Drug-Induced Liver Injury: A Comprehensive Review

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Abstract: Drug-induced liver injury (DILI) is a significant cause of acute liver failure and a major challenge in clinical and regulatory settings. This review provides a comprehensive overview of DILI, discussing its epidemiology, types, mechanisms, clinical presentation, risk factors, management, and prevention. DILI is broadly classified into intrinsic (dose-dependent) and idiosyncratic (dose-independent) types. Intrinsic DILI is predictable and typically associated with overdose, as seen with acetaminophen toxicity, whereas idiosyncratic DILI is unpredictable and influenced by genetic and immune factors. The mechanisms underlying DILI involve metabolic bioactivation leading to direct hepatocellular damage and immune-mediated responses resulting in liver inflammation. Diagnosis is based on clinical history, exclusion of alternative liver diseases and biomarkers. Risk factors can be divided into factors specific to the patient (e.g., age, genetics, pre-existing liver diseases) and drug-related factors (e.g., dose, drug-drug interactions). Management consists in the prompt identification and cessation of the offending drug, with emphasis on supportive care. In WHO candidate malaria vaccines, preventive strategies highlight close monitoring of liver function during therapy and the careful selection of medicines. However, the understanding of DILI, which is bimodal, and nuanced, is of significant importance for improving patient outcomes and developing safer therapeutic agents. Further studies will have to provide robust biomarkers and clarify underlying molecular pathways to improve prediction of this kind of DILI and possibly prevent occurrence of such adverse events.

Keywords: Drug-induced liver injury, DILI, hepatotoxicity, bioactivation, immune-mediated liver injury, acetaminophen toxicity, idiosyncratic DILI

1. INTRODUCTION TO DRUG-INDUCED LIVER INJURY (DILI)

Drug-induced liver injury or DILI is an acute clinical challenge affecting most of the patients worldwide [1]. The liver, considered a primary site for metabolic breakdown and detoxification processes for drugs, is exceptionally sensitive to injury from any sort of pharmaceutical agents and substances, herbal products, or certain environmental toxins [2]. DILI can arise with a spectrum of liver abnormalities as mild, transient elevation in liver enzymes to severe potentially lethal conditions such as acute liver failure [3]. This introduction attempts to overview the epidemiology, types, mechanism, clinical presentation and importance of DILI in the context of modern medicine.

2. EPIDEMIOLOGY AND SIGNIFICANCE OF DILI

DILI is a common cause of acute liver failure in many countries and is often the reason drugs with potential benefits are withdrawn from development [4]. The rate of DILI is highly variable and depends on the population studied and the definition of the syndrome [5]. The annual incidence has been estimated at 14 to 19 cases per 100,000 persons exposed to drugs [6]. DILI imposes a significant burden on healthcare systems because of the requirement for extensive diagnostic evaluations and long-term monitoring of affected patients [7].

3. TYPES OF DILI

Drug induced liver injury is mainly classified into two main types; out of which one is intrinsic and other is idiosyncratic [8]. Intrinsic DILI is predictable and dose-dependent [9]. It usually occurs within a short period of exposure to a high dose of a drug and is a common example of acetaminophen toxicity [10]. Acetaminophen is a widely prescribed drug for its analgesic and antipyretic effects, but at an overdose, it results in severe liver injury with acute liver failure [11]. Idiosyncratic DILI is unpredictable and dose-independent [12]. It occurs in a few patients and can be prompted by many factors, which include genetic predispositions, underlying liver disease, and concurrent use of multiple drugs [13]. Idiosyncratic DILI presents a important diagnostic challenge because of its unpredictable nature and lack of reliable biomarkers for its early detection [14].

4. MECHANISMS OF DILI

The mechanisms of DILI are complex and multifactorial [15]. The livers role in the metabolism of drug and detoxification includes the drugs biotransformation to more water-soluble metabolites

for easy excretion [16]. However, some drugs undergo bioactivation, with resultant formation of reactive metabolites that can covalently bind to cellular macromolecules and cause direct hepatocellular damage [17]. Metabolic bioactivation is one mechanism through which intrinsic DILI is triggered. The liver's immunological environment is also unique, which makes it prone to immune-mediated liver injury [18]. Drugs and their metabolites can act as haptens, which binds to proteins and trigger immune responses that results in inflammation of liver and injury of liver [19]. This immune-mediated mechanism is concerned in idiosyncratic DILI, where the immune system targets liver cells, which leads to hepatotoxicity [20].

5. CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of DILI varies widely, ranging from asymptomatic elevations in liver enzymes to jaundice, coagulopathy, and acute liver failure. Common symptoms of this include fatigue, nausea, abdominal pain, and jaundice [21]. Diagnosis of DILI is challenging and often relies on a combination of clinical history, exclusion of other causes of liver disease, and temporal association with drug exposure [22]. In some instances, a liver biopsy can be carried out to establish the level of liver injury and rule out other diseases affecting the liver [23]. Although the commonly used biomarkers in monitoring the functioning of the liver are ALT and AST, the development of more specific biomarkers in the prediction and early diagnosis of DILI is recommended [24].

6. RISK FACTORS

The risk of Drug induced liver injury is dependent on both the patient-related factors and drug-related factors. Patient-related factors include age, sex, genetic predisposition, pre-existing liver disease, and comorbid conditions [25]. For example, elderly persons and those with existing conditions of the liver such as hepatitis or NAFLD are at higher risk [26]. Genetic polymorphisms in drug-metabolizing enzymes and immune-related genes also play a role in determining susceptibility to DILI [27]. Drug-related factors include the chemical structure of the drug, dose, duration of therapy, and interactions with other drugs. Some drug classes, like antibiotics, anticonvulsants, and NSAIDs, are more commonly associated with DILI [28].

7. MANAGEMENT AND PREVENTION

Early recognition, discontinuation of the offending drug, and supportive care are considered essential in the management of DILI [29]. For severe liver injury, hospitalization and close monitoring of the patient may be required [30]. Preventive measures include careful selection of drugs, especially in patients at risk, and monitoring of liver function in the course of treatment with drugs known to have a hepatotoxic potential [31]. Research is still underway in developing safer drugs with a reduced hepatotoxic potential and in identifying biomarkers for early detection of DILI [32].

8. CONCLUSION

Drug-induced liver injury continues to be a challenging problem in clinical and regulatory realms. Although mechanisms and risk factors have been greatly elucidated, early detection and effective management of DILI remain problematic. This area of research into elucidating molecular pathways of DILI and identifying reliable biomarkers is crucial for patient improvement. Clinicians, researchers, and regulatory authorities must work together to develop strategies to minimize the incidence and impact of DILI, ensuring the safe use of medications and protecting public health.

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