing age also increases the risk for hepatotoxicity from amoxicillin/clavulanate.[23] The cholestatic type of DILI is more common among the elderly, whereas hepatocellular DILI appears to be more common in younger individuals.[10,24] The reasons that age affects DILI phenotypes are unclear. Although older age can affect the clearance of certain CYP3A substrates,[25] older age does not significantly alter the activity or expression of phase I or phase II drug-metabolizing enzymes.[26] Renal function is impaired in the elderly, which might increase drug concentrations in the liver; liver volume and liver blood flow have been correlated inversely with age.[27] However, in the elderly these physiologic alterations would account for intrinsic DILI rather than idiosyncratic DILI. It is unclear if the elderly produce more reactive metabolites or have increased immune response to these metabolites. The increased risk of hepatotoxicity from some drugs might result from polypharmacy among the elderly.[1,2] Although the incidence of certain adverse effects can increase with the use of multiple medications, there is little evidence to support polypharmacy as a predisposing factor for DILI. Combinations of 2 or more hepatotoxic drugs increased the risk for DILI by a factor of 6 in one study.[4] However, a subsequent prospective study did not show a significant relationship between polymorbidity or polypharmacy and the risk for DILI.[28]

Sex

Women are believed to be at higher risk for idiosyncratic DILI than men, based on a higher prevalence of women in published DILI studies.[1] However, recent stud-

Download English Version:

https://daneshyari.com/en/article/3296078

Download Persian Version:

https://daneshyari.com/article/3296078

Daneshyari.com