Review

Drug-induced liver injury

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Drug-induced liver injury: Diagnosis, management and the role of liver transplantation

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Abstract

Drug-induced liver injury (DILI) is caused by various medications or herbals/nutritional supplements resulting in liver test abnormalities or hepatic dysfunction. DILI can be categorized as direct (intrinsic), idiosyncratic, or immune-mediated (indirect), and patterns of injury can be categorized as hepatocellular, cholestatic, or mixed injury. DILI is diagnosed after excluding other causes of liver injury. Cessation of the suspected drug along with supportive care is recommended for most DILI cases. In life-threatening situations, liver transplantation (LT) can be considered; however, the risks with LT and lifelong immunosuppression should be considered. In this paper, we summarize the pathophysiology, diagnosis, medical management, and LT for DILI.

Keywords: Liver failure; liver injury; toxic hepatitis.

Introduction

Drug-induced liver injury (DILI) refers to liver damage caused by various medications or herbals/dietary supplements (HDS), resulting in liver test abnormalities or hepatic dysfunction, after excluding other possible causes of liver injury. DILI accounts for approximately 10–15% of the cases of acute liver failure (ALF) and presents a major challenge for drug safety and development.[1] DILI can be classified into three groups including direct (intrinsic), idiosyncratic, and immune-mediated (indirect).[2–4] Direct hepatotoxicity is common, largely dose-dependent, predictable, and rapid in latency. Direct hepatotoxins such as acetaminophen (APAP) can lead to liver injury after a certain threshold dose in nearly all individuals.[2] Idiosyncratic hepatotoxicity is rare, largely dose-independent, unpredictable, and has variable latency.[2] Immune-mediated DILI is related to the pharmacodynamic properties of the drug rather than direct or idiosyncratic liver injury, is not dose-related, but partially predictable, and arises when the host immune system leads to liver injury following medication administration.[3,5]

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Mechanisms of Drug-Induced Liver Injury

Molecular mechanisms involved in DILI include mitochondrial dysfunction, increased reactive oxygen species generation, depletion of ATP, increased apoptosis and necrosis, altered bile acid homeostasis/bile duct injuries, and, as a result, cell death by apoptosis or necrosis (Fig. 1). [6–8] Patterns of liver injury can be categorized as hepatocellular, cholestatic, or mixed depending on the R-ratio. R-ratio can be calculated with the formulation (alanine aminotransferase (ALT) /upper limit of normal (ULN) for ALT)/(alkaline phosphatase (ALP)/ULN for ALP). If R-ratio is ≥5 the liver injury is classified as hepatocellular, if ≤2 cholestatic, and if 2–5 mixed. Hepatocellular or cytolytic injury is characterized by significant elevations in serum aminotransferase levels, which are typically followed by elevated total bilirubin levels and minor elevation in ALP levels. Typical agents causing hepatocellular injury include those caused by valproic acid, isoniazid, or nitrofurantoin.[4] Cholestatic liver injury is characterized by elevated ALP levels that precede or are more prominent than elevations in ALT or aspartate aminotransferase (AST), and is associated with drugs such as amoxicillin-clavulanic acid or chlorpromazine. An allergic or immune system reaction is often delayed or seen after repeated exposure to a medication, and may be accompanied by fever, rash, or eosinophilia. This type of liver injury can worsen with repeated exposure to the agent, and is often related to phenytoin, nitrofurantoin, or halothane, referred to as a drug hypersensitivity syndrome. Lastly, mitochondrial injury with microvesicular steatosis on liver biopsy, lactic acidosis, and minor elevations of aminotransferase levels could be induced by medications such as valproic acid or high-dose parenteral tetracycline. Other medications/herbals/nutrients including aspirin, amiodarone, chemotherapeutic agents, paraquat, carbon tetrachloride, and mushroom poisons can also lead to DILI.[9] Several risk factors including age, gender, and genetic factors have been suggested for DILI; however, no definite risk factor for all-cause DILI exists.[10]

Acetaminophen Hepatotoxicity

APAP overdose is the most common cause of ALF in the USA and Western Europe.[11] APAP causes liver injury predictably and in a dose-related manner, typically with doses exceeding 4 g/day at a single time point or with excessive doses over several days/weeks. APAP hepatotoxicity can be seen at lower doses in patients who are malnourished or those with alcohol-use disorder. APAP overdose can be seen with intentional or unintentional attempts. In cases of APAP overdose, patients may initially be asymptomatic but can rapidly progress to liver failure within 3–4 days.[12]

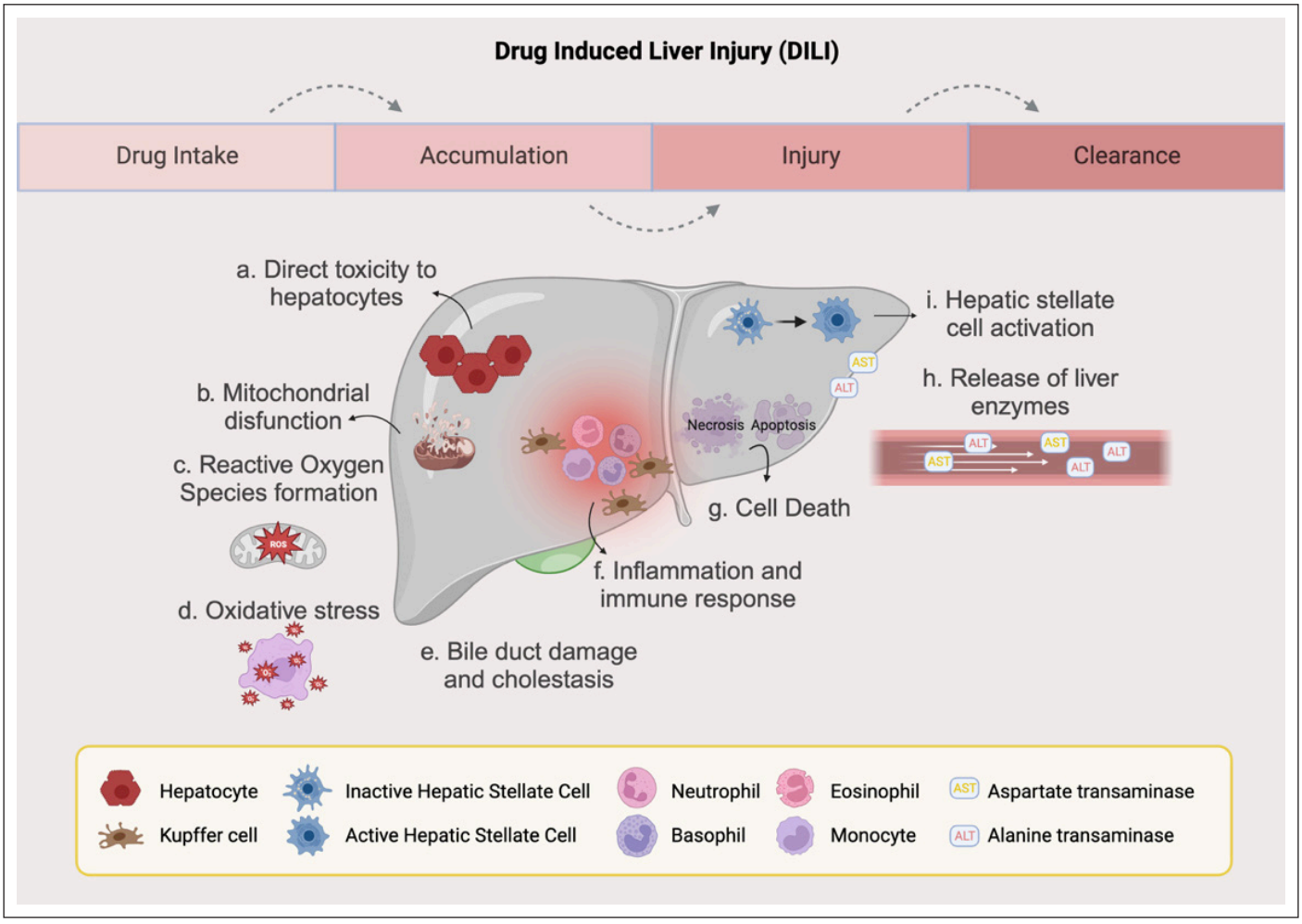

Figure 1. Pathogenesis of DILI.

APAP hepatotoxicity often presents with very high transaminase levels, relatively low bilirubin levels, and elevated INR. Serum APAP level after a single-time-point acute ingestion can aid in identifying patients with the highest risk of developing liver injury, and the use of the modified Rumack-Matthew nomogram is recommended in patients with single-point APAP ingestion to guide N-acetylcysteine (NAC) therapy.[2] Early medical intervention is crucial for suspected APAP overdose and hepatotoxicity. Gastric lavage and activated charcoal can be given to patients presenting within 4 hours of ingestion of a single-time-point APAP ingestion, and oral or IV NAC given within 12 hours of ingestion starting with a loading dose followed by the maintenance dose. NAC is the only effective antidote for severe hepatic necrosis due to APAP overdose. NAC is also recommended if patients present later than 12 hours after ingestion. With advances in intensive care, especially in the past 2 decades, the outcomes of patients with APAP hepatotoxicity have improved. However, if patients progress to ALF, approximately one-third of the patients require LT or die.[2]

Idiosyncratic DILI

Idiosyncratic DILI is rare and reported to occur in 1 to 1,000–1,000,000 people.[2] It is characterized by variable drug latency, clinical presentation, and liver histopathology findings, and is thought to be due to an aberrant host immune response to the drugs.[2] Most commonly implicated medications for idiosyncratic DILI are antimicrobials, immunomodulatory agents, and central nervous system agents.[2,10,12,13] HDS constitute the majority of the idiosyncratic DILI in many Asian countries including China and Korea, while they are responsible for the minority of DILI cases in the United States (US).[2,10,14] HDS account for approximately 20% of all liver injury cases in the US based on Drug-Induced Liver Injury Network (DILIN) Registry data.[15] Although idiosyncratic DILI often has a good prognosis, rates of transplant-free survival at 3 weeks in people who develop ALF are 23.5%–38.7%.[16] Amoxicillin-clavulanate is the most common medication to be implicated with idiosyncratic DILI in the US and Western countries, while anti-tuberculosis medications are the most commonly implicated medications in Asia, along with HDS.[17] Approximately 80% of patients with idiosyncratic DILI have resolution without long-term sequelae, and 10% of patients with idiosyncratic DILI are at risk of severe adverse hepatic outcomes including ALF and need for LT.[2] Patients with ALF due to idiosyncratic DILI have a 25% chance of spontaneous survival without LT, and early transfer to an LT center is critical for these patients.[11]

Causality Assessment Tools

Several clinical models have been developed to assess the likelihood that a drug or HDS is the cause of liver injury.[2] Structural causality assessment models include Roussel-Uclaf Causality Assessment Method (RUCAM), The Maria-Victorino Clinical Diagnostic Scale,

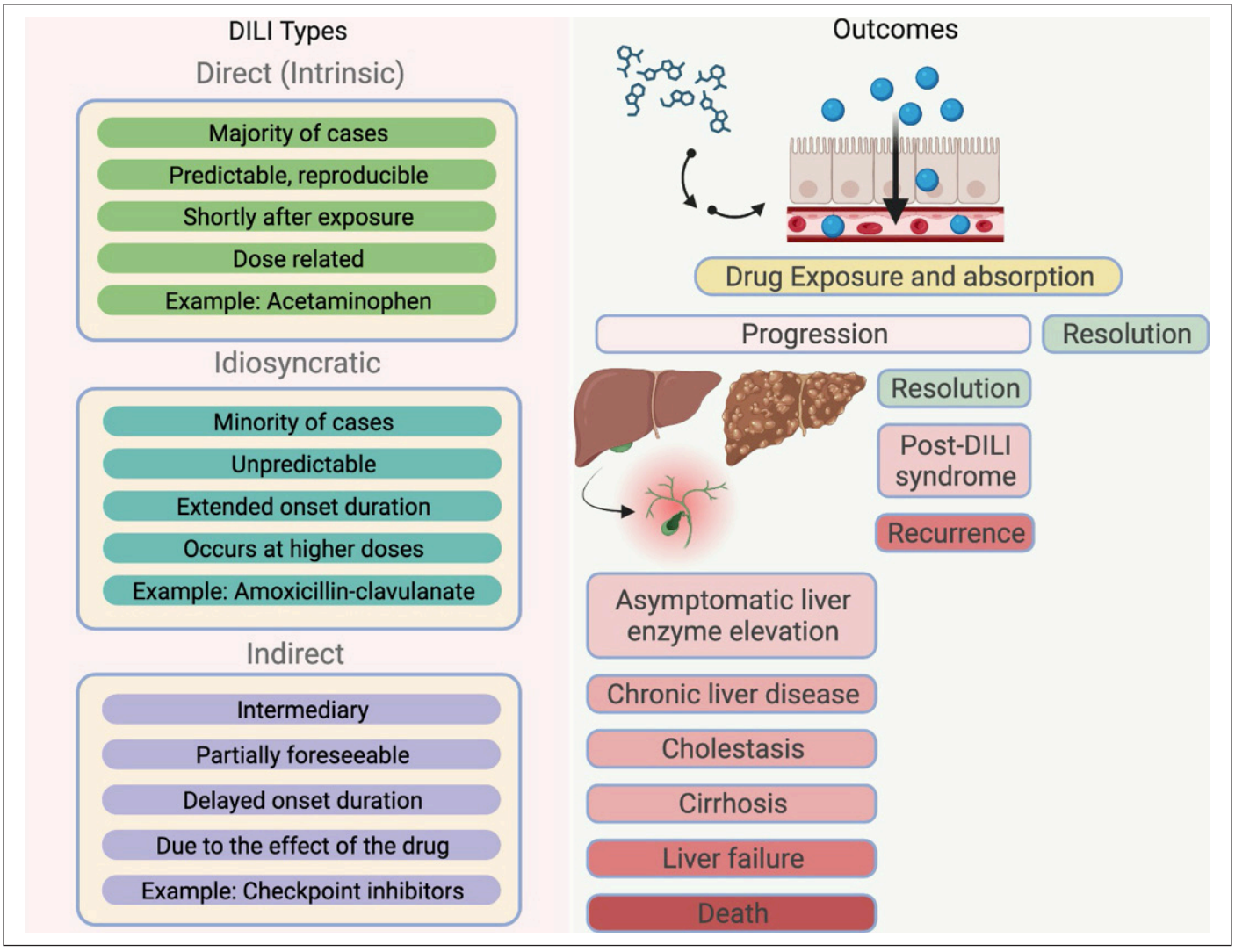

Figure 2. Types of DILI and schematic of the outcomes.

Digestive-Disease Week-Japan 2004 (DDW-J) score, and the Revised Electronic Causality Assessment Method (RECAM).[18] Generic causality assessment models include the World Health Organization Collaborating Center for International Drug Monitoring system by the Uppsala Monitoring Center. However, there is a lack of consensus in the literature regarding which method of causality assessment is superior. Despite these tools, most cases of DILI are diagnosed by excluding other causes of liver injury and by considering the temporal relationship of liver injury and initiation of the suspected drug.[8]

Medical Management of Non-Acetaminophen DILI

Supportive medical care with analgesia, antiemetics, and parenteral hydration is recommended for all patients with DILI. In patients with ALF due to non-acetaminophen DILI, a 3-day course of NAC can be considered, as a large randomized controlled trial reported improved transplant-free survival, especially in patients with early-stage hepatic encephalopathy.[19] Another trial including 102 patients with DILI due to antituberculosis medications reported a shorter length of stay, but no survival benefit with NAC.[20] Ursodeoxycholic acid may improve pruritus and DILI recovery, but large randomized controlled trials are lacking for the optimal dose and duration.[21] Corticosteroid therapy may be effective in cases with hypersensitivity or autoimmune features.

Role of Corticosteroids

Methylprednisolone 1 mg/kg is often used in patients with severe immune-mediated hypersensitivity reactions and for those with drug reactions with eosinophilia and systemic symptoms. In patients with autoimmune features on liver biopsy, DILI due to immune checkpoint inhibitors or tyrosine kinase inhibitors, a 1–3-month course of corticosteroids with rapid taper may be beneficial, and the dose depends on the severity of hepatitis.[22] Data on corticosteroid use in DILI is scarce with no randomized controlled studies to evaluate their efficacy and safety; however, there are reports of corticosteroids having beneficial effects in patients with moderate or severe DILI.[18,23] In addition, patients with drug-induced autoimmune hepatitis have a good response to corticosteroids.[23] Despite this, the majority of patients with DILI recover spontaneously without treatment as reported in several studies. Due to the lack of large randomized clinical trials, there is no clear evidence-based recommendation for the indication, dose, and duration of treatment.[23]

Outcomes

The majority of patients with DILI recover without lasting complications after stopping the suspected medication and supportive care; however, ALF or chronic liver injury ranging from asymptomatic liver test elevations, to vanishing bile duct syndrome and cirrhosis can also be seen with DILI (Fig. 2).[24]

Role of Liver Transplantation

Overall, a 10% mortality rate is reported for DILI.[25–27] Hospitalized patients with DILI with coagulopathy and hepatic encephalopathy should promptly be considered for LT evaluation as their likelihood of spontaneous recovery is <30%.[26,28] A prospective study investigating the fatalities of patients with DILI reported that 7.6% of patients died mainly or partially due to DILI within 2 years, and 40% of the patients had non-ALF courses.[26] Patients with chronic DILI, bile duct loss with progression to vanishing bile duct syndrome, or progressive portal hypertension may also be considered for LT.[28,29] In a study from the European Liver Transplantation Registry over 20 years, out of all LTs performed for ALF, 18% was due to DILI.[30] In an observational retrospective study from China conducted between 2012–2014, out of 25,927 patients, 280 (1.08%) patients developed ALF, and of those with ALF, 2 patients (0.01%) underwent LT and 102 (0.30%) died (10). In this study, ALF was defined as INR ≥2, the presence of HE, total bilirubin ≥10 times upper limit of normal or daily elevations ≥1 mg/dL, and the disease duration of <26 weeks, and DILI was the main reason for death in 52 (70.59%) of the patients. The US Acute Liver Failure Study Group (ALFSG) analyzed 386 patients who were hospitalized with acute liver injury due to DILI showed a 3-week transplant-free survival rate of 87%.[31] In contrast, patients with elevated INR and hepatic encephalopathy had higher mortality.[32] In the US, idiosyncratic DILI constitutes approximately 13% of all ALF cases, with a 3-week transplant-free survival rate of 27%.[33] Emergency LT offers a significant survival benefit of 3-week survival of 88% following LT.[34] In the US, select patients with ALF are priority in the LT waitlist and given Status 1A priority if the life expectancy is <7 days without LT and no preexisting diagnosis liver disease is present.[35,36] In countries with limited access to deceased-donor LT, living-donor LT can be considered for patients with ALF.[35] Apart from patients with DILI requiring LT, DILI after LT is also important to recognize as it is under-recognized in the setting of potential graft rejection or infection.[37,38]

Conclusions

Clinical characteristics and presentation of DILI are variable, and a lack of a specific diagnostic tool presents a major challenge for diagnosis and management. With a reported 10% mortality rate for DILI, LT is reserved as a last-resort option in life-threatening situations, underscoring the gravity of extensive and irreversible liver damage leading to ALF or chronic disease. LT is typically reserved for circumstances with life-threatening complications and when additional medical interventions are unsuccessful. The decision for LT is made on a case-by-case basis, taking into consideration the patient's overall clinical status, severity of liver damage, and probability of LT-free recovery.

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