An Update on Drug-induced Liver Injury

Harshad Devarbhavi

Department of Gastroenterology, St. John's Medical College Hospital, Sarjapur Road, Bangalore, India

Idiosyncratic drug-induced liver injury (DILI) is an important cause of morbidity and mortality following drugs taken in therapeutic doses. Hepatotoxicity is a leading cause of attrition in drug development, or withdrawal or restricted use after marketing. No age is exempt although adults and the elderly are at increased risk. DILI spans the entire spectrum ranging from asymptomatic elevation in transaminases to severe disease such as acute hepatitis leading to acute liver failure. The liver specific Roussel Uclaf Causality Assessment Method is the most validated and extensively used for determining the likelihood that an implicated drug caused DILI. Asymptomatic elevation in liver tests must be differentiated from adaptation. Drugs producing DILI have a signature pattern although no single pattern is characteristic. Antimicrobial and central nervous system agents including antiepileptic drugs are the leading causes of DILI worldwide. In the absence of a diagnostic test or a biomarker, the diagnosis rests on the evidence of absence of competing causes such as acute viral hepatitis, autoimmune hepatitis and others. Recent studies show that antituberculosis drugs given for active or latent disease are still a major cause of drug-induced liver injury in India and the West respectively. Presence of jaundice signifies a severe disease and entails a worse outcome. The pathogenesis is unclear and is due to a mix of host, drug metabolite and environmental factors. Research has evolved from incriminating candidate genes to genome wide analysis studies. Immediate cessation of the drug is key to prevent or minimize progressive damage. Treatment is largely supportive. *N*-acetylcysteine is the antidote for paracetamol toxicity. Carnitine has been tried in valproate injury whereas steroids and ursodeoxycholic acid may be used in DILI associated with hypersensitivity or cholestatic features respectively. This article provides an overview of the epidemiology, the patterns of hepatotoxicity, the pathogenesis and associated risk factors besides its clinical management. (J Clin Exp Hepatol 2012;2:247–259)

Idiosyncratic drug-induced liver injury (DILI) or hepatitis are alteration in liver biochemical tests that occur as an unintended off target response to exposed drug(s) at appropriate or recommended doses for treatment or prophylaxis of diseases.[1,2] Predictable or toxic DILI, in contrast occur when individuals are exposed to intentional and deliberate overdose of drugs.

Clinically, idiosyncratic DILI may take many forms, varying from asymptomatic, often self-limiting, and transient elevation in liver biochemical tests to jaundice and severe life threatening acute liver failure and rarely to chronic liver disease.[3] Presently, hepatotoxicity or cardiac toxicity is the leading cause of withdrawal from the market or termination in drug development in phase I-III.[4] The consequences following DILI, both economic and human are substantial resulting in loss of millions of dollars and hundreds of lives. This review encompasses the epidemiology, causes, risk factors and, causality assessment on DILI and discusses the recent experience from India and the West. The pathogenesis and treatment aspects are also reviewed.

SCOPE AND BURDEN OF THE PROBLEM

Drug-induced hepatitis is vastly unrecognized and underreported, such that the true incidence is unknown. Reported estimates range from 1:10,000 cases to 1:100,000 cases. In reality, this could be more common given that in large areas of the world, the number of people taking drugs which includes complementary or over the counter

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Address for correspondence: Harshad Devarbhavi, Professor, Department of Gastroenterology, St. John's Medical College Hospital, Sarjapur Road, Bangalore, India. Fax: +91 8025520499
E-mail: harshad.devarbhavi@gmail.com
Abbreviations: DILI: idiosyncratic drug-induced liver injury; NRH: nodular regenerative hyperplasia; ADR: adverse drug reaction; RUCAM: Roussel Uclaf Causality Assessment Method; INH: isoniazid; RIF: rifampicin; PZA: pyrazinamide; CIOMS: Council for International Organization of Medical Sciences; CDS: clinical diagnostic scale; NAPQI: *N*-acetyl-p-benzoquinone imine; LPS: lipopolysaccharide; MHC: major histocompatibility complex; HIV: human immunodeficiency virus; HBV: hepatitis B virus; DIAIH: drug-induced autoimmune hepatitis; BSEP: bile salt export pump; MRP: multi-drug resistance proteins; FXR: farnesoid X receptor; PXR: pregnane X receptor; CXR: constitutive androstane receptor; DIALF: drug-induced acute liver failure; TEN: toxic epidermal necrolysis; NRH: nodular regenerative hyperplasia; GWAS: genome wide association studies; AED: antiepileptic drugs; NAC: *N*-acetylcysteine; UDCA: ursodeoxycholic acid
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medicines cannot be estimated. Depending upon the setting, in which it is sought, the incidence of DILI varies.

Pirmohamed et al prospectively identified 1225 cases of adverse drug reaction among 18,820 (6.5%) admitted patients.[5] Although overall fatality was only 0.15%, the financial burden was substantial.[5] Paradoxically most adverse drug reactions could easily have been be avoidable.[5]

The incidence of DILI in an in-patient setting in France was 1.4% (95% CI 1.0–1.7). Fifty-seven cases out of a cohort of 4209 patients developed DILI,[6] whereas the incidence in an out-patient Hepatology clinic setting was 77 cases of a total of 1164 (6.6%) cases.[7] Sgro et al, in the only prospective study to date, reported an incidence of 13.9 ± 2.4 per 100,000 individuals between 1997 and 2000.[8] They detected 34 cases in a population of 81,301. The figure was 16 times higher than the one spontaneously reported to regulatory authorities and testifies to the gross underreporting of cases of DILI. In a single center study from India, DILI contributed to 1.4% of all gastrointestinal admissions and 2.5% of hepatobiliary admissions with a gradual increase in the numbers over the years.[9] In those presenting to the hospital with jaundice only a small minority of patients (0.7%) were due to idiosyncratic DILI.[10]

The common drugs causing DILI appear geographical. Although antimicrobials are the commonest cause of drugs worldwide, the class of antimicrobials varies geographically, with amoxicillin and flucloxacillin common in the Europe[11] in contrast to antituberculosis drugs in India.[9]

DILI is a leading cause of acute liver failure (ALF) in the Western world, with paracetamol being the commonest drug followed by antimicrobials.[12,13] In India antituberculosis drugs are the commonest cause of drug-induced ALF in adults and children,[14–16] contributing to 5.7–22% of all cases of ALF.[14–16] Paradoxically, many could be preventable, as empirical treatment for tuberculosis in 43–60% drives most of the reasons for antituberculous ALF.[14,17]

A brief summary of drugs causing hepatotoxicity and other demographic characteristics are depicted in Table 1.[9,18–21]

DEFINITION OF DRUG-INDUCED LIVER INJURY

With better understanding of the mechanisms and outcomes of DILI over time, the cut offs and thresholds for transaminase elevation for defining DILI have undergone some modifications.[22–24] An earlier definition set the following threshold for defining DILI: elevation of transaminases (either AST and/or ALT) or bilirubin or alkaline phosphatase >2 ULN (upper limit of normal).[22,23] Given the increasing awareness of the phenomenon of adaptation or tolerance that may occur in over 20% of medications, the levels of AST, ALT elevation have been modified. This includes elevation in ALT or AST > 5 × ULN (upper limit of normal) without symptoms, or rise in alkaline phosphatase >2 × ULN or rise in bilirubin >2 × ULN in bilirubin with any rise in AST and ALT elevation. Alternatively, AST or ALT < 5 ULN with symptoms also defines DILI.[24,25]

PATTERNS OF DRUG-INDUCED LIVER INJURY

Drugs may have a characteristic pattern or signature of hepatotoxicity (Table 2). Although not exclusive, this is based less on the symptoms and signs but more importantly on the ratio of elevation of transaminases and alkaline phosphatase.[22,24,26] Based on the level of elevation of transaminases or alkaline phosphatase and the ratio (R) of elevation of baseline ALT to baseline alkaline phosphatase (ALT/ULN)/(ALP/ULN), drug-induced liver injury is classified as either hepatocellular, cholestatic or mixed types.[22,26] Hepatocellular DILI: ALT ≥ 3 ULN and $R \geq 5$; Cholestatic DILI: ALP ≥ 2 ULN and $R \leq 2$; Mixed DILI: ALT > 3 ULN and ALP > 2 ULN and $R > 2 < 5$. The degree of elevation in liver enzymes has poor correlation with severity of liver disease.[26] Instead, the pattern of liver disease indicates near term and long-term consequences. The cholestatic pattern of hepatitis has the lowest mortality but has a small risk of protracted course leading to a longer time for normalization of liver tests. Additionally, cholestatic and mixed hepatitis pattern have a small but definite risk of evolution to chronicity.[26] Reported mortality figures from the Spanish registry and the drug-induced liver injury network (USA) are 2% and 2.1% respectively for mixed hepatitis pattern; contrastingly, the mortality for hepatocellular hepatitis pattern of DILI are 7% and 7.5% and for the cholestatic hepatitis pattern the mortality reported are 5% and 14.3% respectively.[18,19] The hepatitis pattern is not static and may evolve over time; a hepatocellular hepatitis pattern at initiation may evolve to a cholestatic pattern in the course of the disease.[19,22] As the distinction of the different patterns depends on the timing of the liver tests,[19,22] the liver biochemical pattern at the time of initial presentation should be considered to define the pattern of hepatitis.[27] Of more importance with regard to short term prognosis, is the presence of jaundice (bilirubin more than 3 mg/dl), which entails some risk of mortality. Called the Hy's law after Hyman Zimmerman who made the observation of a high fatality ranging from 5 to 50% in those with jaundice signaling severe disease.[28] For objective reasons, Hy's law has been defined by FDA, as bilirubin > 2 mg/dl and AST or ALT >3 × ULN.[28] In Dr. Hyman Zimmerman's original observation the fatality rate was dependent on individual drugs; 10% for

Table 1 Registries of drug-induced liver injury.

Country	Spain[18]	Sweden[20]	USA[19]	Japan[21]	India[9,a]
Year	1994–2004	1970–2004	2004–2007	1997–2006	1997–2008
No. of cases	461	784	300	1676	313
Mean age (years)	53	58	48	55	39.3
Females (%)	49	58	48	56.3	42
% with jaundice	71		73		65.5
% hospitalized	53		54		78
% dead/ transplanted	7	9.2	9	3.75	17.3
Injury pattern: Hepatocellular Mixed Cholestasis	 55.9 19.3 21.4	 52.2 26.2 21.6		 59 20 21	NA
Implicated drugs	Antibiotics (32%) CNS agents (17%) Musculoskeletal agents (17%) GI drugs (10%) Anti-TB drugs (7.2%)	Antibiotics (27%) NSAID (4.8%)	Antibiotics (45%) CNS agents (15%) Immunomodulators (5%) Analgesics (5%)	Antibiotics (14.3%) CNS agents (10.1%) Dietary supplements (10%) Anti-inflammatory drugs (9.9%) Circulatory/respiratory system (7.5%) Herbal drugs (7.1%)	Anti-TB drugs (58%) Antiepileptic drugs (11%) CNS agents (5.4%) Dapsone (5.4%)

[a]Single center.

Table 2 Patterns of liver disease caused by drugs.

Acute hepatitis	Isoniazid, pyrazinamide, rifampicin, ibuprofen, nimesulide, cotrimoxazole, phenytoin, dapsone
Cholestatic	Chlorpromazine, amoxicillin–clavulanic acid, flucloxacillin, carbamazepine, phenytoin
Autoimmune	Minocycline, nitrofurantoin, alpha methyldopa
Steatohepatitis	Tamoxifen, amiodarone, tetracycline, valproic acid
Granulomatous hepatitis	Dapsone, sulphonamides
Cirrhosis	Methotrexate, amiodarone
Bland cholestasis	Anabolic steroids, danazol
Nodular regenerative hyperplasia	Didanosine, stavudine
Vanishing bile duct syndrome	Carbamazepine, cotrimoxazole
Peliosis hepatis	Anabolic steroids, azathioprine
Hepatic adenoma	Oral contraceptive, anabolic steroids

isoniazid, 10% for methyldopa, 40% for phenytoin and 50% for halothane hepatitis.[29] Hy's law has been corroborated in several studies[18–20] including a recent single center study from India, which found a mortality of 21.5% in a setting where transplantation was not available.[9]

Some drugs producing hepatotoxicity do not fit into a particular pattern, taking months and years of cumulative use to produce injury (Table 2). Often they cause very minimal or no rise in liver enzymes. Drugs in this category include methotrexate (fibrosis/cirrhosis), azathioprine (NRH-nodular regenerative hyperplasia), oral contraceptives (hepatic adenoma), tamoxifen (fatty liver).[26,28]

PRESENTATION AND SEVERITY OF DRUG-INDUCED LIVER INJURY

There is a wide variation in terms of presentation; this could range from asymptomatic elevation in liver test abnormalities to acute hepatitis to acute liver failure. Many of the asymptomatic elevation seen in individuals exposed to drugs could be the phenomena of adaptation or tolerance, where the liver tests normalize while continuing the drug, a phenomenon seen in approximately 5–50% of subjects taking drugs.[30] When symptomatic, the symptoms range from non-specific symptoms of nausea, vomiting, anorexia, to specific symptoms of right upper quadrant pain, skin rashes, itching, to jaundice, ascites and encephalopathy. The diagnosis of severe DILI is often clinical such that patients require hospitalization.[19,31] The indications of hospitalization vary geographically. Nevertheless, the presence of ascites, encephalopathy and an INR >1.5 is a sign of severe disease.[27] Notably, in one study, ascites was observed in 12.5% of survivors vs. 32% of non-survivors ($p < 0.001$), attesting to the importance of this clinical finding in assessing severity.[9]

Patients presenting with hypersensitivity DILI have a milder disease and a better survival, particularly in children.[16,18] Hypersensitivity DILI is often accompanied by immunoallergic features such as skin rashes, eosinophilia or lymphadenopathy. These characteristics may aid in the differentiation of hypersensitivity DILI from the metabolic idiosyncrasy variety (Table 3). It is likely that skin rashes draw a patient earlier to a hospital resulting in earlier discontinuation of the offending drug and an earlier diagnosis.[16] Failure to stop the drug with the onset of DILI often results in high morbidity, mortality or chronicity.[18,32]

Drug-induced Liver Injury Severity Index

Elevated transaminases or alkaline phosphatase alone without jaundice or hyperbilirubinemia qualifies as mild disease. Elevated liver enzymes without symptoms may be part of an adaptation process especially when transaminases are less than 5 × ULN (upper limit of normal). Presence of hyperbilirubinemia with a bilirubin of >2 mg/dl qualifies as moderately severe disease. Presence of prolonged international normalized ratio (>1.5), encephalopathy or ascites with or without hospitalization accompanied by hyperbilirubinemia or jaundice connotes severe disease. Mortality in the latter category varies depending on the exposed drug, being 21% for antituberculosis drug-induced liver injury[9] and 9–17% in non-tuberculosis drug-induced liver injury.[9,18]

CAUSALITY ASSESSMENT METHODS

Unlike other causes of hepatitis, DILI is a diagnosis of exclusion, such that common causes of hepatitis and liver test abnormalities need to be excluded before a diagnosis of DILI can be made.[23,24,33–35] A detailed clinical history is of paramount importance including those of herbs and complementary medicines for establishing a diagnosis of DILI.[35] The expertise of the clinician plays a role in establishing the diagnosis. DILI is often but incorrectly used as a default diagnosis, when liver test abnormalities or hepatitis occurs in patients receiving drugs. Studies by Sarda et al demonstrate that up to 15.7% of patients with LFT abnormalities may have hepatitis E infection in northern India.[36] A recently study highlights the small but important role of concomitant hepatitis E even in western countries; 3% (9 of 318) of patients with a diagnosis of DILI were found to have acute hepatitis E infection.[37] This finding has implications on treatment, such that same drug/drugs can be continued or restarted once the hepatitis episode has abated.

Table 3 Types of idiosyncratic drug-induced liver injury (Adapted from Ref. [29]).

Basis for injury	Latency period	Dose related	Skin rashes, fever, LNE, eosinophilia	Rechallenge	Drugs
Hypersensitivity	1–6 weeks	No	Yes	No	Phenytoin Carbamazepine Lamotrigine
Metabolic	1–52 weeks, variable	Yes	No	Yes	INH, PZA

Abbreviations: LNE: lymph node enlargement, INH: isoniazid, PZA: pyrazinamide.

Several causality assessment methods have been established as tools in the accurate diagnosis of DILI. The earliest by Naranjo et al is a generic assessment tool for adverse drug reaction (ADR) and is not limited to DILI.[33] Although simple to use, it was primarily designed for use in clinical trials, much less in clinical practise and has been supplanted by others, which are more specific for DILI. These include the Roussel Uclaf Causality Assessment Method (RUCAM),[23] Maria and Victorino (M and V) method[34] and the more recent DILIN (Drug-Induced Liver Injury Network) expert opinion.[35] The DILIN expert opinion scale although has a better predictive value is limited by the need for a group of experts for validation and hence difficult in a hospital settings or in solo practise. When RUCAM was compared with M and V method, RUCAM was more reliable and correlated better than expert review.[38] The RUCAM by contrast can be used by non-experts and physicians in solo practice. Established in 1993, it has its limitations, which include the allocation of negative points for multiple drugs and for rechallenge, often resulting in underestimating causality. This is particularly problematic for drugs used in the treatment of tuberculosis, which includes three hepatotoxic drugs namely, isoniazid (INH), rifampicin (RIF), and pyrazinamide (PZA). When given together, it is impossible to identify the implicated drug in cases of hepatotoxicity. Furthermore, most patients (~90%) when rechallenged with these drugs tolerate the drugs without developing DILI. The mechanism of tolerance is not clear unknown and the reasons behind the breakdown of tolerance is a subject of much investigation.[25,26]

A recent publication has attempted to rectify some of the limitations with RUCAM.[27] For example, in patients with DILI exposed to combination antituberculous agents (isoniazid, rifampicin and pyrazinamide), all 3 drugs are taken as a single entity in causality assessment.[26] This appears reasonable given the interactive and overlapping toxicities between the individual drugs.

Roussel Uclaf Causality Assessment Method (RUCAM): The RUCAM was established following an international meeting of 12 European and American experts organized by the Council for International Organization of Medical Sciences (CIOMS) in 1990.[23] The RUCAM score has a set of 7 domains which include time of onset of liver disease, duration of disease, risk factors, concurrent use of drugs, exclusion of competing non drug causes, previous history of the culprit drug causing hepatotoxicity, and response to rechallenge.[23] Each of these domains are assigned points ranging from −3 to +3 depending upon the probability of a drug's involvement in DILI and the final score tallied to yield scores between −7 and +14. The final scores are graded into five categories of likelihood of disease: Highly probable; score >8, probable; score 6–8, possible; score 3–5, unlikely; score 1–2, excluded; score <0.[23] Shortcomings persist in the revised RUCAM scoring system lending itself to a degree of subjectivity and ambiguity. Points allocated for rechallenge, age criteria and multiple drugs are some of the shortcomings.

Maria and Victorino scale (M and V scale) was devised as an alternative to RUCAM.[34] Also called the Clinical Diagnostic Scale (CDS) it has 5 domains, the striking feature of which was the inclusion of the category of extra hepatic manifestation with symptoms of hypersensitivity or immune allergy such as fever, skin rashes, eosinophilia and arthralgia. Excluded were factors such as alcohol, age, competing drugs, pregnancy, and the pattern of liver disease such as hepatocellular, cholestatic and mixed. Lucena et al performed a comparison between the 2 models and concluded that RUCAM had an overall better performance and was more reliable and consistent.[38] More recently Rockey et al compared the DILIN expert opinion criteria with RUCAM, and found that the DILIN expert opinion process produced higher agreement rates and likelihood scores; however, there was considerable interobserver variation with a kappa score of 0.28–0.38.[35] A recent expert meeting in 2011, observed that RUCAM with certain modifications was still the most widely used causality assessment method.[27]

PATHOGENESIS OF DRUG-INDUCED HEPATITIS

The exact mechanism of DILI is unknown.[39–45] They depend upon whether the hepatotoxicity is predictable or idiosyncratic (Table 4). The predictable (or dose dependent) hepatotoxicity exemplified by paracetamol toxicity has been extensively investigated in animal models. Although safe in appropriate doses, paracetamol produces massive hepatocellular necrosis when consumed in large doses. Its toxic metabolite *N*-acetyl-p-benzoquinone imine

Table 4 Mechanism of drug-induced liver injury (Adapted from Ref. 29).

Mechanism of injury	Experimental reproducibility	Dose related	Human incidence	Latency period	Drugs
Intrinsic hepatotoxicity	Yes	Yes	High	Usually short (days)	Paracetamol, Phosphorus
Idiosyncratic hepatotoxicity	Lacking[a]	Usually no	Low	Few days–months	INH, RIF, PZA, Cotrimoxazole, Phenytoin

[a]Few animal models for metabolic idiosyncrasy but not immunoallergic idiosyncrasy.

(NAPQI) depletes the hepatoprotective glutathione resulting in covalent binding to cellular proteins.[29] This in turn results in mitochondrial dysfunction and oxidative stress, culminating in cellular damage and death.[29] However, when taken in gradually increasing doses, adaptive mechanism come into play and may explain the tolerance to large doses often experienced in subjects addicted to the drug.[46]

The second mechanism involving idiosyncratic DILI is limited by the lack of experimental animal models, although the last few years have advanced our understanding of idiosyncratic DILI by studies on murine models.[47,48] One of the important concepts in idiosyncratic DILI is the inflammatory stress hypothesis, wherein bacterial lipopolysaccharide (LPS) released as a result of inflammation, in conjunction with drug metabolites has the potential to precipitate DILI. Inflammagen as a precipitant of liver injury has been described in animal models involving drugs such as diclofenac, sulindac, and trovafloxacin among others.[47,48] In addition there is increasing evidence of the important role of the innate and adaptive immune system through an interdependent pathway in the pathogenesis of DILI.[40,48]

The liver may be considered as an immunologic organ with an important role in immune mediated pathway. The unique cellular and microenvironment in the liver particularly the sinusoids, favor tolerance, such that immunologic tolerance is the default response of the liver to antigens/drugs. The large number of natural killer cells and natural killer T cells which comprise more than 50% of intrahepatic leukocytes play an important role in the process of adaptation.[42] The tolerance environment in the liver helps explain the low occurrence of DILI; DILI only occurs when the tolerance mechanisms are deficient or abrogated in susceptible individuals.[40]

Drugs undergo metabolism to form products, which are cleared by body's defense or excretory systems. Impaired systems result in increased formation or decreased elimination of toxic metabolites which after covalent binding, produce oxidative stress and a chain of events leading to liver injury.

Although the term idiosyncratic refers to characteristics of the host, idiosyncratic DILI occurs due to combination of host, drug and environmental factors often acting in concert.[41] Generally the drugs or its metabolites are not immunogenic. The metabolites bind with the cellular proteins such as CYP enzymes to form hapten which activate the macrophages and the natural killer cells resident in the liver microvascular/sinusoidal system setting in motion the major histocompatibility complex (MHC) class II dependent stimulation of CD4 cells and clonal expansion.[41] The CD4–MHC II interaction may explain in part the extra hepatic reactions such as the skin involvement that occurs in some patients with hypersensitivity DILI. The activated cells migrate from the liver to the skin or start de novo in the skin stimulated by metabolites in the skin. Features of immunoallergic or hypersensitivity reactions are observed more commonly in children, with 41% of 39 children in one study demonstrating immunoallergic features.[16] Presence of hypersensitivity features is often associated with good prognosis[16]; a similar observation was made by the Spanish DILI group in whom this reaction was seen in 23% of their 461patients.[18] An indirect evidence for a better outcome was provided by Bjornsson et al who observed eosinophilia including liver eosinophilia in their patients.[43]

An important hypothesis proposed in the pathogenesis of DILI of clinical significance is the "danger hypothesis" where the role of co-stimulatory triggers is an essential step in the pathogenesis of DILI.[44] In danger hypothesis the cytokines released by stressed or dead cells provide additional stimulation to the antigen presenting cell which leads to a further recruitment of helper and cytotoxic T cells culminating in antibody-dependent cell mediated cytotoxicity. This hypothesis may explain the increased predisposition of hepatotoxicity in patients infected with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) infection; infected cells providing the background co-stimulatory signals (danger) in the form of cytokines.[45]

DRUG-INDUCED AUTOIMMUNE HEPATITIS

Drugs such as minocycline, methyldopa and nitrofurantoin can trigger hepatitis which mimic autoimmune hepatitis clinically, biochemically and serologically.[49] However, cirrhosis is uncommon in DIAIH and there is no recurrence of hepatitis on stopping the responsible drug.[49,50]

MITOCHONDRIAL HEPATOTOXICITY

Drugs responsible for mitochondrial toxicity include tetracycline, valproate, amiodarone, and nucleoside analogs such as zalcitabine, didanosine, stavudine, lamivudine, zidovudine and abacavir.[51] Mitochondrial toxicity is characteriZed by mild elevation of liver enzymes with microvesicular steatosis; yet can be accompanied by lactic acidosis and acute liver failure. Valproate hepatotoxicity may also results in mitochondrial dysfunction due to inhibition of mitochondrial beta-oxidation of fatty acids.[52]

PATHOGENESIS OF DRUG-INDUCED CHOLESTASIS

Drug-induced cholestasis may result from defect in bile formation in the hepatocyte or impairment of bile secretion or flow at the bile duct level. The retention of bile acids leads to liver injury. At the histopathologic level, drug-induced cholestasis may be bland or canalicular.[29] In bland cholestasis there is no histological evidence of inflammation, whereas in the latter bile duct and surrounding hepatocellular inflammation and necrosis may be present.[53] Bland cholestasis is produced by inhibition of bile salt pumps or transporters and is exemplified by drugs such as anabolic steroids, estrogens, danazol, cyclosporine, glibenclamide and rifampicin. In hepatocanalicular cholestasis, the drug metabolite undergoes canalicular excretion, exposing the ductular cells to toxic injury and the onslaught of immune cells. Examples include amoxicillin–clavulanic acid, chlorpromazine, and erythromycin antibiotics. Cholangiocyte injury from the toxic metabolites excreted in bile is exemplified by flucloxacillin and terbinafine.[54,55] This type of injury has a small but definite risk of developing into vanishing bile duct syndrome.

Both genetic and environmental factors in concert play a role in drug-induced cholestasis. The rate limiting step in bile formation is considered to be bile salt export pump (BSEP) mediated translocation of bile salts across the canalicular hepatocyte membrane.[56] Polymorphism of the bile acid transporters or pumps such as BSEP and multi-drug resistance proteins (MRP) when under stress by xenobiotic or drug metabolites could manifest as cholestasis in susceptible individuals.[57] There is emerging literature of the role of nuclear receptors, farnesoid X receptor (FXR), pregnane X receptor (PXR), and constitutive androstane receptor (CXR) in the pathogenesis of drug-induced cholestasis.[58]

RISK FACTORS

The following are some of the risk factors attributable to DILI.

Age

Older age was traditionally thought as a risk factor for DILI, such that older age (>55 years) fetches points in the RUCAM score. Recent reports show that no age is exempt from DILI. Reports from Scandinavian countries and Japan had a disproportionately large number of elderly people with DILI. This is likely due to the demographics of those countries and cannot be generalized (See Table 1). Interestingly drug-induced acute liver failure (DIALF) is commonly seen in the relatively young in India.[14,17] Although considered rare, two reports of DILI in children have recently been described.[16,59] Report from India show that both children and adults are at risk. In the Indian series, the investigators observed DILI in 8.7% of their children ranging from 3 years to 17.[16] Combination antituberculosis drugs and antiepileptics were the leading causes in children.[16] The increasing recognition of children is further corroborated from the DILIN.[59] The type of drugs producing DILI in children and adults appears geographically linked. Antituberculosis drugs are the commonest cause of DILI and DIALF in India[14,17]; contrastingly, antibiotics are the commonest cause of DILI in the West followed by paracetamol as a cause of DIALF.[12]

Gender

Women are generally considered more at risk for DILI. Studies from Japan and Sweden found women constituting 58% and 56% of all cases of DILI respectively and again may suggest demographic peculiarity of those countries.[20,21] This was not corroborated by series from Spain (49%),[18] USA (48%)[19] and India (42%).[9] However, women appear more at risk for DIALF across most studies.[14,18,19]

Alcohol

While alcohol is believed to be a risk factor for DILI, its exact role is debatable. It is unclear which attribute of alcoholism is contributory: whether current or past use or the presence of underlying liver disease. Chronic use of alcohol particularly with under nutrition depletes glutathione stores but a definite link between alcoholism is lacking.[60] In the DILIN study alcohol was a negative predictor for DILI.[19]

Concomitant Medication or Polypharmacy

The interaction between drugs given concomitantly is complex and challenging and complicates causality assessment. Often drugs may have reciprocal interaction such that either drug increases the potential for hepatotoxicity of the other.[61] For example, carbamazepine and INH cause inhibition of metabolism of either drug thereby increasing the blood levels of each of the drug.[62] The complexity of concomitant medication is further illustrated by the combination chemotherapeutics in tuberculosis. Pyrazinamide, isoniazid and rifampicin are hepatotoxic in decreasing order of propensity.[63] The combination of

isoniazid and rifampicin is more hepatotoxic than either drug alone. This is largely due to rifampicin increasing the hepatotoxic potential of isoniazid. The complexity is further compounded by the relative inhibition of toxicity of pyrazinamide by INH.[64] This can be gleaned from the high rates of toxicity including death in patients treated with rifampicin–pyrazinamide combination for latent tuberculosis.[65]

Nutrition

Nutritional deficiency may predispose to DILI as reported in patients with HIV, tuberculosis or alcoholism. This propensity is ascribed to reduced glutathione levels in these patients. Indirect evidence supporting this hypothesis comes from the hypoalbuminemia considered a surrogate marker for malnutrition was observed in patients with antituberculous DILI.[66,67]

Human Immunodeficiency Virus

Patients with HIV infection are on multiple drugs both for the primary HIV infection and also for the opportunistic infection such as tuberculosis, pneumocystis carinii infection and concomitant hepatitis B and C infections.[68] Overlapping toxicities are a major cause with contributions from both drug–drug and drug–disease interaction.[69,70] Diminished reserves of glutathione are cited as a predisposing factor. Drugs associated with an increased risk for DILI include zidovudine, stavudine, nevirapine, efavirenz, abacavir and others.[68,69] Both nevirapine and abacavir produce immunoallergic or hypersensitivity reaction with features of skin rashes, fever, lymphadenopathy and eosinophilia. The immune mediated hypersensitivity reaction associated with nevirapine usually tends to occur within 6 weeks after initiation of treatment and presents with skin rashes and hepatitis. Another variety, believed to be a result of direct effect of nevirapine occurs 6–12 months into therapy.[68] Abacavir hypersensitivity is increased in patients carrying HLA-B*5701, such that testing for HLA-B*5701, is presently recommended before initiation of treatment.[71] These drug needs to be discontinued immediately after clinical suspicion for fear of progression to Stevens–Johnson syndrome or toxic epidermal necrolysis (TEN).

There are increasing reports of portal hypertension secondary to nodular regenerative hyperplasia (NRH) in older patients exposed to cumulative doses of didanosine and stavudine.[72] NRH may persist despite discontinuance of the drug.

Hepatitis B and Hepatitis C

There is ongoing debate about the risk of underlying chronic hepatitis B and chronic hepatitis C and DILI. Chronic hepatitis B and C is considered by some to enhance the risk of DILI particularly from drugs used to treat tuberculosis and HIV[73–75]; however, not all studies have found a positive link between chronic B and C infection and anti-TB related DILI and highly active antiretroviral therapy related DILI.[76] Wong et al found hepatotoxicity following antituberculous drugs in 35% of HBV carriers in contrast to 9.4% non-carriers ($p < 0.001$).[73] However, Hwang et al in a prospective study did not find a difference in anti-TB hepatotoxicity in HBV carriers versus non-carriers (29% vs. 26%); instead they that found age >35 years was the only independent factor predicting anti-TB hepatotoxicity.[76] Another retrospective study found a slightly higher but non significant incidence of anti-TB DILI in inactive carriers with HBV DNA $<10^5$ copies/ml.[77] In the setting of chronic hepatitis B and C, the challenge is to determine whether the rise in transaminases or bilirubin is a signal of drug-induced hepatitis or a flare of underlying hepatitis B or C.[68] Hepatitis B flare is not uncommon as suggested by a recent report,[78] and viral replication status including HBV DNA studies may be necessary to differentiate between virus-induced flare from DILI. Nevertheless, caution should be exercised in carriers with hepatitis B or C, the drugs withheld until such time the adjudication process is complete, and the results of viral DNA or RNA levels are available.

GENETIC FACTORS

Genetic polymorphism of enzymes and proteins linked to the metabolism of drugs are important predisposing factors in susceptibility to DILI. Although candidate genes have been studied extensively, there is an increasing role of the importance of genome wide association studies (GWAS) in predisposition to DILI.

Acetylator status of NAT-2 (*N*-acetyltransferase-2), and others such as CYP and GST M1 and T1 genetic polymorphism have been extensively studied in DILI, particularly in antituberculosis DILI. Individuals with slow acetylator status have increased incidence and severity of INH-induced hepatitis.[79] A recent study from New-Delhi, India showed slow acetylator status in 71% of their patients with TB DILI compared to 45% without DILI.[80] Similarly, some[81,82] but not others[83] have found an association of CYP 2E1 genetic polymorphism and GST M1 "null" mutation and GST T1 "NULL" mutation with hepatotoxicity to antituberculous drug.

Studies exploring HLA (human leukocyte antigen) gene polymorphism and DILI have shown mixed results. Sharma et al[67] observed increased risk of TB hepatotoxicity with HLA-DQB1*0201 with an odds ratio of 1.9. Similarly, results identifying association between HLA gene polymorphism and predisposition to DILI particularly amoxicillin–clavulanic acid hepatotoxicity have been reported in some[84] but not others.[85] HLA class I and II gene polymorphism may have a role in the pathogenesis

and biochemical expression of DILI,[85,86] and in some may have a protective role in DILI. This explains the varied presentations of DILI and why some individuals develop a particular pattern of hepatitis.[87] Yet, despite these advances, its utility in clinical practise is limited because of the low predictive value.[86]

In a GWAS study, Daly et al in a European cohort found an 80 fold increased risk in susceptibility to flucloxacillin hepatotoxicity in the presence of HLA-B*5701.[88] This drug is widely available in Europe and 5% of the population carry this haplotype. Therefore, generalizability to other population may be an issue. Interestingly HLA-B*5701 is also strongly associated with abacavir hypersensitivity and can assist physicians in identifying patients at risk of developing adverse reactions. Individuals with HLA-B*1502 are at increased risk of developing carbamazepine induced Stevens–Johnson syndrome and toxic epidermal necrosis particularly in Asians.[71]

Dose

Although idiosyncratic DILI is by definition caused by the unique characteristics of the host and not the drug, Lammert et al made an interesting observation regarding dose of exposed drug and hepatotoxicity.[89] They observed that drugs administered in doses >50 mg confers an increased risk for DILI.[89] Additionally, drugs metabolized by the liver with its excretion in biliary canaliculi appear to enhance the risk of DILI.[90]

RECHALLENGE

Rechallenge risk may be related to the drug-specific mechanism of injury.[91] The re-occurrence of DILI, following rechallenge to the same drug is variable and probably underreported.[92] When alternate drugs are available, it may not be justifiable to use the implicated drug. However, when alternate drugs are not available or the alternate drugs are less effective such as in TB, the implicated drug/drugs may be reintroduced cautiously. In TB, rechallenge with the original drugs is common. A distinction may be made however, wherein drugs that produce metabolic idiosyncrasy such as antituberculous drugs rarely produce DILI on rechallenge. Rechallenge with drugs that produced immunoallergic manifestations such as skin rashes, fever, lymphadenopathy or eosinophilia is fraught with a potential risk of a severe reaction with a shorter latency period. Often reactions could also occur to cross reacting drugs. Prime examples in this category are the AED (antiepileptic drugs) such as phenytoin, carbamazepine and phenobarbitone.[93] With the advent of newer anti-epileptic drugs such as levetiracetam and clobazam, both having a better safety profile, DILI following exposure to AED may be less of a challenge in the future. For tuberculosis though, the primary drugs are invaluable and cheap. Given the questionable potency of the alternative second line drugs, rechallenge with the primary drugs with or without PZA either simultaneously or sequentially is the usual practise.[94,95] Tolerance to antituberculosis drugs could be a result of adaptation or a change in the environmental factors.[31,45]

Various guidelines have been in place for monitoring of patients with anti-TB drugs.[25] They differ with regard to need for initial evaluation of baseline liver biochemical tests and the subsequent monitoring of these tests during therapy and the type of drugs to be reintroduced after hepatotoxicity. Despite these recommendations, monitoring is often inadequate and underutilized even in those at risk for disease.

PREVENTION OF DRUG-INDUCED LIVER INJURY

Given the idiosyncratic nature of most drugs, it is difficult to predict who and when during the course of treatment will develop hepatotoxicity. Rational drug prescribing is central to minimizing DILI particularly in patients with risk factors such as old age, comorbid diseases, HIV status, daily dose of drug >50 mg, or poly pharmacy.[14–17,59,68,73,74,86,87] Caution should be exercised in the empirical treatment for tuberculosis given the high incidence of severe DILI including acute liver failure. Knowledge of drug–drug interaction and drug–disease interaction is also important. Except for few drugs such as methotrexate, clinically significant DILI is usually accompanied by symptoms, such that vigilance for symptoms is the key in the detection of early onset DILI. Patients and caregivers should be educated about the development of new symptoms such as nausea, vomiting, anorexia, dark urine or jaundice. The suspected drug or drugs should be stopped at the slightest suspicion of DILI, in order to prevent progressive liver damage. Debate continues about the need and the timing of liver function tests particularly in those who need to be on medications for a long duration. There is no clear evidence that such a practise influences much in the detection or prevention of clinically significant liver injury. Additional constraints include the costs and inconvenience of the tests, physician ambiguity and varying guidelines with regard to timing of the tests. Studies by Lammert et al have clearly shown the importance of dose dependent hepatotoxicity.[86]

Patients receiving methotrexate for psoriasis are reported to be at increased risk for fibrosis and/or cirrhosis, such that serial liver biopsies have been recommended.[96] Subsequent studies have questioned the effectiveness of liver biopsies in detecting advanced liver fibrosis and its impact on patient management.[97] Increasing evidence attests to the role of host and environmental factors such as obesity, diabetes mellitus, alcohol or concomitant medications

as playing an important role in the hepatic fibrosis process.[98,99] As liver injury particularly fibrosis is reflected poorly in liver tests, the decision to perform liver biopsies in the presence of risk factors must be made on a case by case basis.

MANAGEMENT OF PATIENTS WITH DRUG-INDUCED LIVER INJURY

Once a diagnosis of DILI is suspected, the offending drug(s) is/are discontinued. A vast majority of hepatitis will subside with cessation of drug. The outcome is less favorable in those with marked jaundice, ascites, encephalopathy and coagulopathy. Intensive supportive care and transfer to advanced centers for consideration of transplantation should be undertaken in those with advanced disease. Results of transplantation are similar to those of other acute liver failure.[100]

Once the liver function tests return to normal which usually occurs in days or weeks, considerations may be given for substituting the implicated drug with an alternative drug, particularly in those with immune-allergic DILI. With the widespread availability of newer antiepileptic drugs with good safety profile, there will be a declining use of the older drugs such as phenytoin, carbamazepine and phenobarbitone.

Rechallenge is routine with first line antituberculous agents. Recent studies have shown the feasibility of such an approach. However, in patients who have recovered from severe DILI as manifested by jaundice, ascites and encephalopathy should not be exposed to pyrazinamide.[25,95] Depending on the severity of the earlier episode of DILI either sequential or simultaneous drugs may be administered.

Many agents including *N*-acetylcysteine (NAC), silymarin, antioxidants, S-adenosine methionine, ursodeoxycholic acid or a combination of these have been anecdotally in patients with DILI and other forms of liver toxicity.[100–102] Silymarin alone or silymarin combination with benzylpenicillin has been used in mushroom (Amanita phalloides) toxicity although there is no clear evidence about its efficacy.[102] *N*-acetylcysteine has been extensively evaluated in paracetamol induced ALF and a recent report has demonstrated its utility although not unequivocally, in non-paracetamol drug-induced ALF, particularly in early grade encephalopathy.[100] In another recent series in subjects older than 70 years, NAC showed minimal to no elevation in liver transaminases in patients exposed to TB drugs and simultaneously given oral NAC.[101] Further studies are needed to test its generalizability.

Intravenous carnitine has been shown to be useful in valproic acid induced hepatotoxicity. Valproate inhibits the biosynthesis of carnitine, by affecting the beta-oxidation of fatty acids. Carnitine supplementation circumvents the defect by increasing the beta-oxidation of valproate.[52] In a case controlled study of 92 patients with valproate-induced hepatotoxicity, 42% of the 42 patients treated with L-carnitine survived compared to 10% of the other 50 patients treated with supportive care ($p < 0.001$); intravenous rather than oral administration was associated with greatest survival.[103] In those with valproate DILI, steroids generally are not useful in DILI unless features of drug-induced hypersensitivity features are present.

In patients with cholestasis, a trial of ursodeoxycholic acid (UDCA) may be attempted. UDCA due its membrane stabilizing action protects the hepatocytes and cholangiocytes by replacing the endogenous, cytotoxic bile salts and also by enhancing the function of transporters.[104] Anecdotal reports of UDCA in drug-induced cholestasis in particular vanishing bile duct syndrome attests to its usefulness, albeit in select cases.[105] Cholestyramine may be attempted in those with cholestasis and pruritus. It is particularly useful in leflunomide hepatotoxicity wherein the drug metabolites undergo extensive enterohepatic circulation resulting in a long half life perpetuating liver injury despite discontinuance of the drug.[106] Cholestyramine interrupts the enterohepatic cycle minimizing the liver injury.[106] Corticosteroids too may be attempted in select cases of cholestasis or cholestatic hepatitis particularly those associated with features of hypersensitivity such as skin rashes, and fever.[107] Antiepileptic drugs with its increased predisposition to hypersensitivity syndrome and DILI may particularly respond to steroids. However, the conclusive efficacy of steroids and UDCA await controlled studies.

CONFLICTS OF INTEREST

The author has none to declare.

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