

## REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

## Drug-Induced Liver Injury — Types and Phenotypes

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DRUG-INDUCED LIVER INJURY IS AN UNCOMMON BUT CHALLENGING clinical problem with respect to both diagnosis and management.<sup>1-3</sup> Its incidence is estimated to be 14 to 19 cases per 100,000 persons, with jaundice accompanying 30% of cases.<sup>4,5</sup> Drug-induced liver injury is responsible for 3 to 5% of hospital admissions for jaundice<sup>6</sup> and is the most frequent cause of acute liver failure in most Western countries, accounting for more than half of cases.<sup>7,8</sup> Advances have been made in our understanding of viral, autoimmune, and genetic liver diseases, as well as approaches to their prevention and treatment, but progress on these fronts has been modest in the case of drug-induced liver injury.

The diagnosis of drug-induced liver injury is particularly challenging, since it is based largely on exclusion of other causes. The timing of the onset of injury after the implicated agent has been started (latency), resolution after the agent is stopped (“dechallenge”), recurrence on re-exposure (rechallenge), knowledge of the agent’s potential for hepatotoxicity (likelihood), and clinical features (phenotype) are the major diagnostic elements.<sup>9-11</sup> With few exceptions, there are no specific diagnostic markers for drug-induced liver injury, and special tests (liver biopsy, imaging, and testing for serologic markers) are helpful mostly in ruling out other causes of liver injury. The large number of agents that can cause liver injury highlights these challenges. LiverTox, the National Institutes of Health–sponsored website on hepatotoxicity, has descriptions of more than 1200 agents (prescription and over-the-counter medications, herbal products, nutritional supplements, metals, and toxins), along with their potential to cause liver injury.<sup>12</sup> Among the 971 prescription drugs described, 447 (46%) have been implicated in causing liver injury in at least one published case report.<sup>11</sup> This brief review cannot cover all aspects of drug-induced liver injury but focuses on general principles, newer concepts, and current challenges, with frequent references to the LiverTox website for further detail.

## TYPES OF DRUG-INDUCED LIVER INJURY

Drug-induced liver injury is typically classified as either direct or idiosyncratic,<sup>1</sup> but indirect injury is emerging as a third type (Table 1). Direct hepatotoxicity is caused by agents that are intrinsically toxic to the liver. The injury is common, predictable, dose-dependent, and reproducible in animal models.<sup>1</sup> The latency period is typically short, usually with an onset within 1 to 5 days after high therapeutic or supratherapeutic doses, as in the case of an intentional or accidental overdose.

Idiosyncratic hepatotoxicity is caused by agents that have little or no intrinsic toxicity and that cause liver injury only in rare cases, typically after 1 in 2000 to 1 in 100,000 patient-exposures.<sup>5,13</sup> The injury is unpredictable, not dose-dependent, and not reproducible in animal models. Idiosyncratic liver injury is categorized as hepatocellular, cholestatic, or both (mixed) on the basis of the R ratio, calculated by

**Table 1. Drug-Induced Liver Injury According to Type.\***

Variable	Direct Hepatotoxicity	Idiosyncratic Hepatotoxicity	Indirect Hepatotoxicity
Frequency	Common	Rare	Intermediate
Dose-related	Yes	No	No
Predictable	Yes	No	Partially
Reproducible in animal models	Yes	No	Not usually
Latency (time to onset)	Typically rapid (days)	Variable (days to years)	Delayed (months)
Phenotypes	Acute hepatic necrosis, serum enzyme elevations, sinusoidal obstruction, acute fatty liver, nodular regeneration	Acute hepatocellular hepatitis, mixed or cholestatic hepatitis, bland cholestasis, chronic hepatitis	Acute hepatitis, immune-mediated hepatitis, fatty liver, chronic hepatitis
Most commonly implicated agents	High doses of acetaminophen, niacin, aspirin, cocaine, IV amiodarone, IV methotrexate, cancer chemotherapy	Amoxicillin-clavulanate, cephalosporins, isoniazid, nitrofurantoin, minocycline, fluoroquinolones, macrolide antibiotics	Antineoplastic agents, glucocorticoids, monoclonal antibodies (against tumor necrosis factor, CD20, checkpoint proteins), protein kinase inhibitors
Cause	Intrinsic hepatotoxicity when agent given in high doses	Idiosyncratic metabolic or immunologic reaction	Indirect action of agent on liver or immune system

\* IV denotes intravenous.

dividing the alanine aminotransferase level by the alkaline phosphatase level from the time of initial presentation, with both values expressed as multiples of the upper limit of the normal range.<sup>9</sup> Hepatocellular injury is defined as an R value of more than 5, cholestatic injury as a value of less than 2, and mixed injury as a value of 2 to 5.

Indirect hepatotoxicity is caused by the action of the drug (what it does) rather than by its toxic or idiosyncratic properties (what it is). Indirect injury can represent induction of a new liver condition or an exacerbation of a preexisting condition, such as induction of immune-mediated hepatitis or worsening of hepatitis B or C or fatty liver disease.

#### MAJOR PHENOTYPES

The three types of drug-induced liver injury are manifested by distinctly different patterns of clinical features (phenotypes)<sup>12</sup> (Table 2).

#### DIRECT HEPATOXICITY

Serum enzyme elevations without jaundice constitute the most common pattern of direct drug-induced liver injury, with elevations of alanine aminotransferase or alkaline phosphatase levels but without hyperbilirubinemia and with minimal or no symptoms.<sup>2,12</sup> The elevations resolve when the drug is stopped or the dose is lowered but can also resolve spontaneously, a phenomenon referred to as adaptation.<sup>14</sup> In some cases,

adaptation does not occur, and enzyme elevations worsen and jaundice and symptoms arise. The mechanism or mechanisms underlying adaptation are unknown but may result from changes in drug-metabolizing enzyme activity, up-regulation of hepatoprotective pathways, or down-regulation of hypersensitivity reactions to the drug or its metabolites.

Acute hepatic necrosis is the most common form of clinically apparent direct hepatotoxicity. The injury occurs abruptly, soon after the medication has been started, often after exposure to a single high dose or a dose increase (Fig. 1A). Serum alanine aminotransferase levels rise to high values, whereas alkaline phosphatase levels are minimally elevated. In severe cases, signs of hepatic failure such as coagulopathy, hyperammonemia, or coma arise within days.<sup>7,19</sup> Liver histologic studies show centrilobular or panlobular necrosis with little inflammation, a pattern similar to that of ischemic hepatitis, the major disorder in the differential diagnosis. Acute hepatic necrosis can be fatal, but if it is not, recovery is rapid, and serum enzyme levels fall almost as rapidly as they rose. High doses of acetaminophen, aspirin, niacin, amiodarone, and many antineoplastic agents can cause acute hepatic necrosis.<sup>15,19,20</sup> Typically, these drugs can be restarted at lower doses without a recurrence of injury. Poisonous mushrooms (*Amanita phalloides*) and other environmental toxins can cause a similar syndrome of acute hepatic necrosis.

**Table 2. Phenotypes of Drug-Induced Liver Injury.\***

Phenotype	Type of Liver Injury	Latency	Enzyme Pattern	Typical Agents	Comments
Acute hepatic necrosis	Direct	Days	Marked, abrupt ALT elevations; mild Alk P and bilirubin elevations	Acetaminophen, aspirin, niacin, "Ecstasy"	Often due to overdose
Enzyme elevations	Direct	Days to months	Mild-to-moderate ALT or Alk P elevations	Many agents	Usually transient and asymptomatic
Acute hepatitis	Idiosyncratic, indirect	Days to months	High ALT elevations, modest Alk P elevations	Isoniazid, diclofenac	High death rate
Cholestatic hepatitis	Idiosyncratic	Weeks to months	High Alk P elevations, modest ALT elevations	Amoxicillin–clavulanate, cefazolin	Pruritus, early and prominent
Mixed hepatitis	Idiosyncratic	Days to months	Moderate ALT and Alk P elevations	TMP-SMZ, phenytoin	Usually benign, self-limited
Chronic hepatitis	Idiosyncratic, indirect	Months to years	Moderate ALT elevations with bilirubin elevations	Diclofenac, nitrofurantoin, minocycline	Insidious onset; may require glucocorticoids
Bland cholestasis	Unknown, possibly idiosyncratic	Months	Moderate ALT elevations, mild Alk P elevations	Anabolic steroids, estrogens	Pruritus, prominent and prolonged
Acute fatty liver, lactic acidosis, and hepatic failure	Direct	Days to months	Lactic acidosis, modest ALT elevations, hepatic failure	Stavudine, linezolid, aspirin (Reye's syndrome)	Mitochondrial failure, pancreatitis
Nonalcoholic fatty liver	Indirect, direct	Months	Mild ALT and Alk P elevations	Glucocorticoids, tamoxifen, haloperidol	Asymptomatic; fatty liver seen on ultrasound
Sinusoidal obstruction syndrome	Direct	Weeks	Variable enzyme elevations	Cancer agents, busulfan, gemtuzumab	Hepatomegaly, weight gain, edema, ascites
Nodular regenerative hyperplasia	Direct	Years	Minimal ALT and Alk P elevations	Thioguanine, azathioprine, oxaliplatin	Noncirrhotic portal hypertension

\* The phenotypes are listed very generally in order of frequency; there is some overlap between idiosyncratic and indirect forms of injury. Alk P denotes alkaline phosphatase, ALT alanine aminotransferase, and TMP-SMZ trimethoprim–sulfamethoxazole.

Sinusoidal obstruction syndrome, previously known as veno-occlusive disease, is due to acute injury and loss of intrasinusoidal endothelial cells, resulting in obstruction of sinusoidal blood flow and liver injury.<sup>21,22</sup> Drugs are the usual cause, the most common being myeloablative agents administered in preparation for hematopoietic cell transplantation. Symptoms of abdominal pain, increase in liver size, and weight gain, followed by jaundice, appear 1 to 3 weeks after exposure and may progress rapidly to hepatic failure. Liver histologic studies show dilatation of sinusoids and extravasation of red cells, with hepatocyte necrosis in central areas (zone 3).<sup>22</sup> Drugs that cause sinusoidal obstruction syndrome include alkylating agents such as busulfan or cyclophosphamide and monoclonal antibody–cytotoxic conjugates such as gemtuzumab ozogamicin.<sup>23</sup> The syndrome can also be caused by botanicals (pyrrolizidine alkaloids).<sup>1</sup> Defibrotide, an antithrombotic agent, has recently been approved as therapy for severe sinusoidal ob-

struction syndrome with organ failure, but its use is controversial.<sup>24</sup>

Nodular regenerative hyperplasia is usually manifested as unexplained, noncirrhotic portal hypertension with esophageal varices or ascites. Nodular regeneration can be caused by cancer chemotherapeutic agents given over a long period or in multiple courses (azathioprine, mercaptopurine, or thioguanine)<sup>25</sup> or by first-generation nucleoside antiretroviral agents (zidovudine, stavudine, or didanosine).<sup>26</sup> Nodular regenerative hyperplasia with resultant portal hypertension has also been linked to oxaliplatin infusions for metastatic colon cancer.<sup>27</sup> The pathogenesis of nodular regeneration is unclear, but it may be the result of chronic injury to the hepatic microvasculature. Management should include withdrawal of the medication (and avoidance of similar agents) and treatment of portal hypertension.

Lactic acidosis with microvesicular steatosis and hepatic dysfunction typically occurs with nonspecific symptoms of abdominal discomfort,











the likelihood that they cause injury. The multiple types and phenotypes of injury vary according to the agent, presenting a diagnostic challenge. Recognizing phenotypes of drug-induced liver injury is helpful in establishing the diagnosis, identifying the responsible agent, and providing insights into pathogenesis. A better understanding of the pathogenesis of drug-induced

liver injury should allow for better diagnostics and, ultimately, improved approaches to prevention and treatment.

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## REFERENCES

- Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 1999.
- Navarro VJ, Senior JR. Drug-related hepatotoxicity. *N Engl J Med* 2006;354:731-9.
- Kullak-Ublick GA, Andrade RJ, Merz M, et al. Drug-induced liver injury: recent advances in diagnosis and risk assessment. *Gut* 2017;66:1154-64.
- Sgro C, Clinard F, Ouazir K, et al. Incidence of drug-induced hepatic injuries: a French population-based study. *Hepatology* 2002;36:451-5.
- 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;144:1419-25.
- Vuppalanchi R, Liangpunsakul S, Chalasani N. Etiology of new-onset jaundice: how often is it caused by idiosyncratic drug-induced liver injury in the United States? *Am J Gastroenterol* 2007;102:558-62.
- Reuben A, Koch DG, Lee WM. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. *Hepatology* 2010;52:2065-76.
- Wei G, Bergquist A, Broomé U, et al. Acute liver failure in Sweden: etiology and outcome. *J Intern Med* 2007;262:393-401.
- 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;46:1323-30.
- 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;51:2117-26.
- Björnsson ES, Hoofnagle JH. Categorization of drugs implicated in causing liver injury: critical assessment based on published case reports. *Hepatology* 2016;63:590-603.
- LiverTox: clinical and research information on drug-induced liver injury. Bethesda, MD: National Institutes of Health (<https://www.LiverTox.nih.gov>).
- Chalasani N, Bonkovsky HL, Fontana R, et al. Features and outcomes of 889 patients with drug-induced liver injury: the DILIN Prospective Study. *Gastroenterology* 2015;148(7):1340-52.e7.
- Watkins PB. Idiosyncratic liver injury: challenges and approaches. *Toxicol Pathol* 2005;33:1-5.
- Pye M, Northcote RJ, Cobbe SM. Acute hepatitis after parenteral amiodarone administration. *Br Heart J* 1988;59:690-1.
- Schmeltzer PA, Kosinski AS, Kleiner DE, et al. Liver injury from nonsteroidal anti-inflammatory drugs in the United States. *Liver Int* 2016;36:603-9.
- Alqahtani SA, Kleiner DE, Ghabril M, Gu J, Hoofnagle JH, Rockey DC. Identification and characterization of cefazolin-induced liver injury. *Clin Gastroenterol Hepatol* 2015;13(7):1328-1336.e2.
- Stolz A, Navarro V, Hayashi PH, et al. Severe and protracted cholestasis in 44 young men taking bodybuilding supplements: assessment of genetic, clinical and chemical risk factors. *Aliment Pharmacol Ther* 2019;49:1195-204.
- Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology* 2005;42:1364-72.
- Dalton TA, Berry RS. Hepatotoxicity associated with sustained-release niacin. *Am J Med* 1992;93:102-4.
- McDonald GB. Hepatobiliary complications of hematopoietic cell transplantation, 40 years on. *Hepatology* 2010;51:1450-60.
- DeLeve LD, Shulman HM, McDonald GB. Toxic injury to hepatic sinusoids: sinusoidal obstruction syndrome (veno-occlusive disease). *Semin Liver Dis* 2002;22:27-42.
- Battipaglia G, Labopin M, Candoni A, et al. Risk of sinusoidal obstruction syndrome in allogeneic stem cell transplantation after prior gemtuzumab ozogamicin treatment: a retrospective study from the Acute Leukemia Working Party of the EBMT. *Bone Marrow Transplant* 2017;52:592-9.
- Richardson PG, Riches ML, Kernan NA, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. *Blood* 2016;127:1656-65.
- Suárez Ferrer C, Llop Herrera E, Calvo Moya M, et al. Idiopathic portal hypertension regarding thiopurine treatment in patients with inflammatory bowel disease. *Rev Esp Enferm Dig* 2016;108:79-83.
- Cotte L, Bénet T, Billioud C, et al. The role of nucleoside and nucleotide analogues in nodular regenerative hyperplasia in HIV-infected patients: a case control study. *J Hepatol* 2011;54:489-96.
- Morris-Stiff G, White AD, Gomez D, et al. Nodular regenerative hyperplasia (NRH) complicating oxaliplatin chemotherapy in patients undergoing resection of colorectal liver metastases. *Eur J Surg Oncol* 2014;40:1016-20.
- McKenzie R, Fried MW, Sallie R, et al. Hepatic failure and lactic acidosis due to fialuridine (FIAU), an investigational nucleoside analogue for chronic hepatitis B. *N Engl J Med* 1995;333:1099-105.
- Wei C-M, Chen H-L, Lee P-I, Chen C-M, Ma C-Y, Hwu W-L. Reye's syndrome developing in an infant on treatment of Kawasaki syndrome. *J Paediatr Child Health* 2005;41:303-4.
- Peters RL, Edmondson HA, Mikkelsen WP, Tatter D. Tetracycline-induced fatty liver in nonpregnant patients: a report of six cases. *Am J Surg* 1967;113:622-32.
- Su E, Crowley K, Carcillo JA, Michaels MG. Linezolid and lactic acidosis: a role for lactate monitoring with long-term linezolid use in children. *Pediatr Infect Dis J* 2011;30:804-6.
- Dragovic G, Jevtovic D. The role of nucleoside reverse transcriptase inhibitors usage in the incidence of hyperlactatemia and lactic acidosis in HIV/AIDS patients. *Biomed Pharmacother* 2012;66:308-11.
- Andrade RJ, Lucena MI, Fernández MC, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology* 2005;129:512-21.
- Temple R. Hy's law: predicting serious hepatotoxicity. *Pharmacoepidemiol Drug Saf* 2006;15:241-3.
- de Boer YS, 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.e2.

36. Björnsson E, Talwalkar J, Treeprasert-suk S, et al. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. *Hepatology* 2010;51:2040-8.
37. Russo MW, Hoofnagle JH, Gu J, et al. Spectrum of statin hepatotoxicity: experience of the Drug-Induced Liver Injury Network. *Hepatology* 2014;60:679-86.
38. Ahmad J, Odin JA, Hayashi PH, et al. Identification and characterization of fenofibrate-induced liver injury. *Dig Dis Sci* 2017;62:3596-604.
39. deLemos AS, Ghabril M, Rockey DC, et al. Amoxicillin-clavulanate-induced liver injury. *Dig Dis Sci* 2016;61:2406-16.
40. Kleiner DE, Chalasani NP, Lee WM, et al. Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations. *Hepatology* 2014;59:661-70.
41. Bonkovsky HL, Kleiner DE, Gu J, et al. Clinical presentations and outcomes of bile duct loss caused by drugs and herbal and dietary supplements. *Hepatology* 2017; 65:1267-77.
42. Fontana RJ, Cirulli ET, Gu J, et al. The role of HLA-A\*33:01 in patients with cholestatic hepatitis attributed to terbinafine. *J Hepatol* 2018;69:1317-25.
43. Björnsson ES, Gu J, Kleiner DE, Chalasani N, Hayashi PH, Hoofnagle JH. Azathioprine and 6-mercaptopurine-induced liver injury: clinical features and outcomes. *J Clin Gastroenterol* 2017;51:63-9.
44. Grant LM, Kleiner DE, Conjeevaram HS, Vuppalanchi R, Lee WM. Clinical and histological features of idiosyncratic acute liver injury caused by temozolomide. *Dig Dis Sci* 2013;58:1415-21.
45. Orman ES, Conjeevaram HS, Vuppalanchi R, et al. Clinical and histopathologic features of fluoroquinolone-induced liver injury. *Clin Gastroenterol Hepatol* 2011;9(6):517-523.e3.
46. Martinez MA, Vuppalanchi R, Fontana RJ, et al. Clinical and histologic features of azithromycin-induced liver injury. *Clin Gastroenterol Hepatol* 2015;13(2): 369-376.e3.
47. Devarbhavi H, Karanth D, Prasanna KS, Adarsh CK, Patil M. Drug-induced liver injury with hypersensitivity features has a better outcome: a single-center experience of 39 children and adolescents. *Hepatology* 2011;54:1344-50.
48. Knowles SR, Dewhurst N, Shear NH. Anticonvulsant hypersensitivity syndrome: an update. *Expert Opin Drug Saf* 2012;11: 767-78.
49. Devarbhavi H, Raj S, Aradya VH, et al. Drug-induced liver injury associated with Stevens-Johnson syndrome/toxic epidermal necrolysis: patient characteristics, causes, and outcome in 36 cases. *Hepatology* 2016;63:993-9.
50. Chalasani N, Reddy KR, 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;112:1382-8.
51. Pauli-Magnus C, Meier PJ, Stieger B. Genetic determinants of drug-induced cholestasis and intrahepatic cholestasis of pregnancy. *Semin Liver Dis* 2010;30: 147-59.
52. Robles-Diaz M, Gonzalez-Jimenez A, Medina-Caliz I, et al. Distinct phenotype of hepatotoxicity associated with illicit use of anabolic androgenic steroids. *Aliment Pharmacol Ther* 2015;41:116-25.
53. Kumra S, Herion D, Jacobsen LK, Briguglia C, Grothe D. Case study: risperidone-induced hepatotoxicity in pediatric patients. *J Am Acad Child Adolesc Psychiatry* 1997;36:701-5.
54. Sacks FM, Stanesa M, Hegele RA. Severe hypertriglyceridemia with pancreatitis: thirteen years' treatment with lomitapide. *JAMA Intern Med* 2014;174:443-7.
55. Di Bisceglie AM, Lok AS, Martin P, Terrault N, Perrillo RP, Hoofnagle JH. Recent US Food and Drug Administration warnings on hepatitis B reactivation with immune-suppressing and anticancer drugs: just the tip of the iceberg? *Hepatology* 2015;61:703-11.
56. Kim HN, Harrington RD, Shuhart MC, et al. Hepatitis C virus activation in HIV-infected patients initiating highly active antiretroviral therapy. *AIDS Patient Care STDS* 2007;21:718-23.
57. Nociti V, Biolato M, De Fino C, et al. Liver injury after pulsed methylprednisolone therapy in multiple sclerosis patients. *Brain Behav* 2018;8(6):e00968.
58. Aliberti S, Grignani G, Allione P, et al. An acute hepatitis resembling autoimmune hepatitis occurring during imatinib therapy in a gastrointestinal stromal tumor patient. *Am J Clin Oncol* 2009;32:640-1.
59. Fontana RJ, Hayashi P, Bonkovsky HL, et al. Presentation and outcomes with clinically apparent interferon beta hepatotoxicity. *Dig Dis Sci* 2013;58:1766-75.
60. Ghabril M, Bonkovsky HL, Kum C, et al. Liver injury from tumor necrosis factor- $\alpha$  antagonists: analysis of thirty-four cases. *Clin Gastroenterol Hepatol* 2013; 11(5):558-564.e3.
61. Kleiner DE, Berman D. Pathologic changes in ipilimumab-related hepatitis in patients with metastatic melanoma. *Dig Dis Sci* 2012;57:2233-40.
62. 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;41:760-5.
63. Lammert C, Einarsson S, Saha C, Niklasson A, Björnsson E, Chalasani N. Relationship between daily dose of oral medications and idiosyncratic drug-induced liver injury: search for signals. *Hepatology* 2008;47:2003-9.
64. Regev A. Drug-induced liver injury and drug development: industry perspective. *Semin Liver Dis* 2014;34:227-39.
65. Avigan MI. DILI and drug development: a regulatory perspective. *Semin Liver Dis* 2014;34:215-26.
66. Navarro VJ, Barnhart H, Bonkovsky HL, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. *Hepatology* 2014;60:1399-408.
67. Navarro VJ, Khan I, Björnsson E, Seeff LB, Serrano J, Hoofnagle JH. Liver injury from herbal and dietary supplements. *Hepatology* 2017;65:363-73.
68. Bonkovsky HL. Hepatotoxicity associated with supplements containing Chinese green tea (*Camellia sinensis*). *Ann Intern Med* 2006;144:68-71.
69. Zheng EX, Rossi S, Fontana RJ, et al. Risk of liver injury associated with green tea extract in SLIMQUICK® weight loss products: results from the DILIN prospective study. *Drug Saf* 2016;39:749-54.
70. Dostal AM, Samavat H, Bedell S, et al. The safety of green tea extract supplementation in postmenopausal women at risk for breast cancer: results of the Minnesota Green Tea Trial. *Food Chem Toxicol* 2015;83:26-35.
71. 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: 816-9.
72. Lucena MI, Molokhia M, Shen Y, et al. Susceptibility to amoxicillin-clavulanate-induced liver injury is influenced by multiple HLA class I and II alleles. *Gastroenterology* 2011;141:338-47.
73. Kim SH, Saide K, Farrell J, et al. Characterization of amoxicillin- and clavulanic acid-specific T cells in patients with amoxicillin-clavulanate-induced liver injury. *Hepatology* 2015;62:887-99.
74. Cirulli ET, Nicoletti P, Abramson K, et al. A missense variant in PTPN22 is a risk factor for drug-induced liver injury. *Gastroenterology* 2019;156(6):1707-1716.e2.
75. Stanford SM, Bottini N. PTPN22: the archetypal non-HLA autoimmunity gene. *Nat Rev Rheumatol* 2014;10:602-11.

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