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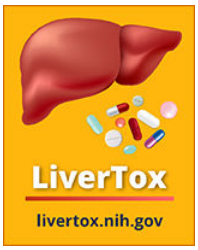



# Atorvastatin

Updated: December 1, 2021.

# OVERVIEW

## Introduction

Atorvastatin is a commonly used cholesterol lowering agent (statin) that is associated with mild, asymptomatic and self-limited serum aminotransferase elevations during therapy and rarely with clinically apparent acute liver injury.

## Background

Atorvastatin (a tor" va stat' in) is a potent, orally available inhibitor of hepatic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the major rate-limiting enzyme in cholesterol synthesis. Like other members of its class (the "statins"), atorvastatin lowers total serum cholesterol and low density lipoprotein (LDL) concentrations, thereby reducing the risk of atherosclerosis and its complications – myocardial infarction and stroke. Atorvastatin was approved for use in the United States in 1996 and has become one of the most commonly prescribed drugs in America, with more than 50 million prescriptions filled yearly. The current primary indication for atorvastatin is the treatment of hypercholesterolemia in persons at high risk for coronary, cerebrovascular and peripheral artery disease. Atorvastatin is available in tablets of 10, 20, 40 and 80 mg generically and under the trade name Lipitor. It is also available in combination with other cardiovascular agents such as amlodipine (Caduet and generics). The recommended dose is 10 to 80 mg once daily based upon tolerability and lipid levels. Common side effects include muscle cramps, headache, joint aches, abdominal pain, nausea, and weakness, symptoms that occur with all of the currently available statins. Rare but potentially severe adverse events include liver injury, myopathy, rhabdomyolysis, and immune-mediated necrotizing myopathy.

## Hepatotoxicity

Atorvastatin therapy is associated with mild, asymptomatic and usually transient serum aminotransferase elevations in 1% to 3% of patients but levels above 3 times ULN in less than 1%. In summary analyses of large scale studies with prospective monitoring, ALT elevations above 3 times the upper limit of normal (ULN) occurred in 0.7% of atorvastatin treated versus 0.3% of placebo recipients. These elevations were more common with higher doses of atorvastatin, being 2.3% with 80 mg daily. Most elevations were self-limited and did not require dose modification.

Atorvastatin is also associated with frank, clinically apparent hepatic injury but this is rare, occurring in ~1:3000 to 1:5000 treated patients. The clinical presentation of atorvastatin hepatotoxicity varies greatly from simple cholestatic hepatitis, to mixed forms, to frankly hepatocellular injury. The latency to onset of injury is also highly variable ranging from 1 month to several years. However, most cases arise within 6 months of starting atorvastatin or several months after a dose escalation. The most common presentation is a cholestatic hepatitis

that tends to be mild to moderate in severity and self-limiting in course (Cases 1 and 2). Atorvastatin hepatotoxicity can also present with a distinctly hepatocellular pattern of injury with marked elevations in serum aminotransferase levels and minimal or no increase in alkaline phosphatase. Rash, fever and eosinophilia are uncommon, but at least one-third of hepatocellular cases have features of autoimmunity, marked by high immunoglobulin levels, ANA positivity and liver biopsy findings of autoimmune hepatitis (Cases 3 and 4). These autoimmune cases usually resolve once atorvastatin is stopped, although they may require corticosteroid therapy for resolution. Strikingly, however, some cases of apparent autoimmune hepatitis caused by atorvastatin do not resolve with stopping the medication but are self-sustained and require long term immunosuppressive therapy. It is unclear whether these cases of persistent autoimmune hepatitis caused by the statin therapy or are triggered by statin in a susceptible host. Another possibility is that the association is coincidental and represents a de novo onset of autoimmune hepatitis in someone who happens to be taking a statin.

Likelihood score: A (well known cause of clinically apparent liver injury).

## Mechanism of Injury

The cause of hepatic injury from atorvastatin is unknown. Atorvastatin is largely metabolized in the liver via CYP 3A4 and excreted in bile. The mild, self-limited ALT elevations are likely due to a toxic intermediate of drug metabolism and the reversal of these elevations due to adaptation. The idiosyncratic, clinically apparent liver injury associated with atorvastatin has many features of autoimmunity and may be immune mediated. Other cases may be due to failure of adaptation.

Because atorvastatin is metabolized by CYP 3A4, it is susceptible to many drug-drug and even drug-food and drug-herb interactions. Strong inhibitors of CYP 3A4 such as clarithromycin, ritonavir (and other HIV protease inhibitors], itraconazole, verapamil and grapefruit juice (high consumption) can increase atorvastatin levels and the dose should be kept to 20 mg daily or less. Cyclosporine, fibrates and niacin can increase the risk of myopathy from atorvastatin. On the other hand, rifampin and other inducers of CYP 3A4 can decrease atorvastatin levels and efficacy. Drug induced liver injury from atorvastatin has sometimes occurred after long term use of the statin, but shortly after additions or discontinuations or modifications of other medications being taken.

## Outcome and Management

The product label for atorvastatin recommends screening for liver test abnormalities before starting therapy and repeating tests as clinically indicated. The mild ALT elevations associated with atorvastatin therapy are usually self-limited and do not require dose modification. Atorvastatin should be stopped if ALT levels rise above 10-fold normal, or persist in being above 5-fold elevated or are associated with symptoms of liver injury. However, prospective monitoring of serum enzymes upon initiating atorvastatin therapy is no longer recommended. Clinically apparent liver injury attributed to atorvastatin is usually self-limited and recovery is complete within 1 to 4 months. Several instances of an autoimmune chronic hepatitis have been reported after atorvastatin therapy that required long term immunosuppressive therapy despite stopping atorvastatin, suggesting that the drug triggered an underlying predisposition to autoimmune hepatitis. In other instances, the liver disease ultimately resolved with stopping atorvastatin. In addition, rare instances of acute liver failure have been attributed to atorvastatin, but in these cases the role of atorvastatin in causing the hepatic injury was not always clear. In view of the wide scale use of atorvastatin, clinically apparent and severe liver injury is extraordinarily rare. Recurrence of injury with rechallenge has been reported and should be avoided. Switching therapy to another statin after atorvastatin induced injury is apparently safe, but few instances have been reported, and it should be done with careful monitoring for recurrence. In cases of autoimmune hepatitis-like injury, corticosteroids have been used but with unclear efficacy. If corticosteroids are used, the dose and duration of treatment should be kept to a minimum, and careful followed up after stopping is essential.

Drug Class: Antilipemic Agents

Other Drugs in the Subclass, Statins: Ezetimibe [used in combination], Fluvastatin, Lovastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin

# CASE REPORTS

## Case 1. Abnormal serum enzymes arising during atorvastatin therapy.(1)

A 71 year old woman was found to have marked elevations in serum ALT and alkaline phosphatase 6 weeks after switching from simvastatin to atorvastatin (80 mg/day) for hyperlipidemia. Her serum ALT levels had been normal on simvastatin (Table). She was asymptomatic and serum bilirubin levels were normal. She had also been taking an herbal weight loss agent which was stopped at the same time as atorvastatin. Serum enzyme levels returned to normal and remained normal during subsequent lovastatin therapy. Switching to atorvastatin again (in lower doses) was followed by a rise in ALT and alkaline phosphatase levels and appearance of pruritus within a week. She was not jaundiced, but direct bilirubin was elevated (total=1.1 and direct=0.6 mg/dL). Atorvastatin was again stopped and serum enzymes fell into the normal range and remained normal on subsequent long term lovastatin therapy.

### Key Points

| | |
|---|---|
| Medication: | Atorvastatin (80 mg daily) |
| Pattern: | Cholestatic (R=1.1 initially; 2.0 on reexposure) |
| Severity: | 1+ (no jaundice) |
| Latency: | 6 weeks initially, <1 week on re-exposure |
| Recovery: | ~1 month |
| Other medications: | Herbal weight loss agent (first exposure only) |

### Laboratory Values

| Time After Starting | Time After Stopping | ALT (U/L) | Alk P (U/L) | Bilirubin (mg/dL) | Other |
|---|---|---|---|---|---|
| Pre | | 12 | | | While on Simvastatin |
| 0 | | Switched to Atorvastatin (80 mg/day) | | | |
| 6 weeks | 0 | 262 | | | Atorvastatin stopped |
| 7 weeks | 6 days | 75 | 694 | 0.5 | Asymptomatic |
| 24 weeks | 23 weeks | 15 | 135 | | On Lovastatin |
| | | Atorvastatin (20 mg/day) restarted | | | |
| 5 days | 0 | 478 | 711 | 1.1 | Atorvastatin stopped |
| 10 days | 5 days | 108 | 404 | 0.5 | Itching |
| 22 days | 17 days | 20 | 223 | | |
| 12 weeks | 11 weeks | 13 | 127 | 0.4 | On Lovastatin |
| **Normal Values** | | **<42** | **<117** | **<1.2** | |

### Comment

The rapid recurrence of liver test abnormalities within days of reexposure is convincing evidence that the initial episode was due to atorvastatin (rather than the herbal weight loss agent) and that the abnormalities were not simple aminotransferase elevations that are common on statin therapy, but rather a manifestation of mild idiosyncratic liver injury with a distinctive cholestatic pattern.

## Case 2. Cholestatic hepatitis due to atorvastatin.(2)

A 72 year old man with hyperlipidemia was treated with atorvastatin (20 mg daily) which he took intermittently for 4 to 5 months. Having stopped therapy for 3 months, he restarted it at a dose of 40 mg daily, and one week later developed dark urine and jaundice. He had no constitutional symptoms of fatigue, nausea or abdominal pain and had no fever or rash. Laboratory testing revealed elevations in ALT, alkaline phosphatase and bilirubin levels (Table). He had no history of liver disease or exposures to viral hepatitis and did not drink alcohol. He took prednisone and folic acid for anemia believed to be due to myelofibrosis. Tests for hepatitis A, B and C were negative as were AMA and SMA. ANA was positive at 1:80, but was known to be elevated for several years before treatment with atorvastatin. Ultrasound of the abdomen and MRCP showed no evidence of biliary disease. A liver biopsy showed intrahepatic cholestasis and mixed inflammatory infiltrates compatible with drug induced liver injury. Stopping atorvastatin was followed by a slow return of laboratory tests to normal. His hyperlipidemia was subsequently managed with ezetimibe.

### Key Points

| | |
|---|---|
| Medication: | Atorvastatin (40 mg daily) |
| Pattern: | Mixed (R=3), later cholestatic |
| Severity: | 3+ (jaundice, hospitalization) |
| Latency: | 1 week on reexposure |
| Recovery: | ~3-6 months |
| Other medications: | Prednisone, folic acid |

### Laboratory Values

| Time After Starting | Time After Stopping | ALT (U/L) | Alk P (U/L) | Bilirubin (mg/dL) | Other |
|---|---|---|---|---|---|
| Pre | Pre | 18 | 282 | 0.9 | |
| Pre | | 40 | 174 | 0.7 | Atorvastatin started |
| 4 months | | 66 | 250 | 0.6 | Atorvastatin stopped |
| 0 | | 49 | 205 | 0.8 | Atorvastatin restarted |
| 8 days | 0 | 538 | 920 | 8.0 | Atorvastatin stopped |
| 14 days | 6 days | 679 | 1259 | 7.4 | Liver biopsy |
| 21 days | 13 days | 441 | 1141 | 3.4 | |
| 35 days | 27 days | 214 | 746 | 1.6 | |
| 3 months | 3 months | 72 | 431 | 1.0 | |
| 9 months | 9 months | 39 | 213 | 1.0 | |
| 12 months | 12 months | 35 | 213 | 1.0 | |
| **Normal Values** | | **<55** | **<270** | **<1.2** | |

### Comment

The rapid development of a cholestatic hepatitis after reintroduction of atorvastatin suggests an immuno-allergic form of idiosyncratic drug induced liver injury. While the serum enzyme elevations qualified as being "mixed", the clinical course was cholestatic.

## Case 3. Self-limited autoimmune hepatitis-like injury arising during atorvastatin and ezetimibe therapy.(3)

A 50 year old woman developed nausea, abdominal pain and jaundice with features of autoimmune hepatitis during combination therapy with atorvastatin (80 mg daily for 16 months) and ezetimibe (10 mg daily for 3 months). There was no previous history of liver disease, and laboratory tests had been normal shortly before ezetimibe was started. She had multiple other medical problems including coronary artery disease, osteoarthritis, hypothyroidism, and gastroesophageal reflux. She drank little alcohol and had no exposures to hepatitis. On presentation, she had epigastric tenderness but no rash or fever. Laboratory tests showed raised bilirubin and serum enzymes (Table). Both ezetimibe and atorvastatin were stopped. Tests for hepatitis A, B and C were negative and ultrasound imaging showed no evidence of biliary obstruction. A liver biopsy showed hepatitis with eosinophils and plasma cells. She tested positive for antinuclear antibody and antibodies to double-stranded DNA (anti-dsDNA). Over the next few weeks, her symptoms resolved and laboratory tests improved. Six weeks after onset, her liver tests were normal and autoantibody levels had fallen. She was started on rosuvastatin for her hypercholesterolemia and did well without recurrence of symptoms or liver test abnormalities.

### Key Points

| | |
|---|---|
| Medication: | Atorvastatin (80 mg daily) and ezetimibe (10 mg daily) |
| Pattern: | Hepatocellular (R=10.7) |
| Severity: | 3+ (jaundice, hospitalization) |
| Latency: | 16 months for atorvastatin; 12 weeks for ezetimibe |
| Recovery: | ~6 weeks |
| Other medications: | Furosemide, diltiazem, diclofenac, acetaminophen, atenolol, ibuprofen, clopidogrel, thyroxine, lactulose, and nitrates |

### Laboratory Values

| Time After Starting | Time After Stopping | AST (U/L) | Alk P (U/L) | Bilirubin (mg/dL) | Other |
|---|---|---|---|---|---|
| Pre | | 17 | 75 | 0.5 | Atorvastatin (~13 months) |
| 0 | | Ezetimibe (10 mg/day) started | | | |
| 12 weeks | 0 | 1626 | 468 | 4.6 | ANA 1:160, anti-dsDNA 38 |
| 13 weeks | 10 days | 858 | 424 | 5.1 | ANA 1:80, anti-dsDNA 31 |
| 14 weeks | 2 weeks | 266 | 340 | 2.7 | |
| 18 weeks | 6 weeks | 20 | 100 | 0.6 | ANA 1:40, anti-dsDNA 6 |
| **Normal Values** | | **<42** | **<130** | **<1.2** | |

### Comment

A well documented example of drug induced autoimmune hepatitis with resolution when the medication was stopped. Particularly convincing was the decrease in autoantibody titers with drug withdrawal. Ezetimibe is

perhaps the most likely candidate to have caused the liver injury, but cases of autoimmune hepatitis-like injury from atorvastatin have been reported with latency to onset of more than a year.

## Case 4. Autoimmune hepatitis requiring long term immunosuppression arising during atorvastatin therapy.(4)

A 65 year old woman developed fatigue and jaundice 3 months after starting atorvastatin (20 mg daily) for long standing hypercholesterolemia for which she had previously been treated with pravastatin [6 months] and fluvastatin [3 years] before switching to atorvastatin. Her only other medication was doxazosin which she had taken for years for hypertension. She had no history of liver disease or exposures to viral hepatitis and did not drink alcohol. On examination, she was jaundiced and had hepatomegaly but no fever, rash or signs of chronic liver disease. Laboratory tests showed a hepatocellular pattern of serum enzyme elevations and mild hyperbilirubinemia (Table). Tests for viral hepatitis were negative, but she had hyperglobulinemia with IgG 6.6 g/dL (normal <1.7) and high titers of both ANA and SMA (>1:1280). A liver biopsy showed chronic hepatitis and lobular collapse and mild fibrosis. She was started on prednisone with improvement in blood tests, but three months later she still had ALT elevations and autoantibody titers had not declined. A repeat liver biopsy showed early cirrhosis.

### Key Points

| | |
|---|---|
| Medication: | **Atorvastatin (20 mg daily)** |
| Pattern: | **Hepatocellular (R=7.5)** |
| Severity: | **3+ (jaundice, hospitalization)** |
| Latency: | **3 months** |
| Recovery: | **Incomplete** |
| Other medications: | **Doxazosin** |

### Laboratory Values

| Weeks After Starting | Weeks After Stopping | ALT* (U/L) | Alk P (U/L) | Bilirubin* (mg/dL) | Other |
|---|---|---|---|---|---|
| 12 | 0 | 510 | 481 | 3.0 | Prothrombin 17% |
| 13 | 1 | 430 | | 2.5 | ANA >1:1280 |
| 14 | 2 | 280 | | 4.4 | First liver biopsy |
| 15 | 3 | 220 | | 5.6 | |
| 16 | 4 | 305 | | 4.3 | Prednisone (1 mg/kg/day) |
| 18 | 6 | 210 | | 2.6 | |
| 19 | 7 | 105 | | 2.4 | |
| 22 | 10 | 80 | | 1.5 | ANA >1:1280 |
| 26 | 14 | 66 | 66 | 1.1 | Second liver biopsy |
| **Normal Values** | | **<40** | **<279** | **<1.2** | |

* Values estimated from Figure 3. Bilirubin converted from μmol to mg/dL.

### Comment

Jaundice and features of autoimmune hepatitis arose after 3 months of atorvastatin therapy in a patient who had been treated with other statins for more than 3 years. Liver tests improved minimally with stopping atorvastatin

and one month later prednisone was started, whereupon serum enzymes decreased from ~8-fold to ~twice normal. However, serum autoantibodies remained present in unchanging titers, and a repeat liver biopsy showed progression of fibrosis with nodularity and incomplete cirrhosis. In this case, atorvastatin appeared to trigger a self-sustained autoimmune hepatitis. An alternative explanation is that atorvastatin was an innocent bystander and the development of autoimmune hepatitis was coincidental and unrelated to the chronic statin therapy.

## PRODUCT INFORMATION

**REPRESENTATIVE TRADE NAMES**

Atorvastatin – Generic, Lipitor®

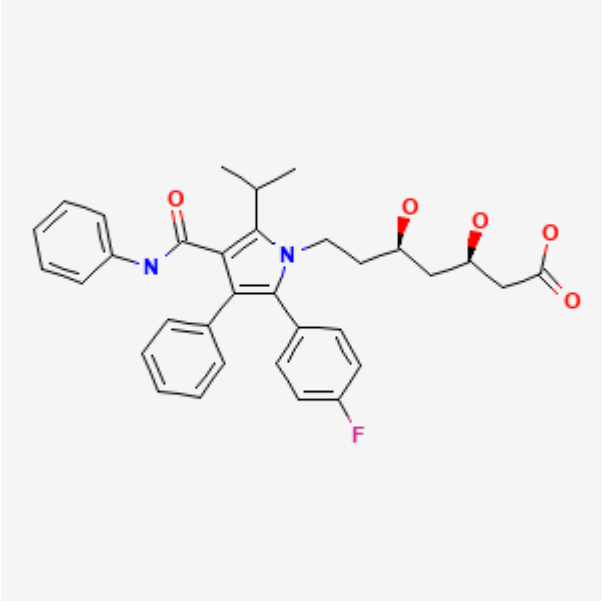
**DRUG CLASS**

Antilipemic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

## CHEMICAL FORMULA AND STRUCTURE

| DRUG | CAS REGISTRY NUMBER | MOLECULAR FORMULA | STRUCTURE |
|---|---|---|---|
| Atorvastatin | 134523-00-5 | C33-H35-F-N2-O5 |  |

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1. Gershovich OE, Lyman AE Jr. Liver function test abnormalities and pruritus in a patient treated with atorvastatin: case report and review of the literature. Pharmacotherapy. 2004 Jan;24(1):150–4. PubMed PMID: 14740794.
2. de Castro ML, Hermo JA, Baz A, de Luaces C, Pérez R, Clofent J. Hepatitis colestásica aguda tras la reintroducción de atorvastatina. Gastroenterol Hepatol. 2006 Jan;29(1):21–4. [Acute cholestatic hepatitis after atorvastatin reintroduction]. Spanish. PubMed PMID: 16393626.
3. van Heyningen C. Drug-induced acute autoimmune hepatitis during combination therapy with atorvastatin and ezetimibe. Ann Clin Biochem. 2005;42:402–4. PubMed PMID: 16168199.
4. Pelli N, Setti M, Ceppa P, Toncini C, Indiveri F. Autoimmune hepatitis revealed by atorvastatin. Eur J Gastroenterol Hepatol. 2003;15:921–4. PubMed PMID: 12867804.

# ANNOTATED BIBLIOGRAPHY

References updated: 01 December 2021

Abbreviations used: ANA, antinuclear antibody; HDL, high density lipoprotein; LDL, low density lipoprotein; OD, odds ratio.

Zimmerman HJ. Drugs used in the treatment of hypercholesterolemia and hyperlipidemia. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 660-2.

*(Expert review of hepatotoxicity published in 1999; the statins have dose related hepatic effects in guinea pigs and rabbits and transient elevations in aminotransferases occur in 1-5% of humans treated; several cases of clinically apparent liver injury from lovastatin and simvastatin have been published).*

De Marzio DH, Navarro VJ. Hepatotoxicity of cardiovascular and antidiabetic medications. Lipid lowering agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 519-40.

*(Review of hepatotoxicity of lipid lowering agents; asymptomatic elevations in aminotransferases are common in patients receiving statins, but clinically significant hepatotoxicity is rare).*

Gurgle H, Blumenthal DK. Drug therapy for dyslipidemias. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 605-618.

*(Textbook of pharmacology and therapeutics; "Serious hepatotoxicity is rare and unpredictable, with a rate of about 1 case per million person-years of use." Multiple academic societies and the FDA recommend testing all patients for routine liver tests before starting statins but monitoring or retesting only if symptoms arise).*

Dart A, Jerums G, Nicholson G, d'Emden M, Hamilton-Craig I, Tallis G, Best J, et al. A multicenter, double-blind, one-year study comparing safety and efficacy of atorvastatin versus simvastatin in patients with hypercholesterolemia. Am J Cardiol. 1997;80:39–44. PubMed PMID: 9205017.

*(In a study comparing atorvastatin [10 to 20 mg] to simvastatin [10 to 20 mg] for 1 year in 177 patients with hypercholesterolemia, there were "no clinically important elevations in ALT, AST or CPK" during treatment with either statin).*

Black DM, Bekker-Arkema RG, Nawrocki JW. An overview of the clinical safety profile of atorvastatin (Lipitor), a new HMG-CoA reductase inhibitor. Arch Intern Med. 1998;158:577–84. PubMed PMID: 9521221.

*(Pooled data of 4271 patients followed for 1845 patient years in 21 clinical trials receiving atorvastatin indicated that 0.7% had ALT elevations >3 times ULN, usually within first 16 weeks, 1 patient had cholestatic hepatitis after 36 weeks, resolving in 14 weeks; dose relationship of rate of ALT elevations; 0.2% with 10 and 20 mg, 0.6% with 40 and 2.3% with 80 mg daily).*

Jiminez-Alonso J, Osorio JM, Gutierrez-Cabello F, Lopez de la Osa A, Leon L, Mediavilla Garcia JD. Atorvastatin-induced cholestatic hepatitis in a young woman with systemic lupus erythematosus. Arch Intern Med. 1999;159:1811–2. PubMed PMID: 10448788.

*(20 year old woman with lupus and complex medical history developed jaundice 2 months after starting atorvastatin despite concurrent prednisone therapy [bilirubin 8.2 mg/dL, ALT 783 U/L, Alk P 669 U/L], resolving within a month of stopping atorvastatin).*

Nakad A, Bataille L, Hamoir V, Sempoux C, Horsman Y. Atorvastatin-induced hepatitis with the absence of cross-toxicity with simvastatin. Lancet. 1999;353:1763–4. PubMed PMID: 10347994.

*(70 year old woman developed nausea and weakness after 12 weeks of atorvastatin therapy [bilirubin not given, ALT 230 U/L, Alk P 591 U/L], returning to normal 2 weeks after stopping and no recurrence with simvastatin).*

Wierzbicki A, Crook MA. Cholestatic liver dysfunction. Lancet. 1999;354:954. PubMed PMID: 10489985.

*(Among 275 patients with familial hyperlipidemia, 3% had ALT elevations and 2 had raised alkaline phosphatase and slight bilirubin elevations during atorvastatin therapy; resolving after switching to fluvastatin).*

Sreenarasinhaiah J, Shiels P, Lisker-Melman M. Multiorgan failure induced by atorvastatin. Am J Med. 2002;113:348–9. PubMed PMID: 12361829.

*(65 year old woman developed jaundice on atorvastatin, resolving when stopping, but recurring in severe form with restarting [bilirubin 25 mg/dL, ALT 290 U/L], progressing to liver and renal failure, myocardial infarction, pancreatitis and death).*

Lewin JJ 3rd, Nappi JM, Taylor MH. Rhabdomyolysis with concurrent atorvastatin and diltiazem. Ann Pharmacother. 2002;36:1546–9. PubMed PMID: 12243603.

*(60 year old man on long term atorvastatin developed rhabdomyolysis 3 weeks after starting diltiazem [bilirubin 0.7 mg/dL, ALT 1610 U/L, Alk P 287 U/L, CPK 1898 U/L and myoglobinemia], resolving rapidly with stopping medications).*

Gagné C, Gaudet D, Bruckert E; Ezetimibe Study Group. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation. 2002;105:2469–75. PubMed PMID: 12034651.

*(Prospective trial comparing the combination of ezetimibe and either atorvastatin or simvastatin to the statin alone in 50 patients with homozygous familial hypercholesterolemia; side effects were similar; two patients on combination therapy had ALT elevations >3 times ULN, but both resolved without stopping therapy).*

Ridruejo E, Mando OG. Acute cholestatic hepatitis after reinitiating treatment with atorvastatin. J Hepatol. 2002;37:165–6. PubMed PMID: 12076881.

*(69 year old man developed jaundice 7 months after starting atorvastatin [bilirubin 2.6 mg/dL, ALT 72 U/L, Alk P 3767 U/L, eosinophilia, ANA negative], resolving within 4 months of stopping; he was previously treated with simvastatin and pravastatin without problems).*

Kiortsis DN, Nikas S, Hatzidimou K, Tsianos E, Elisaf MS. Lipid-lowering drugs and serum liver enzymes: the effects of body weight and baseline enzyme levels. Fundam Clin Pharmacol. 2003;17:491–4. PubMed PMID: 12914553.

*(Among 163 patients treated with various lipid lowering drugs, proportion with elevated ALT levels was 9.1% before treatment, 9.5% at 8 weeks and 9.1% at 24 weeks; similar at all body weights, but ALT elevations more frequent in obese and overweight subjects).*

Graziadei IW, Obermoser GE, Sepp NT, Erhart KH, Vogel W. Drug-induced lupus-like syndrome associated with severe autoimmune hepatitis. Lupus. 2003;12:409–12. PubMed PMID: 12765306.

*(58 year old woman developed abdominal pain after 7 months of atorvastatin with biopsy findings of autoimmune hepatitis, ANA 1:640 and skin rash [lupus], responding poorly to corticosteroids [bilirubin 4.5 mg/dL, ALT 263 U/L, Alk P 270 U/L, IgG 2.7 gm/dL], ultimately requiring long term tacrolimus and mycophenolate for control).*

Pelli N, Setti M, Ceppa P, Toncini C, Indiveri F. Autoimmune hepatitis revealed by atorvastatin. Eur J Gastroenterol Hepatol. 2003;15:921–4. PubMed PMID: 12867804.

*(65 year old woman developed jaundice 3 months after starting atorvastatin [bilirubin 3.0 mg/dL, ALT 510 U/L, Alk P 481 U/L, IgG 6.58 gm/dL, both ANA and SMA >1:1280]; only partial response to prednisone with evolution to cirrhosis and requiring long term corticosteroid therapy: Case 4).*

Perger L, Kohler M, Fattinger K, Flury R, Meier PJ, Pauli-Magnus C. Fatal liver failure with atorvastatin. J Hepatol. 2003;39:1096–7. PubMed PMID: 14642636.

*(85 year old man developed jaundice 2 weeks after starting atorvastatin 20 mg daily [bilirubin 25 mg/dL, ALT 1401 U/L, Alk P 393 U/L], worsened despite stopping drug with subsequent coma, hepato-renal syndrome and death).*

Pelli N, Setti M. Atorvastatin as a trigger of autoimmune hepatitis. J Hepatol. 2004;40:715–9. PubMed PMID: 15030993.

*(Letter in response to Perger [2003], summarizing their previously published case [Pelli 2003).*

Parra JL, Reddy KR. Hepatotoxicity of hypolipidemic drugs. Clin Liver Dis. 2003;7:415–33. PubMed PMID: 12879992.

*(Review and discussion of individual hypolipidemic agents: atorvastatin is associated with ALT elevations >3 times ULN in 0.7%, but only 0.3% stopped therapy because of these abnormalities).*

Bays HE, Dujovne CA, McGovern ME, White TE, Kashyap ML, Hutcheson AG, Crouse JR; Advicor Versus Other Cholesterol-Modulating Agents Trial Evaluation. Comparison of once-daily, niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin(the Advicor Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). Am J Cardiol. 2003;91:667–72. PubMed PMID: 12633795.

*(Controlled trial comparing lovastatin combined with niacin to atorvastatin or simvastatin alone in 315 patients for 16 weeks; no patient had confirmed ALT elevation >3 times ULN).*

Newman CB, Palmer G, Silbershatz H, Szarek M. Safety of atorvastatin derived from analysis of 44 completed trials in 9,416 patients. Am J Cardiol. 2003;92:67–76. PubMed PMID: 12842251.

*(Pooled data from 44 trials which included 9,416 patients treated with atorvastatin; ALT was >3 times ULN in 0.5% of atorvastatin vs 0.3% of placebo recipients; rates rising from 0.13% with 10 and 20 mg, 0.4% with 40 mg and 0.9% with 80 mg of atorvastatin daily).*

Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. Am J Cardiol. 2004;94:1140–6. PubMed PMID: 15518608.

*(Pharmacokinetic studies showing that drugs that inhibit CYP 3A4, the major P450 drug metabolizing enzyme, [itraconazole, clarithromycin, verapamil] cause increases in blood levels of simvastatin and atorvastatin, but have little effect on pravastatin levels).*

Gershovich OE, Lyman AE Jr. Liver function test abnormalities and pruritus in a patient treated with atorvastatin: case report and review of the literature. Pharmacotherapy. 2004;24:150–4. PubMed PMID: 14740794.

*(71 year old woman developed ALT and Alk P elevations after taking atorvastatin for 2 months, which resolved rapidly but recurred after 4 days of restarting drug with itching [bilirubin 1.1 mg/dL, ALT 478 U/L, Alk P 711 U/L], resolving rapidly with stopping and not recurring on switching to lovastatin: Case 1).*

Geoghegan M, Smith V, Green JRB. Acute cholestatic hepatitis associated with atorvastatin. Gut. 2004;53 Suppl.3:A123. [Abstract].

*(Two patients, 1 woman and 1 man, ages 57 and 63 years, developed jaundice 4 and 12 weeks after starting atorvastatin [bilirubin 34.3 and 1.1 mg/dL, ALT 931 and 283 U/L, Alk P 156 and 216 U/L, ANA negative], resolving 8 weeks after stopping).*

Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. Gastroenterology. 2004;126:1287–92. PubMed PMID: 15131789.

*(Retrospective analysis of electronic records found similar rates of severe ALT or AST elevations with or without statin [atorvastatin, simvastatin or fluvastatin] therapy [0.6% vs 0.4%] in those with baseline elevations).*

Kaplowitz N. Statin-induced hepatotoxicity. Gastroenterology. 2004;127:1278. PubMed PMID: 15481021.

*(Letter in response to Chalasani [2004] requesting addition information on cohorts: reply by authors provides what was available).*

de Denus S, Spinler SA, Miller K, Peterson AM. Statins and liver toxicity: a meta-analysis. Pharmacotherapy. 2004;24:584–91. PubMed PMID: 15162892.

*(In 13 controlled trials with 49,275 patients with routine liver test monitoring for an average of 3.6 years, statin therapy was not associated with increased rate of liver test abnormalities [1.14% vs 1.05%: odds ratio = 1.26; 95% CI = 0.99-1.62] compared to placebo).*

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl. 2004;10:1018–23. PubMed PMID: 15390328.

*(Among ~50,000 liver transplants done in the US between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, 3 of which were attributed to statins including simvastatin in 1 and cerivastatin in 2).*

Alsheikh-Ali AA, Karas RH. Adverse events with concomitant amiodarone and statin therapy. Prev Cardiol. 2005;8:95–7. PubMed PMID: 15860984.

*(Review of MedWatch adverse event reports for proportion of cases attributed to different statins that included combination with amiodarone; 1.0% for simvastatin, 0.7% atorvastatin and 0.4% pravastatin; 77% muscle, 30% liver involvement).*

Nissen SE. Effect of intensive lipid lowering on progression of coronary atherosclerosis: evidence for an early benefit from the Reversal of Atherosclerosis with Aggressive Lipid Lowering(REVERSAL) trial. Am J Cardiol. 2005;96(5A):61F–68F. PubMed PMID: 15979434.

*(Controlled trial comparing pravastatin [40 mg] to atorvastatin [80 mg] daily for 18 months in 654 patients; ALT elevations >3 times ULN occurred in 1.6% on pravastatin vs 2.3% on atorvastatin, but no instances of clinically apparent hepatitis).*

van Heyningen C. Drug-induced acute autoimmune hepatitis during combination therapy with atorvastatin and ezetimibe. Ann Clin Biochem. 2005;42:402–4. PubMed PMID: 16168199.

*(50 year old woman developed jaundice 16 months after starting atorvastatin and 3 months after starting ezetimibe [bilirubin 4.6 mg/dL, AST 1626 U/L, Alk P 468 U/L, positive ANA and anti-dsDNA], resolving 6 weeks after stopping both: Case 3).*

Charles EC, Olson KL, Sandhoff BG, McClure DL, Merenich JA. Evaluation of cases of severe statin-induced transaminitis within a large health maintenance organization. Am J Med. 2005;118:618–24. PubMed PMID: 15922693.

*(Among 23,000 patients on statins in a health plan, 17 had an ALT elevation >10 times ULN attributable to statin use; 10 on simvastatin, 5 lovastatin, and 2 atorvastatin; onset 2 days to 4 years after starting; 10 symptomatic; all resolved within 2 to 8 weeks, except one death; 3 of 7 recurred on rechallenge, 5 of 6 tolerated switching to another statin; two atorvastatin cases had ALT 1481 and 478 U/L, bilirubin 1.3 and 1.1 mg/dL, resolved in 5 and 2 weeks).*

Alsheikh-Ali AA, Ambrose MS, Kuvin JT, Karas RH. The safety of rosuvastatin as used in common clinical practice: a postmarketing analysis. Circulation. 2005;111:3051–7. PubMed PMID: 15911706.

*(Review of adverse event reporting for rosuvastatin during first year of marketing; liver related events rates were higher for rosuvastatin [~25/million prescriptions] than other statins [~4/million] and higher for comparable periods for simvastatin, pravastatin and atorvastatin).*

Ballantyne CM, Abate N, Yuan Z, King TR, Palmisano J. Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: the Vytorin Versus Atorvastatin (VYVA) study. Am Heart J. 2005;149:464–73. PubMed PMID: 15864235.

*(Controlled trial of ezetimibe/simvastatin vs atorvastatin in 1902 patients with hypercholesterolemia, ALT elevations >3 times ULN occurred in 1.1% on atorvastatin and none on ezetimibe/simvastatin).*

LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, et al; Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352:1425–35. PubMed PMID: 15755765.

*(Controlled trial of 10 mg or 80 mg of atorvastatin daily in 10,001 patients with coronary artery disease and LDL cholesterol of <130 mg/dL for an average of 4.9 years; rate of confirmed ALT elevation >3 times ULN 1.2% with high dose and 0.2% with low dose atorvastatin; 5 cases of rhabdomyolysis, but no hepatitis reported).*

Andrade RJ, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, García-Ruiz E, García-Muñoz B, et al; Spanish Group for the Study of Drug-Induced Liver Disease. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology. 2005;129:512–21. PubMed PMID: 16083708.

*(Analysis of 461 cases of drug induced liver disease diagnosed between 1994 to 2004 in Spanish Registry; 11 cases were attributed to "statins", but no specific agent caused more than 4 cases).*

Andrade RJ, Lucena MI, Kaplowitz N, García-Munoz B, Borraz Y, Pachkoria K, García-Cortés M, et al. Outcome of acute idiosyncratic drug-induced liver injury: Long-term follow-up in a hepatotoxicity registry. Hepatology. 2006;44:1581–8. PubMed PMID: 17133470.

*(28 of 493 [5.7%] cases of drug induced liver disease were found to have evidence of chronic injury, including 2 cases due to atorvastatin with raised serum enzymes 9 and 17 months after an acute anicteric liver injury).*

Clarke AT, Mills PR. Atorvastatin associated liver disease. Dig Liver Dis. 2006;38:772–7. PubMed PMID: 16777499.

*(7 cases of atorvastatin liver injury from 1 center between 2002-5; ages 50-78 years, arising 3-52 weeks after starting [bilirubin levels ranging from 0.6 to 40.2 mg/dL, AST 76 to 1702 U/L, Alk P 410 to 1935 U/L], resolving within 1-10 months of stopping, 1 death and 1 prolonged).*

Khorashadi S, Hasson NK, Cheung RC. Incidence of statin hepatotoxicity in patients with hepatitis C. Clin Gastroenterol Hepatol. 2006;4:902–7. PubMed PMID: 16697272.

*(Electronic record review of rate of ALT elevations in patients with hepatitis C with or without statin therapy and controls on statin therapy found no differences between the three groups [20%, 24% and 17%]; severe abnormalities most frequent in patients with chronic hepatitis C not on statins [6.6% vs 1.2%]).*

Cohen DE, Anania FA, Chalasani N; National Lipid Association Statin Safety Task Force Liver Expert Panel. An assessment of statin safety by hepatologists. Am J Cardiol. 2006;97(8A):77C–81C. PubMed PMID: 16377288.

*(Expert opinion of panel of academic hepatologists; statins as a class are associated with low rates of moderate ALT elevations during therapy, particularly with higher doses, but these are generally not indicative of significant liver injury, acute liver failure being very rare; routine monitoring of serum aminotransferase levels is not necessary; statins can be used safely in patients with chronic liver disease including nonalcoholic fatty liver).*

Conforti A, Magro L, Moretti U, Scotto S, Motola D, Salvo F, Ros B, et al. Fluvastatin and hepatic reactions: a signal from spontaneous reporting in Italy. Drug Safety. 2006;29:1163–72. PubMed PMID: 17147462.

*(Italian Pharmacovigilance Group review of 35,757 adverse reaction reports; 1260 due to statins of which 178 were hepatic: 69 [36%] fluvastatin, 37 [21%] atorvastatin, 50 [28%] simvastatin, 16 [9%] pravastatin, 6 [3%]*

*rosuvastatin; proportion reporting rate based on number of prescriptions was highest for fluvastatin [~9] compared to other agents [~2-3]; 26 fluvastatin cases described as "hepatitis", but no details given except that most cases occurred within 90 days of starting).*

Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol. 2006;97(8A):52C–60C. PubMed PMID: 16581329.

*(Review of safety of statins; 38 cases of acute liver failure submitted to MedWatch by end of 1999, which gives an estimated rate of 1 per million person years of use; rate of confirmed ALT elevations >3 times ULN is 0.1% with statins and 0.04% with placebo).*

Goldberg RB, Guyton JR, Mazzone T, Weinstock RS, Polis A, Edwards P, Tomassini JE, et al. Ezetimibe/simvastatin vs atorvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia: the VYTAL study. Mayo Clin Proc. 2006;81:1579–88. PubMed PMID: 17165637.

*(Controlled trial of atorvastatin vs simvastatin/ezetimibe in 1229 patients with diabetes and hypercholesterolemia; confirmed ALT elevations >3 times ULN occurred in 0.3% of atorvastatin vs no simvastatin/ezetimibe treated patient, and no clinically apparent liver injury).*

Björnsson E, Olsson R. Suspected drug-induced liver fatalities reported to the WHO database. Dig Liver Dis. 2006;38:33–8. PubMed PMID: 16054882.

*(In WHO database of fatal adverse drug reactions from 1968-2003, there were 4690 reports of drug induced liver fatality; none of the statins were in the top 20 suspected causes).*

Alla V, Abraham J, Siddiqui J, Raina D, Wu GY, Chalasani NP, Bonkovsky HL. Autoimmune hepatitis triggered by statins. J Clin Gastroenterol. 2006;40:757–61. PubMed PMID: 16940892.

*(Three cases of autoimmune hepatitis arising after simvastatin or atorvastatin therapy 6, 20 and 20 weeks after starting [bilirubin 11.3, 3.4 and 5.5 mg/dL, ALT 1749, 1170 and 155 U/L, Alk P of 228, 160, and 203 U/L, all being ANA or SMA positive in titers of 1:40 to 1:160], all responding to prednisone/azathioprine, but remaining on long term therapy with azathioprine or mycophenolate alone).*

de Castro ML, Hermo JA, Baz A, de Luaces C, Perez R, Clofent J. [Acute cholestatic hepatitis after atorvastatin reintroduction](Spanish). Gastroenterol Hepatol. 2006;29:21–4. PubMed PMID: 16393626.

*(72 year old man developed jaundice one week after restarting atorvastatin therapy [bilirubin 8.0 mg/dL, ALT 538 U/L, Alk P 1259 U/L], resolving slowly with stopping therapy: Case 2).*

Clearfield MB, Amerena J, Bassand JP, Hernández García HR, Miller SS, Sosef FF, Palmer MK, et al. Comparison of the efficacy and safety of rosuvastatin 10 mg and atorvastatin 20 mg in high-risk patients with hypercholesterolemia -- Prospective study to evaluate the Use of Low doses of the Statins Atorvastatin and Rosuvastatin (PULSAR). Trials. 2006;7:35. PubMed PMID: 17184550.

*(Controlled trial comparing rosuvastatin [10 mg] vs atorvastatin [20 mg] daily for 6 weeks; one patient on atorvastatin had confirmed ALT elevations >3 times ULN; no clinically apparent liver injury).*

Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, et al; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355:549–59. PubMed PMID: 16899775.

*(Controlled trial of atorvastatin [80 mg] vs placebo for 4-6 years in 4731 patients with cerebrovascular disease and hypercholesterolemia; confirmed ALT elevations >3 times ULN occurred in 2.2% of atorvastatin vs 0.5% of placebo recipients; no cases of liver failure).*

Gómez-Domínguez E, Gisbert JP, Moreno-Monteagudo JA, García-Buey L, Moreno-Otero R. A pilot study of atorvastatin treatment in dyslipidemia, non-alcoholic fatty liver patients. Aliment Pharmacol Ther. 2006;23:1643–7. PubMed PMID: 16696815.

*(Open label study of a one year course of atorvastatin in various doses for nonalcoholic liver disease found some degree of improvement in ALT, AST and GGT levels).*

Silva MA, Swanson AC, Gandhi PJ, Tataronis GR. Statin-related adverse events: a meta-analysis. Clin Ther. 2006;28:26–35. PubMed PMID: 16490577.

*(Metaanalysis of adverse event rates in 18 placebo controlled trials of six statins in 71,108 patients; ALT elevations >3 times ULN in 1.7% of statin vs 1.4% placebo recipients; event rates highest with atorvastatin, lowest with fluvastatin).*

Arca M. Atorvastatin: a safety and tolerability profile. Drugs. 2007;67 Suppl 1:63–9. PubMed PMID: 17910522.

*(Review of safety of atorvastatin; ALT elevations >3 times ULN occur in <1% of statin recipients, but rate may be higher with higher doses of atorvastatin, estimate of rate of acute liver failure is ~1 per million persons years).*

Bhardwah SS, Chalasani N. Lipid-lowering agents that cause drug-induced hepatotoxicity. Clin Liver Dis. 2007;11:597–613. PubMed PMID: 17723922.

*(Review of hepatotoxicity of statins; reported rates of ALT or AST elevations >3 times ULN; atorvastatin 0.7%, fluvastatin 1.2%, lovastatin 0.6%, pravastatin 1.4%, rosuvastatin 0% and simvastatin 1.8%; usually asymptomatic, individual case reports of autoimmune hepatitis).*

Alsheikh-Ali AA, Maddukuri PV, Han H, Karas RH. Effect of the magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis, and cancer: insights from large randomized statin trials. J Am Coll Cardiol. 2007;50:409–18. PubMed PMID: 17662392.

*(Systematic review of relationship between LDL cholesterol lowering effects and adverse events in 23 statin treatment arms representing 309,506 person years of therapy; positive and graded relationship between statin dose [simvastatin, lovastatin and atorvastatin] and rates of ALT elevations, but no independent relationship to degree of LDL cholesterol decrease).*

Dale KM, White CM, Henyan NN, Kluger J, Coleman CI. Impact of statin dosing intensity on transaminase and creatine kinase. Am J Med. 2007;120:706–12. PubMed PMID: 17679130.

*(Metaanalysis of rates of ALT and CPK elevations in nine controlled studies comparing low vs high doses of statins; ALT elevations >3 times ULN occurred in 1.5% of high- and 0.4% of low-intensity statin groups, effect particularly seen with hydrophilic [pravastatin and atorvastatin] compared to lipophilic agents [simvastatin and lovastatin]).*

Silva M, Matthews ML, Jarvis C, Nolan NM, Belliveau P, Malloy M, Gandhi P. Meta-analysis of drug-induced adverse events associated with intensive-dose statin therapy. Clin Ther. 2007;29:253–60. PubMed PMID: 17472818.

*(Metaanalysis of rates of adverse events in 4 controlled trials in 108,049 patient years comparing standard to intensive-dose statin therapy; increased risk of ALT elevations >3 times ULN with intensive therapy [odds ratio 4.5; absolute risk 1.2%], but no mention of clinically apparent liver injury).*

Alsheikh-Ali AA, Karas RH. Safety of lovastatin/extended release niacin compared with lovastatin alone, atorvastatin alone, pravastatin alone, and simvastatin alone(from the United States Food and Drug Administration adverse event reporting system). Am J Cardiol. 2007;99:379–81. PubMed PMID: 17261402.

*(Analysis of MedWatch reports of adverse events found no excess in liver related adverse event reports per million prescriptions due to lovastatin alone [2.3] vs niacin alone [2.5] vs the combination [3.2], but slightly higher rates with atorvastatin [4.5], simvastatin [5.7] and pravastatin [4.9], but data relied upon spontaneous reporting).*

Segarra-Newnham M, Parra D, Martin-Cooper EM. Effectiveness and hepatotoxicity of statins in men seropositive for hepatitis C virus. Pharmacotherapy. 2007;27:845–51. PubMed PMID: 17542767.

*(Retrospective analysis of electronic records on 146 men with chronic hepatitis C who started statin therapy [simvastatin mostly, but also fluvastatin, lovastatin, pravastatin, and atorvastatin, <4 each], mean ALT levels did not change and percent with ALT >3 times ULN was 8% at baseline, 10% at 3 months, 11% at 6 months and 8% at 22 months; only one patient stopped therapy for ALT elevations).*

Sabaté M, Ibáñez L, Pérez E, Vidal X, Buti M, Xiol X, Mas A, et al. Risk of acute liver injury associated with the use of drugs: a multicentre population survey. Aliment Pharmacol Ther. 2007;25:1401–9. PubMed PMID: 17539979.

*(Among 126 cases of drug induced liver injury seen in Spain between 1993-2000, no cases were attributed to statins).*

Leiter LA, Bays H, Conard S, Bird S, Rubino J, Hanson ME, Tomassini JE, et al. Efficacy and safety of ezetimibe added on to atorvastatin (40 mg) compared with uptitration of atorvastatin (to 80 mg) in hypercholesterolemic patients at high risk of coronary heart disease. Am J Cardiol. 2008;102:1495–501. PubMed PMID: 19026303.

*(Controlled trial of adding ezetimibe vs increasing atorvastatin dosage in 579 patients; ALT or AST elevations >3 times the ULN occurred in 1 patient in both groups).*

Escobar C, Echarri R, Barrios V. Relative safety profiles of high dose statin regimens. Vasc Health Risk Manag. 2008;4:525–33. PubMed PMID: 18827903.

*(Review of efficacy and safety of use of higher doses of statins to achieve lower LDL cholesterol levels; ALT elevations are more frequent [2-3%] with higher than lower [~1%] doses).*

Hyogo H, Tazuma S, Arihiro K, Iwamoto K, Nabeshima Y, Inoue M, Ishitobi T, et al. Efficacy of atorvastatin for the treatment of nonalcoholic steatohepatitis with dyslipidemia. Metabolism. 2008;57:1711–8. PubMed PMID: 19013295.

*(Open labeled trial of 24 month course of atorvastatin [10 mg daily] in 31 patients with nonalcoholic steatohepatitis; improvements in serum ALT levels [mean 98 to 36 U/L], cholesterol and triglyceride levels and steatosis, but apparent worsening of fibrosis in some patients; no hepatotoxicity).*

Rahier JF, Rahier J, Leclercq I, Geubel AP. Severe acute cholestatic hepatitis with prolonged cholestasis and bile-duct injury following atorvastatin therapy: a case report. Acta Gastroenterol Belg. 2008;71:318–20. PubMed PMID: 19198578.

*(52 year old developed severe liver injury 5 weeks after starting atorvastatin, 10 mg daily [bilirubin 5.9 rising to ~29 mg/dL, ALT 6838 U/L, Alk P ~150 U/L, ANA negative, INR 1.9], severe itching and slow recovery requiring 6 months for normalization of bilirubin).*

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology. 2008;135:1924–34. PubMed PMID: 18955056.

*(Among 300 cases of drug induced liver disease collected from 2004 to 2008 in the US, 9 [3%] were attributed to statins, including 3 to atorvastatin, 3 to simvastatin/ezetimibe, and one each to pravastatin, fluvastatin, and simvastatin, but most cases were mild and some were not clearly attributable to the statin therapy).*

Martin JE, Cavanaugh TM, Trumbull L, Bass M, Weber F Jr, Aranda-Michel J, Hanaway M, et al. Incidence of adverse events with HMG-CoA reductase inhibitors in liver transplant patients. Clin Transplant. 2008;22:113–9. PubMed PMID: 18217912.

*(Retrospective review of adverse events associated with statin and fibrate use in 69 patients with liver transplants; myalgias problematic in 5, myopathy in 1, but none had significant ALT elevations or hepatitis related to medication).*

Robinson JG, Ballantyne CM, Grundy SM, Hsueh WA, Parving HH, Rosen JB, Adewale AJ, et al. Lipid-altering efficacy and safety of ezetimibe/simvastatin versus atorvastatin in patients with hypercholesterolemia and the metabolic syndrome(from the VYMET study). Am J Cardiol. 2009;103:1694–702. PubMed PMID: 19539078.

*(Controlled trial of ezetimibe/simvastatin versus atorvastatin alone in 1128 patients with metabolic syndrome and hypercholesterolemia; adverse event rates were similar in the two groups, but confirmed ALT or AST elevations >3 times ULN occurred in 0.3% of atorvastatin vs 1.4% of ezetimibe/simvastatin treated patients).*

Koren MJ, Feldman T, Mendes RA. Impact of high-dose atorvastatin in coronary heart disease patients age 65 to 78 years. Clin Cardiol. 2009;32:256–63. PubMed PMID: 19452483.

*(Controlled trial of high [up to 80 mg daily] vs standard dose [10 mg] atorvastatin in 2442 patients, analysis of subgroup of 1001 who were 65 to 78 years of age; ALT elevations >3 times ULN occurred in 1.3% in younger vs 14% in older cohort receiving high dose atorvastatin; no mention of clinically apparent liver disease).*

Minha S, Golzman G, Adar I, Rapoport M. Cholestatic jaundice induced by atorvastatin: a possible association with antimitochondrial antibodies. Isr Med Assoc J. 2009;11:440–1. PubMed PMID: 19911499.

*(68 year old man developed fever, rash and jaundice while taking atorvastatin for unknown duration [bilirubin 7.4 mg/dL, ALT 250 U/L, Alk P 555 U/L, ANA and AMA positive], recovering upon stopping but recurring three times after restarting atorvastatin, eventually resolving completely on stopping permanently).*

Russo MW, Scobey M, Bonkovsky HL. Drug-induced liver injury associated with statins. Semin Liver Dis. 2009;29:412–22. PubMed PMID: 19826975.

*(Review of statin hepatotoxicity and the several forms of liver injury that can occur with atorvastatin, including silent aminotransferase elevations, cholestatic and hepatocellular hepatitis and an autoimmune hepatitis-like syndrome, all of which are rare; two case reports, one with an autoimmune hepatitis [bilirubin 1.0 rising to 12.5, ALT 1750 U/L, Alk P 285 U/L, ANA 1:160] responding to prednisone and one with an acute hepatitis-like onset, but subsequent cholestatic hepatitis [bilirubin 7.8 rising to 30 mg/dL, ALT 6200 U/L, Alk P 280 U/L, ANA negative], with slow but ultimately complete recovery).*

Athyros VG, Tziomalos K, Gossios TD, Griva T, Anagnostis P, Kargiotis K, Pagourelias ED, et al; GREACE Study Collaborative Group. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. Lancet. 2010;376(9756):1916–22. PubMed PMID: 21109302.

*(Among 1600 patients with coronary artery disease treated with statins or standard therapy, mean ALT levels decreased in statin treated patients [57 to 37 U/L], but not in controls [56 to 63 U/L]; 7 of 880 statin treated patients stopped therapy because of ALT elevations, but none developed clinically apparent liver injury).*

Liu Y, Cheng Z, Ding L, Fang F, Cheng KA, Fang Q, Shi GP. Atorvastatin-induced acute elevation of hepatic enzymes and the absence of cross-toxicity of pravastatin. Int J Clin Pharmacol Ther. 2010;48:798–802. PubMed PMID: 21084035.

*(Two men, ages 58 and 53 years, developed ALT elevations within 3 days of starting atorvastatin [peak ALT 120 and 278 U/L], resolving on stopping and not recurring on starting pravastatin).*

Athyros VG, Tziomalos K, Karagiannis A, Mikhailidis DP. Atorvastatin: safety and tolerability. Expert Opin Drug Saf. 2010;9:667–74. PubMed PMID: 20553090.

*(Review of safety of atorvastatin concluded that liver toxicity is rare).*

Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ. 2010;340:c2197. PubMed PMID: 20488911.

*(Among 225,992 new users of statins in a UK health database, there was an increased relative risk of "moderate or serious liver dysfunction" [ALT > 3 times ULN] in the range of 1.4- to 2.0-fold compared to nonusers, being higher with higher doses and during the first year of treatment; rates were highest for fluvastatin and lowest for pravastatin; rates for atorvastatin were 0.15%-0.17% per person year).*

Merli M, Bragazzi MC, Giubilo F, Callea F, Attili AF, Alvaro D. Atorvastatin-induced prolonged cholestasis with bile duct damage. Clin Drug Investig. 2010;30:205–9. PubMed PMID: 20155993.

*(72 year old man developed jaundice 6 weeks after starting atorvastatin [bilirubin 22 mg/dL, ALT 81 U/L, Alk P 816 U/L, ANA negative], ALT elevations resolving in 5 and Alk P in 8 months).*

Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol. 2010;105:2396–404. PubMed PMID: 20648003.

*(Among 313 cases of drug induced liver injury seen over a 12 year period at a large hospital in Bangalore, India, 5 [2%] were attributed to atorvastatin, but no other statin listed].*

Idilman R, Bektas M, Cinar K, Toruner M, Cerit ET, Doganay B, Erden E, et al. The characteristics and clinical outcome of drug-induced liver injury: a single-center experience. J Clin Gastroenterol. 2010;44:e128–32. PubMed PMID: 20551776.

*(Among 170 patients with drug induced liver injury seen at a single referral center in Turkey between 2001 and 2007, 14 were attributed to statins which were hepatocellular in 10 and cholestatic in 4; no details provided).*

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010;52:2065–76. PubMed PMID: 20949552.

*(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 [11%] were attributed to drug induced liver injury, of which 6 [4.5%] were attributed to statins: 2 atorvastatin, 2 simvastatin [one with ezetimibe] and 2 cerivastatin).*

Conard S, Bays H, Leiter LA, Bird S, Lin J, Hanson ME, Shah A, Tershakovec AM. Ezetimibe added to atorvastatin compared with doubling the atorvastatin dose in patients at high risk for coronary heart disease with diabetes mellitus, metabolic syndrome or neither. Diabetes Obes Metab. 2010;12:210–8. PubMed PMID: 20151997.

*(Randomized trial comparing addition of ezetimibe to atorvastatin versus doubling the dose [40 to 80 mg daily] in 556 patients; only 1 patient in each group had ALT or AST elevations >3 times ULN during a 6 week period).*

Saku K, Zhang B, Noda K; The PATROL Trial Investigators. Randomized Head-to-Head Comparison of Pitavastatin, Atorvastatin, and Rosuvastatin for Safety and Efficacy (Quantity and Quality of LDL). Circ J. 2011;75(6):1493–505. PubMed PMID: 21498906.

*(Among 298 patients treated with one of three statins for 16 weeks, ALT elevations occurred in 5% on atorvastatin, 1% on rosuvastatin and 4% of pitavastatin, but overall the three agents had similar efficacy and similar rates of toxicity).*

Foster T, Budoff MJ, Saab S, Ahmadi N, Gordon C, Guerci AD. Atorvastatin and antioxidants for the treatment of nonalcoholic fatty liver disease: the St Francis Heart Study randomized clinical trial. Am J Gastroenterol. 2011;106:71–7. PubMed PMID: 20842109.

*(Among 1005 patients given atorvastatin with vitamin C and E for up to 4 years, 3 patients had ALT elevations >2 times ULN, but therapy appeared to decrease intrahepatic fat as assessed by CT scans).*

Mackay J, Fenech M, Myint K. Acute rhabdomyolysis caused by combination therapy with atorvastatin and warfarin. Br J Hosp Med (Lond). 2012;73:106–7. PubMed PMID: 22504754.

*(69 year old man on long term atorvastatin therapy developed rhabdomyolysis and marked rise in INR after starting warfarin, suggesting a drug-drug interaction).*

Jackevicius CA, Chou MM, Ross JS, Shah ND, Krumholz HM. Generic atorvastatin and health care costs. N Engl J Med. 2012;366:201–4. PubMed PMID: 22149736.

*(Atorvastatin became available generically in 2011 which may result in considerable health care savings).*

Bergmann OM, Kristjansson G, Jonasson JG, Björnsson ES. Jaundice due to suspected statin hepatotoxicity: a case series. Dig Dis Sci. 2012;57:1959–64. PubMed PMID: 22075853.

*(3 women and 1 man, ages 55 to 85 years, developed jaundice 3, 3, 11 and 30 months after starting atorvastatin [n=3] or simvastatin [n=1], with hepatocellular or mixed injury [peak bilirubin 4.0-7.4 mg/dL, ALT 446-2987 U/L, Alk P 174-716 U/L, ANA positive in 1], all resolving spontaneously in 1-3 months).*

Björnsson E, Jacobsen EI, Kalaitzakis E. Hepatotoxicity associated with statins: reports of idiosyncratic liver injury post-marketing. J Hepatol. 2012;56:374–80. PubMed PMID: 21889469.

*(Between 1988 and 2010, the Swedish registry received 217 adverse event reports possibly related to statins, 124 [57%] being liver related, 73 of which could be evaluated: 2 were fatal and one led to liver transplant; 3 had positive rechallenge; 43 [59%] were hepatocellular, 22 [30%] cholestatic and 8 [11%] mixed; 30 were due to atorvastatin, 28 simvastatin, 11 fluvastatin, 2 pravastatin and 2 rosuvastatin, arising after 30-248 days; atorvastatin injury was more likely to be cholestatic and was estimated to occur in 2.9 per 100,000 person years).*

Han KH, Rha SW, Kang HJ, Bae JW, Choi BJ, Choi SY, Gwon HC, et al. Evaluation of short-term safety and efficacy of HMG-CoA reductase inhibitors in hypercholesterolemic patients with elevated serum alanine transaminase concentrations: PITCH study (PITavastatin versus atorvastatin to evaluate the effect on patients with hypercholesterolemia and mild to moderate hepatic damage). J Clin Lipidol. 2012;6:340–51. PubMed PMID: 22836071.

*(Among 189 patients with hypercholesterolemia and ALT elevations [50-100 U/L] treated with pitavastatin vs atorvastatin for 12 weeks, there were minor ALT decreases in both groups; no placebo arm was included).*

Berkelhammer C, Lerma EV. Statin treatment in patients with elevated liver enzymes: pitch to proceed. J Clin Lipidol. 2012;6:310–1. PubMed PMID: 22836066.

*(Editorial regarding Han [2012] stressing that chronic but stable ALT elevations are not a contraindication to use of statins).*

Kwon H, Lee SH, Kim SE, Lee JH, Jee YK, Kang HR, Park BJ, Park JW, Hong CS. Spontaneously reported hepatic adverse drug events in Korea: multicenter study. J Korean Med Sci. 2012;27:268–73. PubMed PMID: 22379337.

*(Summary of 2 years of adverse event reporting in Korea; of 9360 reports, 567 were liver related, including 7 [1.2%] attributed to statins).*

Scarpini F, Cappellone R, Auteri A, Puccetti L. Role of genetic factors in statins side-effects. Cardiovasc Hematol Disord Drug Targets. 2012;12:35–43. PubMed PMID: 22524173.

*(Genetic variants in several genes appear to affect the frequency of side effects of statins, but to varying degrees with various statins and with different side effects).*

DeGorter MK, Tirona RG, Schwarz UI, Choi YH, Dresser GK, Suskin N, Myers K, et al. Clinical and pharmacogenetic predictors of circulating atorvastatin and rosuvastatin concentrations in routine clinical care. Circ Cardiovasc Genet. 2013;6:400–8. PubMed PMID: 23876492.

*(Measurement of plasma levels of atorvastatin and rosuvastatin in two cohorts [299 and 576 patients] found levels varied 45-fold and were consistently higher in Chinese and Japanese compared to European subjects and that*

*differences could not be completely explained by racial variation in frequencies of SLCO and ABCG2 polymorphisms known to affect peak drug levels).*

Liu Y, Su Q, Li L. Efficacy of short-term high-dose atorvastatin pretreatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a meta-analysis of nine randomized controlled trials. Clin Cardiol. 2013;36:E41–8. PubMed PMID: 24038054.

*(Metanalysis of 3 trials of high dose, short term atorvastatin in 333 patients with an acute coronary event undergoing percutaneous coronary interventions stenting found no increase in rate of serum ALT elevations [10% vs 7%], but no details provided and no mention of clinically apparent liver injury).*

Wiliński J, Dabrowski M. Safety and tolerability of the use of atorvastatin 40 mg in common daily practice in short-term observation in 3,227 patients. Przegl Lek. 2013;70:373–6. PubMed PMID: 24052972.

*(Abstract: Prospective questionnaire study of 3227 patients treated with atorvastatin [40 mg daily] found that 0.4% had discontinued therapy because of serum aminotransferase elevations).*

Wu du C. Hepatitis B virus reactivation associated with atorvastatin. Int J Infect Dis. 2013;17:e1069–70. PubMed PMID: 23725984.

*(48 year old man with HBsAg [HBeAg negative] and coronary artery disease had worsening of hepatitis B after 8 months of atorvastatin therapy [ALT rising from 41 to 322 U/L and HBV DNA from 3.3 to 6.8 log10 IU/mL], improving upon stopping and not worsening when treated with simvastatin).*

Tikkanen MJ, Fayyad R, Faergeman O, Olsson AG, Wun CC, Laskey R, Kastelein JJ, et al. IDEAL Investigators. Effect of intensive lipid lowering with atorvastatin on cardiovascular outcomes in coronary heart disease patients with mild-to-moderate baseline elevations in alanine aminotransferase levels. Int J Cardiol. 2013;168:3846–52. PubMed PMID: 24001698.

*(Post hoc analysis of the IDEAL study of 8863 patients with hypercholesterolemia treated with simvastatin [20-40 mg daily] vs atorvastatin [80 mg daily], comparing those with normal ALT levels [7782, mean = 26 U/L] to those with elevated levels [1081, mean = 61 U/L], found improvement in cardiovascular outcomes with atorvastatin in both the normal [12.7% vs 13.9%] and high ALT [6.5% vs 11.5%] groups, rates being higher and the effect greater in the elevated ALT cohort).*

Thapar M, Russo MW, Bonkovsky HL. Statins and Liver Injury. Gastroenterol Hepatol (N Y). 2013;9:605–6. PubMed PMID: 24729773.

*(Review of the hepatotoxicity of statins including both serum enzyme elevations and clinically apparent liver injury).*

Demyen M, Alkhalloufi K, Pyrsopoulos NT. Lipid-lowering agents and hepatotoxicity. Clin Liver Dis. 2013;17:699–714. PubMed PMID: 24099026.

*(Review of hepatotoxicity of statins, fibrates, niacin, bile acid resins and ezetimibe).*

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology. 2013;144:1419–25. PubMed PMID: 23419359.

*(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, including 2 cases attributed to atorvastatin [one with jaundice] for an estimated rate of 1:3693 persons treated).*

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A, Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol. 2014;13:231–9. PubMed PMID: 24552865.

*(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, none of which were attributed to statins or lipid lowering agents).*

Russo MW, Hoofnagle JH, Gu J, Fontana RJ, Barnhart H, Kleiner DE, Chalasani N, et al. Spectrum of statin hepatotoxicity: Experience of the drug-induced liver injury network. Hepatology. 2014;60:679–86. PubMed PMID: 24700436.

*(Among 1,188 cases of drug induced liver disease collected in the US between 2004 to 2012, 22 [2%] were attributed to statins, including atorvastatin [8], simvastatin [5], rosuvastatin [4], fluvastatin [2], pravastatin [2] and lovastatin [1]; median age was 60 years and 68% were women; 9 cases were cholestatic and 12 hepatocellular [6 with autoimmune features]; the latency ranged widely, from 1 month to 10 years; only one case was fatal [a man with preexisting cirrhosis presenting with acute-on-chronic liver failure]).*

Bays H, Cohen DE, Chalasani N, Harrison SA. An assessment by the Statin Liver Safety Task Force: 2014 update. J Clin Lipidol. 2014;8(3 Suppl):S47–57. PubMed PMID: 24793441.

*(Review of the safety of statins including their use in patients with liver disease recommending that liver tests be obtained before therapy, but that routine monitoring is not necessary and that statins can be safety used in patients with nonalcoholic liver disease, and are probably safe in other forms of chronic liver disease and after liver transplantation).*

Ooba N, Sato T, Wakana A, Orii T, Kitamura M, Kokan A, Kurata H, et al. A prospective stratified case-cohort study on statins and multiple adverse events in Japan. PLoS One. 2014;9:e96919. PubMed PMID: 24810427.

*(Among 6877 patients started on statins between 2008 and 2010, 139 developed an increase in ALT or AST deemed likely due to the drug with no significant differences among those treated with pra-, ator-, flu-, pita- or rosuvastatin).*

Macedo AF, Taylor FC, Casas JP, Adler A, Prieto-Merino D, Ebrahim S. Unintended effects of statins from observational studies in the general population: systematic review and meta-analysis. BMC Med. 2014;12:51. PubMed PMID: 24655568.

*(Systematic review of 90 studies of 48 different "unintended effects" of statins with evidence of an increased risk of myopathy [Odds Ratio: OR=2.6] and raised liver enzymes [OR=1.5]).*

Drugs for lipids. Treat Guidel Med Lett. 2014;12(137):1–6. PubMed PMID: 24419209.

*(Concise recommendations on management of hyperlipidemia mentions that 1-2% of patients on high doses of statins develop ALT elevations [above 3 times ULN], but that there is not always cross sensitivity to this side effect and that patients with mild-to-moderate ALT elevations can tolerate statins; no discussion of clinically apparent liver).*

Vishwakarma P, Nehra R, Kumar A. Acute hepatic injury with atorvastatin: an unusual occurrence. Indian J Pharmacol. 2014;46:343–4. PubMed PMID: 24987187.

*(63 year old man developed jaundice 2 months after starting 20 mg daily of atorvastatin [bilirubin 5.2 mg/dL, ALT 1124 U/L, Alk P 214 U/L], falling to normal within a month of switching to 10 mg daily of rosuvastatin).*

Bastida C, Also MA, Pericas JM, Letang E, Tuset M, Miró JM. Enferm Infec Microbiol Clin. 2014;32:579–82. [Rhabdomyolysis and severe hepatotoxicity due to a drug-drug interaction between ritonavir and simvastatin]. Spanish.

*(52 year old woman with HIV infection on darunavir/ritonavir, lamivudine and raltegravir was switched from atorvastatin [40 mg] to simvastatin [80 mg] daily and developed rhabdomyolysis 3 weeks later [bilirubin 0.5 mg/dL, ALT 787 U/L, CK 34,960 U/L], possibly due to drug-drug interactions between simvastatin and ritonavir).*

Ivandić E, Bašić-Jukić N. Acta Med Croatica. 2014;68:175–8. [Liver damage caused by atorvastatin and cyclosporine in patients with renal transplant]. Croatian. PubMed PMID: 26012156.

*(61 year old male renal transplant recipient on cyclosporine developed elevations in liver tests 3 months after starting atorvastatin for hypercholesterolemia [ALT 424 U/L, Alk P 261 U/L, bilirubin not given], which fell to normal after stopping the statin and switching from cyclosporine to everolimus).*

Kalantari S, Naghipour M. Statin therapy and hepatotoxicity: appraisal of the safety profile of atorvastatin in hyperlipidemic patients. Adv Biomed Res. 2014;3:168. PubMed PMID: 25221771.

*(Among 206 patients started on atorvastatin in a "semi-experimental" study, "in general ALT and AST remained in the normal range").*

Perdices EV, Medina-Cáliz I, Hernando S, Ortega A, Martín-Ocaña F, Navarro JM, Peláez G, et al. Hepatotoxicity associated with statin use: analysis of the cases included in the Spanish Hepatotoxicity Registry. Rev Esp Enferm Dig. 2014;106:246–54. PubMed PMID: 25075655.

*(Among 858 cases of drug induced liver injury enrolled in a Spanish Registry between 1994 and 2012, 47 [5.5%] were attributed to statins [16 atorvastatin, 13 simvastatin, 12 fluvastatin, 4 lovastatin and 2 pravastatin], usually with a hepatocellular pattern of injury, 8.5% with autoimmune features, chronic injury in 19%, and no liver related deaths).*

Chen GL, Hsiao FY, Dong YH, Shen LJ, Wu FL. Statins and the risk of liver injury: a population-based case-control study. Pharmacoepidemiol Drug Saf. 2014;23:719–25. PubMed PMID: 24829162.

*(Among 2165 Taiwanese patients hospitalized for liver injury between 2002 and 2009, use of statins was not more frequent than among 16,600 hospitalized controls, except for use of high doses of rosuvastatin [adjusted odds ratio of 2.29]).*

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology. 2015;148:1340–52.e7. PubMed PMID: 25754159.

*(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 31 cases [3.4%] were attributed to statins, including 8 to atorvastatin, 8 simvastatin, 7 rosuvastatin, 4 pravastatin, 2 fluvastatin and 2 lovastatin).*

Carrascosa MF, Salcines-Caviedes JR, Lucena MI, Andrade RJ. Acute liver failure following atorvastatin dose escalation: is there a threshold dose for idiosyncratic hepatotoxicity? J Hepatol. 2015;62:751–2. PubMed PMID: 25463547.

*(85 year old woman on atorvastatin for more than a year developed jaundice after increasing dose from 40 to 80 mg daily [bilirubin 4.1 mg/dL, ALT 909 U/L, Alk P 415 U/L, CK 4753 U/L, INR 1.71], with transient worsening, but ultimate improvement and resolution).*

Chang CH, Chang YC, Lee YC, Liu YC, Chuang LM, Lin JW. Severe hepatic injury associated with different statins in patients with chronic liver disease: a nationwide population-based cohort study. J Gastroenterol Hepatol. 2015;30:155–62. PubMed PMID: 25041076.

*(Among 37,929 Taiwanese persons with chronic liver disease started on statin therapy for hyperlipidemia between 2005 and 2009, there were 912 incident cases of hospitalization for liver injury, rates being similar for the 6 different statins used [1.94-2.95 per 100,000 person-days], but higher in those on high doses of atorvastatin [40 or 80 mg daily]).*

Birmingham BK, Bujac SR, Elsby R, Azumaya CT, Wei C, Chen Y, Mosqueda-Garcia R, et al. Impact of ABCG2 and SLCO1B1 polymorphisms on pharmacokinetics of rosuvastatin, atorvastatin and simvastatin acid in Caucasian and Asian subjects: a class effect? Eur J Clin Pharmacol. 2015;71:341–55. PubMed PMID: 25673568.

*(Among 96 subjects treated in an open-label, 3-way crossover study of a single oral dose of rosuvastatin [20 mg], atorvastatin [40 mg], or simvastatin [40%], Chinese and Japanese subjects had higher plasma levels than European subjects, and the differences could not be attributed entirely to hepatic transporter polymorphisms {SLCO1B1*1a and ABCG2c.421] known to be associated with higher statin levels).*

Kim HS, Lee SH, Kim H, Lee SH, Cho JH, Lee H, Yim HW, et al. Statin-related aminotransferase elevation according to baseline aminotransferases level in real practice in Korea. J Clin Pharm Ther. 2016;41:266–72. PubMed PMID: 27015878.

*(Among 21,233 Korean patients starting statin therapy between 2009 and 2013, abnormal ALT or AST values above 3 times ULN were more frequent among those with mild baseline elevations).*

Clarke AT, Johnson PC, Hall GC, Ford I, Mills PR. High dose atorvastatin associated with increased risk of significant hepatotoxicity in comparison to simvastatin in UK GPRD cohort. PLoS One. 2016;11:e0151587. PubMed PMID: 26983033.

*(Analysis of the Clinical Practice Research Database of UK patients initiating statin treatment between 1997 and 2006 identified 71 of 76,411 developing liver dysfunction while on atorvastatin [0.09%] vs 101 of 164,407 on simvastatin [0.06%], rates being higher with higher [40 or 80 mg] vs lower [10 or 20 mg] doses of atorvastatin [0.44% vs 0.07%], but not with higher vs lower doses of simvastatin [0.09% vs 0.05%]).*

Wang LY, Huang YS, Perng CL, Huang B, Lin HC. Statin-induced liver injury in an area endemic for hepatitis B virus infection: risk factors and outcome analysis. Br J Clin Pharmacol. 2016;82:823–30. PubMed PMID: 27197051.

*(Analysis of the Taipei Veterans Hospital database from 2008 to 2012 identified 108 patients with statin-associated liver injury [including 28 rosu-, 20 flu-, 17 sim-, 11 pra-, 8 lo-, and 8 pita-vastatin] most of which 75 [69%] were mild and only one fatal [80 year old on rosu-], and there were no differences in disease features or peak enzyme or bilirubin levels between HBsAg positive vs negative subjects [n=16 vs 92]).*

Björnsson ES. Hepatotoxicity of statins and other lipid-lowering agents. Liver Int. 2017;37:173–8. PubMed PMID: 27860156.

*(Review of the hepatotoxicity of statins mentions that atorvastatin has been the most frequently implicated statin [accounting for 30-40% of cases] in drug induced liver injury estimated to arise in 1 in 17,000 users, cholestatic in 56% and with autoimmune features in 10% and rarely fatal).*

Bergland Ellingsen S, Nordmo E, Lappegård KT. Recurrence and severe worsening of hepatotoxicity after reintroduction of atorvastatin in combination with ezetimibe. Clin Med Insights Case Rep. 2017;10:1179547617731375. PubMed PMID: 28979175.

*(After an acute myocardial infarction, a 70 year old woman was treated with simvastatin in doses of 40 and 80 mg and then with atorvastatin [40 mg], but developed elevated ALT levels [69 to 123 U/L] and was switched to pravastatin, but then was switched to atorvastatin with ezetimibe and developed fatigue and weakness 2 months later [bilirubin 4.3 mg/dL, ALT 2003 U/L, Alk P 164 U/L], which resolved rapidly once atorvastatin was again discontinued).*

Liang X, He Q, Zhao Q. Effect of stains on LDL reduction and liver safety: a systematic review and meta-analysis. Biomed Res Int. 2018;2018:7092414. PubMed PMID: 29693013.

*(In a systematic review of 16 controlled trials of statins in 74,078 patients, rates of liver test abnormalities were higher with statin therapy [odds ratio, OR=1.18] but this was significant only for fluvastatin [OR=3.5] and with higher doses [40-80 mg daily] [OD=3.6] and was not significant for statins used at low or moderate doses).*

Teschke R. Top-ranking drugs out of 3312 drug-induced liver injury cases evaluated by the Roussel Uclaf Causality Assessment Method. Expert Opin Drug Metab Toxicol. 2018;14:1169–1187. PubMed PMID: 30354694.

*(A compilation of national and international databases on drug induced liver injury identified the ten top-ranking causes which included two statins, atorvastatin [ranking 3rd] and simvastatin [ranking 6th]).*

Moore N, Duret S, Grolleau A, Lassalle R, Barbet V, Duong M, Thurin N, et al. Previous drug exposure in patients hospitalised for acute liver injury: a case-population study in the French National Healthcare Data System. Drug Saf. 2019;42:559–572. PubMed PMID: 30361989.

*(Analysis of a French nationwide health database for medication use and hospitalizations for unexplained acute liver injury identified 4807 cases, 76% of which had been exposed to at least one medication in the previous 7-60 days, 263 cases [5.5%] had taken atorvastatin, but the exposed/case ratio was 15,742; 182 cases [3.8%} had taken rosuvastatin, the exposed/case ratio being 20,359; while only 10 cases had taken pyrazinamide but with an exposed/case ratio of 770).*

Yebyo HG, Aschmann HE, Kaufmann M, Puhan MA. Comparative effectiveness and safety of statins as a class and of specific statins for primary prevention of cardiovascular disease: A systematic review, meta-analysis, and network meta-analysis of randomized trials with 94,283 participants. Am Heart J. 2019;210:18–28. PubMed PMID: 30716508.

*(Metaanalyses of 40 trials of statins that enrolled 94,283 patients followed for a median of 1 year for efficacy and safety reported that statins as a class increased the risk of hepatic dysfunction by 6% with fluvastatin having the highest relative risk).*

Godinho R, Bugnon S, Gracin T, Tataw J. Severe rhabdomyolysis-induced acute kidney injury following concomitant use of Genvoya® (EVG/COBI/FTC/TAF) and simvastatin; a case report. BMC Nephrol. 2019;20:69. PubMed PMID: 30808332.

*(54 year old man with HIV infection, chronic hepatitis C, acute hepatitis A and hypercholesterolemia on simvastatin developed myalgias, weakness and worsening jaundice 10 days after switching antiretroviral regimen to a fixed combination of elvitegravir, emtricitabine, tenofovir and cobicistat a potent inhibitor of CYP 3A4 [ALT 2081 U/L, AST 7017 U/L, GGT 198 U/L, bilirubin 7.6 mg/dL, CPK 185,190 U/L and creatinine 6.1 mg/dL], improving ultimately after stopping the antiretroviral combination regimen).*

Lipid-lowering drugs. Med Lett Drugs Ther. 2019;61(1565):17–24. PubMed PMID: 30845106.

*(Concise review of the mechanism of action, relative efficacy, safety and costs of lipid lowering drugs including statins, ezetimibe, PCSK9 inhibitors, bile acid sequestrants, fibric acid derivatives niacin and fish oil, mentions that statin therapy is associated with ALT elevations above 3 times ULN in 1-3% of patients but "whether statins actually cause liver damage is unclear").*

Laube R, Liu K. An unwanted complement: rare case of potential liver injury induced by an interaction between ginseng and atorvastatin. Br J Clin Pharmacol. 2019;85:1612–1613. PubMed PMID: 30980549.

*(82 year old man on atorvastatin [80 mg daily] for 5 years with normal ALT levels found to have elevated values 1 week after starting a herbal product with ginseng [ALT 931 U/L, Alk P 253 U/L, bilirubin 2.4 mg/dL, INR 1.1, CPK 350 U/L], resolving rapidly on stopping both the statin and ginseng which may have altered metabolism of atorvastatin by inhibition of CYP 3A4 and OATP1B1).*

Hung TH, Tsai CC, Lee HF. Statin use in cirrhotic patients with infectious diseases: A population-based study. PLoS One. 2019;14:e0215839. PubMed PMID: 31017946.

*(Analysis of the Taiwan National Health Insurance Database identified 816 patients with cirrhosis receiving statins [including atorvastatin] who were hospitalized for bacterial infections and similar number of cirrhotic controls not on statins, found a lower 30-day mortality with statins: 5.3% vs 9.8%).*

Mohamed MFH, Salameh OK, Saeed AAM. Statin-induced rhabdomyolysis, acute kidney injury, and hepatitis leading to death. Am J Case Rep. 2019;20:709–712. PubMed PMID: 31101801.

*(67 year old man with coronary artery disease developed muscle pains 2 months and jaundice 4 months after starting atorvastatin in a dose of 40 mg daily [bilirubin 7.2 mg/dL, ALT 1325 U/L, Alk P 249 U/L, CPK 18,267 U/L, creatinine 5.5 mg/dL], with progressive renal and hepatic failure; death from cardiac arrest).*

Kuniyoshi N, Miyakawa H, Matsumoto K, Tsunashima H, Sekine K, Tsujikawa T, Mabuchi M, et al. Detection of anti-mitochondrial antibodies accompanied by drug-induced hepatic injury due to atorvastatin. Intern Med. 2019;58:2663–2667. PubMed PMID: 31178503.

*(44 year old Japanese woman developed fatigue 10 months after starting atorvastatin [bilirubin 07 mg/dL, ALT 84 U/L, Alk P 1557 U/L, AMA 1:40, ANA 1:40, immunoglobulins normal], with slow recovery after stopping).*

Simon TG. When less is more: dosing simvastatin in decompensated cirrhosis. Lancet Gastroenterol Hepatol. 2020;5:3–5. PubMed PMID: 31607676.

*(Editorial in response to Pose et al [2020] discusses the possible beneficial effects of statins in patients with cirrhosis and the issue of increased rate of muscle toxicity with 40 vs to 20 mg daily).*

Pose E, Napoleone L, Amin A, Campion D, Jimenez C, Piano S, Roux O, et al. Safety of two different doses of simvastatin plus rifaximin in decompensated cirrhosis (LIVERHOPE-SAFETY): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Gastroenterol Hepatol. 2020;5:31–41. PubMed PMID: 31607677.

*(Among 50 patients with decompensated cirrhosis treated with simvastatin [20 or 40 mg daily] and rifaximin vs placebo for 12 weeks, 3 of 16 patients on 40 mg of simvastatin developed muscle pains and marked elevations in CPK, ALT and AST whereas the 14 patients on 20 mg did not develop signs of either muscle or liver toxicity).*

Abdallah MA, Ahmed KM, Gohar A, Abdalla AO, Waqas Q, Elgouhari H, Huntington MK. Elevated liver enzymes unmask severe statin-induced muscle injury. Am J Ther. 2020;27:e420–e422. PubMed PMID: 31180927.

*(57 year old woman with coronary artery disease developed fatigue and muscle weakness 12 months after starting atorvastatin [40 mg daily] with elevations in ALT and AST [values not provided], which did not improve with stopping and CPK values found high [5523 U/L] with anti-HMG-CoA, muscle biopsy showing necrosis without inflammation and responding to corticosteroids and IVIG).*

Chapman G, Tanner S. An unusually impressive atorvastatin-induced elevation of serum alkaline phosphatase. BMJ Case Rep. 2020;13:e231839. PubMed PMID: 32047080.

*(90 year old woman with transient ischemic attack developed abnormal liver tests 2 months after starting atorvastatin [40 mg daily] [bilirubin 0.7 mg/dL, ALT 187 U/L, Alk P 940 U/L, GGT 1189 U/L, INR 1.0, ANA and AMA negative], with slow but full recovery 1-3 months after stopping).*

Menon PD, Singh T, Hubbard H, Hackman S, Sharkey FE. Cholangiolytic changes in statin-induced liver injury. Case Rep Pathol. 2020;2020:9650619. PubMed PMID: 32099709.

*(A 58 year old Hispanic woman with diabetes developed abdomen pain and abnormal liver tests having been on atorvastatin for several years [bilirubin 1.5 mg/dL, ALT 748 U/L, Alk P 826 U/L, AMA and ANA negative, IgG 2700 mg/dL], abnormalities persisting until atorvastatin was stopped, 3 months after which liver tests fell to normal).*

Courlet P, Livio F, Alves Saldanha S, Scherrer A, Battegay M, Cavassini M, Stoeckle M, et al; Swiss HIV Cohort Study. Real-life management of drug-drug interactions between antiretrovirals and statins. J Antimicrob Chemother. 2020;75:1972–1980. PubMed PMID: 32240298.

*(Assessment of lipid levels in person living with HIV who were taking atorvastatin found that one-third had suboptimal lipid control despite high doses, perhaps due to drug-drug interactions including inhibition of OATP1b1 causing poor hepatic uptake of statins).*

Kawasaki E, Fukuyama T, Kuriyama E, Uchida A, Sagara Y, Tamai H, Nakano Y, et al. Statin-induced autoimmune hepatitis in patients with type 1 diabetes: A report of two cases and literature review. J Diabetes Investig. 2020;11:1673–1676. PubMed PMID: 32277861.

*(Two men, ages 46 and 54, with type 1 diabetes developed hepatitis 6 and 8 months after starting atorvastatin and rosuvastatin [bilirubin 5.1 and unknown mg/dL, ALT 1632 and 709 U/L, Alk P not given and 2055 U/L, ANA 1:80 and negative, IgG 1495 and 1857 mg/dL], both with autoimmune hepatitis like features on liver biopsy and both with response to corticosteroid therapy).*

Khan AA, Ahmed S, Mohammed A, Elzouki AY. Autoimmune-like drug-induced liver injury caused by atorvastatin and demonstration of the safety profile of pravastatin: a case report and literature review. Cureus. 2020;12:e7299. PubMed PMID: 32313740.

(57 year old woman was found to have abnormal liver tests 3 months after starting 40 mg of atorvastatin daily [bilirubin 7.2 mg/dL, ALT 3195 U/L, Alk P 435 U/L, ANA pos, SMA 1:640, IgG 1210 mg/dL], resolving within 3 months of stopping [SMA 1:80] and later tolerating pravastatin [dose not given]).

Hopewell JC, Offer A, Haynes R, Bowman L, Li J, Chen F, Bulbulia R, et al. Independent risk factors for simvastatin-related myopathy and relevance to different types of muscle symptom. Eur Heart J. 2020;41:3336–3342. PubMed PMID: 32702748.

*(In a combined analysis of 3 large clinical trials in patients with cardiovascular disease treated with simvastatin for a mean of 3.4 years, 171 of 58,390 participants [0.1%] developed myopathy [muscle pain and CK levels above 10 times ULN], and risk was higher with higher doses, in Asian subjects, women, and persons with higher BMI and multiple comorbidities as well as with SLCO1B1 genotype).*

Weersink RA, Alvarez-Alvarez I, Medina-Cáliz I, Sanabria-Cabrera J, Robles-Díaz M, Ortega-Alonso A, García-Cortés M, et al. Clinical characteristics and outcome of drug-induced liver injury in the older patients: from the young-old to the oldest-old. Clin Pharmacol Ther. 2021;109:1147–1158. PubMed PMID: 33179256.

*(Analysis of 882 cases of drug induced liver injury enrolled in the Spanish DILI Registry between 1994 and 2018 analyzed by 4 age groups [<65, 65-74, 75-84, ≥85 years] showed that average severity increased with older age and cases were more likely to be cholestatic, the most frequent causes being amoxicillin-clavulanate, atorvastatin, levofloxacin, ibuprofen and ticlopidine).*

Balasubramanian R, Maideen NMP. HMG-CoA reductase inhibitors (statins) and their drug interactions involving CYP enzymes, P-glycoprotein and OATP transporters-an overview. Curr Drug Metab. 2021;22:328–341. PubMed PMID: 33459228.

*(Systematic review of literature on drug-drug interactions with statins and their clinical significance mentions that toxicity can be enhanced by inhibitors of CYP3A4 [ator-, sim- and lo-vastatin] as well as by inhibitors of P glycoprotein and OATP1B1 [most statins including atorvastatin], with specific recommendations for the most common inhibitors).*

Pedraza L, Laosa O, Rodríguez-Mañas L, Gutiérrez-Romero DF, Frías J, Carnicero JA, Ramírez E. Drug induced liver injury in geriatric patients detected by a two-hospital prospective pharmacovigilance program: a comprehensive analysis using the Roussel Uclaf Causality Assessment Method. Front Pharmacol. 2021;11:600255. PubMed PMID: 33613279.

*(Among 458 cases of drug induced liver injury in elderly patients [age 65 or older] seen at two Spanish medical centers over a 2- and 8-year period, the most frequent causes were acetaminophen [n=50], amoxicillin-clavulanate [n=42] and atorvastatin [n=37], the latter being mostly mild [65%], mean age 77 years, 51% hepatocellular, none fatal, and all except one resolving; among hospitalized subjects the estimated incidence was 37 per 10,000 defined drug-days).*

Sung S, Al-Karaghouli M, Kalainy S, Cabrera Garcia L, Abraldes JG. A systematic review on pharmacokinetics, cardiovascular outcomes and safety profiles of statins in cirrhosis. BMC Gastroenterol. 2021;21:120. PubMed PMID: 33726685.

*(Systematic review of literature suggests that rosuvastatin and pitavastatin pharmacokinetics are unchanged in patients with Child's Class A cirrhosis as opposed to atorvastatin and pravastatin, although unlike rosuvastatin, simvastatin, atorvastatin and pravastatin have been assessed in clinical trials in cirrhotic patients).*

Onfiani G, Nascimbeni F, Carubbi F. A case of statin-induced liver injury with positive rechallenge with a second statin. Is there a class effect? J Basic Clin Physiol Pharmacol. 2021 Apr 21. Epub ahead of print. PubMed PMID: 33882199.

*(58 year old woman on long term simvastatin therapy developed ALT elevations 2 months after dose increase from 10 mg to 20 mg daily [ALT 314 U/L] without symptoms, Alk P or bilirubin elevations which was normal 2 months after stopping but was elevated again without symptoms or jaundice 2 months after starting rosuvastatin in a dose of 5 mg daily [ALT 542 U/L], slowly falling to normal 5 months after stopping statins a second time).*

Saha A, Garg A. Severe liver injury associated with high-dose atorvastatin therapy. J Investig Med High Impact Case Rep. 2021;9:23247096211014050. PubMed PMID: 33966478.

*(71 year old man with hyperlipidemia, diabetes, hypertension and chronic renal dysfunction developed abnormal liver tests 3 months after starting pioglitazone and atorvastatin [80 mg daily], having tolerated simvastatin in doses of 20 to 40 mg daily for years [bilirubin 1.5 mg/dL, ALT 1385 U/L, Alk P 265 U/L, INR 1.0], with rapid improvement and normal tests one month after stopping both drugs, but later tolerating restarting simvastatin and pioglitazone).*

Ortland I, Mirjalili M, Kullak-Ublick GA, Peymani P. Drug-induced liver injury in Switzerland: an analysis of drug-related hepatic disorders in the WHO pharmacovigilance database VigiBase™ from 2010 to 2020. Swiss Med Wkly. 2021;151:w20503. PubMed PMID: 34000058.

*(Analysis of the global VigiBase for drug induced liver injury identified 2042 cases reported from Switzerland, the most commonly implicated agents being acetaminophen, amoxicillin-clavulanate, esomeprazole, and atorvastatin).*

Lu B, Sun L, Seraydarian M, Hoffmann TJ, Medina MW, Risch N, Iribarren C, et al. Effect of SLCO1B1 T521C on statin-related myotoxicity with use of lovastatin and atorvastatin. Clin Pharmacol Ther. 2021;110:733–740. PubMed PMID: 34114646.

*(Among 233 patients with statin associated myopathy and 2342 controls selected from an aging cohort with genetic testing, the allele frequency of c.521T>C in SLCO1B1 [rs4149056] was higher in those with myopathy, C allele frequency being 14%-15% of controls compared to 17% of atorvastatin [p=0.4], 19% of lovastatin [p<0.001], and 25% of simvastatin [p<0.001] myopathy cases).*

Cai T, Abel L, Langford O, Monaghan G, Aronson JK, Stevens RJ, Lay-Flurrie S, et al. Associations between statins and adverse events in primary prevention of cardiovascular disease: systematic review with pairwise, network, and dose-response meta-analyses. BMJ. 2021;374(n1537) PubMed PMID: 34261627.

*(Systematic review of placebo controlled trials of statins for cardiovascular disease prevention identified 62 publications with 120,456 patients and found an increased risk of muscle symptoms, liver test abnormalities, renal insufficiency and eye conditions for all 7 statins, but not muscle disorders or diabetes; rosuvastatin having relatively high risk for muscle symptoms and renal abnormalities and also was also associated with eye conditions and diabetes while atorvastatin and lovastatin had highest risk for liver abnormalities).*