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Risk Factors for Idiosyncratic Drug-Induced Liver Injury

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Abstract

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

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Conflicts of interest

Dr Chalasani has served as a paid consultant within the preceding 12 months to Teva, Eli Lilly, Karobio, Salix, Debiovision, Amylin, Genentech, Abbott, and Gilead on issues related to drug safety, and has research support from Eli Lilly and Monarch LifeSciences; and Dr Björnsson has served as a paid consultant for Astellas Pharma Europe, AstraZeneca, and Karobio.

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 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).

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 studies have not shown that women are systematically at greater risk; in reviewing the published literature, Shapiro and Lewis[29] did not find female sex to be a risk factor for DILI. In a landmark prospective study, Lucena[24] reported that of 603 patients with DILI, 51% were male and 49% were female. Similarly, a population-based prospective study reported an annual incidence of 10.4 ± 3.0 per 100,000 women and 17.1 ± 3.6 per 100,000 men.[5] In this study, the standardized female to male incidence ratio increased from 0.86 (0.26 –2.90) in women younger than 50 years of age to 2.62 (1.0 – 6.92) in women older than age 50. However, this observation was not reproduced by Lucena.[24]

Men and women might have differences in susceptibility to DILI caused by different medications. For example, women are more susceptible to liver injury associated with halothane, flucloxacillin, isoniazid, nitrofurantoin, chlorpromazine, or erythromycin,[1,2,4,12] whereas men have an increased risk of azathioprine-induced liver injury.[1,2] Zimmerman[12] observed that autoimmune-type DILI occurred almost exclusively in women; this observation has been confirmed.[30]

Recent studies have shown a relationship between female sex, the hepatocellular pattern of DILI, and poor outcome (eg, acute liver failure, liver transplantation, and death).[9–11] A prospective trial of the DILI network reported a significantly greater number of women with hepatocellular DILI than men (65% vs 35%; $P < .05$).[11] A similar trend was observed by Lucena et al[24] when the analysis of their cohort was restricted to patients younger than the age of 60 years. De Valle et al[31] found hepatocellular injury to be more common among women, which could not be attributed to differences in the consumption of drugs that might have caused the reaction. It is not clear why hepatocellular DILI occurs more frequently in women. Lucena et al[24] reported a relationship between female sex and DILI severity; nearly 90% of patients with fulminant liver failure from DILI were women. Similarly, more women patients with severe DILI underwent liver transplantation in the United States.[32]

Daily Dose

There is a traditional view that idiosyncratic DILI cannot be predicted based on dose,[12] although a relationship to dose was observed for some medications, such as diclofenac, amoxicillin/clavulanate, and flucloxacillin.[4] Idiosyncratic liver injury associated with bosentan also has been shown to have dose dependency.[33] There are case reports in which dose reduction led to improvement and disappearance of hepatotoxicity caused by mianserin, [34] and an increased dose of duloxetine was associated with liver injury in a patient who had no signs of hepatotoxicity at a lower dose.[35] The concept of idiosyncratic drug reactions of being entirely dose-independent might be incorrect. Uetrecht[19] observed that idiosyncratic drug reactions were rare among patients given drug doses of less than 10 mg per day; conversely patients given drug doses of 1 gram or more per day were more likely to have idiosyncratic drug reactions.[20] Therefore, some relationship exists between daily dose of a drug and the chances of liver injury. This hypothesis recently was tested in a systematic fashion.[35] Data from 2 pharmaceutical databases were used to examine the relationship between daily dose of commonly prescribed oral medicines in the United States and their reported frequency of hepatotoxicity.[35] Furthermore, previously reported cases of DILI and concomitant jaundice[9] were analyzed for a relationship between daily dose and idiosyncratic DILI.[35] Among US prescription medicines, daily doses of oral medications were associated significantly with liver failure, liver transplantation, and death from DILI (Table 2).[35] In a study of approximately 600 DILI cases, only 9% of patients received less than 10 mg/day of medication, whereas 14% received 11–49 mg/day and 77% received more than 50 mg/day.[15] In the Spanish Hepatotoxicity Registry, 77% of patients with DILI received medications with daily doses greater than 50 mg.[24] Supporting these results, among nonacetaminophen cases of DILI that required liver transplantation in the United States from 1990 to 2002, 81% were reported to be caused by compounds that were taken in daily doses of greater than 50 mg/day.[32] Further studies of the relationship between drug doses and DILI risk are important for the development of safe medications.

Metabolism Characteristics

In associating the risk of DILI with hepatic metabolism of 207 of the most commonly prescribed oral medications in the United States, compounds with 50% or greater hepatic metabolism caused a significantly higher frequency (compared with drugs with less hepatic metabolism) of alanine aminotransferase (ALT) levels greater than 3 times the upper limit of normal (34% vs 10%; $P = .007$), liver failure (28% vs 9%; $P = .001$), liver transplantation (9% vs 1%; $P = .045$), and fatal DILI (23% vs 4%; $P = .0003$), but not jaundice (43% vs 34%; $P = .2$).[36] Twelve compounds with no hepatic metabolism (risedronate, alendronate, hydrochlorothiazide, nadolol, cefdinir, cefprozil, gabapentin, metformin, cephalexin, benzonatate, cefuroxime, and sotalol) were not found to cause liver failure, liver transplantation, or fatal DILI.[36] In analyses of the relationships between hepatic adverse events, hepatic metabolism, and daily dose, compounds with significant hepatic metabolism that were given at daily doses greater than 50 mg were significantly more hepatotoxic than compounds from all other groups.[36] Compared with medications without biliary excretion, compounds with biliary excretion significantly increased the incidence of jaundice (67% vs 33%; $P = .0006$). There were potential differences among associations between cytochrome P450 enzymes (CYPs) and liver failure from DILI and fatal DILI; CYP 2C9 and 2C19 pathways generally were associated with more DILI than CYP3A and CYP2D6 pathways.[36]

Cross-Sensitization and Class Effect

Cross-sensitization means the risk of hepatotoxicity for agents with close chemical structure, whereas class-effect means hepatotoxicity risk for agents within a narrow therapeutic class (eg, cyclooxygenase-2 inhibitors or 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors). Although there are some examples of drug hepatotoxicity linked to cross-

sensitivity and class effect, their overall impact on DILI is not well understood. Hypersensitivity from aromatic anticonvulsants might share common mechanisms and some patients could have cross-sensitivity to these drugs—cross-sensitivity frequently is observed between phenytoin and carbamazepine. [37] Cross-sensitivity has been reported from erythromycin derivatives,[38] phenothiazines,[39] haloalkane anesthetics,[40] and anti-androgens.[41] There is a case report of DILI that arose from cross-sensitivity between the propionic acid derivatives naproxen and fenoprofen.[42] Cross-sensitivity also has been reported between tricyclic antidepressants such as amineptine and clomipramine[43] as well as from trimipramine and despiramine.[44] It might be reasonable to closely monitor for DILI in patients who restart tricyclic antidepressants who have had previous liver injury from tricyclic antidepressant agents.[45] However, recent reports showed a lack of cross-hepatotoxicity among antifungal drugs; patients did not experience cross-hepatotoxicity between fluconazole and voriconazole[46] or between voriconazole and posaconazole.[47]

Drug Interactions

The formation of toxic reactive metabolites during hepatic metabolism is believed to be the main pathogenic mechanism for DILI.[12,48,49] Most drugs are bio-transformed by phase I and/or phase II metabolic reactions. Oxidation, reduction, and hydrolytic reactions are included in the phase I reactions, whereas phase II reactions include conjugation reactions and involve either esterification of the parent compound or a metabolite created by the phase I reactions. There are more than 20 different CYPs in the CYP450 family in human liver.[50] CYPs are responsible for the most phase I reactions, and formation of reactive intermediates is more abundant in the centrilobular zone than in the periportal zone. Centrilobular necrosis is one of the characteristic features of severe DILI, so drug-metabolizing enzymes might mediate the pathogenesis of DILI.[12,51] Certain drugs can modify the hepatotoxic potential of other drugs by enzyme induction and lead to formation of reactive metabolites. [52] Examples of CYP inducers are rifampicin, phenytoin, isoniazid, smoking, and ethanol. Some drug metabolizing and detoxification pathways might increase the risk for hepatotoxicity from other drugs, but there is little in vivo evidence to support this model. In a meta-analysis of studies of hepatotoxicity from isoniazid and rifampicin, the incidence of liver injury was significantly greater among patients who received this drug combination than those who received either as a single agent.[53] Rifampicin, which can induce microsomal enzymes, seems to increase the risk of liver injury from isoniazid in frequency and latency.[53,54] Pyrazinamide was reported to increase the hepatotoxicity of isoniazid.[55]

The neuroleptic agent thioridazine is a potent inhibitor of CYP2D6 that increases the plasma concentrations of the antidepressant trazodone.[56] Interestingly, a combination of these drugs was reported to cause a case of fatal liver injury.[57] Simvastatin is metabolized primarily by CYP3A4 and amiodarone is a recognized inhibitor of this enzyme; and interaction between these 2 might have accounted for hepatotoxicity in a 72-year-old man with concomitant rhabdomyolysis.[58] Similarly, severe hepatotoxicity likely resulted from an interaction between raloxifene and fenofibrate because of CYP3A4 inhibition.[59]

The risk of valproate hepatotoxicity is increased by concomitant use of other anticonvulsants, presumably because of increased formation of reactive intermediaries during valproate metabolism.[60,61] Covalent binding of these reactive metabolites normally is prevented by their conjugation with glutathione and subsequent urinary excretion because N-acetylation (NAC) conjugates (NAC I and II) in states of their increased formation.[62] One study demonstrated high levels of NAC I and II in patients given valproate in combination with other anticonvulsants.[61] Failure to detoxify these intermediates (eg, decreased glutathione pool or genetic variants) might lead to their accumulation, binding to liver proteins, and hepatotoxicity. However, another study did not associate serum or urine levels of 4-ene valproate with hepatotoxicity.[62]

Alcohol Consumption

Although the effects of acute and chronic alcohol use on the risk of acetaminophen hepatotoxicity are well established,[63] the role of alcohol in idiosyncratic DILI is less clear. Alcohol consumption is one of the criteria in the RUCAM causality assessment instrument, although there is no evidence that alcohol consumption increases the risk of liver injury from medications other than methotrexate, isoniazid, or halothane.[12] Consumption of large amounts of alcohol increases the risk of fibrosis/cirrhosis in long-term users of methotrexate.[64,65] However, methotrexate alone might not cause severe liver fibrosis, other risk factors such as diabetes mellitus type 2, overweight, and heavy use of alcohol might contribute. [66,67] Chronic alcohol abuse might increase the hepatotoxicity of antituberculosis (anti-TB) drugs,[68,69] possibly from alcohol-mediated induction of hepatic CYP2E1. However, other studies have shown that alcoholics might not have an increased risk of hepatotoxicity from isoniazid or other anti-TB drugs.[22,70,71] Studies that associated alcohol with risk for idiosyncratic DILI[12] might have been confounded by patients' poor nutritional status and older age. Prospective registries did not find a significant association between alcohol consumption and the severity or chronicity of DILI.[10,72] Although the package insert for duloxetine states that to prevent hepatotoxicity individuals with substantial alcohol consumption should not take the drug, there are no published data to show that alcoholism increases the risk of duloxetine hepatotoxicity. Additional studies are needed to determine the relationship between alcohol consumption and idiosyncratic DILI.

Underlying Disease States

There is controversy about whether chronic liver disease increases the risk for DILI. There is a belief that patients with chronic liver disease and cirrhosis are not necessarily prone to DILI,[12,73,74] but patients with preexisting liver disease are at higher risk for complicated courses and adverse outcomes from DILI. A limited number of studies systematically have evaluated the safety of drugs in patients with pre-existing liver disease. Patients with increased baseline levels of aminotransferases have an increased risk of statin-induced hepatotoxicity.[75] Several other studies confirmed the safety of statins in patients with chronic liver disease, including nonalcoholic fatty liver disease and hepatitis C.[76–78] One study reported that nonalcoholic fatty liver disease significantly increased the risk of DILI in middle-aged men,[68] compared with men with hepatitis C (2.4% vs 0%; $P < .05$).[79] Small sample sizes and other methodologic issues limit the validity of these observations. In a study of the clinical characteristics and outcome of disulfiram-associated liver injury, no differences in outcomes were related to pretreatment levels of enzymes.[80] Some studies indicated that hepatitis B or C might be risk factors for hepatotoxicity of anti-TB agents,[81–83] whereas others did not confirm these findings.[84] Many confounding factors must be considered in interpreting results from these studies; patient groups were not stratified according to hepatitis B virus (HBV) replication status and fluctuations in HBV-DNA levels and aminotransferase activities are common in these patients.[85] The increased levels of ALT might have arisen from viral replication rather than hepatotoxicity. A greater proportion of patients with hepatitis C who were given anti-TB drugs developed hepatotoxicity than those without hepatitis C.[86] Highly active antiretroviral therapy has been associated with hepatic adverse reactions in patients co-infected with hepatitis B or C and human immunodeficiency virus, compared with patients without chronic viral hepatitis. [87–91] Furthermore, patients co-infected with human immunodeficiency virus and hepatitis C virus but cured of hepatitis C by interferon therapy were significantly less likely to show signs of hepatotoxicity to highly active antiretroviral therapy than nonresponders.[92] However, patients with chronic hepatitis C have spontaneous fluctuations in levels of ALT and aspartate aminotransferase, so these factors are difficult to associated with drug-induced hepatotoxicity.[93] Hepatitis B and C might increase susceptibility to DILI from anti-TB agents and highly active antiretroviral therapy, but studies are needed to specifically address

this hypothesis. A recent case series illustrated the difficulties in interpreting abnormal liver test results in patients with human immunodeficiency virus and HBV co-infection.[94] In these patients, aminotransferase levels increased significantly 6–12 weeks after highly active antiretroviral therapy began[94]; however, during the follow-up period, liver test results improved despite restarting or continuing the implicated medications.[94]

Other diseases might increase the risk of DILI, such as the higher risk of methotrexate-induced liver injury observed in patients with psoriasis, compared with patients with rheumatoid arthritis.[95,96] However, confounding factors such as age, obesity, diabetes mellitus, and use of other potentially hepatotoxic drugs limit the validity of these observations. Obesity and diabetes mellitus are risk factors for methotrexate-induced hepatotoxicity.[65,66] In 2 studies that tested rifampin for treating pruritus in patients with primary biliary cirrhosis, there was an increased frequency of hepatotoxicity (12.5% and 7.3%)[97,98]; similarly, rifampin might have caused DILI in 5% of patients when administered to treat brucellosis.[99]

Genetic Risk Factors

Because of their rarity and unpredictability, idiosyncratic DILI events are considered to have a strong genetic basis,[12,15–19] but significant association between certain genetic traits and DILI has been shown for only a few compounds.[15–18,100] Even when such an association has been observed, generally the odds ratio (OR) of a given haplotype to increase the risk of DILI has been rather low (with the exception of flucloxacillin).[100] DILI is likely a complex genetic disorder in which multiple genetic variants along with environmental risk factors are responsible for liver injury. Unraveling the genetic basis for DILI has been and will remain challenging because of the vast number of compounds that can cause DILI, its rarity and variable clinical presentation, and diagnostic difficulties.

Genetic studies conducted to date largely have been hypothesis-driven and involved a candidate compound–candidate gene approach.[15–19] These studies predominantly have focused on drug disposition and immunologic mechanisms. More recently, a few genome-wide association studies of DILI caused by individual compounds have been published (vide infra). Several consortia (DILI network, DILIGEN, Spanish Hepatotoxicity Registry, and Serious Adverse Event Consortium) are collecting genomic DNA from patients with well-phenotyped DILI and novel observations are starting to emerge from their work.[101–103] A multistep model of the mechanistic and genetic basis for idiosyncratic DILI has been proposed.[15,16,21] It involves upstream drug-specific pathways that generate reactive metabolites and downstream common pathways that cause cell stress and death, either directly or through immune-mediated mechanisms.

Variations in Phase 1 Drug-Metabolizing Enzymes

Formation of toxic reactive metabolites by cytochrome P450 enzymes (CYPs) is considered to be required for the pathogenesis of DILI.[19–21] There is considerable interindividual variation in the activity of different CYPs and many CYPs are polymorphic. Several studies have investigated their role in the pathogenesis of idiosyncratic DILI, but evidence is not strong to support their role, except for a few compounds.[16]

CYP3A is the most abundant and most important phase 1 enzyme; it consists of 3 isoforms: 3A4, 3A5, and 3A7. *CYP3A4* is not polymorphic whereas *CYP3A5* and *CYP3A7* are. There is no evidence to associate variations in *CYP3A* with DILI.

CYP2C9 is an important phase 1 enzyme involved in the metabolism of several important therapeutic agents such as nonsteroidal anti-inflammatory drugs, phenytoin, and warfarin.

CYP2C9 shows functional polymorphism (CYP2C9*1,*2, and *3)[104]; some polymorphisms initially were associated with diclofenac hepatotoxicity,[105] but subsequent studies failed to confirm any significant association.[106–108]

CYP2C19 is another important phase 1 enzyme that also has functional polymorphisms. It metabolizes proton pump inhibitors, antidepressants, and antiepileptics. A case-series study of 3 patients with atrium hepatotoxicity[109] and a small case-series study of troglitazone hepatotoxicity indicated a role for CYP2C19 polymorphisms, [110] but there are no other strong data to implicate CYP2C19 genetic polymorphism in causing DILI. The Spanish registry failed to show significant enrichment of CYP2C9 and CYP2C19 polymorphisms in a well-characterized cohort of DILI patients.[111]

CYP2D6 is highly polymorphic and metabolizes opiates, antidepressants, β-blockers, and anti-arrhythmic agents. Polymorphisms in CYP2D6 have been associated with hepatotoxicity from perhexiline, senna, chlorpromazine, and other drugs.[16] *CYP2E1* is polymorphic but it is not clear how variants affect the function of the gene or its product. Nonetheless, there is some evidence that CYP2E1 mutant genotypes can lower the risk of isoniazid hepatotoxicity, compared with the CYP2E1*1A/*1A genotype (vide infra).[112–114] *CYPs* are the usual and first suspects in DILI pathogenesis, but studies do not support a major role for their variants in this process.

Variations in Phase 2 and Detoxifying Enzymes

N-acetylation is an important phase II reaction and N-acetyltransferase 2 (NAT2) has been implicated in DILI.[115–119] NAT2 is highly polymorphic and there is interindividual variability in its metabolic activity. NAT2*4 has the highest acetylation activity, whereas *5,*6, and *7 reduced enzymatic activity. Slow rates of acetylation have been associated with increased risk of hepatotoxicity from sulfonamides and isoniazid[115,117] and also were associated with severe isoniazid hepatotoxicity. [112] Isoniazid is metabolized primarily in the liver, initially by NAT2 into acetyl-isoniazid; this is hydrolyzed rapidly into acetyl-hydrazine, which is either oxidized by CYP2E1 into toxic reactive metabolites or acetylated to form diacetyl-hydrazine.[112,120] “Slow acetylators” presumably do not detoxify acetyl-hydrazine rapidly, promoting oxidation by CYP2E1 into toxic intermediaries. A recent meta-analysis showed a strong relationship between *NAT2* genotype and isoniazid hepatotoxicity in Asians (OR, 2.52).[114] *NAT2* and *CYP2E1* polymorphisms might act synergistically to affect predisposition to isoniazid hepatotoxicity.[112] Huang et al[112] showed that NAT2 slow acetylators (*CYP2E1* c*1/c1* genotype) were at significantly higher risk of isoniazid hepatotoxicity than rapid acetylators (*CYP2E1 c1/c2 or c2/c2* genotypes; OR, 7.43).

Glutathione S-transferase and manganese superoxide dismutase (MnSOD) defend against cellular oxidative stress, so their roles in DILI have been explored. In human beings, cytosolic glutathione S-transferases T1 and M1 enzymes are polymorphic; their reduced expression could affect these pathways. This hypothesis recently was tested in 154 patients with idiosyncratic DILI caused by multiple agents, 250 age- and sex-matched population controls, and 88 medication-matched controls. [121] Individuals with *glutathione S-transferase T-* and *glutathione S-transferase M1*-null genotypes had significantly higher risk of DILI compared with individuals who expressed these gene products (OR, 2.70). This relationship persisted for DILI caused by antibacterials (n = 44; OR, 3.12) and nonsteroidal anti-inflammatory drugs (n = 19; OR, 5.61). However, it is possible that the relationship between these null genotypes and DILI could be accounted for by the relationship between null genotype and antibacterial and nonsteroidal anti-inflammatory drug DILI. When investigators reanalyzed the data, they found no significant association between null

genotypes and DILI from agents other than antibacterials and nonsteroidal anti-inflammatory drugs (n = 92; OR, 1.97) (Dr Lucena, personal communication).

MnSOD is a mitochondrial enzyme that detoxifies reactive oxygen species into hydrogen peroxide, which is reduced to water by either catalase or glutathione peroxidase. *MnSOD* is functionally polymorphic and specific alleles (*genotypes C/C or C/T*) import greater levels of MnSOD protein into the mitochondrial matrix, with 30%–40% increases in activity. In a study of 115 patients with DILI caused by multiple agents (63 from anti-TB agents) and 115 matched controls, individuals with the *MnSOD C/C* or *C/T* genotypes had a significantly higher risk for overall DILI (OR, 2.44) or DILI from anti-TB medications (OR, 2.47).[122] It is unclear how increased MnSOD activity might increase the risk of hepatotoxicity, but there might be increased production of hydrogen peroxide.[122]

Although glucuronidation is a detoxification process, it sometimes can generate toxic reactive intermediaries. Diclofenac undergoes glucuronidation by UGT2B7 to produce acyl glucuronide[123]; acyl glucuronides of diclofenac can undergo acyl migration and imine formation or nucleophilic displacement—either can cause irreversible binding to hepatic macromolecules.[124] In a rat model of diclofenac hepatotoxicity, formation of diclofenac adducts was prevented by glucuronidation inhibitors, indicating that glucuronidation of diclofenac might induce formation of adducts.[125] Furthermore, these adducts were localized mostly in zone 3 of the liver lobule, indicating that diclofenac adducts might have a role in the hepatotoxicity.[125] Although diclofenac predominantly is metabolized by CYP2C9, polymorphisms do not appear to be a risk factor for diclofenac hepatotoxicity.[126] In contrast, polymorphisms in UGT2B7 and CYP2C8, enzymes that generate reactive diclofenac metabolites, were risk factors for diclofenac hepatotoxicity.[123] In the same study, an allelic variant of *ABCC2*, which encodes multidrug resistance protein (MRP2), which mediates biliary excretion of reactive metabolites, was associated with diclofenac hepatotoxicity.[123] Patients with at least one *UGT2B7*2* allele were at significantly higher risk for diclofenac-induced hepatotoxicity (OR, 8.5) compared with patients who took diclofenac but had no liver injury or healthy controls.[123] It is conceivable that patients who develop diclofenac hepatotoxicity are rapid glucuronidators who have high concentrations of the unstable and reactive acyl glucuronide in their hepatocytes.

Hepatobiliary Transporters

Hepatic detoxification of xenobiotics results in their anionic conjugates with glutathione, sulfate, and glucuronate. These conjugated xenobiotics become substrates for hepatic drug transport, another potential step for drug hepatotoxicity.[127,128] Drug metabolites actively are transported across hepatocyte membranes by transporters (uptake or efflux transporters) on the canalicular or the apical membranes.[127,128] In the liver, transport at the basolateral membrane involves the organic anion-transporting polypeptide and in the organic anion transporter. [127] Limited data exist on defects in these uptake transporters and associated hepatotoxicity.[127] Basolateral transport processes probably determine hepatic exposure to drugs and their metabolites, which reach the canalicular membrane,[129] but their inhibition does not appear to increase the risk of hepatotoxicity.[130] However, inhibition of efflux proteins can lead to cholestatic liver injury caused by certain compounds or their metabolites. [128] The efflux of drugs into bile involves canalicular transporters of the MRP family, which includes the glycoproteins MDR1 (*ABCB1*), MDR3 (*ABCB4*), MRP2 (*ABCC2*), and bile salt export pump (BSEP, *ABCB11*).[128] Drugs that inhibit export on the canalicular side through inhibition of BSEP can lead to cholestasis in susceptible subjects.[128] Cholestatic liver injury from sulindac, flucloxacillin, terbinafine, and bosentan have been associated with inhibition of the canalicular BSEP.[131–133] The endothelin antagonist, bosentan (used to treat pulmonary hypertension) inhibits BSEP, leading to accumulation of toxic bile acids within the hepatocytes.[134,135] In a recent study of 110

human liver samples obtained at the time of resection for focal lesions, there was significant interindividual variability in canalicular levels of BSEP, MDR3, MDR2, and MRP2 proteins. For example, 30% of samples contained high levels of these transporters whereas 32% had low or very low levels.[136] Limited data are available on the relationship between their polymorphisms and susceptibility to DILI.[137] However, familial intrahepatic cholestasis and intrahepatic cholestasis of pregnancy have been associated with polymorphisms or mutations in BSEP and MDR3[137,138]; patients with intrahepatic cholestasis during pregnancy are at increased risk for cholestatic liver injury when they take oral contraceptives.[139,140] Furthermore, mutations in BSEP have been associated with cholestatic episodes in patients taking antibiotics or nonsteroidal anti-inflammatory drugs.[141] Mutations that disrupt BSEP function have been identified in patients with a history of drug-induced cholestasis.[142] Patients who carry mutations in genes that encode BSEP or MDR3 have a 3-fold increase in risk of cholestatic liver injury from oral contraceptives, certain antibiotics, proton pump inhibitors, and psychotropic drugs.[142] Further studies are needed to identify defects in the transporter proteins that can mediate pathogenesis of DILI.

Immunologic Mechanisms

The innate and acquired immune systems are each involved in the pathogenesis of idiosyncratic DILI; these might represent the most important events in the pathogenesis of DILI.[19–21] Eosinophilia in peripheral blood and/or in the liver of a patient with acute liver injury supports a diagnosis of DILI.[51] Hypersensitivity features such as rash, fever, and eosinophilia are observed in 25%–30% of patients suspected of having DILI.[10,143] However, liver injury might have an immunologic basis in patients without obvious clinical or biochemical evidence of hypersensitivity reactions.[144,145] Most patients suspected to have DILI from hepatotoxic drugs have evidence of an inflammatory response in liver biopsy samples, [145] but this response could be a consequence of liver injury rather than a cause of DILI. A number of studies have shown a strong relationship between genetic polymorphisms that influence immune function (eg, HLA class II antigens or cytokines) and risk of DILI.[15–18] The hapten, danger, and pharmacologic interaction hypotheses all have been proposed to mediate DILI pathogenesis (for review see Uetrecht,[19,20] Kaplowitz,[21] and Pichler[146]). Idiosyncratic DILI from hepatotoxic drugs might arise from immune-mediated haptenization of reactive metabolites and subsequent danger signals that activate the immune response.

Association Between DILI and Specific HLA Haplotypes

There is evidence for an association between polymorphisms in HLA class II antigens and adverse drug reactions; specific HLA haplotypes have been associated with nonhepatic[147,148] and hepatic adverse reactions (Table 3).[144,149–151] An association between *HLA-B*5701* and abacavir hypersensitivity led to the concept that prospective testing for this allele might minimize the risk of abacavir hypersensitivity.[152] In a prospective, doubleblind study of a predominantly white population, not administering abacavir to individuals with the *HLA-B* 5701* allele virtually eliminated the immunologically confirmed hypersensitivity reactions (OR, 0.03).[152]

One of the first HLA haplotypes associated with DILI, *HLA B1*1501-DRB5*0101-DQB1*0602*,[149] is carried by approximately 57% of patients with amoxicillin/clavulanate-induced DILI, but in only 12% of healthy bone-marrow donors.[149] Two subsequent studies from the United Kingdom confirmed the association between *HLA DRB1*15* and liver injury amoxicillin/clavulanate.[101,153] A more recent study based on the Spanish Registry did not confirm this association, but patients with amoxicillin/clavulanate-associated DILI had a significantly higher prevalence of *HLA-DQR1*06* than controls.[154] Liver injury from anti-

TB reagents has been associated with specific HLA II alleles[150]; in a study of 56 North Indian patients with DILI and 290 controls (also exposed to anti-TB medicines), the presence of the *HLA-DQB1*0201* allele (adjusted OR, 1.9) or a lack of *HLA-DQA1*0102* (adjusted OR, 4.0) were associated independently with liver injury from anti-TB medicines.[150] These observations require validation.

In 2 case series consisting of a relatively modest number of patients with DILI suspected to be caused by different agents, no specific HLA alleles were associated with DILI.[154,155] However, Andrade et al[154] reported a potential association between specific HLAs and DILI phenotype. Compared with patients with hepatocellular DILI, those with cholestatic/mixed DILI had a significantly higher frequency of *HLA-DRB1*15* and *HLA-DQB1* 06* alleles and a lower frequency of *DRB1*07* and *DQB1*02* alleles.[154] Further studies are warranted to investigate the relationship between genetic variations and DILI phenotype.

Recent genome-wide association studies associated specific HLA alleles with DILI caused by ximelagatrin and flucloxacillin.[102,144] Ximelagatran is an oral thrombin inhibitor that was withdrawn from the market because of serious hepatotoxicity—a somewhat surprising finding because it is not metabolized by the liver. Kindmark et al[144] conducted genome-wide association studies and a large, candidate gene analysis study of DNA from 74 patients with ALT levels greater than 3 times the upper limit of normal with ximelagatran and 130 treated individuals without hepatotoxicity. Increased levels of ALT were associated with the major histocompatibility complex alleles *DRB1*07* (OR, 4.41) and *DQA1*02* (OR, 4.41) and this association was validated in a study of 10 cases and 16 controls.[144] They also reported corroborative immunologic studies supporting the biological significance of *DRB1*07* in ximelagatran-induced liver injury. Daly et al,[102] under the auspices of the DILIGEN and International SAE consortium, recently reported the results of their landmark genome-wide association studies of flucloxacillin DILI (51 cases, 282 matched controls, and 64 controls who received flucloxacillin without liver injury). This study showed an association peak in the major histocompatibility complex region with the strongest association observed for rs2395029 [G] ($P = 8.7 \times 10^{-33}$), a marker in complete linkage disequilibrium with *HLA-B* 570.1*.[102] Direct genotyping for *HLA-B*5701* in 51 cases and 63 drug-exposed controls revealed a very strong relationship between this allele and flucloxacillin-induced liver injury (OR, 80.6). This finding was confirmed in 23 replication cases (OR, 100), but unfortunately a separate control group was not used for this comparison.[102] There were additional significant single nucleotide polymorphisms (*HLA DRB1*0701*, *tumor necrosis factor rs361525*, *tumor necrosis factor rs1799964*, HSPAIL *rs2227956*), but their significance was deemed not independent of *HLA-B* 5701*. Although the association between *HLA-B*5701* and DILI was a remarkable discovery, it was estimated that only 1 in every 500–1000 individuals who carry *HLA-B*5701* will develop liver injury upon receiving flucloxacillin (an estimated population attributable fraction was 0.64).[102] Many other undiscovered genetic variations are likely to be determinants of flucloxacillin-induced liver injury.

Dysregulation of Cytokines

Dysregulation of cytokine production also might mediate the pathogenesis of DILI in a non–medication-specific manner. Aithal et al[125] investigated polymorphisms in interleukin (IL)-10, IL-4, and IL-4 receptors in 24 patients with diclofenac-induced liver injury, 48 diclofenac-exposed controls, and as many as 321 healthy controls; they observed a higher frequency of IL-10 and IL-4 variants in patients with diclofenac-induced DILI compared with controls. The investigators speculated that polymorphisms that increase IL-10 or reduce IL-4 expression might contribute to a T-helper cell 2–mediated antibody response to diclofenac-induced neoantigens. Pachkoria et al[156] investigated IL-10, IL-4, and tumor necrosis factor-α genetic polymorphism in 140 patients with DILI from different agents and

268 healthy controls. IL-10 haplotypes that reduced expression levels were more common in patients with DILI without peripheral eosinophilia (OR, 5.29). All DILI cases with serious outcomes carried haplotypes that resulted in low or intermediate levels of IL-10 expression, and had normal or low numbers of eosinophils.[156] The investigators attempted to correlate *IL-10* genotypes with the severity of liver injury, but the study included too few cases of severe liver injury for this analysis.

Mitochondrial DNA Mutations

Some drugs (eg, valproate, salicylate, and antiretroviral agents) cause liver injury through mitochondrial toxicity; a recent preliminary study associated mitochondrial DNA mutations with liver injury caused by some compounds.[103] Seventeen patients with suspected valproate hepatotoxicity enrolled in the DILI network studies were assessed for genetic variations in the *mitochondrial DNA polymerase gamma* (*POLG*) gene. *POLG* was sequenced and the frequency of genetic variants was compared between cases and historical controls. Common heterozygous genetic variants of POLG were associated significantly with valproate hepatotoxicity (OR, 23.6). The investigators speculated that impaired liver regeneration caused by genetically impaired POLG activity may play a role in the pathogenesis of valproate hepatotoxicity.[103]

Future Directions

DILI is a problem that is important not only to patients, but also to physicians, regulatory agencies, and drug developers. Although we have gained insight into its pathogenic mechanisms, we have much to learn about its clinical manifestations and factors that might be used in the diagnosis and determination of prognosis. Prospective registries are an important source of data, but firm and systematically established postmarketing surveillance methods urgently are required. Pharmaceutical companies and regulatory agencies have large amounts of data from early- and late-stage clinical trials, but because of confidentiality and proprietary issues it is difficult to evaluate and compare these data and there is no easy access for academic investigators. The annual workshops organized by the United States Food and Drug Administration/CDER-AASLD-PhRMA HepTox Steering Group might be a starting point for initiating discussions on data sharing and building partnerships beyond the current boundaries. Liver injury from dietary supplements is another area that requires more data collection and analysis to better understand its epidemiology and pathogenic mechanisms.

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.

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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.

Table 2

Relationship Between Daily Doses of Oral Medications and Hepatic Adverse Events

Outcome	≤10 mg (n = 54)	10–50 mg (n = 83)	≥50 mg (n = 93)	*P* value
ALT > 3 × ULN, n (%)	10 (19)	22 (27)	29 (31)	.10
Jaundice, n (%)	18 (33)	33 (40)	42 (45)	.16
Liver failure, n (%)	9 (17)	10 (12)	30 (32)	.009
Death, n (%)	6 (11)	9 (11)	26 (28)	.004
Transplant, n (%)	0 (0)	2 (2)	12 (13)	<.001

ULN, upper limit of normal.

Reproduced from Lammert et al.[35]

Table 3

Summary of Various Studies That Investigated or Identified Relationships Between HLA Antigens and DILI

Study and location	DILI compound	Cases and controls	Type of study	Significant HLA allele(s)	Frequency cases vs controls	Result *P* value, OR (95% CI)
Hautekeete et al,[149] 1999 Belgium	Amox/clav	35 cases 60 bone marrow donors	CGAS	HLAB1*1501	57% vs 12%	*P*c < .0002
O'Donohue et al,[153] 2000 UK	Amox/clav	22 cases 134 controls	CGAS	HLAB1*1501	70% vs 20%	$P = 2.5 \times 10^{-6}$ OR, 9.25 (95% CI, N/A)
Donaldson et al,[101] 2008 UK	Amox/clav	52 cases 39 controls 189 population controls	CGAS	DRB1*15 DRB1*07 (protective allele)	50% vs 30% N/A	*P* = .0032 OR, 2.45 (95% CI, 1.37–4.8) Versus community controls 0.2 (0.02–0.59, *P*c = .02) Versus exposed controls 0.13 (0.04–0.44, *P*c = .0062)
Andrade et al,[154] 2004 Spain	Amox/clav	27 cases 635 controls	CGAS	DQB1*06	74% vs 41%	*P*c = .015 OR, 4.14 (1.73–9.95)
Sharma et al,[150] 2002 India	Anti-TB	56 cases 290 controls	CGAS	DQB1*0201 DRA1*0103 (protective allele)	52% vs 23% 6% vs 39%	2.1 (1.0–4.18) 0.2 (0.04–0.69); *P*c = .01
Donaldson,[151] 2008 UK	Diclofenac	4 cases 189 population controls	GGAS	DRB1*13 (protective) DRB1*04	0% vs 18% 45% vs28%	OR, 0.19 (0.02–1.45) Not significant
Berson et al,[155] 1994 France	Different compounds	71 2163 population controls	CGAS	HLA-A11	23% vs 12%	<.01 but *P*c = NS No significant differences in HLA B antigen, HLD DR and DQ antigens tested
Andrade et al,[154] 2004 Spain	Different compounds	140 cases 635 healthy controls	CGAS	No differences in DRB1 and DQB antigens between cases and controls		Compared with hepatocellular DILI, cholestatic/mixed had significantly higher prevalence of DRB1*15 and DQB1*06 and significantly lower prevalence of DQB1*02 antigens
Kindmark et al,[144] 2008 Northern Europe	Ximelagatran	74 cases 130 treated controls	GWAS	DRB1*07 DQA1*02	26% vs 8.5%	4.41 (2.22–8.87) ($P = 9.1 \times 10^{-6}$) 4.41 (2.21–8.8) ($P = 1.3 \times 10^{-5}$)
Daly et al,[102] 2009 UK	Flucloxacillin	51 original and 21 replication cases 282 population controls 64 drug exposure controls	GWAS	DRB1*5701	83% vs 6.3% 87% replication cases vs 6.3% controls	80.6 (22.8–284.9) $P = 8.7 \times 10^{-33}$ 100.0 (20.6–485.8)

Amox/clav, amoxicillin/clavulanate; CGAS, candidate gene association study; GWAS, genome-wide association study; *P*c, corrected *P* value.