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General Concepts of Drug Induced Liver Injury

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ABSTRACT

Drug-induced liver injury (DILI) is a problem of increasing significance, but has been a long-standing concern in the treatment of tuberculosis (TB) infection. The liver has a central role in drug metabolism and detoxification, and is consequently vulnerable to injury. The pathogenesis and types of DILI are presented, ranging from hepatic adaptation to hepatocellular injury. Knowledge of the metabolism of anti-TB medications and of the mechanisms of TB DILI is incomplete. Understanding of TB DILI has been hampered by differences in study populations, definitions of hepatotoxicity, and monitoring and reporting practices. Available data regarding the incidence and severity of TB DILI overall, in selected demographic groups, and in those coinfected with HIV or hepatitis B or C virus are presented. Systematic steps for prevention and management of TB DILI are recommended. These include patient and regimen selection to optimize benefits over risks, effective staff and patient education, ready access to care for patients, good communication among providers, and judicious use of clinical and biochemical monitoring. During treatment of latent TB infection (LTBI) alanine aminotransferase (ALT) monitoring is recommended for those who chronically consume alcohol, take concomitant hepatotoxic drugs, have viral hepatitis or other preexisting liver disease or abnormal baseline ALT, have experienced prior isoniazid hepatitis, are pregnant or are within 3 months postpartum. During treatment of TB disease, in addition to these individuals, patients with HIV infection should have ALT monitoring. Some experts recommend biochemical monitoring for those older than 35 years. Treatment should be interrupted and, generally, a modified or alternative regimen used for those with ALT elevation more than three times the upper limit of normal (ULN) in the presence of hepatitis symptoms and/or jaundice, or five times the ULN in the absence of symptoms. Priorities for future studies to develop safer treatments for LTBI and for TB disease are presented.

KEYWORDS: Alanine Aminotransferase, Aspartate Aminotransferase, Drug-induced liver injury, Hepatitis, Hepatotoxicity, Tuberculosis

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1.0 INTRODUCTION

This review addresses recent advances in specific mechanisms of drug induced liver toxicity (DILI). Because of its unique metabolism and relationship to the gastrointestinal tract, the liver is an important target of the toxicity of drugs, xenobiotics, and oxidative stress. In cholestatic disease, endogenously generated bile acids produce hepatocellular apoptosis by stimulating Fas translocation from the cytoplasm to the plasma membrane where self-aggregation occurs to trigger apoptosis. Kupffer cell activation and neutrophil infiltration extend toxic injury. Kupffer cells release reactive oxygen species (ROS), cytokines, and chemokines, which induce neutrophil extravasation and activation. The liver expresses many cytochrome P450 isoforms, including ethanol-induced CYP2E1. CYP2E1 generates ROS, activates many toxicologically important substrates, and may be the central pathway by which ethanol causes oxidative stress. In acetaminophen toxicity, nitric oxide (NO) scavenges superoxide to

produce peroxynitrite, which then causes protein nitration and tissue injury. In inducible nitric oxide synthase (iNOS) knockout mice, nitration is prevented, but unscavenged superoxide production then causes toxic lipid peroxidation to occur instead. Microvesicular steatosis, nonalcoholic steatohepatitis (NASH), and cytolytic hepatitis involve mitochondrial dysfunction, including impairment of mitochondrial fatty acid β-oxidation, inhibition of mitochondrial respiration, and damage to mitochondrial DNA. Induction of the mitochondrial permeability transition (MPT) is another mechanism causing mitochondrial failure, which can lead to necrosis from ATP depletion or caspase-dependent apoptosis if ATP depletion does not occur fully. Because of such diverse mechanisms, hepatotoxicity remains a major reason for drug withdrawal from pharmaceutical development and clinical use.

The liver synthesizes, concentrates, and secretes bile acids and excretes other toxicants, such as bilirubin. Drug-induced injury to hepatocytes and bile duct cells can lead to cholestasis. Cholestasis, in turn, causes intrahepatic accumulation of toxic bile acids and excretion products, which promotes further hepatic injury. Fortunately, the liver has enormous regenerative capacity, but regeneration of hepatocytes lost by necrotic and apoptotic cell death may mask detection of drug-induced injury. Furthermore, the active proliferative response of hepatocytes makes the liver an important target of carcinogens.

Hepatic nonparenchymal cells, the Kupffer, sinusoidal endothelial, and stellate (fat-storing or Ito) cells, and newly recruited leukocytes, i.e., monocytes and neutrophils, also contribute to the pathogenesis of hepatic toxicity. Kupffer cells and neutrophils are a source of proinflammatory cytokines and chemokines and of reactive oxygen and nitrogen species, which promote oxidative stress in injury induced by toxicants and ischemia/reperfusion. Kupffer cells also play a key role in hepatic injury due to ethanol consumption. The uniquely fenestrated sinusoidal endothelial cell is selectively vulnerable to cold ischemia/reperfusion injury to cause graft failure after transplantation and to cancer chemotherapy agents to cause veno-occlusive disease. Activated stellate cells synthesize collagen whose overproduction leads to hepatic fibrosis and cirrhosis.

The splanchnic circulation carries ingested drugs directly into the liver, a phenomenon known as the "first pass" through the liver. Metabolic enzymes convert these chemicals through phase 1 pathways of oxidation, reduction, or hydrolysis, which are carried out principally by the cytochrome P450 class of enzymes. Phase 2 pathways include glucuronidation, sulfation, acetylation, and glutathione conjugation to form compounds that are readily excreted from the body. Other subsequent steps include deacetylation and deaminidation. Many drugs may be metabolized through alternative pathways, and their relative contributions may explain some differences in toxicity between individuals. In phase 3 pathways, cellular transporter proteins facilitate excretion of these compounds into bile or the systemic circulation. Transporters and enzyme activities are influenced by endogenous factors such as circadian rhythms, hormones, cytokines, disease states, genetic factors, sex, ethnicity, age, and nutritional status, as well as by exogenous drugs or chemicals[1]. Bile is the major excretory route for hepatic metabolites. Compounds excreted in bile may undergo enterohepatic circulation, being reabsorbed in the small intestine and re-entering the portal circulation[2].

The goal of this short review is to discuss new developments in our understanding of the mechanisms of liver injury in the context of hepatic physiology, metabolism, and cell biology. The sections that follow emphasize important injury concepts, types, clinical and pathological manifestations and diagnosis which can be a consequence of metabolism and/or direct cell toxicity of chemicals.

2.0 DRUG-INDUCED LIVER INJURY: CONCEPTS

2.1 DEFINITION

Drug-induced liver injury (DILI) is ultimately a clinical diagnosis of exclusion. Histologic specimens of the liver are often not obtained.Other causes of liver injury, such as acute viral hepatitis, should be methodically sought, and their absence makes the diagnosis plausible. Usually, the time of onset to acute injury is within months of initiating a drug. Rechallenge with the suspected offending agent with more than twofold serum alanine aminotransferase (ALT) elevation, and discontinuation leading to a fall in ALT, is the strongest confirmation of the diagnosis[3]. Rechallenge may, in some instances, endanger the patient and is usually confined to essential drugs or usedwhenmultiple potentially hepatotoxic drugs have been administered concomitantly[4].

2.2 DIMENSIONS OF THE PROBLEM

DILI accounts for 7% of reported drug adverse effects, 2% of jaundice in hospitals, and approximately 30% of fulminant liver failure[4, 5]. DILI has replaced viral hepatitis as the most apparent cause of acute liver failure[6]. A brief search of commercial pharmacopoeia databases suggests there are more than 700 drugs with reported hepatotoxicity and approved for use in the United States[7]. With an estimated background rate of idiopathic liver failure of 1 in 1,000,000 (4, 8), the U.S. Food and Drug Administration (FDA) has withdrawn drugs or mandated relabeling for severe or fatal liver injury exceeding 1 in 50,000 individuals[5, 8, 9].

2.3 PATHOGENESIS OF DRUG INDUCED LIVER TOXICITY

DILI may result from direct toxicity of the primary compound, a metabolite, or from an immunologically mediated response, affecting hepatocytes, biliary epithelial cells, and/or liver vasculature. In many cases, the exact mechanism and factors contributing to liver toxicity remain poorly understood. Predictable DILI is generally characterized by certain dose-related injury in experimental animal models, has a higher attack rate, and tends to occurrapidly. Injurious free radicals cause hepatocyte necrosis in zones farthest from the hepatic arterioles, where metabolism is greatest and antioxidant detoxifying capacity is the least[10, 11]. Unpredictable or idiosyncratic reactions comprise most types of DILI. These hypersensitivity or metabolic reactions occur largely independent of dose and relatively rarely for each drug, and may result in hepatocellular injury and/or cholestasis. Hepatocyte necrosis is often distributed throughout hepatic lobules rather than being zonal, as is often seen with predictable DILI. In hypersensitivity reactions, immunogenic drug or its metabolites may be free or covalently bound to hepatic proteins, forming haptens or “neoantigens.” Antibody-dependent cytotoxic, T-cell, and occasionally eosinophilic hypersensitivity responses may be evoked. Released tumor necrosis factor-alpha, interleukin (IL)-12, and IFN- gamma promote hepatocellular programmed cell death (apoptosis), an effect opposed by IL-4, IL-10, IL-13, and monocyte chemotactic protein-1[12]. Metabolic idiosyncratic reactions may result from genetic or acquired variations in drug biotransformation pathways, with synthesis or abnormally slow detoxification of a hepatotoxic metabolite. Metabolic idiosyncratic reactions may have a widely variable latent period, but recur within days to weeks after re-exposure[4].

2.4 HEPATIC ENZYME MEASUREMENT

An increase in serum ALT, formerly known as serum glutamate pyruvate transaminase (SGPT), is more specific for hepatocellular injury than an increase in aspartate aminotransferase (AST or serum glutamic oxaloacetic transaminase [SGOT]), which can also signify abnormalities in muscle, heart, or kidney[13, 14]. Serum enzyme concentrations are measured by functional catalytic assays with normal values established from "healthy" populations. The normal range lies within 2 standard deviations of the mean of the distribution, with 2.5% of persons who are otherwise healthy having concentrations above and below the limits of normal on a single measurement[15]. Populations used to set standard values in the past probably included individuals with occult liver disease, whose exclusion has led to decreases in the upper limit of normal (ULN)[16]. Interlaboratory variation in assay results can be substantial. Consequently, comparison of multiples of the ULN has become standard[13, 14]. In an individual, transaminases may vary as much as 45% on a single day, with the highest levels occurring in the afternoon, or 10 to 30% on successive days. ALT and AST elevation may occur after exercise, hemolysis, or muscle injury. Serum hepatic transaminase concentration tends to be higher in men and in those with greater body mass index. Children and older adults tend to have lower transaminase concentrations. The National Academy of Clinical Biochemistry recommends that laboratories establish reference limits for enzymes adjusted for sex in adults, and for children and adults older than 60 years[13, 14]. Increases in alkaline phosphatase and/or bilirubin with little or no increase in ALT indicate cholestasis. Alkaline phosphatase concentration may also increase because of processes in bone, placenta, or intestine. An increased concentration of serum _-glutamyl transpeptidase, an inducible enzyme expressed in hepatic cholangioles, is useful in distinguishing liver-related from other organ-related alkaline phosphatase increases[5, 18]. Jaundice is usually detectable on the physical examination when serum bilirubin exceeds 3.0 mg/dl.

2.5 LABORATORY MONITORING

A benefit of ALT and/or bilirubin monitoring in preventing or alleviating drug-induced liver injuryhas not been rigorously tested. A recent small non randomized report suggested that monitoring may decrease the severity of pyrazinamide-induced liver injury[19]. Disadvantages of laboratory monitoring include questionable cost-efficacy of frequent testing for rare adverse events, development and progression of injury between testing events, unclear enzyme thresholds for medication discontinuation, and confusion of hepatic adaptation with significant liver injury. The cost of obtaining AST with ALT is often marginal and may be useful in identifying alcoholrelated Transaminase elevation, where the AST is characteristically higher than the ALT. The diagnosis of a superimposed injury may be difficult with initially abnormal or fluctuating transaminases. Prior laboratory data may be of use in this regard. Monitoring and the use of a Potentially less hepatotoxic regimen is generally recommended for those with preexisting liver disease in the hope that superimposed DILI may be detected preclinically and mitigated. Transaminases elevation during the course of anti-TB therapy may in some instances actually represent coincidentally developed hepatitis A, B, or C[20, 21].

3.0 TYPES OF DRUG INDUCED LIVER TOXICITY

A variety of clinical syndromes may be seen with DILI, even with a single drug.

3.1 HEPATIC ADAPTATION

Exposure to certain drugs may evoke physiologic adaptive responses[18]. The induction of survival genes, including those that regulate antioxidant, antiinflammatory, And antiapoptotic pathways may attenuate toxin-related injurious responses. Such injury may also stimulate hepatocyte proliferation and protective adaptation. Asymptomatic, transient Elevations of ALT may reflect slight, nonprogressive injury to hepatocyte mitochondria, cell membranes, or other structures. Such injury rarely leads to inflammation, cell death, or significant histopathology changes. Certain toxins, such as ethanol, possibly interfere with these adaptive protective responses. Excessive persistence of an adaptive response may, in some instances, render hepatocytes more vulnerable when they are subjected to additional new insults[22]. The induction of hepatic microsomal (cytochrome P450) enzymes, capable of metabolizing the inducing medication[4, 18], is another form of hepatic adaptation.

3.2 DRUG-INDUCED ACUTE HEPATITIS OR HEPATOCELLULAR INJURY

A transaminases threshold for clinic pathologically significant drug induced hepatitis has not been systematically determined for most medications. Patients who take phenytoin often have transaminases elevation up to three times the ULN, but liver biopsies do not reveal significant pathology[23]. However, in patients Treated for rheumatoid arthritis with methotrexate, microscopic evidence of liver injury has been found for any transaminases elevation above the ULN[24]. Patients with acute hepatocellular injury may be asymptomatic or may report a prodrome of fever and constitutional symptoms, Followed by nausea, vomiting, anorexia, and lethargy. Histopathology may reveal focal hepatic necrosis, with bridging in severe cases[4]. Markedly increased transaminases concentrations followed by jaundice imply severe liver disease with a 10% possibility of fulminant failure, a maxim known as “Hy’s Law,” after the late hepatologist and DILI expert Hyman Zimmerman. Coagulopathy may develop 24 to 36 hours after onset, although this can subsequently resolve. Coagulopathy persisting beyond 4 days is a poor prognostic sign in acetaminophen-related hepatotoxicity[13, 14].

3.3 NONALCOHOLIC FATTY LIVER DISEASE

Steatosis, or simple fatty liver, is most commonly caused by obesity, insulin resistance, and probably alterations in triglyceride metabolism. Ethanol, steroids, And highly active antiretroviral therapy (HAART) areassociated with the development and exacerbation of nonalcoholic fatty liver disease[25–28]. Constitutional symptoms, nausea, vomiting, or abdominal pain are uncommon. Laboratory findings in severe cases include hypoglycemia, increased serum transaminases concentrations, prolonged coagulation times, and metabolic acidosis[4, 27, 29]. Most instances of drug- induced steatosis are reversible, if the offending agent is stopped. Persistent steatotic injury may progress to steatohepatitis, characterized histopathologically by hepatic inflammatory and fatty infiltration, and by a subsequently higher risk of cirrhosis[30].

3.4 GRANULOMATOUS HEPATITIS

Granulomata are common, nonspecific findings in liver histology and are potentially related to infectious, inflammatory, or neoplastic etiologies. Hypersensitivity reactions to drugs, such as allopurinol, quinidine, sulfonamides, and pyrazinamide, are a common cause of this type of lesion. Patients may have fever, lethargy, myalgias, rash, lymphadenopathy, Hepatosplenomegaly with increased serum ALTconcentration, and even vasculitis[4, 31].

3.5 CHOLESTASIS

Bland cholestasis, typically reported with estrogen treatment, consists of asymptomatic, usually reversible, increases in serum alkaline phosphatase and bilirubin concentration, caused by a failure of bilirubin transport. There is a lack of inflammation in liver tissue[4].

3.6 CHEMICAL COFACTORS FOR DRUG INDUCED LIVER TOXICITY

Ethanol induces cytochromeP450 2E1, which promotes metabolism of ethanol itself, acetaminophen, and others[32]. Ethanol metabolism yields acetaldehyde, which contributes to glutathione depletion, protein conjugation, free radical generation, and lipid peroxidation. Chronicethanol abuse activates hepatic collagen-producing sinusoidal (stellate) cells, potentially contributing to fibrosis[33]. Some medications, such as calcium channel blockers, may influence cytochromeP450 metabolism of potentially hepatoxic drugs, such as Simvastatin, which may lead to DILI[34].

3.7 PREEXISTING LIVER DISEASE

Abnormal baseline transaminases are an independent risk factor for DILI (35–39). Patients with HIV and hepatitis C, however, appear to have increased frequency of antiretroviral medication–related DILI[26, 27]. The severity of DILI, when it occurs, may be greater in patients with underlying liver disease, likely reflecting a summation of injuries.

4.0 CLINICAL AND PATHOLOGICAL MANIFESTATIONS OF DRUG IN DUCED LIVER TOXICITY

Drug hepatotoxicity manifests with clinical signs and symptoms caused by an underlying pathological injury. The clinical presentation may or may not suggest the underlying liver injury, and therefore, the types of injuries are sometimes described separately. Some drugs usually cause one clinical and pathologic injury and other drugs can cause a variety of injuries, often making the diagnosis more challenging[21- 38].

4.1 CLINICAL MANIFESTATIONS

The manifestations of drug-induced hepatotoxicity are highly variable, ranging from asymptomatic elevation of liver enzymes to fulminant hepatic failure. The injury may suggest a hepatocellular injury, with elevation of aminotransferase levels as the predominant symptom, or a cholestatic injury, with elevated alkaline phosphatase levels (with or without hyperbilirubinemia) being the main feature. In addition, drugs that cause mild aminotransferase elevations with subsequent adaptation are differentiated from those that result in true toxicity that require discontinuation.

Asymptomatic elevations in aminotransferase: Some drugs cause asymptomatic elevations of liver enzymes that do not progress despite continued use of the drug.

- As many as 50% of patients receiving tacrine for Alzheimer disease have elevated enzyme levels. Alkaline phosphatase and bilirubin levels are rarely elevated, and severe injury is rare. Rechallenging a patient with this medication may even be appropriate, and in more than 80% of cases, the alanine aminotransferase (ALT) abnormalities resolve or do not reoccur.
- This tolerance is also observed in 25-50% of the patients taking drugs such as methyldopa or phenytoin, and it is especially well described with INH.
- 5-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors are also associated with a mild elevation in enzyme levels in less than 5% of cases.
- Other drugs include sulfonamides, salicylates, sulfonylureas, and quinidine.
- If the clinician is not familiar with the drug or if any question remains about the safety of continuing a drug, consultation with a hepatologist should be considered.

Elevated aminotransferase levels with acute hepatocellular injury: Drug-induced liver injury is designated hepatocellular if the ALT levels are increased to more than twice the upper limit of the reference range, with alkaline phosphatase levels that are within the reference range or are minimally elevated. Elevation of aspartate aminotransferase (AST) greater than ALT, especially if more than 2 times greater, suggests alcoholic hepatitis. Elevation of AST less than ALT is usually observed in persons with viral hepatitis. In viral and drug-induced hepatitis, the AST and ALT levels steadily increase and peak in the low thousands range within 7-14 days. Many medications can cause increases in AST, such as acetaminophen, NSAIDs, ACE inhibitors, nicotinic acid, INH, sulfonamides, erythromycin, and antifungal agents such as griseofulvin and fluconazole. In acetaminophen overdose, transaminase levels greater than 10,000 IU/L are also noted.

Elevated aminotransferase and bilirubin levels suggestive of subfulminant or fulminant necrosis

- With increasing hepatocellular injury, bilirubin levels are invariably increased, suggesting a worse prognosis. Normally, the total bilirubin level is less than 1.1 mg/dL and approximately 70% is indirect (unconjugated) bilirubin. Unconjugated hyperbilirubinemia (>80% of the total bilirubin is indirect) suggests hemolysis or Gilbert syndrome. Conjugated hyperbilirubinemia (>50% of the total bilirubin is direct) suggests hepatocellular dysfunction or cholestasis. When the bilirubin level is above 25-30 mg/dL, extrahepatic cholestasis is an unlikely diagnosis; because the predominantly conjugated bilirubin is water soluble, it is easily excreted by the kidney in extrahepatic cholestasis.
- Subfulminant hepatic failure most commonly results from acetaminophen, halothane, methoxyflurane, enflurane, trovafloxacin, troglitazone, ketoconazole, dihydralazine, tacrine, mushroom poisoning, ferrous sulfate poisoning, phosphorus poisoning, and cocaine toxicity. Drugs that result in massive necrosis are propylthiouracil, INH, phenytoin, phenelzine, sertraline, naproxen, diclofenac, kava kava, and ecstasy.

Elevated alkaline phosphatase (acute cholestatic injury) levels: Acute intrahepatic cholestasis is divisible into 2 broad categories, (1) cholestasis without hepatocellular injury (bland jaundice or pure cholestasis) and (2) cholestasis with variable hepatocyte injury.

- The most common biochemical abnormality is elevation of the alkaline phosphate level, usually without hyperbilirubinemia. Men and older patients are more prone to these adverse effects. The interval of developments is usually less than 4 weeks and may be as long as 8 weeks. Fever, rash, and eosinophilia may be observed in as many as 30% of individuals, but these findings do not define the disorder.
- Some common drugs associated with cholestatic injury include chlorpromazine, ciprofloxacin, ofloxacin, cimetidine, phenytoin, naproxen, captopril, erythromycin, azithromycin, and dicloxacil-

lin. Amoxicillin-clavulanic acid is also an important cause of cholestatic jaundice. Extrahepatic cholestasis secondary to biliary sludge or calculi is caused by sulindac or octreotide.

Extrahepatic manifestations: Some drugs cause systemic reactions associated with hepatic injury. Extrahepatic manifestations of drug-induced hepatotoxicity are as follows:

- Chlorpromazine, phenylbutazone, halogenated anesthetic agents, sulindac - Fever, rash, eosinophilia
- Dapsone - Sulfone syndrome (ie, fever, rash, anemia, jaundice)
- INH, halothane - Acute viral hepatitis
- Chlorpromazine, erythromycin, amoxicillin-clavulanic acid - Obstructive jaundice
- Phenytoin, carbamazepine, phenobarbital, primidone - Anticonvulsant hypersensitivity syndrome (ie, triad of fever, rash, and liver injury)
- Para-amino salicylate, phenytoin, sulfonamides - Serum sickness syndrome
- Clofibrate - Muscular syndrome (ie, myalgia, stiffness, weakness, elevated creatine kinase level)
- Procainamide - Antinuclear antibodies (ANAs)
- Gold salts, propylthiouracil, chlorpromazine, chloramphenicol - Marrow injury
- Amiodarone, nitrofurantoin - Associated pulmonary injury
- Gold salts, methoxyflurane, penicillamine, paraquat - Associated renal injury
- Tetracycline - Fatty liver of pregnancy
- Contraceptive and anabolic steroids, rifampin - Bland jaundice
- Aspirin - Reye syndrome
- Sodium valproate - Reyelike syndrome

4.2 PATHOLOGICAL MANIFESTATIONS

Besides the use of clinical and laboratory data, the pattern of liver histology may be classified into categories (31-38) as described below.

Acute hepatocellular injury: Manifestations of acute liver injury may range from spotty necrosis to fulminant liver failure. Spotty necrosis resembles classic viral hepatitis and involves all acinar zones. Hepatocellular injury consists of ballooning degeneration or apoptosis with eosinophils, especially in cases of peripheral eosinophilia. Drugs that can cause this type of injury are INH, halothane, phenylbutazone, indomethacin, and disulfiram. Submassive necrosis, as the name suggests, may affect zone 1 (periportal) or zone 3 (central necrosis). Periportal changes occur with ferrous sulfate poisoning, phosphorus poisoning, and cocaine toxicity. Central necrosis occurs with acetaminophen, halothane, methoxyflurane, trovafloxacin, ketoconazole, dihydralazine, tacrine, and mushroom poisoning. Massive necrosis is an extension of submassive necrosis and manifests as fulminant failure.

Chronic hepatocellular injury: Drug-induced chronic changes manifest many forms.

- Pigment accumulation: Lipofuscin pigment storage in the liver cells has been reported with phenothiazines, phenacetin, aminopyrine, and cascara sagrada. Hemosiderin accumulation in the liver cells may result from excessive iron ingestion or parenteral iron therapy in patients undergoing hemodialysis.
- Steatosis, steatohepatitis, and phospholipidosis: Steatosis secondary to drug toxicity may be in the form of medium-sized and large droplets (macrovesicular) or small droplets (microvesicular). Microvesicular steatosis is observed with alcohol, aspirin, valproic acid, amiodarone, piroxicam, stavudine, didanosine, nevirapine, and high doses of tetracycline. Drugs that can cause macrovesicular steatosis include alcohol, corticosteroids, methotrexate, minocycline, nifedipine, parenteral nutrition, and perhexiline maleate. Steatohepatitis has been reported with amiodarone, nifedi-

pine, synthetic estrogens, and didanosine. Phospholipidosis results from lysosomal phospholipid storage secondary to inactivation of lysosomal phospholipases by drugs. Common causes are perhexiline maleate, amiodarone, total parenteral nutrition (TPN), trimethoprim-sulfamethoxazole, and chloroquine.

- Hepatic fibrosis and cirrhosis: Most hepatic drug reactions of minimal-to-moderate severity are followed by recovery and no significant fibrosis. Any drug causing submassive hepatocellular injury may be followed by fibrosis, nodular regeneration, and cirrhosis. However, some agents produce an increase in collagen deposition, with minimal or absent features of necrosis or inflammation. Drugs leading to fibrosis include methotrexate, hypervitaminosis A, vinyl chloride, thorotrast, and heroin. Prolonged therapy with methotrexate, INH, ticrynafen, perhexiline, enalapril, and valproic acid may lead to cirrhosis.

Acute cholestasis: Cholestasis is defined as a reduction in bile flow resulting from reduced secretion or obstruction of the biliary tree. If any evidence indicates hepatocellular injury, it is called cholestatic hepatitis. Histology shows apoptotic bodies, small foci of necrosis, and, less often, ballooning with or without zone 3 necrosis. Bile accumulates in the cytoplasm of the liver cells, canaliculi, and Kupffer cells. Drugs that lead to a pure cholestatic reaction include anabolic steroids (eg, methyl testosterone, oxymetholone, fluoxymesterone) and contraceptive steroids. Drugs that can cause cholestatic hepatitis include erythromycin, azithromycin, ciprofloxacin, ofloxacin, ranitidine, cimetidine, phenytoin, gold salts, and terbinafine. Intrahepatic cholestasis may be accompanied by acute cholangitis and is observed in patients taking chlorpromazine, allopurinol, chlorpropamide, and hydralazine.

Chronic cholestasis: Histology shows chronic portal inflammation and degeneration of the bile duct referred to as progressive ductopenia or vanishing bile duct syndrome. Most cases of drug-induced cholestasis are followed by rapid clinical and biochemical recovery upon withdrawal of the drug. However, approximately 1% of patients may continue to have abnormal liver test results and some may progress to a condition resembling primary biliary cirrhosis. Causes of intrahepatic cholestasis include chlorpropamide, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, carbamazepine, and TPN. Floxuridine causes intrahepatic and extrahepatic cholestasis.

Granulomatous hepatitis: Most of these reactions consist of noncaseating epithelioid granulomas located in periportal or portal areas. This injury is usually transient and causes no sequelae. Drugs implicated include sulfonamide, sulfonylurea, phenytoin, quinidine, and hydralazine. Long-term use of mineral oil for constipation can cause lipogranulomas. Allopurinol is known to cause granulomas with a fibrin ring, whereas gold salts may lead to the formation of lipogranulomas with black pigment. Carbamazepine is a common cause of granulomatous hepatitis.

Autoimmune hepatitis: Histology reveals active necroinflammatory lesions with prominent plasma cells. Females are affected more often than males. Autoimmune hepatitis manifests insidiously as fatigue, anorexia, weight loss, jaundice, ascites, portal hypertension, hepatomegaly, and splenomegaly. The serology may be positive for ANA, anti–smooth muscle antibody (ASMA), or lupus erythematosus factor with elevated gamma globulin levels. Examples of commonly implicated drugs include methyldopa, minocycline, nitrofurantoin, dihydralazine, lisinopril, sulfonamides, and trazodone.

Vascular lesions/venoocclusive disease: Drugs can injure any component of the liver, including the sinusoids, hepatic veins, and hepatic arteries. Azathioprine has been associated with hepatic venoocclusive disease in patients with a renal transplant, bone marrow transplant, and on long-term treatment for inflammatory bowel disease. Alcohol, excess vitamin A, floxuridine, and dacarbazine may lead to venoocclusive disease with or without acinar zone 3 necrosis. Herbal tea preparations (alkaloids) may

cause acute ascites, rapid weight gain, abdominal pain, and hepatomegaly, which are reversible but sometimes fatal. Oral contraceptives can cause focal sinusoidal dilatations. Both contraceptives and anabolic steroids may lead to peliosis hepatis, ie, extrasinusoidal blood-filled spaces.

Neoplastic lesions: Focal nodular hyperplasia and hepatocellular adenomas have been well described since the advent of oral contraceptive steroids. Many agents are linked to malignant hepatic neoplasms, including angiosarcoma from vinyl chloride and thorium dioxide.

5.0 DIAGNOSIS

When a single agent is involved, the diagnosis may be relatively simple, but with multiple agents, implicating a specific agent as the cause is difficult. To facilitate the diagnosis of drug-induced hepatic injury, several clinical tools for causality assessment have been developed to assist the clinician.

History: History must include dose, route of administration, duration, previous administration, and use of any concomitant drugs, including over-the-counter medications and herbs. Knowing whether the patient was exposed to the same drug before may be helpful. The latency period of idiosyncratic drug reactions is highly variable; hence, obtaining a history of every drug ingested in the past 3 months is essential.

- Onset: The onset is usually within 5-90 days of starting the drug.
- Exclusion of other causes of liver injury/cholestasis: Excluding other causes of liver injury is essential.

Dechallenge: A positive dechallenge is a 50% fall in serum transaminase levels within 8 days of stopping the drug. A positive dechallenge is very helpful in cases of use of multiple medications.

Track record of the drug: Previously documented reactions to a drug aid in diagnosis.

Rechallenge: Deliberate rechallenge in clinical situations is unethical and should not be attempted; however, inadvertent rechallenge in the past has provided valuable evidence that the drug was indeed hepatotoxic.

6.0 CONCLUSIONS

Many unanswered questions will always be there regarding DILI in an aging population, in an increasingly complex medical environment, with evolving demographics. Understanding of the basic mechanisms and genetic factors associated with DILI is nascent. Such information should eventually allow identification of those most likely to suffer increased incidence and/or severity of DILI. The existing data are, in some instances, insufficient to come to strong conclusions regarding hepatotoxicity risks and monitoring. In the future, issues related to DILI will need to be reevaluated as new data become available. Safe systems for treating patients, patient and staff education, appropriate selection of patients for treatment, careful regimen selection, and monitoring help minimize risks.

7.0 CONFLICT OF INTEREST STATEMENT

The authors do not have any financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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