

A CLINICAL APPROACH TO DRUG-INDUCED LIVER INJURY

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ABSTRACT

Drug-Induced Liver Injury (DILI) may cause substantial harm to patients and places a considerable burden on the healthcare system. DILI can be classified as non-idiosyncratic (predictable) or idiosyncratic (unpredictable). The focus of this review is on Idiosyncratic DILI. An update on the epidemiology of DILI will be presented. An overview of current knowledge of DILI risk factors, pathogenesis, classification and clinical presentation will be given. An approach to DILI diagnosis and management using DILI due to tuberculosis (TB) treatment, which is a common severe adverse drug reaction in South African patients, as a practical example, will be outlined.

INTRODUCTION

Drug-Induced Liver Injury (DILI) is liver injury due to prescription and non-prescription medicines, herbal or dietary substances.¹ Over the past decade there has been an increasing recognition of herbal and dietary substances as causes of DILI. There is variation in regional distribution of the offending agents, with antimicrobial, antiepileptic and psychotropic drugs most commonly implicated in North America, in contrast with Asia, where herbs and dietary substances are the common offending agents.² In South Africa, which has a high burden of both tuberculosis (TB) and Human Immunodeficiency Virus (HIV) infection, with substantial comorbidity, DILI is commonly associated with exposure to tuberculosis treatment (TB-DILI) and/or antiretroviral drugs.

EPIDEMIOLOGY

The incidence of DILI is estimated to be 14-19 per 100 000 persons.^{3,4} However, the incidence may be underestimated in part due to underreporting and uncertainties regarding diagnosis.^{1,2} Although local data is limited, DILI is reported to complicate TB treatment in 5 to 33% of patients.⁵ DILI, as with adverse drug reactions (ADRs) in general, may be associated with considerable morbidity and mortality resulting in hospitalisation with associated costs.^{6,7} ADRs are implicated in up to 18% of deaths in hospitalised patients worldwide.⁸⁻¹² In a recent survey of medical wards at four South African hospitals, ADRs contributed to the death of 2.9% of hospitalised patients. DILI, most commonly due to TB treatment, was the second most common ADR contributing to death of medical inpatients.¹³ In addition, DILI has implications for drug development.

Emerging evidence of hepatotoxicity is a common reason for drug developers deciding not to proceed further with the development and clinical trials of a new drug.¹⁴

CLASSIFICATION OF DILI

DILI is mechanistically divided into non-idiosyncratic and idiosyncratic reactions.¹⁵ Non-idiosyncratic reactions are often predictable and tend to be dose-related, e.g. DILI due to paracetamol overdose. In contrast, idiosyncratic reactions are unpredictable, occurring in less than 1% of those exposed, and generally considered to be dose-independent.

RISK FACTORS OF IDIOSYNCRATIC DILI

Risk factors may influence the likelihood of developing DILI as well as the severity of DILI. DILI occurs more commonly in adults than children. Whether there is a true biological basis for the higher prevalence in adults, or whether it simply reflects greater drug exposure in adults, is not clear.^{16,17} Females appear to be at higher risk of DILI than males. Genetic factors may contribute to risk of DILI due to a variety of mechanisms. Genetic differences in phase 1 and phase 2 drug metabolising enzymes within the liver may increase the risk of DILI, e.g. isoniazid DILI and N-acetyltransferase 2 gene polymorphism. Secondly, specific Human Leukocyte Antigen (HLA) haplotypes have been implicated in the development of DILI, e.g. HLA-*B5701 genotype and abacavir as well as flucloxacillin.¹⁸ Underlying infection with hepatitis B or hepatitis C virus has been shown to be a risk factor for DILI in patients commencing antituberculous or antiretroviral drugs.^{19,20} Malnutrition is thought to increase risk of DILI.²¹ There is a

lack of data regarding whether or not concomitant alcohol exposure increases risk of development of idiosyncratic DILI.¹

PATHOGENESIS OF DILI

The pathogenesis of DILI is complex and not entirely understood. DILI is thought to result from interplay between the individual, the drug, and the environment. The parent molecule or a drug metabolite may cause the initial insult culminating in hepatic injury. Idiosyncratic DILI may result from either immunologic (allergic) or metabolic (non-allergic) mechanisms, however, distinction is not always clear-cut and there may be an overlap.²² Adaptation may explain why DILI occurs in a small percentage of individuals. Adaptation is characterised by transient minor abnormalities in LFTs without symptoms of DILI, occurring shortly after drug initiation, and resolving in the presence of continued drug exposure. A number of mechanisms are thought to explain adaptation, including optimised drug processing by the liver, development of tolerance by the adaptive immune system, as well as recruitment of antioxidant defences.²³

ALLERGIC DILI

Allergic DILI is a drug hypersensitivity reaction characterised by immune-mediated hepatotoxicity. Haptenisation of hepatic cells by the parent drug or a metabolite leads to the formation of neoantigens. Subsequent neoantigen presentation via major histocompatibility complex (MHC) class II leads to immune activation and hepatocyte destruction mediated by T-lymphocytes, B-lymphocytes and Natural Killer cells.²⁴ Allergic DILI occurs within 1-8 weeks of exposure. Patients may present with features of a hypersensitivity reaction, such as fever, skin rash, arthralgia and eosinophilia but this does not occur in all cases. Recurrence of symptoms on repeat exposure is a key finding that is highly suggestive of allergic DILI.

NON-ALLERGIC DILI

Non-allergic DILI is thought to result from covalent binding of a toxic drug metabolite to hepatic cells, resulting in oxidative cell damage and eventual cell death. In contrast with allergic DILI, non-allergic DILI tends to have a long latency (months) before DILI occurs with a notable absence of systemic features of hypersensitivity. Rechallenge with the offending drug in non-allergic DILI generally does not result in recurrence.¹⁵

CLINICAL PRESENTATION OF DILI

SYMPTOMS

Symptoms may include:

- Malaise;
- Loss of appetite;
- Nausea;
- Vomiting;
- Abdominal or right upper quadrant pain;

- Jaundice;
- Features of drug hypersensitivity, e.g. fever and rash.

ABNORMALITIES IN LIVER FUNCTION TESTS

DILI presents with abnormalities in Liver Function Tests (LFTs) that reflect an underlying pattern of liver injury. The pattern of injury is categorised into hepatocellular, cholestatic, or mixed.²⁵ A markedly elevated alanine aminotransferase (ALT) is characteristic of hepatocellular injury, whereas, marked elevation in alkaline phosphatase (ALP) characterises cholestatic injury. The mixed presentation usually includes elevations in both ALT and ALP. Importantly, the serum bilirubin may be elevated across all presentations. The development of jaundice, in association with hepatocellular injury, has clinical significance. The physician Hy Zimmerman, observed a higher risk of mortality (>10%) in patients with DILI, if they developed jaundice in association with raised transaminases. "Hy's law" refers to the increased mortality associated with an ALT ≥ 3 times the upper limit of normal (ULN) in combination with a serum bilirubin level ≥ 2 times the ULN.²⁶

An awareness of the pattern of injury is of some utility in that some drugs tend to be associated with a specific pattern. Table I provides examples of drugs categorised according to their common pattern of injury.²⁵

HISTOLOGY

DILI may be classified on the basis of histology and some drugs cause distinct histologic patterns of injury. Histologic patterns of injury include hepatocellular, cholestatic and steatosis. The limitation of histology in determining the cause of liver injury is that, as with derangements in LFTs, histological findings are generally not drug-specific. Nonetheless, the pattern of LFT derangement together with histological features may assist with causality assessment where there are multiple drug suspects.

APPROACH TO THE PATIENT WITH SUSPECTED DILI

Consultation with experts routinely involved in the management of DILI including hepatologists, clinical pharmacologists and infectious diseases specialists, is advised.

DIAGNOSIS

DILI is largely a diagnosis of exclusion. The aim is to exclude pre-existing liver disease and rule out other forms of liver disease.

The diagnostic work-up in suspected TB-DILI should give consideration to other potential causes of liver disease such as chronic and acute alcohol use, pre-existing liver disease, viral hepatitis, other hepatotoxic drugs, hepatic TB and Immune Reconstitution Inflammatory Syndrome (IRIS). In TB-DILI, isoniazid, rifampicin and pyrazinamide are the common offending agents. Asymptomatic elevations in serum aminotransferase levels may occur with

TABLE I: CLASSIFICATION OF DILI ACCORDING TO PATTERN OF INJURY

HEPATOCELLULAR (ALT ELEVATED)	CHOLESTATIC (ALP AND BILIRUBIN ELEVATED)	MIXED (ELEVATED ALP AND ALT)
Aspirin Allopurinol Amiodarone Bupropion Ciprofloxacin Isoniazid Ketoconazole Losartan Methotrexate Nevirapine NSAIDs Paracetamol Protease inhibitors Pyrazinamide Rifampicin Risperidone Sertraline Statins Valproic acid Venlafaxine	Chlorpromazine Clopidogrel Amoxicillin/clavulanic acid Co-trimoxazole Efavirenz Erythromycin Nevirapine Oral contraceptives Phenothiazines Terbinafine	Amitriptyline Azathioprine Cyclosporine Carbamazepine Clindamycin Co-trimoxazole Enalapril Erythromycin Phenobarbital Phenytoin Sulphonamides Trazodone Verapamil

Adapted and expanded from: Navarro VJ, Senior JR. Drug-related hepatotoxicity. *N Engl J Med* 2006;16;354(7):731-739.

isoniazid and rifampicin. This reflects hepatic adaptation and does not require treatment cessation. In addition, rifampicin may also cause asymptomatic unconjugated hyperbilirubinaemia shortly after commencing treatment.

HISTORY AND CAUSALITY ASSESSMENT

A comprehensive history should be obtained in the patient with suspected DILI. The patient should be asked about co-morbidities and pre-existing liver disease. Moreover, there should be an evaluation of risk factors for DILI, as well as a thorough history of drug use that includes an assessment of the timing of all recent drug exposures.

For patients with suspected TB-DILI, it is essential to review the details of the TB diagnosis including results of drug susceptibility testing, and to determine if the patient is in the intensive phase or continuation phase of TB therapy. Patients should also be asked about exposure to other hepatotoxic drugs including HIV antiretrovirals, cotrimoxazole, as well as traditional or herbal substances and over the counter medication.

Various causality assessment tools have been developed to assist in the diagnosis of DILI. None replace the need to seek expert advice for complex cases.²⁷

INVESTIGATIONS

We currently rely on abnormalities in LFTs (ALT, ALP and Bilirubin) to aid in the diagnosis and management of DILI. There is currently no universal definition for DILI on the basis of abnormalities in LFTs. However, the following definition of DILI requiring treatment interruption, is advocated for use in South Africa:^{5,28}

- ALT level >3 times ULN and symptomatic (nausea,

vomiting, abdominal pain, jaundice); or

- ALT level >5 times ULN and asymptomatic; or
- Total serum bilirubin concentration >2 times ULN.

Although indicative of liver injury, abnormalities in LFTs are not specific for DILI. The presence of a specific biomarker for DILI could aid in diagnosis and potentially improve our understanding of the pathogenesis of DILI.²² However, there are currently no specific biomarkers for DILI. The search for specific biomarkers of DILI remains an active research area with liver-specific micro RNAs (miR-122 and miR-192) showing a great deal of promise.^{1,22}

OTHER INVESTIGATIONS

Viral hepatitis is common in South Africa and needs to be excluded. Patients presenting with suspected DILI should be screened for Hepatitis A, B, C and E. The International Normalised Ratio (INR) is a marker of synthetic liver function and aids in assessing the severity of liver injury. The need for further investigations, including imaging modalities and/or liver biopsy, will be guided by the clinical presentation. Choice of investigations should be guided by advice from experts in DILI diagnosis and management.

In patients with suspected TB-DILI, additional investigations should be considered:

- Testing to confirm TB diagnosis if there is uncertainty regarding TB diagnosis;
- Review of available TB culture results and drug susceptibility testing;
- Request an abdominal ultrasound if the ALP or Bilirubin is elevated in order to exclude IRIS, disseminated TB and extrahepatic biliary obstruction.

MANAGEMENT

For DILI in general, management can be grouped into dechallenge, specific treatment and rechallenge.

For TB-DILI, there are specific considerations that impact on management decisions. These include severity of DILI, timing of onset of DILI (during initiation phase vs. continuation phase) and the use of concurrent HIV antiretrovirals and co-trimoxazole. In many cases causality assessment is complicated because of multiple drug suspects, which may include rifampicin, isoniazid, pyrazinamide, cotrimoxazole and a number of antiretrovirals, in particular efavirenz, nevirapine and protease inhibitors.

DECHALLENGE

Immediate cessation of the offending drug or drugs is the first step following diagnosis of DILI. Dechallenge of the offending drug will usually result in improvement of liver injury. However, the rate of improvement following dechallenge can be variable. In cases of DILI with a predominantly cholestatic picture, the bilirubin can take many weeks or months to return to normal. In cases of TB-DILI in patients co-infected with HIV, antiretrovirals,

TB treatment and cotrimoxazole may all be implicated. All potential causes should be stopped.

TREATMENT

Treatment is largely supportive with regular monitoring of the patient to ensure recovery. Specific drug therapies for the treatment of DILI are limited and include N-acetylcysteine for paracetamol-induced DILI.²⁹ In addition, carnitine is used for valproic acid toxicity, although robust evidence is lacking.³⁰ There is a lack of robust evidence concerning the use of corticosteroids in the treatment of DILI, and their use is generally not recommended.

Patients with TB-DILI require ongoing combination treatment for their TB while recovering from the liver injury. Patients are switched to a background regimen including three antituberculosis drugs, generally, an aminoglycoside, fluoroquinolone, and ethambutol, for example:

Amikacin 15 mg/kg daily PLUS

Moxifloxacin 400 mg daily

OR

Levofloxacin 750 mg daily (weight <50 kg) or 1000 mg daily (weight >50 kg) PLUS

Ethambutol 800 mg daily (weight 40 kg to 54 kg) or 1200 mg daily (weight 55 kg to 80 kg)

This regimen should be continued throughout the duration of rechallenge (see below).

RECHALLENGE

Rechallenge should only be attempted after confirming the diagnosis of TB. As a rule, rechallenge with the offending agent causing DILI should be avoided in view of the possibility that DILI will recur, and may be more severe on recurrence. However, there are currently very limited options for TB treatment. If rifampicin and isoniazid are not included in the treatment regimen, protracted courses of therapy (up to 18 months duration) are required, and cure rates suffer. Therefore, patients are frequently rechallenged with first-line TB treatment, specifically rifampicin and isoniazid in South Africa. Pyrazinamide rechallenge is more controversial, but is performed in cases where benefit is thought to outweigh risk (e.g. disseminated TB). It is important to remember that rechallenge with TB drugs is only performed because of the lack of effective alternative drugs, and because of the high risk of morbidity and mortality associated with untreated or incompletely treated TB. Furthermore, unlike many other drugs, there is some evidence to support rechallenge with antituberculous drugs in patients with TB-DILI.^{28,31,32} TB DILI recurs in 11% of patients rechallenged.³³ Rechallenge should always be performed with close supervision and monitoring, so that recurrence is detected early.

In patients with antituberculous DILI, rechallenge is usually undertaken once the ALT is <100 IU/l and total bilirubin has normalised. A small randomised controlled trial conducted in 175 patients in India, found no difference in recurrence rates between three approaches:

- Rechallenging with agents one by one with gradually incrementing dose;
- Rechallenging one by one with full doses;
- Rechallenging all drugs together.³²

Rechallenging with individual drugs and gradually increasing the dose requires prolonged hospital stay. Rechallenging with all drugs together makes causality assessment in cases of recurrence very difficult. Therefore, in South Africa, the strategy of rechallenging in a stepwise fashion with full doses is frequently used. A commonly used first-line antituberculous drug rechallenge regimen is as follows:⁵

- Day 1: Rifampicin 450 or 600 mg daily (depending on weight);
- Day 3: Check ALT;
- Day 4-6: Add 300 mg Isoniazid daily;
- Day 7: Check ALT;
- Day 8: Consider a Pyrazinamide rechallenge (in cases of TB meningitis or intolerance/resistance to other drugs after discussing with an expert);
- Check ALT at Day 10 if Pyrazinamide is rechallenged;
- Monitor ALT twice weekly for the first 3 weeks, then every two weeks for a month, then monthly until 3 months.

In patients taking ARVs that were interrupted due to DILI, ARVs should generally only be reintroduced once TB drug rechallenge is complete.

CONCLUSION

DILI may be associated with substantial morbidity and mortality. Awareness of the clinical presentation and common offending agents is therefore important to facilitate early diagnosis, which may improve outcomes. Research into specific biomarkers is progressing and may hold the key to understanding the complex pathogenesis and aid in diagnosis. In view of the lack of specific therapies for DILI, management of DILI is primarily focused on withdrawal of the offending agent and the provision of supportive treatment. Rechallenge should rarely be done but is justified in many cases of DILI, due to first line TB treatment, because of limited alternative treatment options.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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