



Brief Clinical Observation

Atorvastatin associated liver disease

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Abstract

Atorvastatin, a HMG-CoA reductase inhibitor, is widely used in the treatment of dyslipidaemia. A transient rise in serum transaminases occurs in up to 3% of patients using atorvastatin but this is usually self-limiting and inconsequential. Recent literature has indicated some potential for more serious but rare idiosyncratic reactions related to this drug.

Seven patients with significant liver dysfunction from one centre during 2002–2005 are reported, with one death, that raises some concern over the safety of atorvastatin. A total of seven other patients are reported in the literature. The 14 patients were usually over 60 years, had a female:male ratio of 2:1 and showed a mixed cholestatic/hepatocellular reaction. The mean interval to onset of reaction was approximately 9 weeks and the liver often took several months to recover. Three deaths occurred.

Adverse drug reaction reports from the UK Committee on Safety of Medicines reveal that four deaths due to hepatobiliary disease (0.5 deaths per annum) have been reported in association with atorvastatin treatment over 8 years. Simvastatin has had no hepatobiliary-related fatalities reported over 15 years.

While acute hepatotoxicity with atorvastatin remains uncommon, any persistent abnormality in liver function should be treated with caution. © 2006 Editrice Gastroenterologica Italiana S.r.l. Published by Elsevier Ltd. All rights reserved.

Keywords: Atorvastatin; Hepatitis; Statins; Toxic

1. Introduction

Atorvastatin, a widely used HMG-CoA reductase inhibitor, has proven benefit in the treatment of dyslipidaemia. It was first licensed in the UK in 1997 and prescriptions in Scotland have increased rapidly from 0.44 million prescriptions in the year ending March 2002 to 0.91 million prescriptions in the year ending March 2005 [1]. All statins can induce asymptomatic mild elevation of serum transaminases with an incidence quoted between 1% and 1.5% but this rarely requires withdrawal of therapy [2,3]. The elevation of serum transaminases is often self-limiting and thought to relate to alteration of the hepatocyte cellular membrane with enzyme leakage rather than direct liver injury. Only 3% of patients with early, minor elevation in

serum transaminases experience a subsequent persistent elevation of greater than three times the upper limit of normal [4]. However, recent literature has raised concern over occasional more serious hepatotoxicity related to atorvastatin [5,10]. The vital importance of clinical case reports in the early detection of serious adverse drug reactions is again emphasised [11].

This paper reports our personal experience of seven patients with significant liver dysfunction related to atorvastatin and reviews similar case reports in the medical literature.

2. Patients

Acute and chronic liver diseases resulting from other causes were excluded in all seven patients (except where stated) by finding normal serum ferritin, albumin, immunoglobulins, alpha-1 antitrypsin, normal prothrombin

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Table 1
Atorvastatin hepatotoxicity: details of patients in this report

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age	78	63	50	73	73	78	73
Sex	Male	Female	Female	Female	Female	Female	Female
Peak bilirubin (<i>N</i> : <18 $\mu\text{mol/l}$)	184	10	33	59	688	26	17
Peak ALP (<i>N</i> : <280 U/l)	1328	1138	727	1096	410	1935	433
Peak AST (<i>N</i> : <40 U/l)	175	108	76	133	1703	138	256
Atorvastatin dose (mg/day)	20	10	20	10	10	80	10
Drug exposure to onset of reaction (weeks)	3	4	12	5	52	1	10
Duration of reaction (months)	10	1	3	>12	1	4	2
Liver histology	Cholestasis	–	–	–	Hepatitis	Cholestasis	–
Outcome	Resolved	Resolved	Resolved	Persistently abnormal LFTs	Died	Resolved	Resolved except GGT
RUCAM score	8	8	5	8	4	9	8

time, negative viral serology (IgM anti-HAV, HBsAg and anti-HCV, with IgM anti-HBc if thought appropriate) and negative liver autoantibodies. Ultrasound examination ruled out biliary obstruction in each case. Complete drug histories are given. One UK unit of alcohol is 8 g. A summary of patients is given in Table 1.

3. Case 1

A 78-year-old male presented with a 10-day history of jaundice, pale stools, dark urine and pruritus. His past medical history included hypertension, ischaemic heart disease, hypercholesterolaemia, polymyalgia rheumatica and renal calculi. Drugs on admission were atenolol, clopidogrel, isosorbide mononitrate, lansoprazole, prednisolone and atorvastatin 20 mg daily. His atenolol, clopidogrel and atorvastatin had been started 1 month prior to presentation. He denied any recent antibiotic use and drank only 7 units (56 g) of alcohol per week. On examination, apart from obvious jaundice, there were no abnormal clinical signs.

Liver function tests (LFTs) showed bilirubin 133 $\mu\text{mol/l}$, alkaline phosphatase (ALP) 1328 U/l, gamma-glutamyl transpeptidase (GGT) 523 U/l, AST 175 U/l and albumin 40 g/l. Serum immunoglobulin A (IgA) was slightly increased at 5.2 g/l. Abdominal ultrasound and computerised tomography revealed a thick-walled gallbladder with multiple calculi. ERCP was performed with a normal biliary tree demonstrated.

His LFTs remained abnormal 4 weeks after admission despite these investigations and liver biopsy was therefore performed. This revealed non-specific cholestasis with distended bile canaliculi, feathery hepatocyte degeneration and a single focus of hepatocyte necrosis.

Atorvastatin was thought to be the most likely cause for the hepatic reaction and this was discontinued along with his clopidogrel 2 weeks after initial presentation. LFTs slowly improved over the following months and had normalised at follow-up 10 months after initial presentation.

4. Case 2

A 63-year-old female with a history of osteoarthritis and peptic ulcer disease was found to have hypercholesterolaemia. Current medication included coproxamol (which had been used for years) and omeprazole. She had no history of previous liver disease and only rarely consumed alcohol. Clinical examination revealed no signs of chronic liver disease. She was started on atorvastatin 10 mg daily. LFTs at baseline were entirely normal, although there was some mild derangement when tested 1 month later, with a raised ALP of 299 U/l and raised GGT of 55 U/l.

At 2 months, her LFTs were found to be more markedly deranged. ALP had risen to 1138 U/l, with GGT of 312 U/l, AST 102 U/l, ALT 139 U/l and bilirubin was normal.

Atorvastatin was discontinued as this was suspected to be the cause of her liver dysfunction. The patient was also advised to discontinue coproxamol. LFTs 1 month after discontinuation of atorvastatin therapy were normal.

5. Case 3

A 50-year-old female with hypertension treated with ramipril was found to have hypercholesterolaemia. She was started on atorvastatin 20 mg daily. Unfortunately, LFTs were not checked prior to commencement of her statin. Three months after starting atorvastatin she had an ALP of 439 U/l, GGT 584 U/l, AST 45 U/l, ALT 104 U/l and bilirubin 32 $\mu\text{mol/l}$. These continued to worsen, leading to the discontinuation of both ramipril and atorvastatin at 4 months. There was no history of abdominal pain or fever and no signs of chronic liver disease. She drank two bottles of wine per week.

LFTs 2 months after stopping the atorvastatin revealed an ALP of 727 U/l, GGT 847 U/l, AST 76 U/l, ALT 139 U/l and bilirubin of 11 $\mu\text{mol/l}$. She had a slightly raised serum IgA (5.4 g/l), a raised serum ferritin (639 ng/ml) and was heterozygous for the *HFE* gene (Cys282Tyr).

The patient was reviewed at 4 and 6 months after stopping atorvastatin and her LFTs had normalised. It was felt at this stage that her previous liver dysfunction was in keeping with a drug reaction to atorvastatin.

6. Case 4

A 73-year-old female was admitted to hospital with a 2-day history of nausea, jaundice, pale stools and pruritus. She had an extensive past medical history including chronic renal failure, ischaemic heart disease, recent coronary angioplasty, hypercholesterolaemia and depression.

She only drank alcohol occasionally and her medication included aspirin, atenolol, bumetanide, nicorandil, ramipril and spironolactone. She was also on atorvastatin 10 mg daily, having commenced the statin 5 weeks prior to admission when LFTs were normal. On examination, she was icteric and apyrexial. There were no signs of chronic liver disease.

LFTs on admission were bilirubin 58 $\mu\text{mol/l}$, ALP 1096 U/l, GGT 309 U/l and AST 125 U/l. Abdominal ultrasound revealed gallbladder stones but no biliary obstruction. Her liver derangement was presumed to be due to her atorvastatin and this was discontinued.

Subsequent follow-up at clinic has shown slow and steady resolution of her LFTs and 1 year later they were normal apart from ALP of 665 U/l and GGT of 223 U/l. At 3 years the LFTs are normal.

7. Case 5

A 73-year-old female was admitted as an emergency with a history of jaundice for 1 week. Her past medical history included ischaemic heart disease, hypertension, peripheral vascular disease, hypercholesterolaemia and osteoarthritis. She had no past history of liver disease.

Medication on admission included amlodipine, aspirin, bendrofluzide, coproxamol (taken for 3 years), doxazosin, gaviscon, lansoprazole and ramipril. She was also taking atorvastatin 10 mg daily which had been commenced 12 months earlier and LFTs checked prior to statin therapy had been normal. LFTs performed 5 months after commencing atorvastatin were mildly abnormal with a bilirubin 15 $\mu\text{mol/l}$, ALP of 286 U/l, GGT 114 U/l and AST 49 U/l.

On examination she was deeply jaundiced, with no signs of chronic liver disease.

LFTs on admission were grossly deranged with bilirubin 401 $\mu\text{mol/l}$, ALP 465 U/l, GGT 202 U/l, AST 1375 U/l, ALT 1355 U/l and albumin of 35 g/l. Prothrombin time was prolonged at 15 s.

Her coproxamol and atorvastatin were discontinued as there was concern that this may be a drug-related hepatitis.

Over the next 3 weeks her bilirubin and prothrombin time continued to deteriorate. Transjugular liver biopsy revealed an acute hepatitis with lobular disarray and swelling of hep-

atocytes. There was a mononuclear cell infiltrate, occasional acidophils and large areas of recent necrosis. Unfortunately, the patient died of acute liver failure 23 days after admission.

8. Case 6

A 78-year-old female was admitted with an uncomplicated acute myocardial infarction. Her baseline LFTs were normal and she was switched from simvastatin to atorvastatin 80 mg daily.

Her past medical history included coeliac disease, hypertension, optic nerve atrophy and paroxysmal atrial fibrillation. Other medication included aspirin, atenolol, nicorandil, omeprazole and warfarin.

LFTs 1 week later showed bilirubin 10 $\mu\text{mol/l}$, AST 109 U/l, ALT 201 U/l, ALP 1134 U/l and GGT 286 U/l. Her atorvastatin and warfarin were discontinued and LFTs gradually resolved to normal at 4 months. Liver biopsy was performed and showed cholestatic features and minimal inflammation. This was felt to be compatible with atorvastatin-induced cholestasis.

9. Case 7

A 73-year-old female was commenced on atorvastatin 10 mg daily after uncomplicated inferior myocardial infarction. Other medical history included hypertension, osteoporosis and previous cerebrovascular disease and medication consisted of aspirin, coproxamol, metoprolol and ramipril.

LFTs prior to commencing atorvastatin were normal except GGT 99 U/l. She took no alcohol. Blood tests at 10 weeks showed bilirubin 17 $\mu\text{mol/l}$, AST 256 U/l, ALT 289 U/l, ALP 433 U/l and GGT 1123 U/l. Autoantibodies revealed a positive smooth muscle antibody. Her atorvastatin was discontinued and LFTs had returned to normal, except for GGT at 306 U/l, when rechecked 2 months later.

10. Current data for statin use and adverse event reporting in UK

Data provided by the Information and Statistics Department of NHS Scotland illustrate the wide use of statins in current clinical practice [1]. Simvastatin is the most commonly prescribed statin in Scotland (population 5.1 million) with 1.62 million prescribed units per annum in the year ending March 2005. Atorvastatin is the second most commonly prescribed statin with pravastatin third and fluvastatin fourth (0.91, 0.38 and 0.03 million units in the same period, respectively). The annual cost of atorvastatin prescriptions in Scotland was £33.4 million in 2004/2005. Similar figures are available for the UK as a whole [12].

Data on suspected adverse drug reaction reports from the UK Committee on Safety of Medicines (CSM) reveal that

Table 2
Features of statin-associated adverse hepatic events

	Atorvastatin	Simvastatin	Pravastatin	Fluvastatin
First adverse reaction report ^a	April 1996	December 1988	July 1990	February 1994
Number of years of adverse reporting	8	15	14	10
Abnormal LFTs	98	125	28	12
Cholestasis and jaundice				
Cholestasis	3	4	1	0
Hepatitis cholestatic	0	2	0	0
Jaundice NOS ^b	24	29	3	7
Jaundice cholestatic	7	14	2	1
Hepatocellular damage				
Hepatic necrosis	0	1	1	0
Hepatic steatosis	2	6	0	0
Hepatitis NOS ^b	17	25	4	3
Hepatitis acute	2	2	1	2
Hepatitis fulminant	0	1	0	0
Hepatic failure	2	3	1	0
Hepatorenal syndrome	0	1	1	0
Deaths	4	0	1	0

Summary of data obtained from the UK CSM. This data has not been corrected for usage or any other reporting biases.

^a Data from the CSM ADROIT database collected between 1 July 1963 and 1 July 2004.

^b Not otherwise specified.

four deaths due to hepatobiliary disease have been reported in association with atorvastatin treatment since the first adverse event 8 years ago was reported for this statin. Simvastatin has had no hepatobiliary-related fatalities reported over 15 years. Pravastatin has had one death reported secondary to hepatorenal syndrome. Suspected adverse hepatobiliary reactions due to statins, reported to the CSM, are summarised in Table 2.

11. Discussion

There is good evidence for the value of HMG-CoA reductase inhibitors in the treatment of dyslipidaemias, and significant reduction in morbidity and mortality is obtained in patients with coronary heart disease [13]. Atorvastatin was initially licensed for use in the UK in 1997 and is now widely used in primary care and hospital settings. Previous litera-

ture has shown it to be generally well tolerated with minimal adverse events. However, this report describes seven patients who appear to have had significant liver dysfunction secondary to atorvastatin therapy, with three patients requiring hospitalisation and one death (Table 1).

A review of published literature also revealed serious hepatotoxicity in seven other patients (Table 3) and reflect our own clinical experience with two fatalities and the other five cases improving on withdrawal of treatment [5–10]. The 14 patients tended to be over 60 years, had a female:male ratio of 2:1 and showed a mixed cholestatic/hepatocellular picture. Six patients had a marked hyperbilirubinaemia (>100 µmol/l) and there were three deaths with a hepatocellular reaction. The duration of exposure prior to hepatic toxicity was variable (mean 9.4 weeks, range 1–52 weeks) and the reaction would often last for several months before recovering. The dose of atorvastatin varied with six patients taking 10 mg daily, four patients taking 20 mg daily, one patient taking 30 mg daily

Table 3
Atorvastatin hepatotoxicity: details of patients from the previous literature

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age	83	65	69	70	20	57	63
Sex	Male	Female	Male	Female	Female	Female	Male
Peak bilirubin (µmol/l)	425	428	44	NR	140	584	18
Peak ALP (U/l)	393	NR	3767	591	669	156	216
Peak AST (U/l)	1312	992	669	151	869	596	241
Atorvastatin dose (mg/day)	20	NR	10	30	20	10	NR
Drug exposure to onset of reaction (weeks)	4	4	1	12	8	4	12
Duration of reaction (months)	2	NR	3	2	1	2	8
Liver histology	Cholestasis	–	–	Hepatitis	–	Cholestasis	Chronic hepatic process
Outcome	Died	Died	Resolved	Resolved	Resolved	Resolved except GGT	Resolved
References	[5]	[6]	[7]	[8]	[9]	[10]	[10]

NR, not reported.

and one patient taking 80 mg daily. Two patients did not have the atorvastatin dose reported [6,10].

A careful drug history is essential in the assessment of all patients presenting with acute liver disease and some of the patients described in our series were prescribed other medication that can also cause drug-related hepatotoxicity. Three patients had been taking regular coproxamol (a combination of paracetamol/dextropropoxyphene) for several years. There had been no hepatotoxicity earlier and while this can cause cholestasis, the timing was suggestive of atorvastatin hepatotoxicity.

Criteria for the diagnosis of drug-induced liver disorders were established following an International Consensus meeting reported in 1990 [14]. These criteria were further developed to produce the Roussel-Uclaf causality assessment method (RUCAM). This scoring system evaluates time to onset, course of reaction, risk factors, concomitant drugs, the search for non-drug causes, previous information on hepatotoxicity of drug and response to readministration [15]. The assessment produces a continuous score ranging from -5 to $+14$. A score of ≤ 0 excludes causality, $1-2$ is unlikely, $3-5$ possible, $6-8$ probable and >8 highly probable [16]. Our patients were scored using the RUCAM system (Table 1) with two possible cases, four probable cases and one highly probable cases.

The discontinuation of atorvastatin for all adverse events has been estimated at between 1% and 2% [3,4] with mild gastrointestinal disturbance the most common reported. Gastrointestinal symptoms include constipation, flatulence, dyspepsia and abdominal pain [3]. The frequency of mild gastrointestinal disturbance with atorvastatin is similar to the other statins [17]. Myalgia and depression have also been reported [4] but the most concerning toxicity is the potential risks of rhabdomyolysis (especially when used in conjunction with fibrates) [6,13,18] and liver dysfunction [4–8,13,19].

Black et al. [4] reported on safety data from 21 completed trials (2502 patients) and 23 ongoing trials (1769 patients) involving patients receiving atorvastatin for moderate-to-severe hypercholesterolaemia. Thirty out of 4271 patients (0.7%) had a persistent significant elevation in serum transaminases (greater than three times the upper limit of normal) across the dose range for atorvastatin. The majority of transaminase elevations occurred in the first 16 weeks of therapy. This incidence rose to 2–3% for the 80 mg daily dose. The rise in serum transaminases was not associated with age (younger/older than 70 years), sex, height, alcohol consumption, body mass index, final plasma LDL cholesterol or percentage reduction of LDL cholesterol. Interestingly, when compared to placebo, the incidence of ‘transaminitis’ in the 10–40 mg dose range of atorvastatin was found to be similar. They found that of 4271 patients, only two had had ‘serious events’ associated with therapy. One patient was admitted to hospital with pancreatitis and the second developed cholestatic jaundice with markedly elevated transaminases. Both patients recovered without sequelae on discontinuation of therapy.

The Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA) reported no difference in hepatic adverse events in 5168 hypertensive patients treated with 10 mg atorvastatin over 3.3 years when compared with 5137 controls receiving placebo [20]. A retrospective analysis of 44 completed clinical trials of 16,495 patients taking atorvastatin was reported by Newman et al. [21]. They reported persistent elevations of serum transaminases in 47 patients (0.5%) compared to five placebo controls (0.3%). They also saw a dose-related increase in the incidence of elevated serum transaminases (0.13%, 0.12%, 0.4% and 0.89% incidence for the 10, 20, 40 and 80 mg doses respectively).

Suspected adverse drug reaction reporting to the CSM (Table 2) is neither systematic nor comprehensive but is driven by individual practitioners observations. It should also be noted that numerical comparisons between different drugs can be misleading. This can be due to variation in the level of reporting (vigilance for, and reporting of, adverse events may be increased among practitioners using a newer agent in comparison to a more established drug) or differences in the overall usage of the different statins. With these considerations in mind, initial analysis of CSM data suggests a higher incidence of hepatobiliary dysfunction with atorvastatin in comparison to other statins, including infrequent deaths. Abnormal LFTs were reported in 98 patients on atorvastatin over 8 years compared with 125 patients in 15 years for simvastatin and 28 patients in 14 years for pravastatin. Simvastatin has had a greater numbers of hepatic adverse events reported in comparison to atorvastatin (Table 2). However, it should be noted that simvastatin reporting has been over 15 years in comparison to 8 years for atorvastatin and that simvastatin is the most commonly prescribed statin in the UK [1,12]. The medical literature also records only infrequent clinical hepatic toxicity with simvastatin [22].

The risk of a significant rise in serum transaminases while using statins, and in particular atorvastatin, is thought to be dose dependent [13,17]. In comparison to other statins (for which the $t_{1/2}$ for HMG-CoA reductase inhibition is generally less than 3 h), atorvastatin is significantly longer acting. It has been postulated that the longer exposure with atorvastatin could explain an increased risk of hepatotoxicity in comparison to other statins [17].

Dujovne [23] comments that recently published data on significant differences in elevation of serum transaminases between atorvastatin and simvastatin may reflect an increased risk of hepatotoxicity at higher doses of atorvastatin. However, he postulates that as atorvastatin has more pronounced activity in lowering serum low-density lipoprotein, this in turn could influence the structure of cellular membranes leading to greater leakage of cellular enzymes and increased incidence of ‘transaminitis’ without direct hepatotoxicity.

Atorvastatin is normally taken in a dose of 10–80 mg/day with 30% of the oral dose absorbed. It undergoes extensive first-pass metabolism and has a bioavailability of approximately 14%. It inhibits HMG-CoA reductase which converts HMG-CoA to mevalonic acid and this appears to be the

rate-limiting step in the formation of endogenous cholesterol [13]. All statins, including atorvastatin, undergo extensive microsomal metabolism by the cytochrome P450 (CYP) system. The CYP 3A4 isoenzyme is mainly responsible for the metabolism of atorvastatin, as well as simvastatin and lovastatin (the CYP 2C9 isoenzyme metabolises fluvastatin) [2,13]. Co-administration of drugs which interact with the CYP 450 system may significantly affect plasma concentrations and potential toxicity of statins. These include calcium channel antagonists, antifungals, macrolides, corticosteroids and amiodarone [2,13]. In our series, one patient was taking a calcium-channel antagonist and one was on long-term prednisolone.

The pathogenesis of atorvastatin-associated liver dysfunction is unclear. Some authors suggest that the induction of the CYP 450 system may be central to these adverse events and indeed, genetic polymorphisms in CYP 3A4 may reflect differences in drug reactions [2]. However, cross-toxicity with simvastatin (also dependent on CYP 3A4) does not appear to be a common phenomenon suggesting that another mechanism is at play. Nakad et al. [8] suggested an immunological basis for such hepatotoxicity and noted an eosinophil infiltrate on liver histology of a 70-year-old patient with atorvastatin-induced hepatitis.

Fatty liver has been demonstrated by ultrasonography in 50% of patients with hyperlipidaemia [24] and there has been concern that the risk of hepatotoxicity due to statins may be higher in patients with non-alcoholic fatty liver disease and abnormal baseline LFTs. However, a recent study demonstrated that individuals with elevated baseline LFTs had no significant increase in hepatotoxicity following the introduction of statin therapy [25]. None of our cases had a history of diabetes mellitus and ultrasound revealed increased echogenicity in only two cases (cases 5 and 7) which could reflect fatty change.

In conclusion, atorvastatin can rarely cause significant acute hepatotoxicity. These serious hepatic reactions tend to occur in females, over 60 years, and persistent elevation in serum transaminases in this group should prompt early review of the need to continue with atorvastatin therapy.

Conflict of interest statement

None declared.

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