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# Review article: drug hepatotoxicity

C. Y. CHANG & T. D. SCHIANO

The Division of Liver Diseases, Department of Internal Medicine, The Mount Sinai School of Medicine, New York, NY, USA

Correspondence to:
Dr C. Y. Chang, Division of Liver Diseases, The Mount Sinai School of Medicine, One Gustave Levy Place, Box 1104, New York, NY 10029-6574, USA
E-mail: charissa.chang@mssm.edu

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## SUMMARY

### Background
Drug toxicity is the leading cause of acute liver failure in the United States. Further understanding of hepatotoxicity is becoming increasingly important as more drugs come to market.

### Aims
(i) To provide an update on recent advances in our understanding of hepatotoxicity of select commonly used drug classes. (ii) To assess the safety of these medications in patients with pre-existing liver disease and in the post-liver transplant setting. (iii) To review relevant advances in toxicogenomics which contribute to the current understanding of hepatotoxic drugs.

### Methods
A Medline search was performed to identify relevant literature using search terms including 'drug toxicity, hepatotoxicity, statins, thiazolidinediones, antibiotics, antiretroviral drugs and toxicogenomics'.

### Results
Amoxicillin-clavulanic acid is one of the most frequently implicated causes of drug-induced liver injury worldwide. Statins rarely cause clinically significant liver injury, even in patients with underlying liver disease. Newer thiazolidinediones are not associated with the degree of liver toxicity observed with troglitazone. Careful monitoring for liver toxicity is warranted in patients who are taking antiretrovirals, especially patients who are co-infected with hepatitis B and C. Genetic polymorphisms among enzymes involved in drug metabolism and HLA types may account for some of the differences in individual susceptibility to drug hepatotoxicity.

### Conclusions
Drug-induced hepatotoxicity will remain a problem that carries both clinical and regulatory significance as long as new drugs continue to enter the market. Future results from ongoing multicentre collaborative efforts may help contribute to our current understanding of hepatotoxicity associated with drugs.

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## INTRODUCTION

Drug hepatotoxicity (due to acetaminophen overdose and idiosyncratic drug reactions) is the leading cause of acute liver failure (ALF) in the United States.[1] While the overall incidence of drug-induced liver injury (DILI) is infrequent (one in 10 000 to 100 000 persons exposed),[2] the impact is significant. Only 20% of patients presenting with ALF because of DILI survive with supportive care; therefore, early diagnosis and referral for liver transplantation is crucial.[1] At a regulatory level, hepatotoxicity is the main reason for postmarketing regulatory decisions including drug withdrawal.[3] Doctors involved in administering new medications must weigh potential risks vs. benefits and be aware of appropriate monitoring guidelines for hepatotoxicity. Factors which limit our understanding of drug hepatotoxicity include the relatively rare incidence of toxicity for most drugs, lack of animal models, underreporting and practical issues of drug–drug interactions which can confound the establishment of causality in cases of suspected toxicity.

Diagnosis of drug hepatotoxicity may sometimes be evident based on a temporal relationship between initiation of a drug followed by liver chemistry test elevations, especially in the case of medications which are classically associated with drug hepatotoxicity (i.e. isoniazid, augmentin, trimethoprim/sulfamethoxazole, phenytoin). Classification of drug-related hepatotoxicity can be delineated based on the pattern of liver chemistry test abnormalities (i.e. hepatocellular, cholestatic or mixed),[4, 5] the mechanism of toxicity (i.e. direct, immune-mediated, idiosyncratic, mitochondrial toxicity), or by histological findings on liver biopsy (i.e. steatosis, sinusoidal obstruction syndrome). As a general rule, clinically significant DILI is often defined as ALT >3 times the upper limit of normal (ULN).[6] Jaundice associated with aminotransferase elevation portends a worse prognosis compared with aminotransferase elevation alone.[7, 8] Table 1 shows a classification of the different types of DILI and drugs that have been associated with each other.

The most commonly implicated drugs involved in acute liver injury as reported from recent studies are summarized in Table 2. Acetaminophen accounts for the majority of cases of drug-induced ALF in the United States.[9, 10] Antimicrobial agents and non-steroidal anti-inflammatory drugs (NSAIDS) account for a large portion of non-acetaminophen-associated DILI. A complete review of all common classes of

**Table 1.** Classification of drug induced liver injury and drugs which have been associated with each pattern

| Pattern of liver injury | Associated drugs |
|---|---|
| Acute | |
| Hepatocellular (ALT >3× ULN) | Acarbose<br>Acetaminophen<br>Allopurinol<br>Buproprion<br>Bromfenac<br>Diclofenac<br>Fluoxetine<br>Isoniazid<br>Ketoconazole<br>Lisinopril<br>Losartan<br>Nefazodone<br>Nevirapine<br>Paroxetine<br>Pyrazinamide<br>Rifampin<br>Risperidone<br>Ritonavir<br>Sertraline<br>Statins<br>Tetracycline<br>Trazodone<br>Troglitazone<br>Trovafloxacin<br>Valproic acid |
| Cholestatic (AP >2× ULN, ALT/AP <2) | Amoxicillin/clavulanate<br>Anabolic steroids<br>Azathioprine<br>Chlorpromazine<br>Clopidogrel<br>Cytarabine<br>Erythromycin<br>Estrogen<br>Fosinopril<br>Irbesartan<br>Phenothiazines<br>Sulindac<br>Terbinafine<br>Tricyclics |
| Mixed (elevated AP and ALT) | Amitryptilline<br>Azathioprine<br>Captopril<br>Carbamazepine<br>Clindamycin<br>Cyprohepatadine<br>Enalapril<br>Flutamide<br>Ibuprofen<br>Nitrofurantoin<br>Phenobarbital<br>Phenytoin |

**Table 1.** (Continued)

| Pattern of liver injury | Associated drugs |
|---|---|
| | Sulfonamides |
| | Trazodone |
| | Trimethoprim/ sulfamethoxazole |
| | Verapamil |
| Chronic | |
| Steatohepatitis | Amiodarone, tamoxifen |
| Microvesicular steatosis | NRTIs, valproic acid, tetracycline |
| Granulomatous hepatitis | Diltiazem, sulfa drugs, quinidine |
| Sinusoidal obstruction syndrome | Busulfan, cyclophosphamide |
| Fibrosis | Methotrexate |
| Hepatic adenoma | Oral contraceptives |
| Autoimmune hepatitis | Nitrofurantoin, minocycline |

potentially hepatotoxic drugs is beyond the scope of a single review. Rather, the purpose of the current review is to highlight updates on select classes of drugs commonly used in patients with metabolic syndrome/ underlying fatty liver disease, viral hepatitis and HIV. We chose to highlight statins, thiazolidinediones (TZD) and antiretroviral agents because of their relevance as agents in which the risk vs. benefit ratio can be difficult to discern in individuals with underlying liver disease. Two antimicrobial agents, amoxicillin/clavulanic acid and telithromycin, will also be addressed in the context of recent updates. Other drugs commonly associated with hepatotoxicity (i.e. acetaminophen, isoniazid, propylthiouracil and NSAIDs) will not be addressed as they have been well-reviewed elsewhere[11–13] although it is worth noting that these account for a large proportion of cases of drug-induced ALF[9] and should not be overlooked.

## STATINS

Statins are prescribed commonly for hyperlipidaemia and play an important role in the prevention of coronary artery disease. Rising trends in obesity and non-alcoholic fatty liver disease (NAFLD) have resulted in a common scenario in which a carer is faced with deciding whether or not to start a statin in a patient with metabolic syndrome, hyperlipidaemia, NAFLD and baseline aminotransferase elevations. While mild aminotransferase elevations occur in patients taking statins, clinically significant elevation leading to ALF is extremely rare, and evidence suggests that hepatotoxicity due to statins has been overstated.[14]

Asymptomatic mild aminotransferase elevation associated with statin use is generally dose-related, occurs within the first 12 weeks of therapy, and improves spontaneously in many cases.[15] The incidence of dose-related mild (2–3× ULN) aminotransferase elevation associated with statins ranges from 0% to 3%.[16] Moderate to severe ALT elevation (ALT >3× ULN) can occur with statins; however, rates are low and have not been shown to differ significantly from placebo in several trials. A meta-analysis involving a total of 49 275 patients enrolled in 13 placebo-controlled statin trials reported no significant difference in the overall incidence of LFT elevation >3× ULN in statin users (pravastatin, lovastatin, simvastatin, fluvastatin) compared with placebo (statins 1.1% vs. placebo 1.1%, OR 1.3, 95% CI: 0.99–1.62). The Pravastatin Pooling Project reported a 0.3% incidence of ALT elevation between 3 and 5× ULN in 9185 individuals who received Pravastatin compared with a 0.2% incidence in the placebo arm.[17] Severe ALT elevation (>9× ULN) among statin users was also no different compared with placebo in the Pravastatin Pooling Project (0.2% in statin users vs. 0.1% in placebo). A case–control study by Chalasani reported similarly low rates of severe ALT elevation in statin users (0.6% incidence of ALT >10× ULN) which did not differ significantly from non-users (0.2%, $P = 0.2$).

In contrast to mild asymptomatic aminotransferase elevation with statins, ALF secondary to statins is rare and likely occurs through an idiosyncratic mechanism. The rate of ALF associated with lovastatin, the first approved statin, is one per 1–1.1 million patient-treatment years, which is the same as the background rate of idiopathic ALF.[15, 18] Statins were identified as the cause of fulminant hepatic failure in only three of 51 741 liver transplant recipients in the United States from 1990 to 2002.[9] While rare cases of ALF have been described with all statins, there is no evidence to suggest that periodic monitoring of liver chemistry tests predicts ALF, and routine monitoring of liver tests may result in high false-positive rates and unnecessary discontinuation of a drug that might otherwise be beneficial.

Statins have been associated with autoimmune hepatitis in several case reports.[19–23] Clinical features in these case reports range from minimal fibrosis on biopsy with normalization of aminotransferases

**Table 2.** Drugs associated with drug induced liver injury (DILI)

| Author | Study design | *n* | Drugs (number of associated cases) |
|---|---|---|---|
| De Valle (2006) | Retrospective cohort<br>1995–2005<br>Out-patient acute DILI<br>Single centre, Sweden | 77 | 1. Diclofenac (14)<br>2. Flucloxacillin (8)<br>3. Azathioprine (5)<br>4. Atorvastatin (4)<br>5. Ciprofloxacin (4)<br>6. Macrolides (3)<br>7. Nitrofurantoin (2)<br>8. Clindamycin (2)<br>9. Disulfiram (2) |
| Andrade *et al.* (2005) | Prospective cohort<br>1994–2004<br>In-patient and out-patient acute DILI<br>Multicentre, Spain | 446 | 1. Amoxicillin/clavulanate (59)<br>2. Ebrotidine (22)<br>3. INH + RIP + PIZ (18)<br>4. Ibuprofen (18)<br>5. Flutamide (17)<br>6. Ticlopidine (13)<br>7. Isoniazid (9)<br>8. Medicinal herbs (9)<br>9. Nimesulide (9)<br>10. Carbamazepine (8)<br>11. Bentazepam (7)<br>12. Tetrabamate (7)<br>13. Azathioprine (6)<br>14. Erythromycin (6)<br>15. Paroxetine (6)<br>16. Valproic acid (5)<br>17. Trovafloxacin (5)<br>18. Thiamazole (5) |
| Galan *et al.* (2005) | Retrospective cohort<br>1993–2002<br>Acute non-fulminant drug-induced hepatitis<br>Out-patients referred to single tertiary centre, United States | 32 | 1. Amiodarone (7)<br>2. Amoxicillin/clavulanate (4)<br>3. Minocycline (4)<br>4. Nitrofurantoin (3) |
| Bjornsson (2005) | Retrospective cohort<br>1966–2002<br>Acute DILI leading to death<br>Multicentre, Sweden | 103 | 1. Halothane (16)<br>2. Paracetamol (12)<br>3. Flucloxacillin (7)<br>4. TMP-SMX (6)<br>5. Diclofenac (4)<br>6. Naproxen (3)<br>7. Ciprofloxacin (3)<br>8. Disulfiram (3)<br>9. Sulfonamides (3) |
| Abajo (2004) | Retrospective case–control<br>1994–1999<br>Acute DILI<br>Population-based registry, UK | 128 | 1. Amoxicillin/clavulanate (13)<br>2. Diclofenac (10)<br>3. Chlorpromazine (6)<br>4. Tetracycline (6)<br>5. Metoclopramide (5)<br>6. Flucloxacillin (4)<br>7. Sulfasalazine (4)<br>8. Erythromycin (4) |

Table 2. (*Continued*)

| Author | Study design | *n* | Drugs (number of associated cases) |
|---|---|---|---|
| Sgro *et al.* (2002) | Prospective cohort<br>1997–2000<br>In-patient and out-patient acute DILI<br>Primary care and referral practitioners in France | 34 | 1. Amoxicillin/clavulanate (4)<br>2. Nevirapine (3)<br>3. Atorvastatin (3)<br>4. Ibuprofen (2)<br>5. Fenofibrate (2) |
| Russo *et al.* (2004) | Retrospective cohort<br>1990–2002<br>Acute drug-induced liver failure leading to liver transplant<br>UNOS database | 270 | 1. APAP (124)<br>2. Isoniazid (24)<br>3. Prophylthiouracil (13)<br>4. Phenytoin (10)<br>5. Nitrofurantoin (7)<br>6. Herbal (7)<br>7. Ketoconazole(6)<br>8. Disulfiram(6)<br>9. Troglitazone(4)<br>10. Halothane, galuridine, sulfasalazine, combination of non-APAP drugs, methyldopa (3 each)<br>11. Nefazodone, labetalol, cerivastatin (2 each) |

Case definitions and sample population vary among studies. Only drugs associated with more than one case in each study are listed.

following treatment with prednisone alone[23] to a lupus-like syndrome with rash, hepatic failure and improvement only with institution of triple immunosuppressive therapy with tacrolimus, mycophenolate mofetil and prednisolone.[22] The cases reviewed by Alla *et al.* were associated with ALT elevation up to 10–20× ULN and jaundice despite discontinuation of statin therapy. Liver biopsies showed advanced fibrosis and all responded to treatment with prednisone and tacrolimus, azathioprine or mycophenolate mofetil. Among four patients in whom HLA typing was available, all four were positive for HLA-DR3, DR4 or DR7.[19] The overall incidence of autoimmune hepatitis due to statins is rare; however, the diagnosis should be considered when aminotransferase elevation is associated with jaundice or other autoimmune features (elevated antinuclear antibody or antismooth muscle antibody titres, skin rash), or when liver test elevations persist despite discontinuation of a statin.

## Safety of statins in patients with underlying liver disease

There is no clear evidence to date that suggests that patients with underlying liver disease are at increased risk for hepatotoxicity from statins. The early statin trials excluded patients with abnormal baseline liver chemistry tests, which led to uncertainty regarding the initiation of statins in patients with underlying liver disease. In a case–control study, Chalasani compared rates of aminotransferase elevation following initiation of statin therapy among patients with normal and abnormal baseline aminotransferases. When patients with elevated baseline liver tests were compared to patients with normal baseline levels, the incidence of elevations in liver enzymes was higher. However, when patients with elevated baseline liver tests treated with statins were compared to a third group of patients with elevated baseline tests who were **not** started on a statin, there was no difference in liver enzyme elevations.[24] This suggested that patients with underlying liver disease have regular fluctuations in their liver tests, and that there is no increased risk of hepatotoxicity with statin use in patients with underlying liver disease. Another recently published case–control study based on Dallas Heart Study participants supports the safety of statin use in patients with underlying hepatic steatosis.[25] Safety of statins in patients with underlying hepatitis C (HCV) infection has also been demonstrated in a recent Veterans Adminstration-based study, where there was no difference in moderate or severe aminotransferase elevations

among patients with HCV who were administered statins when compared to patients without HCV who were administered statins.[26] The existing evidence suggests that statins should not be withheld in patients with underlying chronic HCV or NAFLD when there is a clear indication for statin use.

Statins have been shown to be safe in patients following liver transplantation,[27] in whom the prevalence of hyperlipidaemia ranges from 16% to 43%.[28] Caution is advised regarding potential interactions between statins and other drugs that are metabolized by the CYP3A4 system, including ciclosporin. Of all the statins, pravastatin is not extensively metabolized by the CYP3A4 system, whereas atorvastatin, lovastatin and simvastatin are metabolized by CYP3A4.[29] Although hyperlipidaemia associated with primary biliary cirrhosis (PBC) has not been shown to be associated with an increased risk of atherosclerosis,[30, 31] small studies have demonstrated the safety of statins in patients with underlying PBC to treat hypercholesterolaemia.[32]

### Role of liver chemistry test monitoring

Current recommendations advocate monitoring of liver chemistry tests at 12 weeks following initiation of statin therapy and at least annually thereafter.[33] The utility of periodic liver chemistry test monitoring in patients treated with statins has been challenged by a recent expert panel[34] as well as others.[14, 15, 35, 36] Routine monitoring of liver tests are unlikely to predict rare idiosyncratic toxicity, and premature termination of statins may deprive patients who would otherwise benefit from their use. Furthermore, limited studies suggest additional benefit of statins in patients with underlying liver disease beyond cardiovascular effects. A few pilot studies have shown improved histology in patients with non-alcoholic steatohepatitis (NASH) treated with statins.[37, 38] In addition, a recent study showed *in vitro* evidence of anti-viral activity of statins in a model of HCV replication when used in conjunction with interferon.[39] Statins may also have beneficial immunomodulating effects in transplanted patients, although this is debatable.[40, 41]

### Other lipid-lowering agents

Ezetimibe (Zetia) inhibits intestinal uptake of cholesterol and has been used alone or in conjunction with other lipid-lowering agents (Vytorin) for management of hyperlipidaemia. Clinical trials of ezetimibe in conjunction with statins demonstrated a higher (1.3%) rate of aminotransferase elevation (>3× ULN) compared with statins alone (0.4%).[42] Two non-fatal cases of hepatotoxicity with ezetimibe used in conjunction with simvastatin have been reported recently.[43] Cholestatic hepatitis was described in one patient and a steroid-responsive autoimmune hepatitis was described in another. Prior to these reports, no reports of symptomatic hepatotoxicity had been reported among clinical trials of ezetimibe monotherapy in 666 subjects[44] and combination ezetimibe–statin in 379[45, 90], 900[46] and 305[47] subjects. To our knowledge, no trials to date have explored the safety of ezetimibe in patients with underlying liver disease. While all of the lipid-lowering agents have been associated with some degree of hepatotoxicity, sustained release niacin is worth mentioning due to its association with a high rate of symptomatic hepatoxicity including fulminant hepatic failure and thus should be avoided.[48, 49] Therefore, substitution of other lipid-lowering agents in place of statins does not necessarily obviate the risk of hepatotoxicity.

## THIAZOLIDINEDIONES

The TZDs are a class of insulin-sensitizing drugs used to treat diabetes mellitus through activation of the gamma isoform of the peroxisome proliferator-activated receptor (PPAR$\gamma$). TZDs lower serum glucose and insulin levels, improve peripheral glucose uptake, and decrease triglyceride levels. Troglitazone, the first approved TZD, was withdrawn from the market in 2000 following 94 reported cases of liver failure.[50] An idiosyncratic mechanism of toxicity was suggested based on the delayed (3–7 months) onset of ALT elevation and a lack of dose effect. Rosiglitazone and pioglitazone, so-called second-generation TZDs, were introduced into the market by the time troglitazone was withdrawn. In early clinical trials of rosiglitazone and pioglitazone, rates of AST elevation >3 times the ULN were no different compared with placebo. Since then, case reports of hepatotoxicity with both pioglitazone[51, 52] and rosiglitazone[53–55] have been published, including one report of fulminant hepatic failure with pioglitazone,[56] one case of granulomatous hepatitis with rosiglitazone[57] and one case of fatal liver failure with long-term rosiglitazone use.[58] All but one of the patients recovered following discontinuation of the drug. Baseline and periodic monitoring of liver chemistry tests during therapy with rosiglitazone and pioglitazone is advised by the

manufacturers, along with recommendations to discontinue the drug if ALT levels remain >3 times the ULN or if jaundice occurs.[59, 60] Use of rosiglitazone and pioglitazone in patients with a history of toxicity to troglitazone is not advised; however, it is somewhat debatable whether a true class effect exists.[61]

### Safety in underlying liver disease

TZDs may show some promise in the treatment of NAFLD, a condition which is increasing in prevalence and for which no definitive pharmacological therapies are available.[62] Pilot studies have demonstrated both biochemical and histological improvement in patients treated with TZDs for NASH.[63–67] A total of 94 patients received either roziglitazone or pioglitazone in these studies for a duration of 6 months to 48 weeks. Of these, two patients developed increase in ALT requiring discontinuation. Chalasani followed 210 diabetics with elevated baseline aminotransferases (ALT 1–2.5× ULN) who received rosiglitazone for 12 months and noted no increased incidence of liver chemistry test elevations (10-fold elevation compared with baseline) when compared to diabetics with normal liver enzyme tests at baseline.[68] In a pooled study of Phase 2/3 trials of rosiglitazone in Type 2 diabetic patients, the incidence of ALT elevation >3× ULN was 1.4% in patients with baseline ALT elevation (1.0–2.5× ULN) compared to 0.25% in patients with normal liver tests at baseline ($P = 0.01$). Conversely though, 83% of patients with elevated liver tests at baseline had a **decrease** in ALT while taking rosiglitazone.[69] The combined evidence suggests that TZDs are probably safe in patients with baseline liver chemistry abnormalities, and may actually improve liver tests due to an improvement in underlying fatty liver disease; however, it is still prudent to follow liver tests closely in patients treated with TZDs. There is not enough evidence to date to recommend long-term TZD therapy in NASH; however, TZDs should not be withheld in diabetics with minor LFT elevations (<2.5 ULN) in the setting of NASH, especially given the potential beneficial effects. Rosiglitazone (Avandia) has been used safely to treat diabetes mellitus in liver transplant patients.[70]

### Other antidiabetic agents: metformin

Metformin is an oral biguanide hypoglycaemic agent used in the treatment of non-insulin-dependent diabetes mellitus. Rare hepatotoxocity from metformin has been described in three case reports.[71–73] The case reports suggested an idiosyncratic mechanism, and both cholestatic and hepatocellular toxicity were described. Lactic acidosis is a rare complication associated with metformin use. The overall rate is 3–5 cases per 100 000 patient-years.[74, 75] Hepatic impairment is cited as a risk factor for lactic acidosis; however, pre-existing cardiac disease and renal insufficiency are more commonly implicated risk factors.[75] Metformin is probably safe in the setting of mild hepatic impairment (Child's Class A cirrhosis) and should not be withheld in patients with liver disease who have clear indications for its use. However, metformin should be avoided in patients with significant hepatic impairment (Child's B or C cirrhosis) due a potential increased risk of lactic acidosis.

## ANTIRETROVIRALS

The overall incidence of hepatotoxicity in patients receiving antiretroviral therapy (ART) ranges from 3% to 18%.[76, 77] The incidence of irreversible liver failure leading to death or liver transplantation is uncommon though, and varies in the literature from 1.1 per 1000 person-years to 1.1 per 100 person-years.[78, 79] Hepatoxicity as defined by aminotransferase elevation is generally classified according to a standardized grading system developed by the AIDS Clinical Trials Group.[80] In clinical trials, significant hepatotoxicity often refers to Grade 3 (5.1–10× ULN) or Grade 4 (>10× ULN) elevations in AST and ALT. Patients with elevated pre-treatment AST and ALT, as seen in individuals co-infected with HBV and HCV, are classified based on changes relative to baseline liver tests rather than ULN. All three classes of ART, nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI) have been associated with hepatotoxicity. Some of the more common associations between antiretroviral drugs and hepatotoxicity are described below and are summarized in Table 3.

### Protease inhibitors

All PIs are metabolized by the cytochrome P450 3A4 system and have been associated with hepatotoxicity. Currently approved PIs include indinavir (Crixivan), nelfinavir (Viracept), amprenavir (Agenerase), ritonavir (Norvir), saquinavir (Fortavase), lopinavir/ritonavir (Kaletra) and fosamprenavir (Lexiva). Newer PIs include atazanavir (Reyataz), tipranavir (Aptivus) and

**Table 3.** Antiretrovirals used to treat HIV and specific precautions with regard to hepatotoxicity, as organized by class

| Antiretroviral class | |
|---|---|
| Protease inhibitors | Precautions with regard to hepatotoxicity |
| Ritonavir (Norvir) | Hepatotoxicity with high-dose ritonavir (600 mg b.d.) |
| Lopinavir/Ritonavir (Kaletra) | Less hepatotoxicity with low-dose ritonavir (<200 mg b.d.) used in PI boosting regimens |
| Amprenavir (Agenerase) | Avoid combination amprenavir-ritonavir (competing CYP 450 3A4 metabolism) |
| Saquinavir (Fortavase) | Indirect hyperbilirubinaemia with indinavir and atazanavir. Avoid combination of indinavir with atazanavir |
| Indinavir (Crixivan) | Severe hepatotoxicity with tipranavir has been reported. Caution is advised with use of tipranavir in patients with underlying liver disease |
| Fosamprenavir (Lexiva) | |
| Nelfinavir (Viracept) | |
| Atazanavir (Reyataz) | |
| Tipranavir (Aptivus) | |
| Darunavir (Prezista) | |
| Nucleoside reverse transcriptase inhibitors (NRTI) | |
| Zalcitabine (ddC) | Lactic acidosis (especially with ddC, ddI, d4T) |
| Didanosine (ddi) | Avoid ddI–d4T combination |
| Stavudine (d4T) | Increased risk of lactic acidosis with ribavirin in conjunction with ddI or d4T |
| Lamivudine (3TC) | Avoid ribavirin–ddI combination in advanced fibrosis due to risk of hepatic decompensation |
| Zidovudine (AZT) | |
| Abacavir (Ziagen) | |
| Tenofovir (Viread) | |
| Abacavir/lamivudine/zidovudine (Trizivir) | |
| Abavavir/lamivudine (Epzicom) | |
| Non-nucleoside reverse transcriptase inhibitors (NNRTI) | |
| Nevirapine (Viramune) | Increased risk of hepatotoxicity with nevirapine in patients with HBV/HCV or in women with CD4 >350 or men with CD4 >400 |
| Efavirenz (Sustiva) | |
| Delavirdine (Rescriptor) | |

darunavir (Prezista). Among the PIs, high-dose ritonavir is associated with the highest incidence of hepatotoxicity, with most studies demonstrating a 3–9% incidence of severe hepatotoxicity.[81–84] Lower doses of ritonavir (<200 mg twice daily) used in boosting regimens have largely replaced high-dose ritonavir and have not been associated with increased hepatotoxicity[81, 85] except when used with amprenavir.[86] Tipranavir, a newer PI, has been associated with reports of severe hepatotoxicity.[87] A black box warning was issued in June 2006 warning of an increased risk of hepatitis and hepatic decompensation in patients taking tipranavir and ritonavir, especially in patients with HBV or HCV co-infection.

Both indinavir and atazanavir have been associated with asymptomatic indirect hyperbilirubinaemia due to competitive inhibition of bilirubin uridine diphosphate (UDP)-glucoronosyltransferase (UGT).[88, 89] Homozygosity for the UGT1A1*28 genetic allele associated with Gilbert's syndrome increases the risk of hyperbilirubinaemia from indinavir and atazanavir.[88] Another allele, UGT1A1*6, has been shown to be associated with hyperbilirubinaemia in Thai patients treated with indinavir.[90] Co-infection with viral hepatitis has not been associated as a risk factor for hyperbilirubinaemia in indinavir users.[91] Current guidelines recommend avoiding use of indinavir in combination with atazanavir.[86] Dose adjustments and contraindications to PI use in patients with underlying liver disease are outlined in Table 4.

## Nucleoside reverse transcriptase inhibitors

Nucleoside reverse transcriptase inhibitors include zalcitabine (ddC, Hivid), didanosine (ddI, Videx), stavudine (d4T, Zerit), lamivudine (3TC, Epivir), zidovudine

**Table 4.** Antiretrovirals which require dose adjustments or which should be avoided in patients with cirrhosis having moderate to severe hepatic impairment (Child Turcotte Pugh Class B-C). Adopted from (86)

| Antiretroviral | Usual dose | Dosing in hepatic impairment |
|---|---|---|
| Protease inhibitors | | |
| Amprenavir | 1400 mg b.d. | Avoid use in hepatic failure |
| Atazanavir | 400 mg q.d.s. | CTP Class B: 300 mg daily<br>CTP Class C: not recommended |
| Fosamprenavir | 1400 mg b.d. | CTP Class B: 700 mg b.d.<br>CTP Class C: not recommended |
| Indinavir | 800 mg q8h | Mild to moderate hepatic insufficiency: 600 mg q8h |
| Tipranavir | 500 mg b.d. with ritonavir 200 mg b.d. | CTP Class B and C: combination tipranavir/ritonavir is contraindicated |
| NNRTIs | | |
| Nevirapine | 200 mg b.d. | Avoid use in moderate to severe hepatic impairment |

(AZT, Retrovir), abacavir (Ziagen), emtricitabine (Emtriva) and tenofovir (Viread).

As a class, NRTIs have been associated with hepatic steatosis and lactic acidosis. The spectrum of hyperlactataemia associated with NRTIs ranges from asymptomatic mild lactate elevation to a rare but potentially fatal lactic acidosis syndrome (LAS). Asymptomatic hyperlactataemia without metabolic acidosis is common in HIV-infected patients (8–18%), is often transient, and is non-specific for current NRTI use.[92] Lactate levels are usually between 2 and 5 mM and significant injury is uncommon. This should be distinguished from LAS, which is characterized by lactate levels >5 mM, metabolic acidosis and liver dysfunction which can lead to death or the need for liver transplantation. Liver histology demonstrates mixed microvesicular and macrovesicular steatosis.[93, 94] The incidence of LAS is rare (1.3–3.9 cases per 1000 patient-years).[92] Mortality is high and approaches 100% in some series. Once LAS is identified, prompt discontinuation of NRTI is warranted.

The mechanism of NRTI-associated lactic acidosis is hypothesized to involve mitochondrial toxicity. *In vitro* studies demonstrate that mitochondrial polymerase gamma, the enzyme responsible for replication of mitochondrial DNA, is variably inhibited by NRTIs according to the following order: zalcitabine (ddC) > didanosine (ddI) > stavudine (d4T) > lamivudine (3TC) > zidovudine (AZT) > abacavir.[95] In theory, this might explain the higher rates of lactic acidosis observed with stavudine, zalcitabine and didanosine. Current recommendations advise against co-administration of didanosine and stavudine[86] due to an increased risk of lactic acidosis. Among HCV/HIV co-infected patients, administration of ribavirin in conjunction with didanosine or stavudine has been associated with mitochondrial toxicity and lactic acidosis.[96] Lesser rates of hepatotoxicity have been observed with abacavir, lamivudine and tenofovir.

## Non-nucleoside reverse transcriptase inhibitors

The NNRTI class of antiretroviral agents includes nevirapine (Viramune), efavirenz (Sustiva) and delavirdine (Rescriptor). Of these, nevirapine warrants particular attention with regard to hepatotoxicity. Nevirapine toxicity may manifest as a rash-associated hypersensitivity reaction (with or without concurrent hepatotoxicity) within the first few weeks of starting therapy in 2.3% of patients.[97] A second, late onset toxicity related to cumulative dose over time[98, 99] is more commonly observed than a hypersensitivity reaction.[81, 100] Rare cases of hepatic failure leading to liver transplantation and death[101] have been reported with nevirapine. Risk factors for hepatotoxicity include co-infection with HBV or HCV[99, 100] and higher CD4 counts associated with use in postexposure prophylaxis regimens. Current guidelines recommend avoiding nevirapine in women with CD4 counts >250 and in men with CD4 counts >400.[86]

Two studies demonstrate a significantly lower risk of hepatotoxicity with efavirenz-based regimens compared with nevirapine-based regimens,[100, 102] whereas another study showed no difference.[103] Efavirenz has been safely substituted in patients who developed hepatotoxicity with nevirapine, suggesting that hepatotoxicity due to nevirapine is not class-specific.[104]

Less data are available with delvirapine; however, one study suggests at least a similar safety profile compared with efavirenz.[103]

## Role of hepatitis C and hepatitis B

The prevalence of co-infection with HBV and HCV among persons with HIV is 10–15% and 30–50%, respectively. HBV and HCV co-infection is an independent risk factor for ART-associated hepatotoxicity and is associated with a greater than twofold risk of ART-associated aminotransferase elevation.[91, 105–107] A large, Veterans Administration-based cohort study demonstrated a twofold increased risk of fulminant hepatic failure in patients co-infected with HCV and HIV when compared with HIV alone.[78]

Aminotransferases should be monitored closely in patients treated for HIV/HBV or HIV/HCV co-infection. An elevation in liver chemistry tests should not only raise suspicion of drug toxicity, but should also prompt an evaluation to rule out causes associated with viral hepatitis, including immune reconstitution in the setting of HCV co-infection, and HBV flares following discontinuation of emcitritabine, lamivudine or tenofovir (these have activity against HBV as well as HIV). Drug combinations which should be avoided in HCV co-infected persons undergoing treatment for HCV include didanosine–ribavirin (increased risk of lactic acidosis) and zidovudine–ribavirin (increased risk of anaemia).[86] ARTs which require dose adjustments or which should be avoided in cirrhotic patients having moderate to severe hepatic impairment (Child Turcotte Pugh Class B–C) include nevirapine, amprenavir, atazanavir, fosamprenavir, indinavir and tipranavir. Recommendations are summarized in Table 4.

## HAART in liver transplant patients

The success of HAART has led to longer survival of individuals with HIV and the emergence of end-stage liver disease as a leading cause of death among HIV-infected persons.[108] Once thought to be contraindicated in individuals with HIV, liver transplantation is now performed in carefully selected HIV-positive individuals. PIs and NNRTIs both inhibit and induce cytochrome P450 enzymes, whereas NRTIs are not metabolized by P450 enzymes. This is important in liver transplant recipients who commonly receive calcineurin inhibitor-based immunosuppression regimens using ciclosporin or tacrolimus, which are metabolized by cytochrome CYP3A4. Literature describing interactions between HAART and immunosuppression regimens in liver transplant patients is limited to small case series describing patients on mostly NRTI- and PI-based HAART regimens. Among the PIs, nelfinavir and combination lopinavir/ritonavir in particular have been reported to increase tacrolimus levels.[109–111] Transplanted individuals taking both tacrolimus and PIs may require up to a 10- to 50-fold reduction in tacrolimus dosing to maintain therapeutic levels. Vigilant monitoring of tacrolimus levels following cessation of HAART therapy is important. Acute withdrawal of a PI can result in a sudden decrease in tacrolimus concentration followed by graft loss if timely dose adjustments are not made.[112] Nelfinavir has been shown to increase sirolimus levels in an HIV-positive individual who underwent liver transplantation.[109] Less is known about interactions between HAART therapy and other immunosuppression regimens. NRTI-based regimens in co-infected liver transplant patients should avoid use of zalcitabine (ddC), didanosine (ddI) or stavudine (d4T).

## Recommendations

Liver tests should be monitored closely in all patients commencing ART. The first 4–6 weeks following initiation of therapy warrant vigilant monitoring for development of hypersensitivity reactions, when early diagnosis and discontinuation of the drug must be timely. Lactic acidosis occurs later during the course of therapy and may be either asymptomatic or, if accompanied by metabolic acidosis, potentially fatal. A liver biopsy demonstrating microvesicular steatosis may support evidence of NRTI-associated mitochondrial toxicity. Throughout the course of ART therapy, liver chemistry tests should be monitored regularly. Any increase in aminotransferases should prompt a search to exclude all causes of hepatotoxicity, especially concurrent HBV/HCV infection and other prescription or non-prescription (i.e. herbal or alternative) medications. In general, a threshold aminotransferase elevation of 5–10× ULN should prompt discontinuation of ART. Caution is warranted in patients co-infected with HBV and HCV, who have a higher risk of ART-associated hepatotoxicity, and who have underlying hepatic impairment. Nelfinavir and PIs in particular may interfere with tacrolimus levels in the HIV-positive liver transplant recipient. Individuals with HIV who undergo liver transplantation should

have vigilant monitoring of immunosuppression levels following initiation or discontinuation of HAART.

## ANTIBIOTICS

Antibiotics are a commonly implicated cause of DILI. A recent single US centre experience reported antibiotics as the class of drugs most frequently implicated in non-fulminant drug-induced hepatitis.[113] Amoxicillin/clavulanic acid, minocycline, nitrofurantoin, trimethoprim-sulfamethoxazole and trovafloxacin were the most frequently implicated antibiotics. Antibiotics were cited as the most frequent cause of DILI in a recent Spanish registry,[3] French study,[114] and United Kingdom study.[115] All forms of histological injury ranging from cholestasis (amoxicillin/clavulanic acid) to autoimmune hepatitis (minocycline) to ALF (telithromycin) have been described.

### Augmentin

Amoxicillin-clavulanic acid (augmentin) is the most frequently reported antibiotic associated with drug-induced hepatotoxicity.[3, 114, 115] The overall rate of symptomatic hepatitis due to amoxicillin-clavulanic acid is estimated at <1 in 100 000 persons exposed.[116] The typical pattern of hepatotoxicity is a cholestatic reaction that develops 1–4 weeks after cessation of therapy.[117–120] However, delayed onset of symptoms can be seen up to 8 weeks following discontinuation of therapy[118, 120] and prolonged cholestasis with ductopenia following cessation of therapy has also been described.[121] A recent large prospective case series involving 69 patients with amoxicillin-clavulanate hepatotoxicity suggested that the type of hepatic injury observed varies according to the time from onset of therapy, where hepatocellular injury predominates at 1 week, cholestatic injury at 2–3 weeks and mixed liver injury after 3 weeks. There was a 7% probability of an unfavourable outcome (death, liver transplant or persistent liver damage) and a 3% probability of a severe (death or liver transplantation) outcome in this series.[120] Immunological idiosyncrasy associated with certain HLA haplotypes may play a role in the pathogenesis.[122]

### Telithromycin (Ketek)

Telithromycin is the first FDA approved agent of the ketolide class of antibiotics. It was first approved in 2004 for use in respiratory tract infections, including pneumonia, sinusitis and bacterial exacerbations of chronic bronchitis. Ketolides are semisynthetic derivatives of macrolide antibiotics that have been designed to overcome macrolide resistance. Rates of aminotransferase elevation >3 times the ULN associated with telithromycin are 2% and the reported rate of reversible hepatitis is 0.07%.[123]

In January 2006, three reported cases of severe hepatotoxicity occurring with telithromycin[124] prompted the FDA to issue a label revision warning regarding potential severe liver injury. The case reports describe three patients who developed jaundice and elevated liver enzyme tests within 2–7 days of starting telithromycin. In one case, liver chemistry tests rose to over 10 times the ULN and normalized within 8 weeks after stopping therapy. A second case required orthotopic liver transplantation and a third patient died. Three additional cases have been reported to the FDA Medwatch. A recent editorial compared the reporting rate of ALF with telithromycin as being greater than trovafloxacin and troglitazone, and similar to rates reported with bromfenac.[125] Telithromycin remains on the market at the time of this writing. A label update by the FDA in February 2007 removed bronchitis and sinusitis as indications for its use in the setting of safety concerns. It is now indicated only for community acquired pneumonia.

## TOXICOGENOMICS

Hepatic biotransformation of drugs involves several steps which include oxidation by cytochrome P450 enzymes followed by conjugations through enzymes including *N*-acetyltransferase and glutathione transferase. Genetic polymorphisms among enzymes involved in drug metabolism account for some of the differences in individual susceptibility to drug hepatotoxicity. Certain HLA haplotypes may also predispose individuals to immune-mediated hepatitis. Polymorphisms which have been associated with an increased risk of drug hepatotoxicity are summarized in Table 5.

### Cytochrome P450

Ethnic variations in cytochrome P450 enzyme isotypes including CYP2D6 and CYP2C19[126] contribute to an interesting yet complex canvas from which to understand predictors of drug hepatotoxicity. CYP2D6 deficiency has been associated with perhexiline hepatotoxicity, is inherited in an autosomal recessive

**Table 5.** Select examples of genetic polymorphisms associated with a possible increased risk of hepatoxocity from specific drugs

| Enzyme/HLA allele | Prevalence | Drug associated with hepatotoxicty |
|---|---|---|
| CYP 2D6 deficiency | 8–10% Europe<br><2% Chinese, Japanese, African American | Perhexiline[127] |
| CYP 2C19 deficiency | 3–5% Caucasians<br>20% Asians | ATRIUM[130]<br>Troglitazone[131] |
| *N*-Acetyltransferase: slow acetylator phenotype | 50% Whites<br>41% African-American<br>20% Chinese<br>8–10% Japanese<br>92% Egyptian | Sulfonamides[135]<br>Hydralazine[138]<br>Isoniazid[151] |
| HLA A11 | | Amitryptillline, diclofenac, halothane[144] |
| HLA DR6 | | Chlorpromazine[144]<br>Nitrofurantoin[152] |
| HLA DRB*1501 | | Amoxicillin/clavulanate[122, 142] |
| HLA DR3, DR4, DR7 | | Statins[19] |

manner and is characterized by a phenotype of poor metabolization of debrisoquine.[127] The prevalence of the poor metabolizer phenotype is 5–10% in Europe[128] and ethnic variation among 20 genotypes has been described.[129] CYP2C19 deficiency has been implicated in Atrium hepatotoxicity[130] and troglitazone hepatotoxicity.[131] A recent Taiwan-based study demonstrated a higher risk of isoniazid hepatitis in wild-type CYP2E1 c1/c1 homozygotes compared with CYP2E1 c2/c2 or c2/c1 mutant genotypes.[132]

## Acetylation

Polymorphisms in the gene encoding *N*-acetyltransferase (NAT2) are responsible for the phenotypic classification of individuals as either slow acetylators (individuals with two defective NAT2 alleles) or rapid acetylators (those who are heterozygous or homozygous for wild-type NAT2). Ethnic variation in specific NAT2 mutations has been described.[133] Prevalence of the rapid acetylation phenotype is 30–60% in Western Europe and over 70% in Asia.[134] Slow acetylator status of NAT has been demonstrated to correlate with sulfonamide hepatotoxicity,[135–137] hydralazine hepatotoxicity[138] and isoniazid hepatotoxicity.[132, 139–141]

## HLA haplotypes

HLA haplotypes which have been associated with drug-induced idiosyncratic hepatotoxicity are summarized in Table 5. In particular, amoxicillin/clavulanate has been shown in two studies to be associated with HLA DRB*1501.[122, 142] As noted earlier, recently reported cases of autoimmune hepatitis presumed due to statin use were associated with HLA-DR3, DR4 or DR7.[19] HLA associations with drug hepatotoxicity appear to be specific to particular drugs rather than with drug hepatotoxicity in general;[143, 144] however, one study showed an increased frequency of DRB1*15 and DQB1*06 alleles in individuals with cholestatic/mixed liver damage compared with healthy controls.[143]

## Multifactorial contributors

The association between acetylator status and CYP2E1 genotype with isoniazid hepatotoxicity[132] demonstrates compound effects of different steps involved in drug metabolism. It is this same presence of different steps in metabolism that makes it difficult to identify genetic mutations that significantly contribute to drug hepatotoxicity. Genes which in theory might predict hepatotoxicity often do not translate to *in vivo* findings,[145, 146] likely due in part to polygenic determinants where different steps are involved.[147, 148] In addition, toxicity which is well described in one organ system may not translate to another system. For example, thiopurine methyltransferase deficiency status predicts haematological toxicity with azathioprine but not has not been demonstrated to predict hepatotoxicity.[149, 150] Continued efforts in defining inherited determinants of drug hepatotoxicity may eventually

pave the way towards tailored therapy and monitoring for toxicity.

## CONCLUSIONS

Drug-induced hepatotoxicity will remain a problem that carries both clinical and regulatory significance as long as new drugs continue to enter the market. Unfortunately, recognizing toxicity of specific drugs is limited by the relatively rare overall incidence of hepatotoxicity as well as underreporting. Models of toxicity and genomic predictors hold potential promise in preventing toxicity before it occurs. Collaborative efforts such as the Drug-induced Liver Injury Network[6] and Acute Liver Failure group may help contribute to our current understanding of hepatotoxicity associated with drugs. Administration of drugs in patients with underlying liver disease involves a balanced assessment of risk benefit ratio that may in fact favour judicious use when clear indications are present, as in the case of statins. Careful monitoring for drug interactions is especially important in patients who have undergone liver transplantation.

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