Drug-induced liver injury

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Abstract

Lack of substantial advances in preclinical testing for hepatotoxicity has meant that drug-induced liver injury (DILI) remains an important issue during both the drug development and post-marketing phases. A number of drug-related, genetic and non-genetic host factors influence the risk of DILI in an individual. Demonstration of human leukocyte antigen genotype as a strong risk factor for development of DILI with a range of drugs has highlighted the role of the adaptive immune system in the pathogenesis of DILI; there is accumulating evidence that drug metabolism genes also contribute to some forms of DILI. Early recognition and prompt withdrawal of the drug is essential in preventing serious hepatic failure and is the critical step in the management of adverse reactions. Diagnosis of DILI relies upon index of suspicion, careful evaluation of a temporal relationship between the exposure to a particular drug and the specific clinical event, as well as exclusion of potential alternative diagnoses. A high negative predictive value of genetic tests can be used to rule out DILI due to particular drugs and to identify correctly the agent underlying DILI in a patient exposed to two concomitant medications.

Keywords Adverse drug reaction; drug-induced liver injury; hepatotoxicity; human leukocyte antigen; pharmacogenetics

What's new?

- The incidence of DILI has been estimated to be 19 per 100,000 population and DILI is the second most common cause of hepatocellular jaundice presenting to secondary care
- The strong association between human leukocyte antigen (HLA) genotype and the development of DILI caused by a number of structurally dissimilar drugs indicates that the presentation of a drug—peptide complex to T cells is a key mechanism mediating liver injury
- The majority of HLA alleles associated with DILI have a very high negative predictive value of >0.95; this allows genetic tests to be used to rule out DILI due to particular drugs and to identify the correct agent underlying DILI in a patient exposed to two concomitant medications
- A number of drug-related, genetic and non-genetic host factors that influence the risk of DILI could be incorporated into algorithms that assist accurate evaluation of risk-benefit ratio in an individual requiring drug therapy

Introduction

Idiosyncratic drug-induced liver injury (DILI) is best described as an adverse hepatic reaction that is unexpected on the basis of the pharmacological action of the drug administered; this is distinct and different from liver injury secondary to drug overdosage.[1] Hepatotoxicity includes a wide variety of adverse reactions such as drug-associated chronic liver diseases (drug-associated fatty liver disease, fibrosis, nodular regenerative hyperplasia, secondary sclerosing cholangitis), whereas the term DILI refers to adverse events which are acute in onset.

Thresholds to define DILI include a fivefold elevation above the upper limit of normal (ULN) for alanine transaminase (ALT), twofold elevation for alkaline phosphatase, or a simultaneous threefold elevation in ALT concentration and twofold elevation of bilirubin concentration.[1] Based on the associated biochemical abnormalities DILI is sub-classified as of 'hepatocellular', cholestatic or mixed pattern.

Burden of hepatotoxicity

Because the liver is involved in the biotransformation of the majority of drugs, hepatotoxicity is a potential complication of large number of medications. Owing to their relatively low incidence, hepatic adverse reactions often remain undetected during clinical trials. Even after a drug has been marketed, hepatotoxicity may become apparent only when a large number of people have been exposed to the drug; for this reason, hepatotoxicity has been the second most common reason for withdrawal of drugs from the market worldwide, accounting for 32% of such cases between 1975 and 2007.

A prospective population-based study from Iceland estimated the crude incidence of DILI to be 19 per 100,000 population.[2] The incidence of acute serious liver injury requiring hospitalization has been estimated to be 0.7—1 per 100,000 population per year. In a recent audit from the UK involving 881 consecutive patients presenting with jaundice in whom biliary obstruction had been ruled out by imaging,[3] DILI was the underlying aetiology in 15% of cases; in this case series, DILI was the second most common cause of hepatocellular jaundice after alcoholic liver disease, which accounted for 25% of cases. Idiosyncratic DILI contributes to 7—15% of cases of acute liver failure, highlighting the potentially serious consequences of this adverse reaction. (Table 1).

Risk factors associated with DILI

Drug-related risk factors

Although idiosyncratic DILI is clearly distinguishable from hepatotoxicity related to overdose (e.g. paracetamol), serious DILI occurs more frequently with medications taken in a daily dose of ≥50 mg than those taken in a daily dose of ≤10 mg.[4] There is also a significant relationship between daily dose and reports of liver failure, liver transplantation, and death caused by DILI. In addition, compounds >50% of whose elimination relies upon hepatic metabolism are more likely to be associated with DILI (fatal and non-fatal) and liver failure; lipophilicity of the drug increases the risk of hepatotoxicity.[5] Lengthy duration of exposure to the medication (flucloxacillin and co-amoxiclav) has also been associated with an increased risk of DILI.

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Drugs associated with different forms of hepatotoxicity

Acute hepatocellular pattern of liver injury

NSAIDs: diclofenac, naproxen, nimesulide, piroxicam

Anaesthetics: enflurane, halothane, isoflurane

Antimicrobials: ketoconazole, terbinafine, tetracyclines; anti-tuberculosis drugs such as isoniazid, pyrazinamide, rifampicin; anti-HIV agents such as didanosine, nevirapine, zidovudine

Neuropsychotropics: tricyclics (most), fluoxetine, paroxetine, sertraline; illegal compounds such as cocaine and ecstasy

Anti-epileptics: carbamazepine, phenytoin, valproate

Cardiovascular drugs: bezafibrate, captopril, enalapril, lisinopril, lovastatin, simvastatin, ticlopidine

Antineoplastics: cyclophosphamide, cisplatin, doxorubicin

Others: herbal remedies

Acute cholestatic pattern of liver injury

Hormonal preparations: androgens, anabolic steroids, oral contraceptives, tamoxifen

Antimicrobials: clindamycin, co-amoxiclav, co-trimoxazole, erythromycin, flucloxacillin, troleandomycin

Analgesics/anti-inflammatory drugs: gold salts, sulindac Neuropsychiatric drugs: carbamazepine, chlorpromazine, tricyclic antidepressants

Immunosuppressants: azathioprine, ciclosporin

Others: allopurinol

Auto-immune hepatitis

Minocycline, nitrofurantoin, diclofenac, indometacin, statins, infliximab, halothane, herbal medicine (germander), methyldopa

Chronic drug-associated liver disease and/or cirrhosis

Methotrexate, tamoxifen, vitamin A

Chronic cholestasis and ductopenia

Carbamazepine, chlorpromazine, co-amoxiclav, co-trimoxazole, erythromycin, flucloxacillin, methyltestosterone, phenytoin

Granulomatous hepatitis

Allopurinol, carbamazepine, diltiazem, gold salts, methyldopa, nitrofurantoin, penicillin, penicillamine, phenytoin, sulfonamides, sulfonylureas

Macro and microvesicular steatosis

Amiodarone, corticosteroids, methotrexate, salicylate, tetracycline, valproate, zidovudine

Hepatic vascular lesion

Hepatic vein thrombosis/veno-occlusive disease: azathioprine, combination chemotherapy (carmustine, cytarabine, mitomycin, thioguanine, urethane), oral contraceptives

Sinusoidal dilation/peliosis: anabolic steroids, azathioprine, oral contraceptives

Tumours

Anabolic steroids, oral contraceptives

Table 1

Genetic susceptibility

A series of case control studies in the last decade has demonstrated that allelic variants of UDP-glucuronosyltransferase-2B7, cytochrome P450 (CYP)-2C8 and the ATP-binding cassette, subfamily C -member 2 (*ABCC2*), which may promote formation and accumulation of reactive diclofenac metabolites, are associated with susceptibility to diclofenac hepatotoxicity.[6] In the case of flucloxacillin, a promoter region polymorphism in gene coding for xeno-sensing pregnane X receptor (PXR), which regulates the transcription of phase I and II drug-metabolizing enzymes such as CYPs and glutathione S-transferases (GSTs) as well as transporters, has been associated with DILI.[6]

Several candidate gene and genome-wide association studies (GWAS) have confirmed the major influence of human MHC on individual's susceptibility to DILI. A seminal GWAS demonstrated that possession of *HLA-B*5701* allele was strongly associated with an 81-fold increased risk of flucloxacillin DILI.[7] Several studies have confirmed association of co-amoxiclav DILI with the *DRB1*1501–DQB1*0602* haplotype.[8] HLA variants have also been associated with DILI secondary to a number of drugs including ximelagatran, ticlopedine, lumiracoxib.[6,9]

Pathogenesis

Development of idiosyncratic DILI involves a number of concurrent as well as sequential events determining the direction of the pathways, and the severity of liver injury and its manifestations (Figure 1).[10] The key upstream events include drug-specific pathways triggered by particular drugs or their metabolites. Genetic and environmental factors that influence the expression and activities of proteins involved in drug disposition will determine the rate of formation and accumulation of reactive metabolite. These reactive metabolites induce the production of excessive reactive oxygen species leading to lipid peroxidation and cell death. The cellular environment can modulate the threshold for hepatocyte death secondary to oxidative stress; thus dysregulation of the antioxidant pathway may contribute to the propagation of DILI. In addition, the occurrence and extent of liver injury could be influenced by events downstream; innate immune response can promote or inhibit the inflammatory process and thereby determine the progression and severity of DILI.

Although protein binding of reactive metabolites may impair cellular function to cause toxicity, drug metabolite adducts may