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Short Communication

Standard Diagnosis for Drug Induced Liver Injury

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DESCRIPTION

Drug-induced liver injury (DILI; also known as drug-induced hepatotoxicity) is caused by medications (prescription or over-the-counter), herbal and dietary supplements (HDS), or other xenobiotics that cause abnormalities in liver tests or hepatic dysfunction [1].

DILI is classified into two types: intrinsic and idiosyncratic. Intrinsic DILI is defined as liver damage caused by a medication in a predictable and dose-related way (e.g., acetaminophen [APAP]); idiosyncratic DILI, which occurs less frequently, is characterized by a less consistent dose-toxicity connection and a more variable presentation [2].

Mechanism of DILI

DILI is considered to be caused by a variety of processes. Direct disruption of the liver's structural (e.g., mitochondrial dysfunction) and functional integrity; production of a metabolite that affects hepatocellular structure and function; and synthesis of a metabolite that alters hepatocellular structure and function are some of the examples.

Drugs related to DILI

Antibiotics and antiepileptic drugs are responsible for more than 60% of DILI instances. Some of the clinical recommendations on idiosyncratic DILI have recognized the most prevalent and well-described DILI-associated agents, as well as their pattern of liver damage.

The significance of DILI diagnosis

Drug-induced liver damage (DILI) accounts for just 1% of all instances of acute liver injury treated by gastroenterologists, yet it is the leading cause of acute liver failure in many countries.

DILI has an annual incidence of 14-19 per 100 000 persons, according to surveys in France and Iceland. DILI is also a major source of compound attrition in drug development and one of the two most common causes of medication withdrawals, limitations, and project termination. Between 1969 and 2002, 12 medicines were removed from the market due to liver harm [3]. Whereas liver signals that go undetected during drug approval result in post-marketing restrictions (for example, pazopanib, temozolomide, and flupirtine in 2013), the risk of false-positive DILI adjudication may result in unnecessary attrition, contributing to the significant economic issues associated with DILI.

Patients who take more than 7.5 g of acetaminophen (APAP) in a single dosage develop severe liver damage, especially if plasma concentrations surpass 200 or 100 g/L 4 or 8 hours after consumption, respectively. In one-third of individuals, APAP at the permitted dose of 4 g/day for two weeks causes alanine aminotransferase (ALT) levels above 3 the upper limit of normal (ULN). This type of dose-dependent APAP-induced damage is known as intrinsic DILI: It is predictable, repeatable in preclinical animals, and significant insight into the underlying processes has been acquired.

Standard of diagnosis: Role of currently performed liver tests in assessing DILI

DILI often manifests as an acute viral hepatitis-like illness with no symptoms unique to the drug aetiology, unless rash or other cutaneous signs strengthen the hypothesis of drug poisoning. DILI's clinical range can be similar to that of nearly any other liver disease. Blood eosinophilia is uncommon in large series of DILI patients, although it is strongly indicative of drug allergy. DILI histopathological results can be similar to those of many other liver diseases, limiting the use of liver biopsy in DILI diagnosis. However, when the underlying liver condition worsens (e.g., alcoholic hepatitis, autoimmune hepatitis), a biopsy can be used to establish an alternate diagnosis (AIH)

Although serum aminotransferases (ALT and AST), alkaline phosphatase (ALP), and total bilirubin (TB) levels are not specific for DILI, they remain the gold standard for identifying and assessing liver injury [4]. Minor elevations in aminotransferases caused by drug-induced adaptive and reversible liver responses (eg, statins) or pre-existing liver illness (eg: fatty liver) should not be categorised as DILI. An international expert panel suggested the following criterion for

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DILI diagnosis: (a) ALT value of 5 ULN, (b) ALP value of 2 ULN, or (c) ALT value of 3 ULN and TB value of 2 ULN. The latter constellation is defined by 'Hy's Law,' which predicts a 10% chance of mortality/liver transplantation based on vast databases of DILI cases. The FDA advice for DILI expands on Hy's Law by noting that "there should not be a pronounced cholestatic component" in the hepatocellular character of the liver damage, implying that a cholestatic component, as indicated by high ALP levels, is linked with a lower risk of progression. However, a recent studies found that elevated ALP >2 ULN did not reduce the risk of acute liver failure in instances when Hy's Law was met. A marked increase of AST and an AST/ALT ratio >1.5 at DILI recognition also predict a worse prognosis.

Antinuclear antibodies (ANAs), smooth muscle antibodies (SMAs), and increased IgG levels, as well as histological characteristics of AIH, may lead DILI to be misdiagnosed [5]. Although the usual laboratory and clinical signs of AIH may potentially be medication caused, screening for autoantibodies and serum IgG in hepatocellular damage is required. Furthermore, recurrent DILI caused by a different medication is more likely to have an AIH profile. DILI with autoimmune characteristics should be differentiated from idiopathic AIH, which usually goes away once the causative medication is stopped. There are currently no diagnostic tests available to distinguish between idiopathic and drug-related AIH, however histological findings can aid in the differential diagnosis.

CONCLUSION

Rechallenge with the suspected drug, although considered the gold standard for diagnostic confirmation, carries ethical and practical issues. For starters, it carries a risk that is only justifiable when no other option is available. Second, due to a lack of data on 'negative rechallenge,' the concept of a 'positive rechallenge' is debatable in terms of the needed threshold, if any, of liver enzyme increase and symptoms. The re-exposure test is positive in the RUCAM score if ALT is 2 baseline after re-exposure and ALT was below 5 ULN before re-exposure, and negative if one or both conditions are not met. In individuals with DILI, regular liver biochemistry must be performed until full normalisation. The rapid normalisation of aminotransferases supports the diagnosis, whereas delayed or partial resolution implies other explanations. In such cases, a liver biopsy might be beneficial. Chronic prognosis can be predicted by persistently high TB and ALP 30–60 days following the first DILI diagnosis.

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