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Progress in the study of drug-induced liver damage

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Abstract: Drug metabolism or biotransformation is one of the most important functions of the liver, at the same time the drug itself or metabolites can also cause liver damage, the liver damage caused by drug-induced liver injury (drug-induced liverinjury (DILI)).DILI manifested as acute viral hepatitis symptoms, can be seen in the liver area, discomfort, loss of appetite, malaise, nausea, etc., and severe cases can even be seen in liver failure, bleeding tendency, cerebral encephalopathy and other symptoms. In severe cases, liver failure, haemorrhagic tendency and hepatic encephalopathy can be seen. [1] With the continuous increase of new drugs and the increase of clinical medication, the incidence of drug hepatitis is increasing year by year, especially the vigorous promotion of Chinese medicine, the promotion and development of combined Chinese and Western medicine, the continuous improvement of Chinese and Western medicine dosage forms, and the rise of health care, which further broaden the application of various types of medicines in the clinical treatment and health care, but the drug liver injury caused by the drug is commonplace in clinic and reported more and more, and has become a major cause of liver damage in clinical practice. However, drug-induced liver injury is common in clinical practice, and the number of reports is increasing, and it has become a common clinical disease. In this review, we will make a comprehensive summary of the studies on drug-induced liver injury in the past 10 years.

1. Introduction

Drug-induced liver damage refers to liver damage caused by drugs or their metabolites, which occurs in healthy people with no history of liver disease or patients with pre-existing serious diseases, and occurs to different degrees after the use of certain drugs. Up to now, there are more than 1,000 kinds of drugs causing different degrees of liver damage, including almost all kinds of drugs. With the increasing number of new drugs, the incidence of drug-induced hepatitis is increasing day by day, and it has become a common clinical disease. In this article, we will make a comprehensive summary of the studies on drug-induced liver damage in recent years from various aspects.

2. Pathogenesis and staging of drug-induced liver injury

Drug-related hepatic damage, or colloquially known as DILI, encompasses a wide spectrum of liver impairments triggered by prescribed medications, non-prescription drugs, herbal treatments, and nutritional supplements. Delving into the intricacies of DILI, it is imperative to first distinguish its two primary manifestations: the idiosyncratic and the intrinsic varieties; The intrinsic form is generally believed to be dependent on the dose of the drug, and it is only when a certain dosage is taken that the injury occurs. This is due to the direct toxicity of the substance or its metabolites, and is characterised primarily by the rapid onset of the disease following dose administration, and the onset of clinical signs and symptoms is similar to that of the past, and can be predicted, which is why it is also called the predictable type, characterized by the necrosis of the hepatocytes in certain areas of the liver lobule [2] The mechanism of intrinsic drug-type liver injury is that the drug causes cell membrane peroxidation through free radicals or metabolic mediators, resulting in damage to the hepatic border cells; it can also initiate apoptosis by altering the cell membrane or intracellular structure. [3] Atopic liver damage is usually unpredictable, with an incubation period of days to weeks, no definite causal link between drug dose and disease severity, and with re-dosing of the drug, not only is the disease severity increased, but also the incubation period is shortened, and the pathology manifests itself as a diffuse hepatic damage [4]. Also atopic liver damage can be divided into two subtypes: allergic and non-allergic. The non-allergic type, also known as the metabolic heterogeneous type, is thought to be caused by direct biochemical damage to the liver from the drug, whereas the allergic type acquires immunity at the previous dose of the drug and develops a more rapid liver injury in a shorter period of time at the next dose of the drug. The mechanisms of these two subtypes of liver injury are as follows: 1.1 Mechanisms of metabolic heterogeneous liver injury: CYP450 is the main enzyme that metabolises drugs in the body, and is mainly found in the liver. Metabolic heterogeneous liver injury is mostly related to CYP450 enzyme system, the genetic diversity of CYP450 enzyme system leads to the low metabolism ability of the liver, the accumulation of drugs or intermediates and thus cause liver injury. [5]1.2 Mechanisms of allergic liver injury: two hypotheses for the involvement of immune factors in DILI: (1) a small number of susceptible individuals regard the resurrection of CYP450 enzymes with drugs as a "foreign body", and hepatocytes expressing foreign antigens are subjected to immune cell attack [6]; (2) drugs induce mitochondrial oxidative stress, and the release of inflammatory factors promotes the activation of T-cells cell activation. Han et al [7] suggested that drugs induced mitochondrial oxidative stress and inflammatory factor release which further promoted T cell activation. When hepatocytes are exposed to drugs or their metabolites, if the hepatocytes are not protected by adaptive signalling pathways, the drugs are processed as semi-antigens leading to the activation of CD8+ T cells, which further initiates the apoptotic program.

3. Common medications that cause DILIs

DILI is a common side effect, accounting for about 10% to 15% of all drug-induced adverse drug reactions [8] Currently, more than 1100 marketed drugs worldwide are known to have potential liver toxicityCommon medicines include nonsteroidal anti-inflammatory drugs (NSAIDS), anti-infectious medicines (including antituberculotics), anticancer medicines, central nervous system medicines, cardiovascular medicines, hormonal medicines, certain biologics, natural medicines, health products, food supplements (TCM-NM-HPDS), and so on.[9].Common Western medicine drugs include paracetamol, valproic acid, carbamazepine, methotrexate, tetracycline, zidovudine, ceftriaxone, Bosenan, cyclosporine, balliximab, erythromycin, voriconazole, montelukast sodium, etc. American scholars have found that herbal medicines are the second most common cause of drug-induced hepatitis. The proportion of hepatitis caused by herbal medicines in

China is about 20% to 74.4%, and a large number of plant medicines have been found to be toxic to the liver, with pathogenic mechanisms such as abnormalities in immune function, lipid peroxidation, apoptosis and dysregulation of intracellular calcium homeostasis in hepatocytes. In addition, the liver incidence of botanical drugs containing alkaloids and glycosides is significantly higher than that of drugs containing other components. [10] In terms of Chinese herbs, common single Chinese herbs that have direct toxicity to the liver include polygonum multiflora, cassia seed, coxanthus bark, centipedes, licorice, mint, rhubarb, fish bile, aconite, tripterygium vine, xanthium, senna leaf, etc. Some of these drugs or their metabolites can directly damage the liver. At the same time, liver damage is related to the body's atopy and allergic reaction to Chinese herbs or their metabolites, that is, liver damage through immune-mediated mechanism. The material, storage, transportation and processing of Chinese herbal medicine may affect the drug effect and the occurrence of drug-induced hepatitis, and the excipients and organic solvents used in the processing of Chinese herbal medicine may also be related to drug-induced hepatitis.

4. Risk factors for pharmacological liver injury

(1) Patient's age, sex, etc.: 1.1 1.1. Gender: Women have been shown to be more at risk for certain DILI than men. A number of retrospective studies and one prospective study have reported the predominance of women in DILI. [11] A study in the United States found that DILI was more prevalent among females (59% female, 41% male). In a prospective French study, the average annual DILI rate was 17 for females versus 10 for 100 000 for males, while the Icelandic study indicated that DILI was more evenly distributed among females (56%) compared to males (44%). In the Icelandic and Spanish epidemiological trials, DILI women accounted for 55% and 53%, respectively. [12] Additionally the higher percentage of middle-aged female patients who develop medicated liver may be related to women's focus on health and wellness and inappropriate use of supplements [13]. It may also be related to the fact that females are slightly more sensitive to drugs than males, and the activity of hepatic microsomal enzymes is slightly higher in males than in females. Therefore, the sex of a woman is a DILI risk factor. [14] 1.2: Age: It has been demonstrated that age is a risk factor for DILI, and the risk of DILI is generally lower in children, but a study of non-viral hepatitis in children in China showed that DILI accounted for 1.01% of non-viral hepatitis in 1983-2000, and had risen to 10.0% of all non-viral hepatitis cases in the years 2001-2010. -2010 has increased to 10.53%. [15] Another study also noted that DILI in children accounted for about 10% of liver diseases in the same period, [16] such as paracetamol, tetracycline, zidovudine, ceftriaxone, bosentan, cyclosporine, balexisumab, all of which increase the risk of hepatotoxicity. [17] For elderly patients because of key factors such as absorption, distribution, and metabolism. The increased risk or incidence of DILI in the elderly is biologically plausible

(2) Among DILINs in the United States, 10% of DILI patients had prior liver disease

(3) Other factors: Toxicity of the drug itself, dosage of the drug, Patients with allergic history and immune disorders, Patients taking multiple different drugs at the same time

5. Diagnosis

The diagnostic methods and criteria of drug-induced liver disease are still under constant revision, and the diagnostic criteria of drug-induced liver disease were firstly proposed in Japan in 1978 as follows: (1) Liver damage occurs for some time after the use of medication, and some of them usually have a certain latent period; (2) Initial symptoms include fever, rash, jaundice, itching, etc.; (3) Eosinophils are elevated in the blood; (4) Lymphatic stimulation test of the medication or the skin test is positive; (5) Occasionally, liver damage occurs again after taking medication; (6) Occasional recurrence of liver damage after taking the drug [18]. Referring to the above diagnostic

criteria, as well as the "European Consensus Diagnostic Criteria for Pharmacological Liver Injury" proposed by Danan, Maria's protocol proposed in 1997, and the protocol of the Japanese Society of Hepatology of the DDW-Japan in 2003,the main points of clinical diagnosis are as follows: (1) No history of exposure to hepatitis, no history of alcohol consumption, no history of exposure to toxins, and history of taking traditional Chinese medicines (including soups, granules, pills, tablets, injections, etc). (2) Initial symptoms include gastrointestinal symptoms, such as gastrointestinal discomfort, nausea, vomiting, poor appetite, abdominal distension, and may also be accompanied by yellow urine, fever, rash, and itchy skin. (3) Liver damage, including markedly elevated ALT, AST, GGT, ALP and bilirubin, occurs 1 week to 3 months after taking the drug or after the drug is administered. (4) Pathological and clinical signs of intrahepatic cholestasis or parenchymal cell injury. (5) Negative for various markers of viral hepatitis. (6) Re-administration of the drug and the occurrence of liver injury, judgement criteria: any 2 of (1) to (6), exclude alcoholic hepatitis, infectious toxic hepatitis, autoimmune liver disease, hereditary liver disease, can be diagnosed. [19]

6. Prognosis and treatment of drug-induced hepatitis

6.1 Prognosis

Most DILIs have a favourable prognosis and tend to return to normal within 3 months of drug discontinuation; deaths are most often due to complications of fulminant liver failure and chronic hepatitis. Hepatocellular type has the fastest recovery of liver function after drug discontinuation, cholestatic liver damage and mixed liver damage are slower than hepatocellular type, if DILI is not diagnosed early and continued use of liver damaging drugs for more than 6 months will likely lead to irreversible liver damage. In addition, about 71% of cases in which early manifestations of liver fibrosis are detected on histological tests become chronic. Generally liver biochemical tests recover within 4-14 weeks of drug withdrawal and liver-protective therapy, and some may last up to 12 months, and if these markers do not recover within the normal time frame, it suggests that the liver damage becomes chronic

6.2 Treatment

(1) Once DILI is suspected, it is most important to stop using the culprit's medication in a timely manner. (2) For diseases in which the drug cannot be stopped or changed immediately, if the liver function is not severely impaired, it may be given first to reduce the dosage of the drug, increase the amount of fluids to promote drug elimination, and treat with hepatoprotective, enzyme-lowering, and anti-yellowing therapy [20]. For example, in the treatment of pulmonary tuberculosis, the recommended first-line treatment is the combination of isoniazid (INH), rifampicin (RFP), and vizinophthalein (PZA), and blindly stopping the drugs may lead to worsening of the patient's condition or even the emergence of drug-resistant tuberculosis. In this case can be given first to protect the liver treatment, monitoring liver function, can be symptomatic liver protection before deciding whether to stop the drug. (3) If the use of the drug causes a hypersensitivity reaction in the body and liver function tests cannot be recovered within 8 to 12 weeks after stopping the drug, hormones can be used, or it has been proved that liver damage is due to immune-mediated, cortisol should be used, which can benefit the patient in the early stage [21] (4) Awareness-raising and caution in the use of traditional Chinese medicines (TCMs) are the first choice of treatment for many patients with the emergence of the disease in their opinion. Chinese medicine has less toxic side effects, due to the complexity of the composition of Chinese herbs, many herbal ingredients can cause liver damage, even if commonly used in hepatoprotective treatment of Chinese herbs so far there is no evidence of evidence-based medicine to support. Even some literature has pointed out

that the Chinese herbal medicines commonly used for liver-protection formulae gentian diarrhoea liver soup and Xiao Chaihu Tang can themselves cause DILI [22]. (5) For patients with chronic liver disease or long-term oral medication, liver function tests should be performed routinely, and once liver enzymes exceed three times the upper limit of normal values, the medication should be stopped immediately. On the other hand, the monitoring of drugs with proven hepatic impairment should be strengthened. Diagnosis and appropriate management before irreversible liver function changes will reduce the morbidity and ultimate outcome of DILI [23](6) Liver transplantation can be life-saving in the event of fulminant liver failure

7. Conclusion

Drug-induced hepatitis is a serious adverse drug reaction, which brings great economic burden and psychological pressure to patients, as medical workers should pay great attention to the diagnosis and treatment of drug-induced hepatitis in the clinic, and improve the awareness of medication safety, especially when unavoidably applying hepatotoxic drugs, it is necessary to weigh the advantages and disadvantages and check the liver function on a regular basis, so as to avoid irreversible damage, and if possible, establish the method of blood concentration monitoring of this kind of drug to quantify and monitor the concentration of hepatotoxic drugs in real time, so as to avoid irreversible damage to patients. If possible, a method of blood concentration monitoring can be established for such drugs to quantify and monitor the concentration of hepatotoxic drugs in real time, so as not to cause liver damage to patients. In conclusion, the etiology of drug hepatitis is diversified, but most of them are drugs commonly used in clinical practice, such as anti-tuberculosis drugs, antipyretic and analgesic drugs, anti-inflammatory drugs, antibiotics, anti-tumour drugs and immunosuppressants, Chinese herbal medicines, hypoglycemic drugs, anti-thyroid medicines, etc. With the development of the modern medical industry, it is possible for patients to be treated with these drugs in real time. With the development of the modern medical industry, the pharmacy over-the-counter medication to provide people with the convenience of medication at the same time also increased the arbitrariness of the use of medication, so for the patients it is best to use these drugs under the guidance of the physician and pharmacist, the dose of the drug, time, indications and side effects of the drug to effectively grasp, and on the basis of the medication. For researchers, the listing of new drugs has to go through phase I, II and III clinical trials, through which drugs with obvious hepatotoxicity to the liver can usually be eliminated, but for some patients with specific hepatic injury cannot be eliminated, and need to follow up on the incidence of patients with systematic investigation and research. This is due to the fact that the pathogenesis of specific liver injury is still unclear, and effective monitoring indicators cannot be established, so the immunological study of drug-induced liver disease is a relatively unknown and worthwhile field of research, waiting for researchers to discover.

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