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S Verma and N Kaplowitz

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S Verma,[1] N Kaplowitz[2]

[1] Department of Medicine, Brighton and Sussex Medical School, Brighton, UK; [2] USC Research Centre for Liver Diseases, Keck School of Medicine, University of Southern California, Los Angeles, USA

Correspondence to:
Dr N Kaplowitz, Division of Gastrointestinal and Liver Diseases, Keck School of Medicine, University of Southern California, 2011 Zonal Avenue, HMR 101, Los Angeles, CA 90033, USA; kaplowit@usc.edu

ABSTRACT

Drug-induced liver injury (DILI) is increasingly being recognised as a significant cause of both acute and chronic liver disease. The most commonly implicated agents are paracetamol, antimicrobials, non-steroidal anti-inflammatory drugs, statins, isoniazid and herbal remedies. Drug-induced hepatotoxicity is generally idiosyncratic in nature. The pathogenesis of DILI remains enigmatic, but involves exposure to the toxic agent, mitochondrial injury, failure of adaptation, and innate and adaptive immune responses. Diagnosis of drug-induced liver diseases can be difficult, but the key to causality is to diligently exclude other causes of liver injury, and to identify a characteristic clinical drug-related signature. Management of drug-induced liver injury is symptomatic, with early referral to a liver transplant unit at the first hint of liver failure, especially in those with non-paracetamol-induced liver injury. Prevention of drug hepatotoxicity includes increased vigilance during pre-clinical drug development and clinical trials, alanine aminotransferase monitoring with certain drugs, better marketing strategies, and the future identification of both diagnostic and prognostic biomarkers.

Drug hepatotoxicity, mostly due to paracetamol and idiosyncratic drug reactions, is the leading cause of acute liver failure (ALF) in the US and the UK, accounting for approximately 50% of all cases.[1–3] Drug-induced ALF is also associated with high morbidity and mortality, with only a 20% survival in the absence of liver transplantation, though prognosis is better when the underlying aetiology is paracetamol.[3] In the US, paracetamol overdose is responsible for more than 100 000 calls/year to poison control centres, 56 000 emergency room visits, and 2600 hospitalisations, as well 500 deaths.[4] This exceeds by at least 3-fold the number of deaths related to all idiosyncratic hepatic drug reactions combined.[5] In the UK, paracetamol overdose accounts for 200–500 deaths, and 20–40 liver transplants annually.[6 7]

The overall incidence of drug-induced liver injury (DILI) is variable,[8–11] probably a reflection of the lack of internationally accepted criteria for DILI, under-reporting and selection bias.[12] A meta-analysis from Canada reported the incidence of serious adverse reactions (ADRs) to drugs (defined as those that required hospitalisation, were permanently disabling, or resulted in death) as 6.7%, and of fatal ADRs as 0.32% of hospitalised patients.[8] The best estimates of the incidence of hepatic ADRs were reported by a 3 year French prospective community study where the global crude annual incidence rate was 13.9 (SD 2.4) per 100 000 inhabitants.[10] A more recent French impatient study observed the incidence of DILI to be 1.4%.[11]

At a regulatory level, hepatotoxicity is the single most frequent reason for removing approved medications from the market, or issuing warnings and modifications of use.[13] Between 1975 and 1999, 548 new drugs were approved by the US Food and Drug Administration (FDA), of which 10 received a "black box" warning for potential hepatotoxicity, and an additional four were withdrawn from the market.[14] It is remarkable, however, that in most cases routine animal toxicology failed to identify the risk of subsequent clinical toxicity, or predict post-marketing problems.[13]

A recent US centre reported antibiotics as the class of drugs most frequently implicated in non-fulminant drug-induced hepatitis[15] (amoxicillin/clavulanic acid, minocycline, nitrofurantoin, trimethiprim–sulfamethoxazole, telithromycin and trovafloxacin). Antimicrobials were also the most common cause of DILI in a recent Spanish Registry,[16] and in French and UK studies.[11 17] Another US study with 300 patients conducted by the recently established Drug Induced Liver Injury Network (DILIN),[18] (liver injury due to paracetamol was excluded), reported the aetiology as follows: single prescription medication (73%), multiple agents (18%), and dietary supplements (9%). Antibiotics (45.5%) and central nervous system drugs (15%) were the most common agents.[19] Other drugs associated with significant number of cases of hepatotoxicity include non-steroidal anti-inflammatory drugs (NSAIDs), isoniazid, bentazepam, atorvastatin, captopril and herbal remedies.[13 16 20]

PATHOGENESIS

The pathogenesis of idiosyncratic DILI remains poorly understood.[21] Animal models have not been readily available, which is not surprising as most of the marketed drugs that cause idiosyncratic DILI have not exhibited evidence of liver injury in preclinical animal toxicology. Presumably, this reflects the fact that a unique predisposition is required. Recent progress has been made by employing animals with various gene knockouts. For example, mice which are heterozygous for knockout of superoxide dismutase 2 (SOD2), the

mitochondrial form of SOD which protects against oxidative stress, developed liver injury after 4 weeks of troglitazone administration.[22] Much of the experimental work in this field has focused on paracetamol. These studies provide many insights into mechanisms of liver injury in general, but it is unclear if the insights gained from this model can be extrapolated to idiosyncratic DILI. However, based upon these models, as well as models of inflammation (endotoxin co-treatment potentiates toxicity of drugs), it is possible to list a number of areas which may be very relevant to DILI (table 1).

The liver removes lipophilic chemicals, including drugs, and biotransforms them into water-soluble metabolites which are excreted. This process involves cytochrome P450 (CYP) (phase 1), conjugation (phase 2) and transport (phase 3). The expression of the enzymes and transporters involved in hepatic handling of drug are under the control of transcription factors (nuclear hormone receptors) such as pregnane X receptor (PXR) and constitutive androstane receptor (CAR). In addition, in humans, polymorphisms of these phases 1, 2 and 3 genes and transcription factors affect their activities and expression in response to environmental factors. Therefore, it is likely that the level of exposure to the toxic moiety (usually a reactive metabolite but sometimes the parent drug) as influenced by this system, is the most upstream determinant of DILI.

Following exposure, the toxic moiety induces some type of stress or functional disturbance. Mitochondria have emerged as one of the most important targets. In the case of paracetamol models, cellular necrosis depends upon rapid loss of mitochondrial function, whereas as in the SOD-2+/− model, troglitazone induces a more delayed loss of mitochondrial function.[22] This is best understood as a threshold phenomenon in which mitochondria have a large reserve (many mitochondria per hepatocyte each with many mitochondrial genomes). When sufficient loss of mitochondrial DNA or modification of mitochondrial electron transport proteins (via oxidative stress) accumulates, oxidative stress from increased reactive oxygen species (ROS) overwhelms the antioxidant defence of mitochondria. This renders the mitochondria more vulnerable and allows the ROS to be released to activate cell death pathways (eg, mitogen-activated protein kinases leading to activation of c-jun-N-terminal kinases), which then target these vulnerable mitochondria leading to necrosis and/or apoptosis.[23] With paracetamol the threshold is reached rapidly (hours), whereas with troglitazone it is reached slowly (weeks).

An important concept in DILI is adaptation. This is a situation in which the injury reverses with the continuation of the drug. A number of responses could mediate adaptation. Alterations in phases 1, 2 or 3 could dampen the exposure of hepatocytes to the toxic chemical. Oxidative stress induced by the toxic chemical or its effects on mitochondria can activate nuclear factor erythroid 2-related factor (Nrf-2), a transcription factor which activates the expression of antioxidant genes.[24] Organelle damage can elicit upregulation of chaperones and replacement of organelles. For example, mitochondrial damage induces mitochondrial biogenesis, and endoplasmic reticulum stress induces an adaptive response (unfolded protein response) to modulate stress.[25] Thus, one can speculate that a determinant of idiosyncratic DILI is the inability to appropriately handle various types of stress, due to a failure to express the appropriate adaptation. Finally, the regenerative response may play an important role in adaptation as well as severity of DILI.

Another factor of interest is the innate immune response which can promote or inhibit the extent of inflammation and thereby determine the progression and severity of DILI.[26 27] In immune-mediated DILI, the adaptive immune system may respond to the drug or its metabolite acting as a hapten coupled with danger signals (eg, concomitant inflammation).[28]

Table 1 Pathogenesis of idiosyncratic drug-induced liver injury

- **Exposure to critical entity**: toxic metabolite or parent drug
  - Phases 1, 2, 3 and nuclear hormone receptors
  - Induction, inhibition, genetic polymorphism
- **Mitochondrial impairment**: threshold phenomenon
- **Adaptation** (failure)
  - Dampen exposure to toxic metabolite
  - Response to stress
    - Oxidative – nuclear factor E2-related factor 2 (Nrf-2) → antioxidant gene
    - Mitochondria – chaperones and biogenesis
    - Endoplasmic reticulum (ER) – chaperones ((unfolded protein response, (UPR))
- **Sterile inflammatory/innate and adaptive immune responses**

All factors influenced by environment and genetics

CLASSIFICATION OF DRUG-INDUCED LIVER INJURY

Hepatotoxicity can be classified as predictable or unpredictable (idiosyncratic).[29] The former is dose related, has a high incidence, and occurs with a short latency (within a few days). It results from direct toxicity of the drug or its metabolite and is reproducible in animal models. The classical example of predictable drug toxicity is paracetamol.[30] On the other hand idiosyncratic reactions occur with variable latency (1 week to 1 year or more), with low incidence, and may or may not be dose related. The majority of hepatotoxic drugs cause idiosyncratic reactions. These result in alanine aminotransferase (ALT) elevations, and an ALT>3×upper limit of normal (ULN), or an alkaline phosphatase (ALP)>2×ULN has been somewhat arbitrarily identified as a sensitive but not necessarily specific signal of liver toxicity.[13 31]

DILI can also be classified as immune mediated (allergic) or non-immune mediated (non- allergic)[32] (tables 2 and 3). If immune mediated, the latency is shorter (1–6 weeks) compared to non-immune-mediated reactions (1 month to 1 year).[13 20] However, there are exceptions: immune reactions

Table 2 Classification of drug-induced liver injury

Pattern of liver injury	Examples
Hepatitis	
Immune mediated (allergic)	Allopurinol, diclofenac, dihydralazine, germander, halothane, methyldopa, minocycline, nevirapine, phenytoin, propylthiouracil, trovafloxacin
Non-immune mediated (non-allergic)	Acarbose, amiodarone, bosentan, dantrolene, diclofenac, disulfiram, felbamate, flutamide, HAART, statins, isoniazid, ketoconazole, labetalol, leflunomide, methotrexate, nefazodone, nevirapine, nicotinic acid, paracetamol, pemoline, pyrazinamide, rifampicin, tacrine, tolcapone, troglitazone, sodium valproate, ximelagatran, zafirlukast, zileutin
Cholestatic	
Immune mediated (allergic)	ACE inhibitors, amitriptyline, amoxicillin/clavulanic acid, carbamazepine, chlorpromazine, cotrimoxazole, erythromycins, phenobarbital, sulfonamides, sulindac, tricyclic antidepressants
Non-immune mediated (non-allergic)	Anabolic steroids, azathioprine, cyclosporine, estrogens, oral contraceptives, terbinafine
Fibrosis/cirrhosis	Methotrexate
Granulomas (allergic)	Allopurinol, amoxicillin/clavulanic acid, carbamazepine, hydralazine, methyldopa, penicillamine, phenylbutazone, phenytoin, procainamide, quinidine, sulfonamides
Microvesicular steatosis	NRTIs, sodium valproate
Neoplasms	
Adenomas	Anabolic steroids, oral contraceptives
Angiosarcoma	Anabolic steroids
Cholangiocarcinoma	Anabolic steroids
Hepatocellular cancer	Danazol, anabolic steroids
Non-alcoholic steatohepatitis	Amiodarone, tamoxifen, antipsychotics (insulin resistance)
Phospholipidosis	Amiodarone
Vascular lesions	
Budd–Chiari	Oral contraceptives
Peiliosis hepatis	Anabolic steroids, azathioprine, oral contraceptives
Perisinusoidal fibrosis	Retinol (vitamin A), methotrexate
Veno-occlusive disease	Busulfan, cyclophosphamide

Adapted (with permission) from Abboud, *et al*.[20]
Immune-mediated reactions may be characterised by fever, rash eosinophilia or autoantibodies. Rapid positive re-challenge is expected but generally not advisable.
ACE, angiotensin-converting enzyme; HAART, highly active antiretroviral therapy; NRTIs, nucleoside reverse transcriptase inhibitors

can appear after a very long latency with drugs such as nitrofurantoin, methyldopa, diclofenac and minocycline.[33–38] Some of the immune-mediated reactions due to certain drugs (sulfonamide, erythromycin and amoxicillin/clavulanic acid) may, in fact, result in DILI 3–4 weeks after drug discontinuation.[20] Immune-mediated idiosyncratic reactions can be characterised by presence of fever, rash, eosinophilia and autoantibodies (such as antinuclear and smooth muscle antibodies). Severe cases may be accompanied by Stevens–Johnson syndrome, toxic epidermal necrolysis, and haematological features such as granulocytopenia, thrombocytopenia or haemolytic anaemia.[39] Another feature is rapid reproduction of liver injury upon drug re-challenge, though this approach is rarely, if ever, justified.[39 40] Finally, immune-mediated DILI is not always dose related.[13] However, it is not possible to entirely exclude an immune basis to DILI because of absence of these features. Non-immune-mediated reactions lack the aforementioned characteristics, an important feature being the long latency period (1 month to 1 year).[13 20] This is a puzzling scenario especially when drug pharmacokinetics excludes accumulation of the drug in the liver; amiodarone is an example of accumulation leading to liver injury.[41] Non-immune hepatotoxicity can be independent of dose (eg, troglitazone[42]) or dose related.[43] Rechallenge after injury may not reproduce the disease, suggesting that environmental factors present at the time of original injury are no longer present, or that some type of adaptation has occurred.[13]

A phenomenon common to both immune and non-immune idiosyncratic reactions is a background of more frequent, though transient, and mild asymptomatic abnormalities in the liver panel.[13] Although it is unclear whether the mechanism of mild injury determines the probability of more severe injury, it is possible that concomitant contributions of genetic and environmental factors to an initial injury, as well as individual deficiencies in the adaptive process, could lead to progressive injury.[13]

DIAGNOSIS OF DRUG-INDUCED LIVER INJURY

Establishing with any degree of certainty as to whether the liver disease is drug induced can be very difficult. The issue is further confounded by the relatively rare incidence of DILI, under-reporting, and potential drug interactions, due to which establishing the identity of the culprit drug may be impossible.[12 44] Furthermore, histology is generally not helpful as it just indicates the type and degree of liver injury rather than the aetiology. The key to causality is to assess the temporal relationship between drug initiation and development of an abnormal liver panel, the individual susceptibility to DILI,[20] and to diligently exclude other causes of liver diseases. This includes liver injury induced by alcohol, viral hepatitis (acute hepatitis A, B, C and E), autoimmune, and metabolic disorders, biliary obstruction, sepsis and total parenteral nutrition). Dalton *et al* reported that in their cohort of 47 patients with suspected DILI, 28 were tested for hepatitis E infection, of whom six (21%), had a positive serology.[45] Another challenging scenario is the presence of autoantibodies (antinuclear antibody, smooth muscle antibody), since drugs can cause a clinical–serological picture similar to autoimmune hepatitis (AIH), possibly trigger AIH in patients with underlying genetic predisposition to AIH, or the patient may have AIH related to the drug. In a recent Swedish study, of the 23 patients who developed chronic DILI, five (23.1%) were subsequently diagnosed with AIH, the suspected drugs being ranitidine, enalapril, oestrogen, carbamazepine and oestriol.[46]

Laboratory tests that might aid diagnosis of immune-mediated reactions include the lymphocyte-stimulation test. This involves exposure of peripheral blood mononuclear cells from the patient to the drug, and subsequent determination of lymphocyte proliferation.[47 48] This test, however, needs to be standardised and made more reproducible. The presence of autoantibodies to specific cytochrome P450 (CYP) isoforms has also been associated with hypersensitivity reactions to certain drugs.[49 50] A new assay for the detection of serum paracetamol adducts may prove useful in

Table 3 Characteristic features of immune-mediated (allergic) and non-immune (non-allergic) drug-induced liver injury

	Immune mediated (allergic)	Non-immune mediated (non-allergic)
Latency period	1–6 weeks	1 month to 1 year
Fever, rash, eosinophilia	Yes	Uncommon
Reproduction of liver injury upon drug re-challenge	Yes	Uncommon
Dose related	No	Maybe

diagnosing atypical cases of paracetamol overdose.[51] Finally, individual drugs exhibit a characteristic clinical signature, which may assist in the diagnosis of DILI. The latter is constituted by (1) the pattern of the abnormal liver panel (hepatitis, cholestasis or mixed); (2) duration of latency to symptomatic presentation; (3) presence or absence of immune-mediated hypersensitivity (ie, immune or non-immune reaction); and (4) response to drug withdrawal.[13 20] However, it must be emphasised that the same drug may cause different patterns of liver injury.[20]

Even with these guidelines, assessment for causality for DILI remains challenging and the physician is often left with a scenario in which the causal relationship can be defined as "definitely present", "definitely absent" or "possibly present". In an attempt to overcome this problem, several scoring systems that predict the likelihood of DILI, such as the Roussel Uclaf Causality Assessment Method (RUCAM) have been developed.[52 53] This scoring system is by no means perfect, and a recent study reported it to be of mediocre reliability in predicting drug-induced liver diseases.[54]

PATTERNS OF LIVER PANEL ABNORMALITY AND CLINICAL FEATURES

On the basis of the alanine aminotransferase (ALT) and the alkaline phosphatase (ALP) level, DILI is classified into either acute hepatitis, cholestasis or mixed patterns (table 1). This scheme was first established by the Council for International Organizations of Medical Sciences (CIOMS),[55] and has recently been modified by the US FDA Drug Hepatotoxicity Steering Committee:[56]

$$\text{Hepatitis pattern : ALT} \geqslant 3\text{ULN and } \frac{(\text{ALT/ULN})}{(\text{ALP/ULN})} \geqslant 5$$

$$\text{Cholestasis pattern : ALP} \geqslant 2\text{ULN and } \frac{(\text{ALT/ULN})}{(\text{ALP/ULN})} \leqslant 2$$

$$\text{Mixed pattern : ALT} > 3\text{ULN and ALP} > 2\text{ULN and } \frac{(\text{ALT/ULN})}{(\text{ALP/ULN})} > 2 \text{ to} < 5$$

HEPATITIS PATTERN OF DILI

The hepatitis pattern indicates hepatocellular injury. Patients may be asymptomatic or present with fatigue, right upper quadrant pain, jaundice or ALF. In a recent Spanish DILI Registry, approximately 40% of patients showed hypersensitivity features, with no significant difference between hepatitis, cholestatic or mixed patterns of injury.[16] There is usually poor correlation between degree of ALT elevation and the severity of the liver disease. In fact, clinical and biochemical parameters often underestimate the degree of liver injury, histology being a more accurate indicator.[20] However, one factor that is a good predictor of mortality in drug-induced hepatitis is jaundice. A consistent serum bilirubin $\geqslant 3\times$ULN in the absence of biliary obstruction or Gilbert's syndrome, is associated with a mortality of approximately 10% (range, 5–50%).[57] This is also known as Hy's law, in recognition of the pioneering work done by Hyman Zimmerman, and has been confirmed by recent Spanish, American and Swedish studies.[16 19 58] Hy's law has also been adopted by the FDA as a predictor of severe toxicity during clinical trials, though in the interest of patient safety, the FDA has lowered hyperbilirubinaemia to $2\times$ULN ("modified Hy's law").[59] The hepatitis pattern of liver injury is most commonly accompanied by acute liver failure (ALF), defined as coagulopathy (international normalised ratio (INR)$\geqslant$1.5) and hepatic encephalopathy occurring $<$26 weeks after onset of illness in a patient without pre-existing cirrhosis. This usually has a grave prognosis in absence of liver transplantation.[60] In some cases, due to adaptation, asymptomatic liver test abnormalities resolve despite drug continuation.

CHOLESTASIS PATTERN OF DILI

The cholestatic pattern can be due to canalicular cholestasis or ductular injury. The former usually results from inhibition of bilirubin or the bile-salt transport (eg, cyclosporine or oestrogen metabolite);[61] this is referred to as "bland" cholestasis because histologically there is virtual absence of inflammation or necrosis. More commonly, however, cholestasis is associated with some degree of cholangiocyte injury.[13] The presentation can mimic biliary obstruction or the course can be more indolent with jaundice and pruritus. Mortality appears to be less than with the hepatitis pattern (1–7.8%),[58 62] and death is usually not liver-related, though chronic cholestatic injury can result in ductopenia and, rarely, cirrhosis.[63]

In the mixed pattern of liver injury, patients can present with a combination of acute hepatitis and cholestasis. This pattern of liver injury probably has the lowest mortality. In the studies by Andrade *et al*[16] and Chalasani *et al*[19], the mortality in patients with hepatitis, cholestatic and mixed pattern of DILI was 7%, 5%, 2% and 7.5%, 14.3%, 2.1%, respectively. Drugs that result in a cholestatic liver injury can also cause a mixed pattern and vice versa. Individual drugs produce a signature in this spectrum that is drug characteristic (table 2) but exceptions do occur.[13] For example, troglitazone was mainly associated with a hepatitis injury but rarely resulted in cholestasis,[42] and similarly, amoxicillin–clavulanic acid

usually results in cholestatic injury, but less frequently has been associated with ALF.[64]

Besides hepatitis, cholestatic and mixed-pattern liver injury, on rare occasions drugs can also initiate other forms of hepatotoxicity such as granulomas, fibrosis, neoplasms, steatohepatitis and vascular lesions. Common drugs associated with these forms of liver injury are listed in table 2.

The clinical course after withdrawal of the drug is variable. In most cases the abnormal liver panel resolves after discontinuation of the offending drug, though in some cases liver injury may worsen for weeks before improvement is seen. Overall, the resolution of cholestatic injury is a lengthier process compared to the hepatitis form, maybe because in contrast with the hepatocytes, the cholangiocytes regenerate more slowly.[20] In fact complete recovery from a cholestatic injury may be delayed up to 1 year following de-challenge.[20 39] The Spanish Registry Study (mean duration of follow-up, 20 months) reported that only 5.7% of the 493 idiosyncratic DILI cases had evidence of persistent liver injury 3 months following an acute hepatitis, or 6 months after cholestatic injury. In addition, patients with cholestatic/mixed liver disease were more prone to developing chronic injury (18/194, 9%), than those with the hepatocellular form (10/240, 4%).[16] In the recently published American DILIN study, 6 months after enrolment, 14% of patients had persistent laboratory abnormalities and 8% had died; the cause of death was liver related in 44%.[19] In a study with long follow-up, (mean, 11 years), of a total of 685 patients who had DILI associated with jaundice, eight developed cirrhosis (five had cryptogenic cirrhosis in which DILI may have played a role), and five had liver-related mortality (included two patients with cryptogenic cirrhosis). The authors concluded that the development of clinically important chronic liver disease was rare when a patient survived severe DILI. In concurrence with prior studies, protracted DILI was mostly seen in patients with cholestatic/mixed types of hepatotoxicity.[46]

MANAGEMENT

Once a patient develops DILI, the management includes prompt discontinuation of the offending drug, supportive and symptomatic therapy, and monitoring for the development of ALF. As already stated, after drug withdrawal, the liver injury improves in most cases, though there may be a protracted course in those with a cholestatic liver panel. Use of glucocorticoids for immune-mediated reactions,[65] and ursodeoxycholic acid (UDCA) for cholestatic liver injury[66] remain controversial therapies. In fact, in two ALF trials (included a total of 104 patients of whom 12 had DILI), steroids failed to show a beneficial effect. On the contrary, in the subset with DILI, there was a trend towards a worse prognosis in those on steroid therapy.[65 67] Since UDCA has a good safety profile, and prolonged cholestasis, irrespective of aetiology can be fatal,[68] it may be reasonable to treat prolonged cholestasis due to DILI with UDCA in a dose of 13–15 mg/kg. Similarly, in drug-induced hepatitis with allergic features, with no improvement after drug withdrawal, a short course of steroids may be justifiable.[39] Antioxidants have also been proposed as a treatment modality for severe DILI, and *N*-acetylcysteine (NAC) is the treatment of choice for paracetamol overdose.[7] The role of NAC in non-paracetamol-induced liver failure remains unclear. In a randomised controlled trial with 177 patients with non-paracetamol-induced ALF, a 72 h infusion of intravenous NAC did not improve survival compared to placebo. However, in a subgroup analysis, patients with grade 1 to 2 encephalopathy had a significantly higher rate of spontaneous survival.[69] Despite the fact that both UDCA and NAC are safe and widely prescribed, they have not been licensed for use in cholestatic DILI, and non-paracetamol-induced hepatotoxicity, respectively.

Serious drug-induced liver diseases need to be managed in conjunction with a hepatologist, and at the earliest signs of liver failure (INR>1.5, development of ascites, or any grade of hepatic encephalopathy), prompt referral to a liver transplant unit is indicated. In a recent study on telithromycin-associated liver injury, ascites was observed in 17% of the cohort.[70] An important point that merits consideration is that a reduction in liver enzymes does not always herald a good prognosis. In fact, in some cases, decreasing ALT indicates poor hepatic reserve, as is observed in patients with massive/submassive hepatic necrosis.[20] Overall, survival is better for paracetamol-induced liver failure than for idiosyncratic cases (spontaneous survival, 62% vs 26%).[71] In addition, transplant-free survival rate and rates of liver transplantation are similar between suicidal and unintentional paracetamol-induced ALF groups.[5] The most widely used criteria to list patients with DILI for liver transplantation are those that have been developed (and subsequently revised) by King's College, London (table 4), though they have a low sensitivity (27%) but high specificity (90%) for death or transplantation.[72 73]

The United States Acute Liver Failure Study group (ALFSG) is a network of 23 referral centres that have been prospectively studying the aetiologies and outcomes of ALF since 1998.[1] Between

Table 4 King's College criteria for liver transplantation in acute liver failure

Paracetamol	Non-paracetamol
pH<7.3* or	Prothrombin time greater than 100 s (INR>6.5) (irrespective of grade of encephalopathy) or any three of the following
Arterial lactate >3.5 mmol at 4 h or	1. Age less than 11 years or greater than 40 years
Arterial lactate >3.0 mmol/l at 12 h* or	2. Aetiology of non-A/non-B hepatitis, halothane hepatitis, or idiosyncratic drug reactions
PT>100 s (INR>6.5)	3. Duration of jaundice of more than 7 days before onset of encephalopathy
Serum creatinine >300 mmol/l (3.4 mg/dl)	4. Prothrombin time greater than 50 s (INR>3.5)
Grade 3 or 4 encephalopathy	5. Serum bilirubin level greater than 17 mg/dl (300 μmol/l)

Adapted (with permission) from O'Grady, *et al*[72] and Bernal, *et al*.[73]
*After fluid resuscitation. INR, international normalised ratio.

January 1998 and July 2007, the adult ALF Study Group enrolled 1147 patients at 23 clinical sites. The most common causes of ALF were paracetamol (46%), indeterminate (15%) and idiosyncratic DILI (12%). The drugs implicated in idiosyncratic DILI were antibiotics including anti-tuberculosis drugs (20%), sulfa compounds (12%), phenytoin (10%) and various herbs (10%).[12] Spontaneous survival was highest for paracetamol overdose (63%), and the worst outcome was in idiosyncratic DILI (20%).[71] In a recent study, Russo *et al* analysed data from United Network for Organ Sharing (UNOS), and observed that, between 1990 and 2002, 15% (n = 370) of liver transplants performed for ALF were due to drug-induced hepatotoxicity. A striking female preponderance was noted (76%). Of the 270 subjects in whom complete data were available, a single drug was implicated in 258 (96%) with the remainder having multi-drug associated DILI. Paracetamol was the most common drug responsible (46%) followed by isoniazid (INH) (17.5%), propylthiouracil (9.5%), phenytoin (7.3%) and valproate (7.3%).[74]

RISK FACTORS FOR DILI

Susceptibility to DILI is influenced by an inter-play between many factors, including age, gender, concurrent drugs, co-morbidity and genetics. In general, increased age is a risk factor for DILI (eg, age >49 increases the risk of isoniazid hepatotoxicity).[75] Exceptions to this rule include sodium valproate and erythromycin as they result in hepatotoxicity predominantly in children.[76] Women are widely viewed as more likely to develop DILI and the ALFSG has reported a female preponderance in ALF due to both paracetamol (74%) and idiosyncratic drug reactions (67%).[71] However, a recent examination of a Spanish registry showed no overall gender difference. Rather, men predominated over age 60 and were more likely to have a cholestatic injury, whereas women predominated under age 60, and were more susceptible to a hepatitis-like injury.[77] Combination treatment in certain instances augments risk of drug-induced liver disease; for example, hepatotoxicity is more likely to occur if isoniazid is used concurrently with rifampicin and pyranizamide than when used alone.[78 79] Concomitant problems such as HIV, alcoholism, diabetes mellitus, underlying liver disease, and obesity need to be considered as their presence could predict a poorer outcome.[39 80] In fact, a recent US study has identified chronic hepatitis C infection as a predictor of acute liver injury among patients hospitalised for paracetamol overdose.[81] Although most cases of DILI are not related to the cumulative dose of medication used, it is more likely to occur when drugs are administered in doses exceeding 10 mg/day, but an absolute dose threshold has not been identified.[82] Furthermore, failure to stop the offending drug after development of liver disease is associated with a worse prognosis. In the Spanish Registry study, 60% of the patients with chronic liver injury had continued exposure to drug after onset of DILI.[16] Bjorrnsson *et al* also observed that duration of drug therapy before diagnosis of DILI was considerably longer in those who experienced liver-related morbidity/mortality.[46] This underscores the importance of prompt cessation of drug therapy in cases of suspected DILI.

Genetic factors play an important role in susceptibility to DILI. In immune DILI, HLA associations have been described but tend to be different for different drugs, and generally are not sufficiently predictive to be of value in clinical practice. A recent exception is the striking association of flucloxacillin-induced cholestatic injury with HLA-B*5701,[83] which is the same marker identified as being highly predictive of abacavir skin reactions.[84] In non-immune DILI various associations have been identified with CYPs, glutathione *S*-transferase, *N*-acetyltransferase 2, SOD-2 and cytokines.[85] These reflect toxification and detoxification pathways which determine exposure to toxic metabolites and their consequences (eg, oxidative stress), as well as the innate immune responses to the injury, which can modulate the progression and severity of injury. Thus far, these associations have not been sufficiently robust to be of practical value, although they provide mechanistic clues. Perhaps combinations of these polymorphisms will prove to have a stronger predictive value. Certainly, the occurrence of severe DILI (Hy's law cases) is what we wish to avoid. This occurs far less frequently (1:100 to 1:10 000) with idiosyncratic toxins than the prevalence of individual polymorphisms. Although genome-wide single nucleotide polymorphism (SNP) analysis is a promising approach, and small number of cases may be sufficient for very strong associations such as flucloxacillin, it is likely to require very large number of cases to identify the contribution of multiple SNPs. Table 5 summarises risk factors associated with DILI.

Table 5 Risk factors for drug-induced liver injury

Drug	Risk factors
Paracetamol	Chronic alcohol use, fasting, phenobarbitol and isoniazid use
Diclofenac	Female sex, osteoarthritis, cytokine polymorphisms (interleukins 4 and 10)[86]
Erythromycin	Young age
Halothane	Obesity
Isoniazid	HBV, HCV, HIV, alcohol use, older age, female gender, rifampicin use, *N*-acetyltransferase 2 and CYP2E1 genetic polymorphisms[87]
Methotrexate	Chronic alcohol use, obesity, diabetes mellitus, chronic hepatitis, psoriasis
Sodium valproate	Young age, antiepileptic drug use
Troglitazone and tacrine	Glutathione *S*-transferase polymorphisims[88 89]
Flucloxacillin	HLA-B*5701[83]

Adapted (with permission) from Abboud, *et al*.[20]
HBV, hepatitis C virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

PREVENTION

Nearly all drugs that cause immune or non-immune idiosyncratic hepatotoxicity have been accompanied by an increased frequency of ALT elevations in clinical trials,[13] though ALF is unlikely to occur as it is very rare (1 in ⩽10 000).[90] An ALT elevation of 3×ULN is usually associated with mild injury and may also be seen in placebo controlled trials (in the range of 0.2–1%).[13 20] However, a statistically significant doubling or more in the incidence of ALT

elevation >3×ULN is almost always described with idiosyncratic hepatotoxins.[20] So, though an ALT > 3×ULN has been identified as a sensitive marker for liver toxicity, this threshold is not specific, a good example being statins. Most statins are associated with a dose-related increase in the incidence of ALT elevations of ⩾3×ULN, though ALF occurs approximately 1 in 1 000 000, an incidence no greater than that estimated for idiopathic ALF.[43] More accurate predictors of liver failure are an ALT of 10×ULN (rarely observed in placebo-treated patients), or an ALT of >3×ULN accompanied by serum bilirubin of >2×ULN (modified Hy's law).[59 91] This simply reflects the fact that increased serum bilirubin (excluding Gilbert's unconjugated hyperbilirubinaemia), indicates a major hit to the liver, and that, in general, the higher the serum bilirubin, the more severe the liver injury. Several recent examples of idiosyncratic toxins met the criteria for Hy's law in clinical trials, although ALF usually did not occur (but was observed post-marketing). Examples include troglitazone, trovafloxacin, ximelagatran and bromfenac.[13]

ROLE OF ALT MONITORING

An important issue is whether ALT monitoring during drug therapy can prevent occurrence of life threatening idiosyncratic hepatotoxicity by enabling early detection of injury, and thus prompt drug cessation.[13] Although a rational approach, there may be problems with such a strategy. Drugs that result in predictable injury would not qualify for monthly monitoring, since such reactions occur early, and in a dose-dependent fashion; neither would drugs that cause immune-mediated idiosyncratic reactions, as again the injury occurs relatively early, and usually progresses rapidly to become symptomatic, and is therefore easily recognised.[20] The apparent non-immune cases associated with delayed toxicity may be suitable for such a risk management strategy, though there may still be a number of concerns. First, compliance with monthly monitoring is poor. The FDA reported that even after three warning letters were sent from the manufacturers of troglitazone recommending baseline and monthly ALT monitoring, examination of a health-maintenance organisation database revealed that only 45% had baseline tests, and only 33% and 13% were tested at 1 and 5 months, respectively.[92] However, it is possible that risk-management programmes that limit monthly prescription refills according to ALT results may overcome this problem, but would entail considerable cost, and may inhibit use.[13] Second, such a strategy may lead to premature termination of drugs in patients who would otherwise benefit from their use. Finally, serious DILI can occur despite monitoring of the liver panel. This is well illustrated with troglitazone, where out of the 12 cases of ALF, all of whom were undergoing monthly monitoring, the liver injury progressed rapidly from normal ALT to liver failure within 1 month in nine of the cases.[42] Therefore, waiting for the ALT to exceed 3×ULN might be too late to prevent DILI. We could lower the ALT threshold for drug cessation, but that would be at the cost of increasing the number of patients with unnecessary drug withdrawal. Thus there appear to be pros and cons of monitoring of the liver panel to prevent a serious drug reaction. On the one hand we have unconvincing efficacy, poor compliance, and far more patients withdrawn from treatment than would actually experience a serious adverse reaction. On the other hand, where a benefit–risk analysis would favour continued therapy, monthly monitoring may be beneficial compared with no monitoring at all.[13 20] However, as hepatologists, whatever strategy we adopt, the most useful way to prevent DILI would be to educate our patients about the warning signs of severe drug injury such as abdominal pain, nausea, vomiting and jaundice. The importance of these symptoms cannot be over-emphasised. In the case of isoniazid chemoprophylaxis, reporting of symptoms at monthly visits proved effective in averting serious consequences without the need for ALT measurements.[93] However, it should be noted that the population in this study was young (<35 years), and hence the risk for drug injury was not as great as in an older population.[13 20] Furthermore, as already stated, the incidence of hepatotoxicity from antituberculosis medication increases when they are used in combination,[78 79] so it would be inappropriate to extrapolate from the public-health chemoprophylaxis studies.[13]

Other ways to prevent or reduce the incidence of DILI (especially with drugs like paracetamol) include improving package labels, limiting large volume sales, and unbundling or limiting paracetamol in narcotic preparation.[94] In the UK, blister packs and dispensing restrictions have led to a reduction in the number of patients with intentional paracetamol overdose, and those referred for liver transplantation.[95] Finally, use of cross-reacting sensitivity to drugs should be avoided. This issue is of clinical significance as it indicates that a history of a specific drug toxicity should serve as a red flag for potential toxicity from another structurally similar drug.[39] Examples of such a class effect include aromatic anticonvulsants (phenytoin, phenobarbital and carbamezapine; rates of cross-sensitivity as high as 80%);[96] ACE inhibitors (captopril and enalapril);[97] NSAIDS (naproxen and fenoprofen);[98] erythromycin;[99] phenothiazines;[100] and tricyclic antidepressants (amineptine and clomipramine).[101]

An area of active interest is the identification of biomarkers for both early identification of cases in which liver injury is likely to be severe, and diagnostic markers which distinguish DILI from other causes of liver disease. Potential factors for the former might include modifications of serum proteins, or serum and urine metabolites reflecting a specific process (eg, mitochondrial dysfunction) before overt liver disease occurs; for the latter might include serum protein adducts as have been identified with paracetamol. At present the concept of biomarkers is attractive but far from clinical practice.

Key points

- Drug-induced liver injury due to paracetamol and idiosyncratic drug reactions is the leading cause of acute liver failure in the UK and USA.
- The pathogenesis of idiosyncratic drug-induced liver diseases remains enigmatic, but presumably involves the inter-play of factors that determine exposure of the liver to the inciting chemical moiety (metabolite or parent compound), the balance of injurious and protective responses to cellular stress, and the innate and adaptive immune systems.
- Diagnosis of drug-induced liver injury can be difficult, but rests on identification of a characteristic clinical drug signature and exclusion; a high index of suspicion is prudent in clinical practice.
- Spontaneous recovery from non-paracetamol drug-induced acute liver failure is rare, and early referral for liver transplantation is vital.
- Prevention of drug-induced liver injury includes vigilance, identification of risk factors, ALT monitoring with certain drugs, and safer marketing strategies.

CONCLUSIONS

Drug hepatotoxicity due to paracetamol overdose and idiosyncratic drug reactions is the leading cause of acute liver failure both in the US and the UK, and may contribute to as many as 0.3% of all inpatient deaths. Due to its protean manifestation, drug-induced liver injury must be included as a differential diagnosis in all patients with an abnormal liver panel. Thankfully, serious idiosyncratic hepatotoxicity (Hy's law cases) is rare, occurring in 1 in 100 to 1 in 10 000 of individuals exposed to idiosyncratic hepatotoxins. An inter-play of multiple genetic and environmental factors in combination cause these rare idiosyncratic reactions. Based on the characteristic clinical drug signature, drug-induced liver diseases are classified into hepatitis, cholestatic, or mixed patterns, with the hepatitis form most likely to be associated with acute liver failure. Management of patients with drug-induced liver injury needs increased vigilance, as once liver failure develops spontaneous survival (in the absence of liver transplantation) is rare, except in those with paracetamol-induced hepatotoxicity. Prevention of DILI remains challenging. The FDA has adopted Hy's law as a predictor of severe toxicity during clinical trials. Other strategies at a clinical level include diagnostic biomarkers and assessment of genetic polymorphisms that may predict susceptibility to DILI. At a more cellular level the pharmaceutical industry is making a concerted effort at defining potential characteristics of hepatic toxicity by studying chemical structures, reactive metabolites, oxidative stress, and toxicogenomic/biological signatures in animal and cell models.

Competing interests: SV: none. NK: consults for GlaxoSmithKline, JNJ, King Pharmaceuticals, TEVA, Pfizer, Bristol Myers Squibb, Daiichi Sankyo, ISIS Pharm, Hepregen, Eisai Medical Research, Entelos, Merck, Gilead, Allergan, Amgen, Novartis, Roche, Sanofi-Aventis, Wyeth and Cougan Pharmaceuticals regarding liver safety.

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Editor's quiz: GI snapshot

ANSWER

From the question on page 1537

The patient was diagnosed with the bowel-associated dermatosis arthritis syndrome (BADAS). It was first described in patients undergoing ileojejunal bypass surgery for morbid obesity[1] and since then in various other intestinal disorders,[2] including occasionally in inflammatory bowel disease (IBD).[3 4] Clinical presentation is heterogeneous, but is usually characterised by sterile pustular skin lesions, fever, diarrhoea, arthritis, and eye inflammation. The symptoms generally disappear once the intestinal manifestations ameliorate. Skin lesions characteristically consist of small erythematous lesions with a perivascular neutrophilic infiltrate and dermal oedema (fig 1). Histological features however are non-specific and clinical history is essential for a correct diagnosis. The aetiology is believed to be related to bacterial overgrowth leading to the formation and deposition in skin and synovia of circulating immune complexes and subsequent activation of neutrophilic granulocytes.[5]

As in this patient, BADAS usually responds well to high-dose steroids. It may also respond to antibiotics. Antibiotics have been reported to be beneficial in up to 50% of patients with BADAS after bypass surgery, although the response has been inconsistent.[6] As far as we know, the therapeutic effect of antibiotics in patients with IBD and BADAS has not been evaluated. Since the pathophysiology is presumed to be similar in both disease entities, a course of antibiotics could be tried in patients with IBD and BADAS. The patient presented here had no clinical manifestations that might predispose her to bacterial overgrowth; however, she was not formally tested to exclude this possibility. Given the severity of her symptoms, treatment was initiated with high-dose corticosteroids (40 mg prednison/day). The fever disappeared instantly while the skin manifestations completely resolved within 1 week. Steroids were slowly tapered and symptoms have not recurred since then.

In conclusion, it is important to consider the possibility of a BADAS in patients with IBD who have unexplained fever and skin lesions because treatment may lead to prompt resolution of the symptoms and prevent an exhaustive search for other causes of fever.

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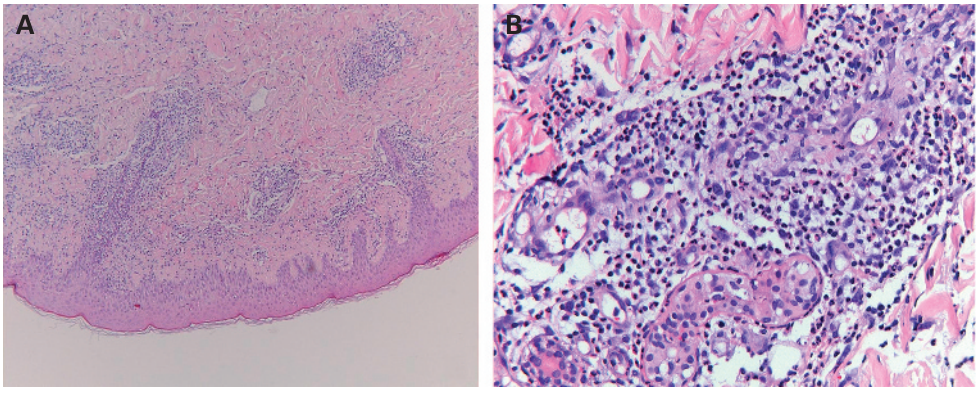

Figure 1 Haematoxylin & eosin stained photomicrograph of the dermis and epidermis demonstrating a perivascular and perifollicular neutrophilic infiltrate. Magnification: (A) ×2.5; (B) ×20.