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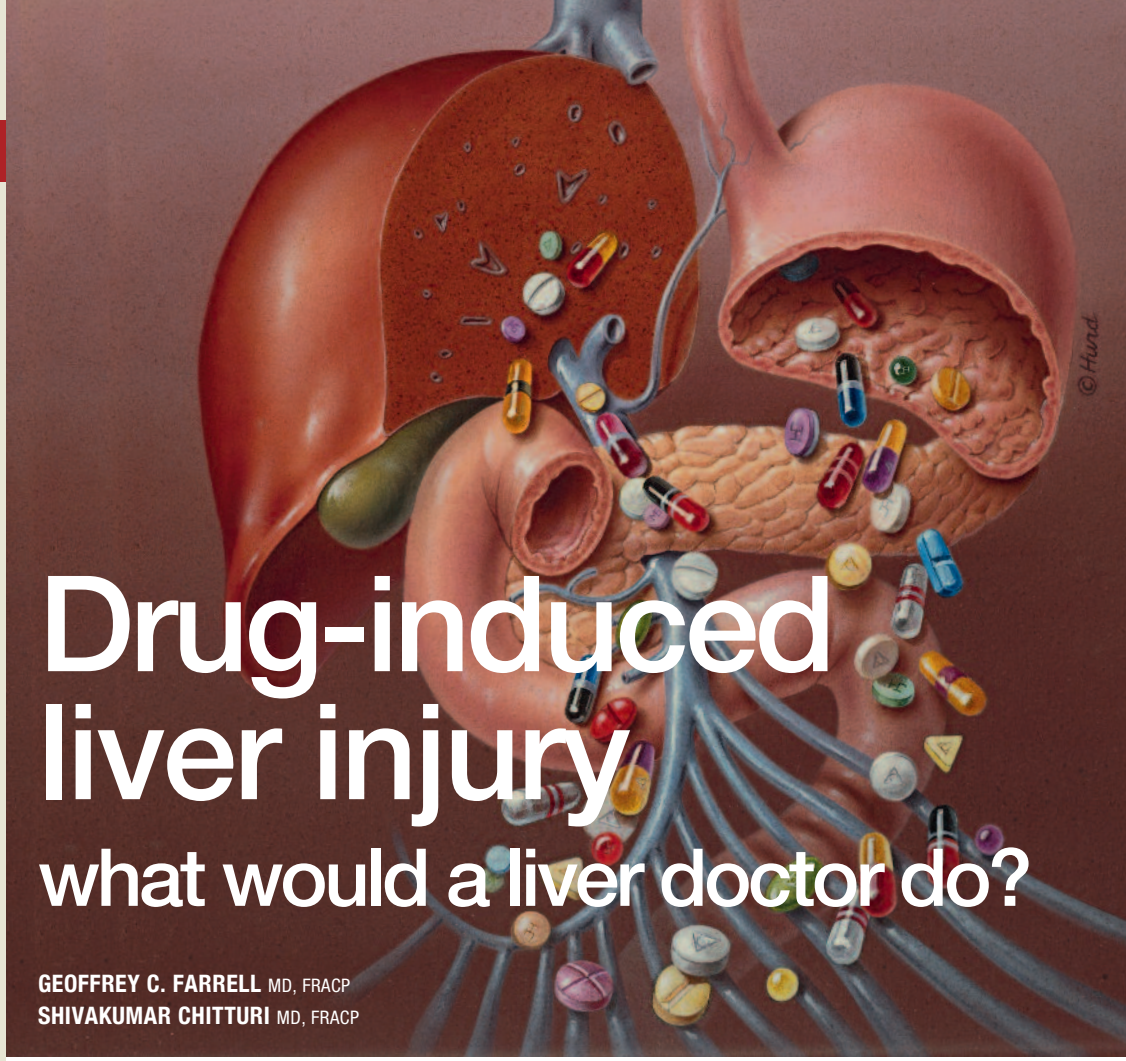

Drug-induced liver injury

what would a liver doctor do?

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Key points

- Drug-induced liver injury (DILI) is a significant cause of morbidity and can lead to liver failure.
- Few of the more than 300 agents implicated as possible causes of DILI are associated with a frequency of drug reactions greater than 0.1%.
- The agents most often responsible in DILI are those most commonly prescribed (i.e. antimicrobials, NSAIDs and anticancer drugs). Generally, the agent started most recently is the most likely culprit.
- Diagnosis is vital as continued drug ingestion after onset of liver injury is a critical factor for poor prognosis.
- Patients are often unaware of the toxicity of large quantities of paracetamol.
- Statins rarely cause liver injury.
- The long-term risks of liver complications from methotrexate treatment should be weighed against the benefits of therapy.

Drug-induced liver injury is a significant cause of morbidity. Practical management strategies for suspected drug-induced liver injury, including useful investigations and appropriate referral, are proposed in this case-based article.

Drug-induced liver injury (DILI) is a significant cause of morbidity and GPs are usually the first point of contact for affected individuals. This article provides an overview of the general practice management of patients with DILI, using four cases to illustrate various scenarios. Consider the following cases before reading the commentaries on each.

CASE SCENARIOS

Case 1

LB, a 52-year-old woman with recurrent depression and type 2 diabetes, was hypertensive (blood pressure [BP] 155/95 mmHg) eight weeks ago and started taking enalapril 10 mg daily. She has also been taking carbamazepine, fluoxetine, metformin, tolbutamide and fluvastatin for at least 18 months. She now

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The views published in this series are those of the authors and not necessarily indicative of those held by all members of the Digestive Health Foundation or GESA.

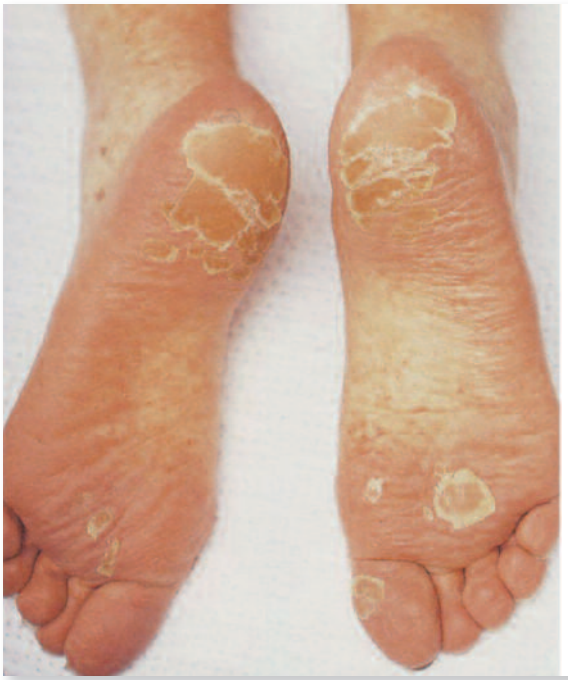

Figure 1. Desquamating erythematous rash of the feet and ankles, with punctuated erythematous or purpuric lesions (which were palpable). The patient, who started taking allopurinol six weeks earlier, has drug-induced liver injury (granulomatous hepatitis) and interstitial nephritis with vasculitis.

presents with three days of fever, anorexia, nausea and dark urine. Dipstick urine test confirms bilirubinuria and a rash is noted, similar to that illustrated for a different patient in Figure 1.

What would you do?

Case 2

You have been called to a nursing home to see MG, a 74-year-old woman who was noticed by her relatives two days ago to be jaundiced (Figure 2). She has early dementia and severe osteoarthritis of both knees and hips. In the preceding two months, she had rejected food and had lost 5 kg in weight. Your colleague ordered an ultrasound, hepatitis serology and liver biochemistry. The ultrasound was normal and the hepatology serology was all negative. The other results were: serum bilirubin 80 mmol/L (upper limit of normal [ULN] less than 20 mmol/L), alanine transaminase (ALT) 3000 U/L (ULN less than 40 U/L), aspartate transaminase (AST) 4000 U/L (ULN less than 40 U/L), albumin 38 g/L (normal range, 35 to 53 g/L), INR 2.5 (ULN less than 1.3).

What would you do?

Case 3

BO is a 64-year-old Indian man with a history of type 2 diabetes, two myocardial infarctions and placement of three coronary artery stents. Apart from his waist circumference of 99 cm, you notice hypercholesterolaemia is the only uncontrolled risk factor (total cholesterol 6.8 mmol/L, HDL cholesterol 0.7 mmol/L (ideally greater than 1.2 mmol/L), LDL cholesterol 6.1 mmol/L (ideally less than 3.0 mmol/L). However, Mr O has been told he cannot take statins because he has liver dysfunction (ALT 150 U/L, gamma glutamyl transferase (GGT) 75 U/L (ULN less than 35 U/L).

Is it appropriate to prescribe a statin?

Case 4

JL is a 45-year-old male taxi driver with psoriatic arthritis and moderately severe psoriasis of the scalp, arms and trunk. He was treated with methotrexate (15 mg once a week) for seven years (total about 5 g) with excellent control. This patient found information on the internet that metho - trexate could cause cirrhosis (of which his father died); he therefore stopped taking methotrexate about 18 months ago.

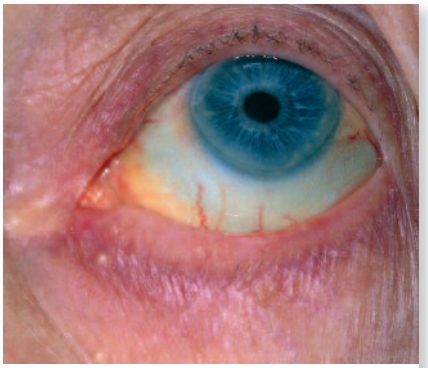

Figure 2. Drug-induced jaundice in an elderly woman.

His hands are now so painful and stiff that he cannot drive and he is therefore unemployed.

Can you safely prescribe methotrexate again?

WHAT WOULD A LIVER DOCTOR RECOMMEND FOR GENERAL PRACTICE MANAGEMENT?

Case 1

LB has symptoms of acute hepatitis, bilirubinuria being consistent with this, together with fever and rash, within eight weeks of starting a new medication. GPs should first exclude other causes of acute hepatitis and jaundice, for example, by hepatitis serology and hepatobiliary ultrasonography before considering drug-induced liver disease.

Prominent anorexia is more in favour of hepatitis than biliary obstruction from, for example, gallstones and pancreatic cancer. However, neither fever nor rash is a usual feature of viral hepatitis. The presence of fever, rash and even relatively nonspecific gastrointestinal symptoms in someone taking a new medication strongly suggest a drug reaction. In this case, the hepatitis symptoms and bilirubinuria make a hepatic drug reaction (or 'drug hepatitis') likely.

Diagnostic tests

Liver function tests (LFTs) will confirm a form of acute liver injury. With the

clustering of LB's clinical features there may be a raised serum bilirubin level and substantial elevation of levels of alanine transaminase (ALT; five-fold or more above upper limit of normal) and/or serum alkaline phosphatase (SAP; to greater than twice the upper limit of normal) but with relatively normal levels of serum albumin and globulins.

Two other features of the biochemistry may be helpful. First, concomitantly major elevations of ALT and SAP, or a 'mixed picture', is particularly common with hepatic drug reactions, and this is why the less committal term 'drug-induced liver injury' (DILI) is now often used. Second, abnormalities of INR (or prothrombin time) reflect severely impaired liver function and commonly occur with severe forms of DILI, such as that caused by isoniazid. Together with the clinical features of jaundice, repeated vomiting or clouding of consciousness and/or confusion, a prolonged INR indicates incipient liver failure; such patients need urgent and immediate referral to a major hospital or a liver transplant centre.

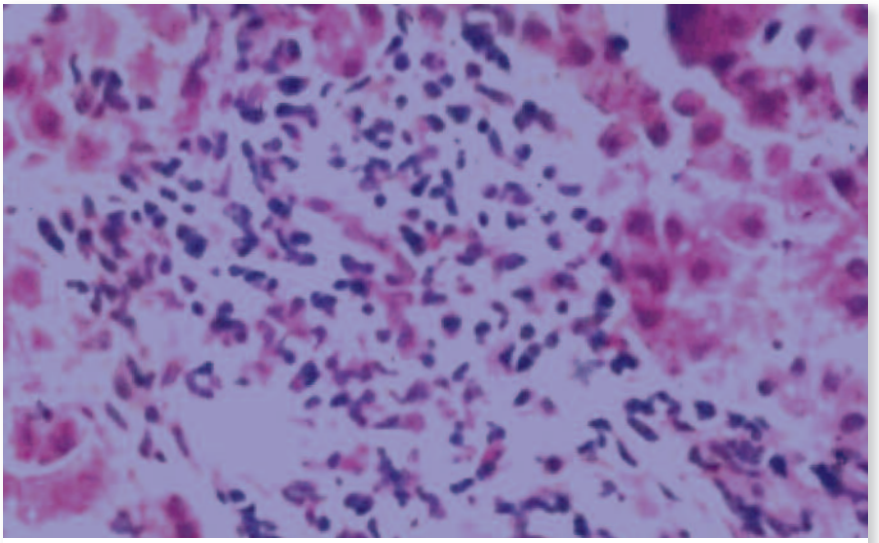

Figure 3. Liver biopsy taken from a patient with a similar history to that of LB (Case 1). This patient had been taking enalapril for six weeks as treatment for hypertension. In addition to liver cell injury and parenchymal inflammation (hepatitis) there is portal tract inflammation (including both neutrophils and eosinophils) with bile duct injury.

Causative agents

Generally, the agent started most recently, particularly when it has previously been implicated in DILI, is the most likely culprit. Typically, the onset of drug hepatitis is between two and 12 weeks after starting exposure, rarely after 12 months.

LB's case is illustrative, the drug she started most recently being enalapril. ACE inhibitors have been associated with cholestatic hepatitis (Figure 3) and other forms of DILI.

ACE inhibitors and other antihypertensive agents are individually rare causes of DILI (less than one per 10,000 persons exposed), but so too are most other drugs. Among more than 300 agents implicated as possible causes of DILI, few are associated with a frequency of drug reactions greater than 0.1%. The agents most often implicated come from the most commonly used groups of drugs, such as antimicrobials (amoxycillin–clavulanate being most often implicated), NSAIDs and anticancer drugs. However, agents from every category, including herbal and other complementary medicines, have been associated with rare instances of DILI.[1] A list of potentially hepatotoxic drugs is provided in the Table.

In LB's case, carbamazepine is a well-known cause of DILI but the fact that she has been taking it for longer than 18 months makes it a highly unlikely cause of her present symptoms.

Management

Diagnosis is the key to management of DILI. Cases not recognised as instances of DILI carry a bad prognosis because continued drug ingestion after onset of liver injury is a critical factor for poor prognosis, as has been well documented for isoniazid.[2] Other prognostic factors include jaundice, particular agents (halothane, mitochondrial toxins such as the older highly active antiretroviral therapy [HAART] agents, and terbinafine), polypharmacy, advanced age and comorbidities.

If LB stops her ACE inhibitor (it can be replaced with a different antihypertensive), rapid recovery (within one to two weeks) would be anticipated. Corticosteroids are not helpful for DILI. Referral is advised if there are adverse laboratory findings or when the clinical course is atypical or prolonged as patients may need a liver biopsy to confirm the diagnosis (Figure 3).

Case 2

MG's extreme elevation of transaminases suggests severe acute liver injury. The pattern of very high elevations of transaminases is found only with hepatic necrosis, ischaemia-reperfusion injury (usually due to acute cardiac failure or other cause of profound hypotension or hypoxia) and DILI (specifically that caused by paracetamol). Higher levels of AST relative to ALT often accompany paracetamol hepatotoxicity, and this is attributable to mitochondrial injury.

TABLE. POTENTIALLY HEPATOTOXIC DRUGS

Drug/drug class	Spectrum of liver injury	Important hepatotoxic representatives of the group	Practice points
Anaesthetic agents	Acute hepatitis; acute liver failure	Halothane Newer agents (desflurane, sevoflurane) very rarely	Important cause of postoperative jaundice; more common in patients over 40 years of age, women, obese individuals, persons with a familial disposition and with repeated use
Antithyroid drugs	Acute or cholestatic hepatitis; acute liver failure	Propylthiouracil Carbimazole	Propylthiouracil more commonly used
Antituberculous drugs	Acute hepatitis; liver failure	Isoniazid, rifampicin (with isoniazid), pyrazinamide (with isoniazid, rifampicin)	Risk increases with age (up to 1%), alcohol intake. Important to educate patients about symptoms of acute hepatitis. LFT monitoring recommended but should not replace early assessment of nonspecific symptoms
Antibiotics	Acute or chronic hepatitis; cholestatic liver injury	Amoxycillin–clavulanate	Most common cause of idiosyncratic DILI; onset can be delayed for several weeks after completing antibiotic course. Genetic predisposition
		Flucloxacillin (cholestatic liver injury), nitrofurantoin, minocycline	Prolonged courses, IV use. Long-term nitrofurantoin and minocycline use can be associated with chronic hepatitis with autoantibodies
		Erythromycins, cephalosporins	Rare cases of cholestasis
Anticonvulsants	Acute hepatitis; granulomatous hepatitis; acute liver failure	Phenytoin	Personal or family history of anticonvulsant hypersensitivity (should avoid these agents)
		Carbamazepine	Granulomatous or cholestatic hepatitis
		Valproate (acute liver failure)	Valproate liver toxicity more common with mitochondrial enzyme deficiencies (and patients carrying certain mitochondrial gene polymorphisms), young children and with polypharmacy
Cardiovascular drugs	Acute hepatitis; cholestatic hepatitis; rarely cirrhosis, acute liver failure	With exception of methyldopa and amiodarone, very rare reactions	–
		Methyldopa	Acute and chronic hepatitis, cirrhosis
		Labetalol	Acute hepatitis, acute liver failure
		Amiodarone	Abnormal liver tests, acute liver failure, steatohepatitis, cirrhosis. Note: opacification on CT due to iodine and not toxicity
		ACE inhibitors	Cholestatic hepatitis
Herbal medicines and other over-the-counter agents	Abnormal liver tests; acute and chronic hepatitis; acute liver failure; hepatic venous outflow obstruction	Germander; pyrrolizidine alkaloids; slimming aids containing usnic acid); black cohosh	Careful enquiry into herbal medicine use is critical. Not always in 'medicine' formulation, therefore ask about herbal tea mixtures, health supplements, over-the-counter medications
Highly active antiretroviral treatment (HAART)	Mitochondrial hepatotoxicity: steatosis, lactic acidosis, acute liver failure with first generation NRTIs; less common with newer NRTIs (tenofovir)	Zidovudine, didanosine, stavudine	Baseline and serial liver test monitoring needed. Educate and encourage patients to report symptoms that could reflect liver injury/lactic acidosis
	Acute hepatitis with non-NRTIs	Nevirapine (acute hepatitis) High-dose ritonavir (acute hepatitis)	Drug interactions with protease inhibitors to be considered when multiple drugs are prescribed

TABLE. POTENTIALLY HEPATOTOXIC DRUGS continued

Drug/drug class	Spectrum of liver injury	Important hepatotoxic representatives of the group	Practice points
Hormonal agents and hormonal antagonists	Cholestasis; hepatic adenoma; hepatocellular carcinoma	Oestrogens, anabolic steroids, antiandrogens: danazol, cyproterone acetate (cholestasis, hepatic adenoma, rarely hepatocellular carcinoma)	Avoid uninterrupted high-dose use of sex steroids. Physical examination (hepatomegaly) and consider serial hepatic imaging in long-term danazol and cyproterone acetate users
	Acute hepatitis; acute liver failure	Tamoxifen (steatohepatitis, rarely cirrhosis)	More common with underlying obesity and metabolic syndrome
Immunosuppressive agents*	Hyperbilirubinaemia	Cyclosporin – not true 'toxicity' or cholestasis (effects on bile canalicular transporters)	May cause raised bilirubin, which does not reflect liver injury (it is a transport defect of no clinical significance)
	Cholestatic hepatitis; hepatic veno-occlusive disease; other vascular disorders of liver	Azathioprine	Particularly after renal transplantation, occasionally after several years
	Fibrosis; steatohepatitis; cirrhosis	Methotrexate	Risk factors: older age, alcohol use (more than 15 g/day), renal failure, obesity, fatty liver. Management: pre-treatment liver biopsy in selected cases; regular LFT monitoring; on treatment liver biopsy based on cumulative dose thresholds; liver tests and checking risk factors
Lipid-lowering drugs	Acute hepatitis; acute liver failure	Statins	Statin-related hepatotoxicity is very rare. Periodic monitoring of liver tests is unhelpful
		Nicotinic acid (acute liver failure)	Nicotinic acid hepatotoxicity is severe and partially dose-dependent
NSAIDs	Acute or chronic hepatitis; acute liver failure; cholestasis	Many potential culprits, including COX-2 inhibitors (lumiracoxib withdrawn because of hepatotoxicity)	Avoid NSAIDs in patients with cirrhosis for risk of causing gastrointestinal bleeding, acute renal failure
		Diclofenac (acute/chronic hepatitis); sulindac (cholestatic liver injury); ibuprofen (rare cholestasis)	Diclofenac hepatitis can mimic autoimmune hepatitis. Increases in serum transaminases reported with ibuprofen in persons with chronic hepatitis C
Paracetamol	Acute liver failure	Dose-dependent but check individual risk factors	Important to consider in cases presenting with an overdose 'staggered' over a few days. Identify individuals at risk of liver injury (prolonged fasting, alcoholics, late presentation or concealed use, concomitant medication use). Have a low threshold for testing paracetamol levels in emergency department
Sedatives, antidepressants	Acute hepatitis; cholestatic hepatitis; cholestasis	Chlorpromazine (still a cause of cholestatic hepatitis) Amitriptyline, imipramine (cholestasis) Trazodone (acute and chronic hepatitis)	Several selective serotonin reuptake inhibitors have been associated with acute hepatitis, but reactions are very rare compared with older agents

* Before prescribing immunosuppressive or anticancer drugs, doctors must know each patient's hepatitis B status. Severe exacerbations, occasionally fatal, can occur with immune modulation for anyone (including 'healthy carriers') with chronic hepatitis B virus infection.

ABBREVIATIONS: ACE = angiotensin converting enzyme; COX-2 = cyclo-oxygenase-2; DILI = drug-induced liver injury; IV = intravenous; LFT = liver function test; NRTI = nucleoside reverse transcriptase inhibitor; NSAIDs = nonsteroidal anti-inflammatory drugs.

This patient's high serum bilirubin and INR prolongation indicate poor liver function and an uncertain prognosis; there may also be impaired renal function. Her higher levels of AST relative to ALT are suggestive of paracetamol hepatotoxicity.

Dose-dependent hepatotoxicity

Although paracetamol is a dose-dependent hepatotoxin, it is important to understand that the difference between a safe dose and a hazardous dose can vary markedly between individuals. First, there is a difference between short-term (a day or two) and more prolonged dosing (several days). Second, a number of host factors modify paracetamol metabolism, and therefore the risk of liver injury, by favouring an increased proportion of the drug being oxidised by the cytochrome P450(CYP)2E1 pathway.

CYP2E1 is induced by alcohol consumption and fasting, which also deplete stores of hepatic glutathione, the antioxidant that protects tissues against oxidative injury. The increased susceptibility of alcohol abusers to paracetamol hepatotoxicity (even at doses not usually regarded as toxic) is well known for these reasons, but the similar susceptibility of children or older patients who have not eaten for several days is not as familiar. It is not uncommon to find that a patient's recommended dosage of 'paracetamol 4 h prn' has resulted in a total ingestion of more than 4 g/day for several days or even weeks.

With her early dementia, MG could easily have been self-administering paracetamol (and/or paracetamol-containing analgesics) in large dosages for her joint pains, perhaps aided and abetted by caring relatives and nursing staff. Avoiding this potentially lethal 'iatrogenic' complication in contemporary medical practice should have greater priority.

Investigations and management

MG needs to have heart failure excluded clinically and with simple tests (such as a chest x-ray). In addition to thoroughly investigating possible exposure to other drugs, serum paracetamol estimation is still worth performing even though the onset of jaundice indicates severe liver injury began two to five days earlier. If paracetamol is still detectable, this is suspicious for paracetamol as the cause of DILI.

Admission of MG to hospital is advisable unless it is against her and her family's expressed wishes (under a living will, for example). Although in this case it is past the optimal first 16 hours since paracetamol ingestion, most medical units would still administer N-acetylcysteine (NAC) as there is some evidence that NAC may ameliorate acute liver failure and it does not increase risks of hepatic coma and other complications. (NAC augments glutathione reserves and hence the inactivation of the toxic metabolites of paracetamol that accumulate when the drug is taken in large quantities.)

Case 3

BO has the odds stacked against him for further cardiac events as he has diabetes, multivessel coronary heart disease and atherogenic dyslipidaemia (low HDL cholesterol and very high LDL cholesterol levels). He should be prescribed a statin, and it is totally inappropriate not to do so. The evidence that statins reduce risk of further cardiac events is overwhelming, and their protective efficacy is considerable. Some patients still get inappropriate advice that they cannot safely use statins because of their abnormal liver test results.

This patient almost certainly has nonalcoholic fatty liver disease (NAFLD); the diagnosis could be partly confirmed by a hepatic ultrasound. At age 64 years, with type 2 diabetes and metabolic syndrome (he has central obesity, diabetes and atherogenic dyslipidaemia) and with markedly abnormal liver tests (particularly his ALT level of 150 U/L), there is a high probability that BO has cirrhosis complicating longstanding NAFLD (or, more specifically, its progressive form termed nonalcoholic steatohepatitis [NASH]).

Statins, however, despite their reputation and the information on the package insert, rarely cause any liver injury: about 3% of patients have raised ALT in clinical trials, with most changes resolving during continued drug administration. Monitoring ALT levels in patients taking statins is inconvenient, costly and ineffective, and in reality, statins are among the rarest causes (less than one case per 100,000 persons exposed) of clinically significant DILI.

Finally, and most cogently for this patient, pre-existing NAFLD, or abnormal liver tests from any cause of liver disease, does not predispose to statin-induced liver injury. The evidence on which the American Association for the Study of Liver Diseases (and all hepatologists) have reached this conclusion is based on millions of person-year exposures and prospective study by the National Institutes of Health DILI Collaborative Research Network.[2-5]

Case 4

JL would like to get back to work so the odds of long-term liver complications from his restarting methotrexate need to be weighed against his clinical issues and social need for disease control.

Risk factor update

Before once-a-week low dose (up to 25 mg) regimens of methotrexate were used, cases of methotrexate fibrosis culminating in cirrhosis, even hepatic decompensation or liver cancer, were not rare. Now that methotrexate is a first-line disease-modifying drug in rheumatoid arthritis and has other important indications including psoriasis, it is prescribed in dosage schedules that are rarely associated with significant liver fibrosis.

Some rheumatologists believe that methotrexate liver disease is a condition of the past but there are important caveats, including the possibility that liver involvement is more common with psoriasis than with rheumatoid arthritis. Hepatology specialists still see rare cases of cirrhosis – but only when guidelines are disregarded.

Recommendations

The previous recommendation was that a liver biopsy is indicated after a patient has taken a total of 2 g methotrexate. However, this is probably not necessary unless the patient has had repeatedly abnormal liver test results (the American Rheumatological Association recommends LFTs every two to three months) and/or there are important risk factors for methotrexate-induced liver fibrosis.[2,6] These risk factors include 'significant alcohol intake' (15 g/day or more), diabetes, renal failure and obesity.

There is a strong suspicion that methotrexate exacerbates NAFLD/NASH, and patients with risk factors for this metabolic liver disease should be monitored closely (regular LFTs and consideration of liver biopsy) when taking methotrexate.

It is advisable that JL considers having a liver biopsy. A finding of his liver being normal after his taking 5 g methotrexate would give reassurance about the safety of restarting methotrexate, assuming there is no evidence of or risk factors for fatty liver disease. JL should be counselled about safe levels of alcohol intake (less than 15 g/day) and have LFTs performed four times a year.[6] The LFT changes are usually nonspecific minor elevations of ALT and/or GGT, but any fall in serum albumin level or platelet count could indicate developing cirrhosis. The indication for and timing of any subsequent liver biopsy will depend on the initial findings, and whether there are risk factors or liver test abnormalities. Thus, it should be an individualised approach and involve discussion between the specialists involved and the patient's GP.

If JL declines the offer of a liver biopsy, most hepatologists would not recommend withholding treatment with methotrexate but clearly monitoring during the treatment and the prevention of risk factors would take on even greater importance. Noninvasive tests, including physical modalities of 'liver stiffness' (such as a transient elastography using Fibroscan) and biochemical markers (such as serum hyaluronan) may soon be more widely applied in this context. Transient elastography using Fibroscan is already available in many specialised liver units and could be valuable for assessment of severe fibrosis, but there is not yet a strong evidence base for the use of biochemical markers of hepatic fibrosis in patients taking methotrexate.

CONCLUSION

The key points about DILI that need to be borne in mind by GPs and all prescribing doctors are highlighted at the beginning of this article. While a vast number of agents have been associated with some form of liver injury, commonly used agents like antimicrobials and NSAIDs are most often involved. Always consider the temporal profile between drug ingestion and liver injury; the agent started most recently is typically the culprit when patients develop hepatitis or jaundice. Although exclusion of common disorders (viral hepatitis, gallstone, fatty liver disease) is an essential step towards diagnosis of DILI, it is helpful for doctors to always ask themselves whether a drug (prescribed or over-the-counter) or herbal remedy could be incriminated as the cause of individual cases of liver disease. MT

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COMPETING INTERESTS: None.