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The diagnosis and management of idiosyncratic drug-induced liver injury

Ammar Hassan | Robert J. Fontana

Division of Gastroenterology, Department of internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan

Correspondence: Robert J. Fontana, MD, Division of Gastroenterology, Department of internal Medicine, University of Michigan Medical School, 3912 Taubman Center, Ann Arbor, MI 48109 (rfontana@med.umich.edu).

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Abstract

Drug-induced liver injury (DILI) is an uncommon but important cause of liver disease that can arise after exposure to a multitude of drugs and herbal and dietary supplements. The severity of idiosyncratic DILI varies from mild serum aminotransferase elevations to the development of severe liver injury that can progress to acute liver failure resulting in death or liver transplantation within days of DILI onset. Chronic liver injury that persists for more than 6 months after DILI onset is also becoming increasingly recognized in up to 20% of DILI patients. Host demographic (age, gender, race), clinical and laboratory features at DILI onset have been associated with the severity and outcome of liver injury in DILI patients. In addition to cessation of the suspect drug, other medical interventions including the use of N-acetylcysteine and corticosteroids in selected patients have shown some clinical benefit, but additional prospective studies are needed. A number of promising diagnostic, prognostic and mechanistic serum and genetic biomarkers may help improve our understanding of the pathogenesis and treatment of idiosyncratic DILI.

KEYWORDS

acute liver failure, drug-induced liver injury, hepatotoxicity, liver transplantation

1 | OVERVIEW

Idiosyncratic drug-induced liver injury (DILI) is an uncommon but important cause of liver disease worldwide. To make a diagnosis of DILI requires a high index of suspicion after ruling out more common causes of liver injury, such as viral hepatitis, alcohol, autoimmune hepatitis and pancreaticobiliary disease. The lack of a confirmatory, objective laboratory test to identify the culprit agent remains problematic, particularly in patients taking multiple medications or herbal and dietary supplements (HDS) and in those with underlying liver disease. Nonetheless, a careful review of the temporal association between medication use and the laboratory and clinical profile at DILI onset allows one to confidently make a diagnosis of DILI.[1] The spectrum of liver injury in DILI patients ranges from mild to moderate serum alanine aminotransferase (ALT) or alkaline phosphatase (ALK) level elevations with or without jaundice that resolves within 6 months of drug discontinuation in most patients. However, some patients may develop rapidly progressive acute liver failure (ALF) or evolve into a smouldering chronic liver injury. A liver biopsy can help exclude competing causes of liver injury and help identify characteristic histological features associated with the suspect drug as well as provide prognostic information.[2]

Two recent population-based studies from Europe estimate that the annual incidence of DILI is 14 to 19 cases per 100 000 inhabitants.[3,4] However, many experts believe that the actual incidence of DILI is higher due to the difficulty in establishing a

Abbreviations: ALF, acute liver failure; ALFSG, acute liver failure study group; ALI, acute liver injury; ALK, alkaline phosphatase; ALT, alanine aminotransferase; AUROC, area under the receiver operating curve; DAMP, damage-associated molecular pattern; DILI, drug-induced liver injury; DILIN, drug-induced liver injury network; DRESS, drug-related eosinophilic systemic syndrome; GLDH, glutamate dehydrogenase; GWAS, genomewide association study; HDS, herbal and dietary supplements; HLA, human leucocyte antigen; HMGB1, high mobility group box 1; INR, international normalized ratio; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NAC, N-acetylcysteine; RUCAM, Roussel Uclaf Causality Assessment Method; SDH, sorbitol dehydrogenase; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

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diagnosis and under-reporting. The implicated agents that cause DILI vary substantially around the world (Table 1). Although antibiotics are the most commonly implicated agents in many DILI series, the most common individual antimicrobial agent varies, with antitubercular agents (particularly isoniazid) being most frequently implicated in Asian countries while amoxicillin-clavulanate is the most common suspect drug in both the USA and Spain.[5-7] Herbal and dietary supplements (HDS) are also widely used in many parts of the world and have accounted for a substantial and increasing proportion of DILI cases in Asia as well as Europe and North America.[8] The Drug-Induced Liver Injury Network (DILIN) recently reported that HDS products were the second leading cause of DILI in the USA accounting for 16% of cases.[6] In comparison, antihypertensives, antidiabetic agents and hypolipidaemic agents (eg statins) are infrequently (< 5%) implicated as a cause of DILI despite their widespread use.

Key points

- Idiosyncratic drug-induced liver injury is an infrequent but important cause of both acute and chronic liver injury.
- Host demographic, clinical and laboratory features at DILI onset are associated with the severity and outcome of liver injury in DILI patients.
- Management of suspected DILI after drug discontinuation is largely supportive, but pilot studies suggest that N-acetylcysteine and corticosteroids may prove safe and effective in selected patients.
- There are a number of promising diagnostic, prognostic and mechanistic serum and genetic biomarkers that may improve our understanding of the pathogenesis and treatment of idiosyncratic DILI

2 | SEVERE DILI

DILI patients with severe nausea and vomiting, coagulopathy or hypoglycaemia may require hospitalization. Patients with acute hepatitis and elevated prothrombin time or international normalized ratio (INR) levels without mental status changes are commonly categorized as having severe acute liver injury (ALI). A large case series of 386 hospitalized ALI patients reported by the US Acute Liver Failure Study Group (ALFSG) demonstrated a 3-week transplant-free survival rate of 87% in patients with idiosyncratic DILI.[9] In contrast, hospitalized patients with an elevated INR who develop hepatic encephalopathy have ALF and a much higher mortality.[10] In the USA, idiosyncratic DILI accounts for 13% of all ALF cases and is associated with a 3-week transplant-free survival rate of only 27%.[11] The most commonly implicated agents leading to ALF-related DILI in the USA are isoniazid, bactrim, nitrofurantoin and HDS products.[12] However, emergency liver transplantation offers an excellent survival benefit in these patients with an 88% 3-week survival after transplantation.[12] Series from countries with limited access to transplantation also demonstrate a low rate of spontaneous survival in ALF patients with DILI (9% vs 17%) (Table 2).[13]

TABLE 1 Aetiologies and outcomes of DILI in studies from around the world

Series	Chalasani et al (ref[6])	Andrade et al (ref[7])	Bjornsson et al (ref[3])	Suk et al (ref[8])	Takikawa et al (ref[85])	Devarbhavi et al (ref[13])
Country	USA	Spain	Iceland	Korea	Japan	India
Patients (n)	899	461	96	371	1,676	313
Mean age (years)	49	53	40-59	49	55	39
% female	59%	49%	56%	63%	57%	42%
Agents implicated	Antimicrobials (45%)	Antimicrobials (32%)	Antimicrobials (37%)	HDS (28%)	Antimicrobials (14%)	Antimicrobials (31%)
	HDS (16%)	CNS drugs (17%)	HDS (16%)	Non-HDS (17%)	CNS drugs (10%)	CNS drugs
	CVS agents (10%)	Musculoskeletal (17%)	NSAIDs (6%)	Pills, powder (6%)	HDS (10%)	(11%)
%HC/Chol/Mix	54%, 23%, 23%	58%, 20%, 22%	42%, 32%, 26%	76%, 9%, 15%	59%, 21%, 20%	58%, 23% 19%
% Txp or Death	9%	7%	1%	2%	2%	3%
% Chronic	17%	6%	7%	NA	NA	NA

HC, hepatocellular; Chol, cholestatic; Mix, mixed; CNS, central nervous system; NSAID, nonsteroidal anti-inflammatory drugs; HDS, herbal and dietary supplements.

TABLE 2 Outcomes of patients with ALF due to idiosyncratic DILI

Series	Reuben et al (ref[11])	Hillman et al (ref[86])	Zhao et al (ref[87])
Country	USA	USA	China
Total ALF cases	1198	2626	117
% ALF due to DILI	11%	8%	44%
% female	71%	33%	54%
% spontaneous recovery	27%	35%	23%
% requiring Txp	42%	36%	NA
% overall mortality	33%	31%	38%

In the USA, liver transplant candidates with chronic liver failure are prioritized for deceased donor liver transplantation (LT) using the Model for End-Stage Liver Disease (MELD) scoring system that is derived from bilirubin, INR, creatinine and sodium levels. However, highly selected patients in the intensive care unit with new-onset ALF of any aetiology are granted a MELD exception score of 40 and have greater access to emergency liver transplantation as a "Status 1" patient.[14] In Asia where access to deceased donor LT is more limited, some centres consider living donor LT for selected ALF patients.[15] Although living donor LT can be safely performed for ALF patients with survival rates similar to those undergoing deceased donor LT, concerns remain about whether donor candidates can be safely evaluated in a highly compressed time frame without undue coercion.[14,15]

3 | OUTCOMES IN PATIENTS WITH SEVERE DILI

Recently, DILIN reported on 24-month outcomes in 1089 consecutive high causality DILI patients enrolled into the ongoing Prospective registry study between 2003 and 2015.[16] This study showed a 10% fatality/transplant rate with the majority of adverse outcomes (92%) occurring within 6 months of DILI onset. However, not all cases of severe DILI rapidly progress to the loss of significant hepatic function that culminates in death or liver transplantation. In addition, ALF secondary to DILI can have a delayed or subacute presentation, with hepatic encephalopathy manifesting up to 26 weeks after jaundice onset.[17]

4 | DEMOGRAPHICS OF PATIENTS WITH SEVERE DILI

In a recent study of 771 Spanish DILI patients, 64% of those who progressed to ALF were female[18] while an even greater percentage (70%) of fulminant DILI cases were women in the ALFSG cohort of 113 patients.[12] However, the DILIN prospective registry study failed to show a significant association between female gender and outcomes in 899 consecutive DILI cases.[19] The basis for a possible gender predisposition to severe DILI may be related to differences in drug metabolism or hepatic adaptation to injury and regeneration.

Prior studies have also demonstrated that the age of ALF patients is inversely associated with the likelihood of liver regeneration and recovery. In addition, older individuals with DILI appear to be at increased risk for adverse clinical outcomes.[16] There are growing data on the role of racial and ethnic differences as well in patients with DILI.[20,21] A recent publication from DILIN found that not only did the causative agents differ between African Americans and Caucasians, African Americans were also more likely to have more severe cutaneous reactions and a greater degree of liver injury leading to worse outcomes.[20] The relationship between alcohol consumption and DILI susceptibility and outcome remains unclear. In a recent study of 1198 DILIN patients, heavy alcohol consumers had significantly higher serum ALT and total bilirubin levels compared to nondrinkers but the risk of a fatal outcome was not increased.[22]

In both animal and human studies, diabetes mellitus is an independent risk factor for severe DILI outcomes.[19,23-25] For example, one recent study demonstrated that overweight or obese patients were more likely to develop acetaminophen hepatotoxicity.[23] In addition, a recent study of 259 patients with inflammatory bowel disease receiving immunosuppressants demonstrated that those with baseline steatosis were more likely to develop liver injury.[24] The mechanism by which diabetic patients and those with underlying hepatic steatosis may be more susceptible to DILI remains unclear but possibly related to altered cytochrome-P450 or transporter expression resulting in aberrant drug pharmacokinetics or disposition. In addition, differences in hepatocyte autophagy, intrahepatic oxidative stress and ferroptosis in the setting of hepatic steatosis may play a role.[25]

Recent studies also demonstrate that individuals with certain class I and II human leucocyte antigen (HLA) alleles may be at increased risk of developing idiosyncratic DILI such as those with HLA-A*33:01 developing terbinafine and fenofibrate DILI.[21] However, there is less evidence supporting a link between specific genetic polymorphisms and poor outcomes in DILI patients.[26]

5 | INITIAL LABORATORY FEATURES IN PATIENTS WITH SEVERE DILI

Serum AST and ALT elevations do not reliably correlate with the degree of hepatic impairment, while increases in the INR are more indicative of loss of hepatic functional mass. Nonetheless, the degree of ALT elevation, as well as the serum AST/ALT ratio, was associated with the development of ALF and chronic liver injury in some DILI patients.[21,26-28]

In 1978, the late Hyman Zimmerman noted that the development of jaundice (ie total bilirubin >2.5 mg/dL) in DILI patients with acute hepatocellular liver injury (ie serum ALT > 3× upper limit of normal (ULN)) was associated with an estimated mortality of 10%.[27] This observation has been clinically evident in retrospective studies of

TABLE 3 Models to predict adverse outcomes in the setting of severe DILI

	Robles- Diaz M et al[18]		
	ALF/Txp = 32 (4.1%) of 771 DILI patients		
Model	ALT > 3 × ULN + TBL > 2 × ULN (Hy's law)	R ≥ 5 +TBL > 2 × ULN	Nr ≥ 5 + TBL >2 × ULN (New Hy's law)
Sensitivity	90%	83%	90%
Specificity	44%	67%	63%
AUROC	0.67	0.74	0.77

	Hayashi et al[16]		
	ALF/Txp = 68 (6.2%) of 1089 DILI patients		
Model	ALT > 3 × ULN + TBL > 2 × ULN (Hy's law)	Nr ≥ 5 + TBL >2 × ULN (New Hy's law)	MELD score
Sensitivity	52%	79%	90%
Specificity	71%	69%	75%
AUROC	0.60	0.73	0.83

DILI patients from Sweden and Japan.[3,29] However, the utility of "Hy's law" is limited in the clinical setting due to its low specificity for death.[30] To overcome this limitation, alternative models utilizing laboratory parameters at DILI onset have been developed to more accurately prognosticate clinical outcomes. These models include the *Nr* model (ALT or AST, whichever is highest, X ULN/ALP X ULN), which showed the best sensitivity and specificity in predicting ALF in the setting of severe DILI in a Spanish cohort[18] (Table 3).

Interestingly in the ongoing DILIN registry study, 64% of the deaths were primarily attributed to the DILI event while DILI had a secondary or contributory role in 14% and a nonhepatic cause of death was identified in the remaining 20% with advanced medical comorbidities (eg cancer, heart failure). Apart from older age, no significant demographic differences were seen between those with and without fatal outcomes. The study also assessed several different prognostic scores (Hy's Law, nR Hy's Law and MELD) at DILI onset as a predictor of liver-related death/transplant. The area under the receiver operating curve (AUROC) to predict mortality from DILI was 0.60 for Hy's law, 0.73 for nR Hy's Law, and 0.83 with a MELD score of >19 (Table 3).

6 | MANAGEMENT OF SEVERE DILI

Making a diagnosis of DILI requires a high index of suspicion due to the wide range of clinical manifestations and large number of culprit agents that can cause DILI. In that regard, utilizing resources such as the LiverTox database can provide clinicians with up-to-date diagnostic criteria and published clinical, laboratory and histological features of DILI attributed to over 900 drugs and 30 HDS products.[31] This e-textbook also includes annotated references and has new sections describing hepatotoxicity from selected HDS products (see https://livertox.nih.gov). A drug likelihood scale has also recently been developed that categorizes the hepatotoxicity potential of drugs according to the total number of published reports of bonafide hepatotoxicity with that agent.[32]

The current recommended treatment for all patients with DILI is to immediately withhold the offending drug once the diagnosis is suspected. Early discontinuation of the offending agent may help prevent the development and progression of further liver injury. However, the liver damage in many DILI patients is perpetuated after drug cessation via activation of the innate immune system and the development of a cytokine-driven acquired immune response.[28] Therefore, avoidance of exposure to other potentially hepatotoxic medications and substances, including alcohol, is also recommended for all DILI patients. Furthermore, oral enteral nutrition may be considered in severely ill hospitalized patients with inadequate caloric intake and fat-soluble vitamin replacement is advisable in patients with prolonged cholestasis at risk of developing micronutrient deficiencies.[33]

Gastric lavage and administration of activated charcoal that are used in acute acetaminophen overdose[31] and heavy metal poisoning[34] do not have a role in the primary management of idiosyncratic DILI as most drugs have been metabolized and cleared from the body by the time that DILI becomes apparent. While N-acetylcysteine (NAC) is of proven benefit in the treatment of acetaminophen overdose, recent data also support its use in preventing the development of ALF due to other drugs. A randomized controlled trial showed that prophylactic use of oral NAC reduced the incidence of hepatotoxicity associated with the use of antituberculosis medications.[35] Another double-blind randomized controlled study in 173 patients with non-acetaminophen–related ALF demonstrated that those treated with NAC had significant improvement in transplant-free survival as well as lower bilirubin and ALT levels compared to placebo-treated patients.[36] Similar findings have been reported in a recently published meta-analysis.[37] However, use of NAC in non-APAP–related ALF in children was not efficacious and therefore is not recommended.[38]

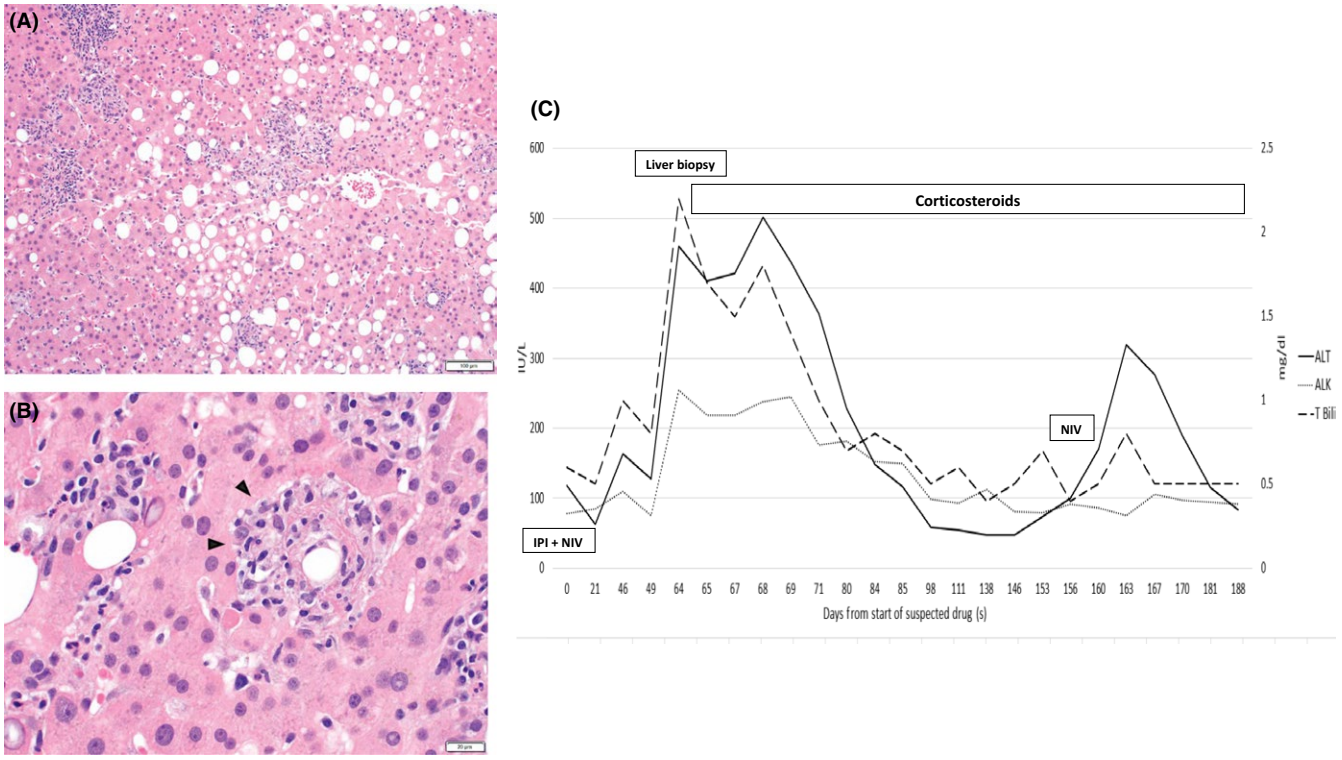

FIGURE 1 A 55-year-old man with metastatic melanoma to the liver was prescribed ipilimumab (IPI) and nivolumab (NIV) infusions at day 1 and day 21. At day 60, he presented to the emergency room with weakness and hypotension with ALT 460 IU/L, alk phos 255 IU/L and total bilirubin of 2.2 mg/dl. Initial ANA, SmAb and quantitative immunoglobulins were normal and a liver biopsy on day 64 after DILI onset showed (A) Active hepatitis and steatosis. The portal and lobular inflammation was composed mostly of macrophages and lymphocytes. (B). There were also multiple granulomas in the lobules, many with fibrin-ring granuloma morphology characterized by a central lipid vacuole, surrounding ring of fibrin, and epithelioid macrophages mixed with lymphocytes (arrowheads). MRI of the liver confirmed progression of his intrahepatic metastases and he was discharged home on high dose steroids. Due to disease progression (C) he was given another infusion of nivolubumab alone at day 156. However, his ALT increased to 170 IU/l and prednisone was increased to 100 mg per day and mycophenolate was added. However, disease progressed further with portal vein thromboses and he died at day 263 of metastatic disease with ALT of 135 U/L and total bilirubin of 5.8 mg/dl. (hematoxylin-eosin stain, original magnification x100 [A] and x400 [B]). Photomicrographs courtesy of Karen Choi, MD, University of Michigan.

Corticosteroids have been used in the setting of drug-induced hypersensitivity syndromes for many years.[39] In addition, prolonged high-dose corticosteroids are recommended in patients with drug-related eosinophilic systemic syndrome (DRESS) who frequently have concomitant hepatic biochemical abnormalities.[40] However, not all cases of drug-induced hypersensitivity reactions respond to corticosteroid administration, particularly in the setting of prolonged jaundice.[41] Corticosteroids have also been used in the treatment of DILI secondary to the use of tyrosine kinase inhibitors.[42] Lastly, ipilimumab, a monoclonal antibody that inhibits cytotoxic T-lymphocyte antigen-4 (CTLA-4), and the PD-1 inhibitors, nivolumab and pembrolizumab, are increasingly being used in the treatment of solid organ tumours.[43] These agents can cause a moderate-to-severe hepatitis in up to 10% to 20% of treated patients that present with severe acute hepatocellular injury within 6 months of treatment. Many of the patients in clinical trials with liver injury were treated with high-dose corticosteroids and/or mycophenolic acid once the serum ALT exceeded 3 × ULN. However, liver biopsy may be of benefit in oncology patients with suspected DILI to insure other causes of liver injury are excluded and stratify the risk for immune-mediated versus other histological phenotypes of injury[44,45] (see Figure 1).

The utility of ursodeoxycholic acid (UDCA) is largely provided via case reports and observational studies in patients with cholestatic DILI. Uncontrolled data suggest that UDCA may hasten liver injury recovery[46] or attenuate the risk of developing vanishing bile duct syndrome in some patients.[47] However, more recent studies from DILIN have failed to demonstrate similar benefits.[19] Bile acid binding resins such as cholestyramine are frequently used in DILI patients with severe cholestasis and pruritus.[48] These agents may also be beneficial in the "washout" of hepatotoxic drugs that have a long half-life and undergo enterohepatic circulation, such as leflunomide.[49]

Various nonpharmacological treatment strategies have also been studied in DILI patients. Silymarin is a combination of three flavonoids (silybin, silydianin and silychristin) that are the active ingredients of milk thistle which has shown promise in animal models of DILI.[50] However, prophylactic studies in patients receiving antituberculosis medications have been conflicting and inconclusive.[51] Glycyrrhiza

TABLE 4 Phenotypes of chronic DILI

Chronic DILI subtype	Commonly involved drugs	Clinical features
Autoimmune DILI (AI-DILI)	Nitrofurantoin Minocycline Statins Methyldopa	• Reactive hepatic metabolites bind to cellular proteins leading to immune activation. • Frequency of AI-DILI among those diagnosed with AIH is 9-13%.[88] • Diagnosis of AI-DILI remains difficult as it presents similarly to sporadic AIH regarding serum ALT levels and presence of autoantibodies (ANA, SMA)[89] • Immunosuppressive therapy indicated if injury does not resolve with drug cessation.[90]
Drug-induced hepatic steatosis	Microvesicular steatosis: Valproic acid Diltiazem Interferon NSAIDs Hypervitaminosis A Macrovesicular Steatosis: Oestrogen Tamoxifen Both macro- and microvesicular Steatosis: Amiodarone Methotrexate Didanosine	• (Microvesicular steatosis) Mitochondrial dysfunction with inhibition of beta-oxidation of fatty acids leads to diffuse deposition of lipid droplets in hepatocytes without displacement of nucleus.[91] • With extensive mitochondrial dysfunction, systemic complications such as hypoglycaemia, lactic acidosis and encephalopathy.[92] • (Macrovesicular steatosis) Intracellular drug deposition can lead to accumulation of intracellular phospholipids and/or altered hepatic lipid trafficking. • Large intracellular fat deposits with displacement of nucleus.[93]
Vanishing bile duct syndrome (VBDS)	Amoxicillin Ciprofloxacin Azithromycin Allopurinol Carbamazepine	• Typically occurs after a bout of severe cholestatic hepatitis.[94] • Progressive loss of intrahepatic bile ducts with cholestasis that can lead to hepatic failure.[95]
Drug-induced nodular regenerative hyperplasia (DI-NRH)	Thiopurines Platinum-based chemotherapy Hypervitaminosis A antiretroviral drugs (didanosine, stavudine)	• Latency of 6 months or more, minimal elevations in ALT and ALK <3 × ULN with clinical, radiological or endoscopic features of portal hypertension. • Liver biopsy shows nodularity with no or minimal inflammation.[96]
Drug-induced peliosis hepatitis	Anabolic steroids Oral contraceptive (Oestrogen) Tamoxifen Azathioprine	• Acquired vascular disorder with sinusoidal dilation and loss of endothelial barrier.[97] • Usually asymptomatic, mild ALT elevation but can present with vascular collapse due to intraabdominal bleeding[98] or progression to cirrhosis.[99]

glabra is a licorice derivative that has been used as a single agent or in combination with cysteine and glycine for the management of DILI, particularly in India and Japan.[52] A combination of monoammonium glycyrrhizinate-glycine-L-cysteine HCl (Monofit 20 mL/day) is also commonly used to treat acute DILI in Japan.[53] Glycyrrhizin is an aqueous extract of the licorice root and has exhibited in vitro hepatoprotection through cell membrane stabilization.[54] An European randomized controlled trial of glycyrrhizin showed improvement in serum ALT and hepatic necroinflammation and fibrosis in patients with chronic hepatitis C who were nonresponders to interferon.[55] Similarly, studies from Asia have shown beneficial effects with glycyrrhizin in patients with chronic hepatitis B.[56,57]

7 | CHRONIC DILI

While most cases of DILI resolve after discontinuation of the suspect drug, a minority of patients may go on to develop chronic liver injury. There is currently a lack of a consensus definition of what constitutes chronic DILI. DILIN has defined chronic DILI as persistent elevation

TABLE 5 Proposed DILI biomarkers

Biomarker	Clinical significance	Characteristics/limitations
Liver injury markers		
Sorbitol dehydrogenase (SDH)	Marker of hepatocyte injury	• Early marker of acute liver injury • Nonspecific
Glutathione S-transferase alpha (GSTα)	Elevated in liver injury (centrilobular hepatocytes) and renal injury	• Early marker of acute liver injury (serum) • Early marker of acute kidney injury (urine)
Bile acids	Elevated levels of endogenous bile acids due to impaired excretion from injured hepatocytes	• More specific indicator of liver injury than bilirubin • Elevated in other liver diseases (IHCP)
Glutamate dehydrogenase (GLDH)	Reflective of mitochondrial dysfunction	• Elevated in chronic liver disease not due to DILI
Micro-RNAs		
miR-122 miR-192	Noncoding, liver-specific RNAs released from damaged hepatocytes	• Elevated levels secondary to acute and chronic liver injury • Further validation analytical methods needed
Mechanistic biomarkers		
HMGB1	Marker of tissue necrosis	• Not liver specific
Acetylated HMGB1	Marker of activation of innate immune system	• Not liver specific • Requires mass spectrometry
Cytokeratin 18 fragments	Marker of tissue apoptosis (caspase-cleaved proteins)	
M-30	Marker of apoptosis	• Not liver specific • Prognostic validation ongoing
M-65	Marker of total apoptosis and necrosis	
Serum Cys-APAP adducts	Sensitive and specific marker of acetaminophen overdose	• Point of care testing in development • Therapeutic dosing vs intentional/unintentional overdose
Metabolomics		
Urine or serum metabolome	Measurement of endogenous metabolites generated in relation to drug exposure	• Still exploratory • Confounding by dietary, environmental, microbiome factors
Genetic polymorphisms		
HLA- B * 57:01	Flucloxacillin DILI (odds ratio 80)	• Strong NPV in flucloxacillin-treated Caucasians with unexplained cholestasis
HLA- A * 33:01	Mixed/ cholestatic DILI susceptibility (odds ratio 5.0) Terbinafine DILI (odds ratio 40)	• Identified with DILI due to multiple drugs in a large Caucasian cohort
HLA- B * 35:02	Minocycline DILI (odd ratio 29)	• Requires validation in other cohorts

of serum ALT, ALK or total bilirubin levels >1.25 × ULN or the baseline if abnormal at 6 months after DILI onset.[58] The DILI Expert Working Group use a shorter time period of 3 months of continued liver injury after recognition to classify a case as chronic DILI.[59] In contrast, the Spanish DILI registry defines chronic DILI as persistently elevated aminotransferase levels for more than 3 months after drug withdrawal in patients with hepatocellular injury or persistently elevated liver biochemistries for more than 6 months in patients with cholestatic/mixed liver injury.[7] A more recent analysis from the Spanish group suggested that persistence of liver biochemical abnormalities at 1 year after DILI onset may be more clinically relevant.[60]

Regardless of the definition of chronic DILI, a substantial number of patients who experience acute DILI progress to chronic liver injury during follow-up. The incidence of chronic DILI in DILIN, the Spanish registry and Iceland was reported at 19%, 6% and 7% respectively.[3,6,7] In the DILIN study, chronic DILI was more commonly seen in African American patients and those with a cholestatic laboratory profile at presentation.[6] Although a large number of drugs have been implicated in the development of chronic DILI, the most commonly identified agents in the DILIN study were amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole and azithromycin and antibiotics were over-represented in the Spanish study as well.[6,60] The phenotypes of persistent liver injury after acute DILI encompass a spectrum of clinical disorders (Table 4). Autoimmune-like DILI and cholestatic liver injury with progressive loss of intrahepatic bile ducts (vanishing bile duct syndrome) are well documented but infrequent long-term clinical and histological subtypes of chronic DILI.[59] Drugs that are more likely to lead to an autoimmune phenotype include minocycline, methyldopa, nitrofurantoin and hydralazine. However, whether drug-induced autoimmune hepatitis can be reliably distinguished from

sporadic AIH based upon liver histology and the types of infiltrating leucocytes, HLA genotype or outcomes after steroid withdrawal remain unclear.[61-63] A recent systemic review on chronic DILI described drug-induced fatty liver, focal nodular hyperplasia and peliosis hepatitis as additional subtypes that are increasingly recognized in long-term cancer survivors who received chemotherapy.

Currently, there are limited data on the long-term clinical outcomes of patients who develop chronic DILI.[60,64,65] A paper from DILIN that prospectively followed 99 patients with evidence of liver injury 6 months after DILI onset found that the majority (75%) had persistent liver damage 12 months after DILI onset. Older patients and those who had higher serum ALK levels at presentation were more likely to continue to have evidence of liver injury 12 months after DILI onset. Importantly, in those patients with baseline and follow-up liver biopsies, fibrosis progression was seen in two-thirds of cases. These findings suggest that patients with chronic DILI should be followed up closely to assess for late clinical and histological progression of liver disease.[66]

8 | NEW BIOMARKERS FOR DILI DIAGNOSIS AND PROGNOSIS

Establishing a diagnosis of DILI requires the exclusion of more common causes of liver injury, a temporal association between drug exposure and DILI onset, and compatible laboratory, clinical and pathological features during follow-up.[67] Causality assessment in DILI provides a semiquantitative estimate of the likelihood that a drug was involved in the observed illness and is essentially based upon "circumstantial evidence." To improve standardization and reproducibility in DILI diagnosis, liver-specific causality assessment instruments such as the Roussel Uclaf Causality Assessment Method (RUCAM) were developed from a consensus opinion of an expert panel in 1990 and "validated" from a group of 49 published DILI cases which had been rechallenged and compared to 28 controls.[68] Limitations of the RUCAM include ambiguous instructions for use, reliance on rechallenge, and lack of evidence supporting the weighting and selection of domains. In addition, the RUCAM performs poorly in the most severe cases of DILI that resulted in death, transplant or prolonged cholestasis mostly due to the lack of dechallenge data.[7] DILIN has developed causality assessment scales (range 1 = definite to 5 = unlikely) based on expert opinion that are more reliable and reproducible than the RUCAM.[69,70] However, expert opinion is not generalizable and requires knowledge of prior cases of liver injury for pattern recognition.

Currently available laboratory markers of liver injury (ie serum AST, ALT, ALK) are not sensitive or specific enough to detect early DILI nor are they able to reliably prognosticate the outcomes of such injury. This has led to a great interest in identifying novel serum biomarkers for DILI diagnosis and prognosis.[71] Biomarkers in development broadly fall into three categories: (A) dynamic liver injury markers that identify and quantify the degree of hepatocyte damage, (B) mechanistic markers that aim to elucidate the underlying cause of liver injury and (C) prognostic markers.[67] Serum biomarkers such as sorbitol dehydrogenase (SDH),[72] glutathione S-transferase[73] and glutamate dehydrogenase (GLDH)[74] have been studied in various forms of liver injury, including ischaemic hepatitis and DILI (Table 5). In particular, GLDH and microRNA-122 (miR-122) show promise as being more sensitive and specific biomarkers of liver injury than ALT, with promising results in animal models and clinical studies in patients with liver damage from various aetiologies.[75] However, further replication and validation studies are needed before these can be incorporated into clinical practice.

The nature of hepatocyte death, necrosis vs apoptosis, has been shown in animal models to be associated with a worsened laboratory and clinical course in the former. To this end, the use of an "apoptotic index" (AI) based on serum biomarkers has been proposed to estimate the relative contributions of apoptosis and necrosis in the setting of liver injury. This index utilizes assessment of the ratio of full-length cytokeratin 18 (K18) that is passively released from the liver in the setting of hepatocyte necrosis and caspase-cleaved cytokeratin 18 (ccK18) formed by caspase-mediated cleavage during apoptosis. Quantification of both total and caspase-cleaved K18 has been shown to exhibit enhanced sensitivity in the detection of DILI when compared to serum ALT.[76] The apoptosis index has also been studied as a prognostic tool, with a lower value (greater necrosis) indicative of a poorer likelihood of survival in patients with acetaminophen overdose.[77] A pilot study from DILIN also suggests that a lower apoptosis index may be associated with poorer outcomes in patients with idiosyncratic DILI.[78]

An important step in the presumed pathogenesis of idiosyncratic DILI is the release of damage-associated molecular patterns (DAMPs) that activate innate immune cells to release cytokines and chemokines that draw inflammatory cells into the liver, a prerequisite for a targeted, adaptive immune attack of the liver. Biomarkers reflecting the initiation and maintenance of an immune-based inflammatory process secondary to drug exposure can not only help in the earlier identification of such injury (before liver enzyme elevation) but may also help differentiate transient elevation of liver enzymes reflecting adaptation from the development of significant DILI. In this regard, high mobility group box 1 (HMGB1), a DAMP that can be detected in the serum in various isoforms demonstrates great promise.[79-81]

9 | GENETIC BIOMARKERS

Due to its low incidence in the general population, genetic variation in host receptors, metabolic pathways and immune response have been implicated in DILI pathogenesis. The first successful genomewide association study (GWAS) in DILI identified a very strong association between flucloxacillin-induced liver injury and HLA-B * 57:01, which was subsequently replicated in independent cohorts with an odds ratio of 80.[82] Currently, some experts advocate using HLA genotyping in flucloxacillin-treated patients who develop cholestasis as a diagnostic biomarker to help exclude the drug as a suspect agent (ie high negative predictive value).[83] More recently, Nicoletti et al demonstrated that HLA-A * 33:01 was a risk factor for cholestatic and mixed DILI in Caucasians from a number of drugs, including terbinafine, fenofibrate and ticlopidine.[21] Finally, we recently showed that HLA-B *35:02 was

over-represented in Caucasian patients with minocycline hepatotoxicity.[84] However, due to the small number of minocycline cases, replication cohorts are needed to confirm the value of testing for this allele in minocycline-treated patients presenting with liver injury.

Limitations in the current utilization of DILI biomarkers include (a) limited knowledge of performance characteristics of the tests in patients with idiosyncratic DILI versus other causes of liver injury and (b) lack of standardized assay methods and normal values. Nonetheless, novel biomarkers represent an exciting opportunity for us to improve the detection, prognostication and even treatment of patients at risk for severe idiosyncratic DILI.

10 | SUMMARY

Although DILI is an uncommon cause of liver injury associated with a variety of clinical phenotypes, substantial progress into the aetiologies, natural history and treatment of DILI has been made. Host demographic (age, gender, race), clinical (diabetes) and laboratory features (serum ALT, bilirubin, INR) at DILI onset have been associated with the severity and outcomes of liver injury in DILI patients. Pilot studies suggest that medical interventions such as the use of n-acetylcysteine and corticosteroids may provide benefit to some patients, but additional studies are needed. Lastly, the application of powerful genomic, proteomic and transcriptomic technologies holds promise to identify improved diagnostic, prognostic and mechanistic biomarkers that will enhance our understanding of DILI susceptibility and outcomes.

CONFLICT OF INTEREST

Dr. Fontana has received research grants from Abbvie, Gilead Sciences and Bristol-Myers Squibb. He also provides consulting services for Alnylam Pharmaceuticals. Dr. Hassan has no conflict of interests.

ORCID

Robert J. Fontana http://orcid.org/0000-0001-9161-5892

REFERENCES

1. Lee WM, Senior JR. Recognizing drug-induced liver injury: current problems, possible solutions. *Toxicol Pathol*. 2005;33(1):155-164.
2. Kleiner DE, Chalasani NP, Lee WM, et al. Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations. *Hepatology*. 2014;59(2):661-670.
3. Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology*. 2013;144(7):1419-1425. e1413.
4. Sgro C, Clinard F, Ouazir K, et al. Incidence of drug-induced hepatic injuries: a French population-based study. *Hepatology*. 2002;36(2):451-455.
5. Van Boeckel TP, Gandra S, Ashok A, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infect Dis*. 2014;14(8):742-750.
6. Chalasani N, Bonkovsky HL, Fontana R, et al. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. *Gastroenterology*. 2015;148(7):1340-1352. e1347.
7. Andrade RJ, Lucena MI, Kaplowitz N, et al. Outcome of acute idiosyncratic drug-induced liver injury: long-term follow-up in a hepatotoxicity registry. *Hepatology*. 2006;44(6):1581-1588.
8. Suk KT, Kim DJ, Kim CH, et al. A prospective nationwide study of drug-induced liver injury in Korea. *Am J Gastroenterol*. 2012;107(9):1380.
9. Koch DG, Speiser J, Durkalski V, et al. The natural history of severe acute liver injury. *Am J Gastroenterol*. 2017;112(9):1389.
10. Bernal W, Wendon J. Acute liver failure. *N Engl J Med*. 2013;369(26):2525-2534.
11. Ostapowicz G, Fontana RJ, Schiødt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med*. 2002;137(12):947-954.
12. Reuben A, Koch DG, Lee WM. Drug-induced acute liver failure: results of a us multicenter, prospective study. *Hepatology*. 2010;52(6):2065-2076.
13. Devarbhavi H, Dierkhising R, Kremers WK, Sandeep M, Karanth D, Adarsh C. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. In: Nature Publishing Group; 2010.
14. de Villa VH, Lo C-M, Chen C-L. Ethics and rationale of living-donor liver transplantation in Asia. *Transplantation*. 2003;75(3):S2-S5.
15. Liou IW, Larson AM. Role of liver transplantation in acute liver failure. *Semin Liver Dis*. 2008 May;28(2):201-209.
16. Hayashi PH, Rockey D, Fontana RJ, et al. Death and liver transplantation within two years of onset of drug-induced liver injury. *Hepatology*. 2017;66(4):1275-1285.
17. Bernal W, Auzinger G, Dhawan A, Wendon J. Acute liver failure. *Lancet*. 2010;376(9736):190-201.
18. Robles-Diaz M, Lucena MI, Kaplowitz N, et al. Use of Hy's law and a new composite algorithm to predict acute liver failure in patients with drug-induced liver injury. *Gastroenterology*. 2014;147(1):109-118. e105.
19. Chalasani N, Fontana RJ, Bonkovsky HL, et al. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology*. 2008;135(6):1924-1934. e1924.
20. Chalasani N, Reddy KRK, Fontana RJ, et al. Idiosyncratic drug induced liver injury in African–Americans is associated with greater morbidity and mortality compared to Caucasians. *Am J Gastroenterol*. 2017;112(9):1382.
21. Nicoletti P, Aithal GP, Bjornsson ES, et al. Association of liver injury from specific drugs, or groups of drugs, with polymorphisms in HLA and other genes in a genome-wide association study. *Gastroenterology*. 2017;152(5):1078-1089.
22. Dakhoul L, Ghabril M, Gu J, Navarro V, Chalasani N, Serrano J. Heavy consumption of alcohol is not associated with worse outcomes in patients with idiosyncratic drug-induced liver injury compared to non-drinkers. *Clin Gastroenterol Hepatol*. 2018;16(5):722-729.e2.
23. Chomchai S, Chomchai C. Being overweight or obese as a risk factor for acute liver injury secondary to acute acetaminophen overdose. *Pharmacoepidemiol Drug Saf*. 2018;27(1):19-24.
24. Schröder T, Schmidt KJ, Olsen V, et al. Liver steatosis is a risk factor for hepatotoxicity in patients with inflammatory bowel disease under immunosuppressive treatment. *Eur J Gastro Hepatol*. 2015;27(6):698-704.
25. Dara L, Liu ZX, Kaplowitz N. Mechanisms of adaptation and progression in idiosyncratic drug induced liver injury, clinical implications. *Liver Int*. 2016;36(2):158-165.
26. Kindmark A, Jawaid A, Harbron C, et al. Genome-wide pharmacogenetic investigation of a hepatic adverse event without clinical signs

of immunopathology suggests an underlying immune pathogenesis. *Pharmacogenomics J*. 2008;8(3):186.
27. Zimmerman HJ. *Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver*. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.
28. Mosedale M, Watkins PB. Drug-induced liver injury: advances in mechanistic understanding that will inform risk management. *Clin Pharmacol Ther*. 2017;101(4):469-480.
29. Ohmori S, Shiraki K, Inoue H, et al. Clinical characteristics and prognostic indicators of drug-induced fulminant hepatic failure. *Hepatogastroenterology*. 2002;50(53):1531-1534.
30. Senior JR. Drug hepatotoxicity from a regulatory perspective. *Clin Liver Dis*. 2007;11(3):507-524.
31. Hoofnagle JH. LiverTox: a website on drug-induced liver injury. In: Kaplowitz N, DeLeve L, eds. *Drug-Induced Liver Disease*, 3rd edn. Amsterdam, The Netherlands: Elsevier; 2013:725-732.
32. Björnsson ES, Hoofnagle JH. Categorization of drugs implicated in causing liver injury: critical assessment based on published case reports. *Hepatology*. 2016;63(2):590-603.
33. Moreno C, Deltenre P, Senterre C, et al. Intensive enteral nutrition is ineffective for patients with severe alcoholic hepatitis treated with corticosteroids. *Gastroenterology*. 2016;150(4):903-910. e908.
34. Flora SJ, Pachauri V. Chelation in metal intoxication. *Int J Environ Res Public Health*. 2010;7(7):2745-2788.
35. Baniasadi S, Eftekhari P, Tabarsi P, et al. Protective effect of N-acetylcysteine on antituberculosis drug-induced hepatotoxicity. *Eur J Gastro Hepatol*. 2010;22(10):1235-1238.
36. Lee WM, Hynan LS, Rossaro L, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. *Gastroenterology*. 2009;137(3):856-864. e851.
37. Hu J, Zhang Q, Ren X, Sun Z, Quan Q. Efficacy and safety of acetylcysteine in "non-acetaminophen" acute liver failure: a meta-analysis of prospective clinical trials. *Clin Res Hepatol Gastroenterol*. 2015;39(5):594-599.
38. Squires RH, Dhawan A, Alonso E, et al. Intravenous N-acetylcysteine in pediatric patients with nonacetaminophen acute liver failure: a placebo-controlled clinical trial. *Hepatology*. 2013;57(4):1542-1549.
39. Knowles SR, Shapiro LE, Shear NH. Anticonvulsant hypersensitivity syndrome. *Drug Saf*. 1999;21(6):489-501.
40. Avancini J, Maragno L, Santi C, Criado P. Drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome: clinical features of 27 patients. *Clin Exp Dermatol*. 2015;40(8):851-859.
41. Lee T, Lee YS, Yoon S-Y, et al. Characteristics of liver injury in drug-induced systemic hypersensitivity reactions. *J Am Acad Dermatol*. 2013;69(3):407-415.
42. Shah RR, Morganroth J, Shah DR. Hepatotoxicity of tyrosine kinase inhibitors: clinical and regulatory perspectives. *Drug Saf*. 2013;36(7):491-503.
43. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol*. 2012;30(21):2691-2697.
44. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(1):23-34.
45. Huffman BM, Kottschade LA, Kamath PS, Markovic SN. Hepatotoxicity after immune checkpoint inhibitor therapy in melanoma: natural progression and management. *Am J Clin Oncol*. 2018;41(8):760-765.
46. Katsinelos P, Vasiliadis T, Xiarchos P, et al. Ursodeoxycholic acid (UDCA) for the treatment of amoxycillin-clavulanate potassium (Augmentin (R))-induced intra-hepatic cholestasis: report of two cases. *Eur J Gastro Hepatol*. 2000;12(3):365-368.
47. O'Brien CB, Shields DS, Saul H, Rajender Reddy K. Drug-induced vanishing bile duct syndrome: response to ursodiol. *Am J Gastroenterol*. 1996;91(7):1456-1457.
48. Tani M, Hayashi Y, Okamoto S, et al. Rapid improvement of icterus and pruritus by the oral administration of colestimide in two cases of drug-induced hepatitis. *Intern Med*. 2001;40(11):1098-1103.
49. Wong SP, Chu CM, Kan CH, Tsui HS, Ng WL. Successful treatment of leflunomide-induced acute pneumonitis with cholestyramine wash-out therapy. *J Clin Rheumatol*. 2009;15(8):389-392.
50. Abenavoli L, Capasso R, Milic N, Capasso F. Milk thistle in liver diseases: past, present, future. *Phytother Res*. 2010;24(10):1423-1432.
51. Gu J, Tang S-J, Tan S-Y, et al. An open-label, randomized and multi-center clinical trial to evaluate the efficacy of Silibinin in preventing drug-induced liver injury. *Int J Clin Exp Med*. 2015;8(3):4320.
52. Koga K, Kawashima S, Shibata N, Takada K. Novel formulations of a liver protection drug glycyrrhizin. *Yakugaku Zasshi*. 2007;127(7):1103-1114.
53. Wang G, Han Z. The protective action of glycyrrhiza flavonoids against carbon tetrachloride hepatotoxicity in mice. *Acta Pharm Sin*. 1992;28(8):572-576.
54. Crance J-M, Lévêque F, Biziagos E, van Cuyck-Gandré H, Jouan A, Deloince R. Studies on mechanism of action of glycyrrhizin against hepatitis A virus replication in vitro. *Antiviral Res*. 1994;23(1):63-76.
55. Manns M, Wedemeyer H, Singer A, et al. Glycyrrhizin in patients who failed previous interferon alpha-based therapies: biochemical and histological effects after 52 weeks. *J Viral Hepatitis*. 2012;19(8):537-546.
56. Hung C-H, Kee K-M, Chen C-H, et al. A randomized controlled trial of glycyrrhizin plus tenofovir vs. tenofovir in chronic hepatitis B with severe acute exacerbation. *Clin Transl Gastroenterol*. 2017;8(6):e104.
57. Sato H, Goto W, J-i Y, et al. Therapeutic basis of glycyrrhizin on chronic hepatitis B. *Antiviral Res*. 1996;30(2-3):171-177.
58. Fontana RJ, Hayashi PH, Gu J, et al. Idiosyncratic drug-induced liver injury is associated with substantial morbidity and mortality within 6 months from onset. *Gastroenterology*. 2014;147(1):96-108. e104.
59. Aithal G, Watkins P, Andrade R, et al. Case definition and phenotype standardization in drug-induced liver injury. *Clin Pharmacol Ther*. 2011;89(6):806-815.
60. Medina-Caliz I, Robles-Diaz M, Garcia-Muñoz B, et al. Definition and risk factors for chronicity following acute idiosyncratic drug-induced liver injury. *J Hepatol*. 2016;65(3):532-542.
61. de BY, Kosinski AS, Urban TJ, et al. Features of autoimmune hepatitis in patients with drug-induced liver injury. *Clin Gastroenterol Hepatol*. 2017;15(1):103-112. e102.
62. Björnsson E, Talwalkar J, Treeprasertsuk S, et al. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. *Hepatology*. 2010;51(6):2040-2048.
63. Foureau D, Walling T, Maddukuri V, et al. Comparative analysis of portal hepatic infiltrating leucocytes in acute drug-induced liver injury, idiopathic autoimmune and viral hepatitis. *Clin Exp Immunol*. 2015;180(1):40-51.
64. Björnsson E, Davidsdottir L. The long-term follow-up after idiosyncratic drug-induced liver injury with jaundice. *J Hepatol*. 2009;50(3):511-517.
65. Aithal P, Day C. The natural history of histologically proved drug induced liver disease. *Gut*. 1999;44(5):731-735.
66. Fontana RJ, Hayashi PH, Barnhart H, et al. Persistent liver biochemistry abnormalities are more common in older patients and those with cholestatic drug induced liver injury. *Am J Gastroenterol*. 2015;110(10):1450.
67. Fontana RJ. Pathogenesis of idiosyncratic drug-induced liver injury and clinical perspectives. *Gastroenterology*. 2014;146(4):914-928. e911.

68. Danan G, Benichou C. Causality assessment of adverse reactions to drugs—I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol*. 1993;46(11):1323-1330.
69. Rockey DC, Seeff LB, Rochon J, et al. Causality assessment in drug-induced liver injury using a structured expert opinion process: comparison to the Roussel-Uclaf causality assessment method. *Hepatology*. 2010;51(6):2117-2126.
70. Hayashi PH, Barnhart HX, Fontana RJ, et al. Reliability of causality assessment for drug, herbal and dietary supplement hepatotoxicity in the Drug-Induced Liver Injury Network (DILIN). *Liver Int*. 2015;35(5):1623-1632.
71. Pisetsky DS, Jiang W. Role of Toll-like Receptors in HMGB1 Release from Macrophages. *Ann N Y Acad Sci*. 2007;1109(1):58-65.
72. Zhang C, Li X, Liu Q. Sorbitol dehydrogenase inhibitor protects the liver from ischemia/reperfusion-induced injury via elevated glycolytic flux and enhanced sirtuin 1 activity. *Mol Med Rep*. 2015;11(1):283-288.
73. Zhang J, Jin Z, Hu X-X, et al. Efficient two-photon fluorescent probe for glutathione S-transferase detection and imaging in drug-induced liver injury sample. *Anal Chem*. 2017;89(15):8097-8103.
74. Church RJ, Watkins PB. The transformation in biomarker detection and management of drug-induced liver injury. *Liver Int*. 2017 Nov;37(11):1582-1590.
75. Harrill A, Roach J, Fier I, et al. The effects of heparins on the liver: application of mechanistic serum biomarkers in a randomized study in healthy volunteers. *Clin Pharmacol Ther*. 2012;92(2):214-220.
76. Thulin P, Nordahl G, Gry M, et al. Keratin-18 and microRNA-122 complement alanine aminotransferase as novel safety biomarkers for drug-induced liver injury in two human cohorts. *Liver Int*. 2014;34(3):367-378.
77. Rutherford A, King LY, Hynan LS, et al. Development of an accurate index for predicting outcomes of patients with acute liver failure. *Gastroenterology*. 2012;143(5):1237-1243.
78. Church RJK-UG, Kleiner DE, Bonkovsky HL, et al. Candidate liver safety biomarkers Provide Prognostic and Mechanistic insights in patients with DILI. *Hepatology*. 2017;66:24A.
79. Antoine DJ, Dear JW, Lewis PS, et al. Mechanistic biomarkers provide early and sensitive detection of acetaminophen-induced acute liver injury at first presentation to hospital. *Hepatology*. 2013;58(2):777-787.
80. Antoine DJ, Jenkins RE, Dear JW, et al. Molecular forms of HMGB1 and keratin-18 as mechanistic biomarkers for mode of cell death and prognosis during clinical acetaminophen hepatotoxicity. *J Hepatol*. 2012;56(5):1070-1079.
81. Antoine DJ, Williams DP, Kipar A, et al. High-mobility group box-1 protein and keratin-18, circulating serum proteins informative of acetaminophen-induced necrosis and apoptosis in vivo. *Toxicol Sci*. 2009;112(2):521-531.
82. Daly AK, Donaldson PT, Bhatnagar P, et al. HLA-B* 5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. *Nat Genet*. 2009;41(7):816.
83. Aithal GP. Pharmacogenetic testing in idiosyncratic drug-induced liver injury: current role in clinical practice. *Liver Int*. 2015;35(7):1801-1808.
84. Urban TJ, Nicoletti P, Chalasani N, et al. Minocycline hepatotoxicity: clinical characterization and identification of HLA-B* 35: 02 as a risk factor. *J Hepatol*. 2017;67(1):137-144.
85. Takikawa H, Murata Y, Horiike N, Fukui H, Onji M. Drug-induced liver injury in Japan: an analysis of 1676 cases between 1997 and 2006. *Hepatol Res*. 2009;39(5):427-431.
86. Hillman L, Gottfried M, Whitsett M, et al. Clinical features and outcomes of complementary and alternative medicine induced acute liver failure and injury. *Am J Gastroenterol*. 2016;111(7):958.
87. Zhou Y, Yang L, Liao Z, He X, Zhou Y, Guo H. Epidemiology of drug-induced liver injury in China: a systematic analysis of the Chinese literature including 21 789 patients. *Eur J Gastro Hepatol*. 2013;25(7):825-829.
88. Heurgué A, Bernard-Chabert B, Diebold M, et al. Drug-induced autoimmune hepatitis: a frequent disorder. *Gut*. 2007;56(Suppl III):A271.
89. Foureau DM, Jacobs C, Ahrens W, Russo MW, Bonkovsky HL. Drug-induced liver injury with autoimmune features. *Semin Liver Dis*. 2014;34(2):194-204.
90. Stine JG, Chalasani N. Chronic liver injury induced by drugs: a systematic review. *Liver Int*. 2015;35(11):2343-2353.
91. Amacher DE, Chalasani N. Drug-induced hepatic steatosis. *Semin Liver Dis*. 2014;34(2):205-214.
92. Begriche K, Massart J, Robin M-A, Borgne-Sanchez A, Fromenty B. Drug-induced toxicity on mitochondria and lipid metabolism: mechanistic diversity and deleterious consequences for the liver. *J Hepatol*. 2011;54(4):773-794.
93. Day CP, James OF. Steatohepatitis: a tale of two "hits"? *Gastroenterology*. 1998;114:842-845.
94. Forbes GM, Jeffrey GP, Shilkin KB, Reed WD. Carbamazepine hepatotoxicity: another cause of the vanishing bile duct syndrome. *Gastroenterology*. 1992;102(4):1385-1388.
95. Danica J, Irena H, Davor R, et al. Vanishing bile duct syndrome associated with azithromycin in a 62-year-old man. *Basic Clin Pharmacol Toxicol*. 2010;106(1):62-65.
96. Ghabril M, Vuppalanchi R. Drug-induced nodular regenerative hyperplasia. *Semin Liver Dis*. 2014;34(2):240-245.
97. Tsokos M, Erbersdobler A. Pathology of peliosis. *Forensic Sci Int*. 2005;149(1):25-33.
98. Loomus GN, Aneja P, Bota RA. A case of peliosis hepatis in association with tamoxifen therapy. *Am J Clin Pathol*. 1983;80(6):881-883.
99. Van Erpecum K, Janssens A, Kreuning J, Ruiter D, Kroon H, Grond A. Generalized peliosis hepatis and cirrhosis after long-term use of oral contraceptives. *Am J Gastroenterol*. 1988;83(5):572-575.

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