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Fluvastatin

Updated: December 1, 2021.

OVERVIEW

Introduction

Fluvastatin 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

Fluvastatin (floo" va stat' in) is an 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"), fluvastatin lowers total serum cholesterol and low density lipoprotein (LDL) concentrations, thereby reducing the risk of atherosclerosis and its complications – myocardial infarction and stroke. Fluvastatin is indicated for treatment of hypercholesterolemia in persons at high risk for coronary, cerebrovascular and peripheral artery disease and to decrease the risk of mortality from cardiovascular disease. Fluvastatin is available in capsules of 20 and 40 mg and as extended release tablets of 40 and 80 mg generically and under the brand names Lescol and Lescol XL. The recommended daily dose is 20 to 80 mg in one or two divided doses based upon tolerability and lipid levels. Fluvastatin was approved for use in the United States in 1993 and remains a commonly prescribed drug with more than one million prescriptions filled yearly. Common side effects include muscle cramps, joint aches, abdominal pain, nausea, headache 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

Fluvastatin therapy is associated with mild, asymptomatic and usually transient serum aminotransferase elevations in 1% to 5% of patients but in levels above 3 times ULN is approximately 1%. In summary analyses of large scale studies with prospective monitoring, ALT elevations above normal occurred in up to 5% of patients; ALT levels of above 3 times the upper limit of normal (ULN) occurred in 1.1% of fluvastatin treated versus 0.3% of placebo recipients. These elevations were more common with higher doses of fluvastatin. Most of these elevations were self-limited and did not require dose modification. Fluvastatin is the statin most commonly associated with serum aminotransferase elevations and the highest rates of symptomatic liver injury, yet frank, clinically apparent hepatic injury from fluvastatin is still quite rare estimated to occur in 1.7 per 10,000 person years of use. In the few cases that have been reported, the onset of clinical injury has been within 1 to 4 months, the pattern of injury is typically cholestatic or mixed. Rash, fever and eosinophilia are uncommon. At least one

case with features of autoimmunity has been described. Most cases resolve within a few months of onset. Rare cases of acute liver failure and death have been attributed to fluvastatin.

Likelihood score: B (likely rare cause of clinically apparent liver injury).

Mechanism of Injury

The cause of hepatic injury from fluvastatin is unknown. Fluvastatin is largely metabolized in the liver (via several P450 enzymes, largely CYP 2C9) and excreted in bile. The mild, self-limited ALT elevations are likely due to direct hepatotoxicity from an intermediate of drug metabolism and the reversal of these elevations due to adaptation. The idiosyncratic, clinically apparent liver injury associated with fluvastatin may be due to hypersensitivity or to a failure of adaptation.

Outcome and Management

The product label for fluvastatin recommends screening for liver test abnormalities before starting therapy and repeating tests as clinically indicated. In most instances, the minor elevations in serum ALT levels that occur during fluvastatin therapy are self-limited and resolve even with continuation of the drug. Discontinuation is recommended for any elevation above 10 times and for persistent elevations above 5 times the ULN. Cases of clinically apparent hepatic injury from fluvastatin are also usually self-limited and resolve within 1 to 2 months. Cases of chronic hepatitis and vanishing bile duct syndrome have not been reported. In view of the wide scale use of fluvastatin, 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 fluvastatin induced injury is apparently safe, but few instances have been reported, and it should be done with careful monitoring for recurrence.

Drug Class: Antilipemic Agents

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

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Fluvastatin – Generic, Lescol®

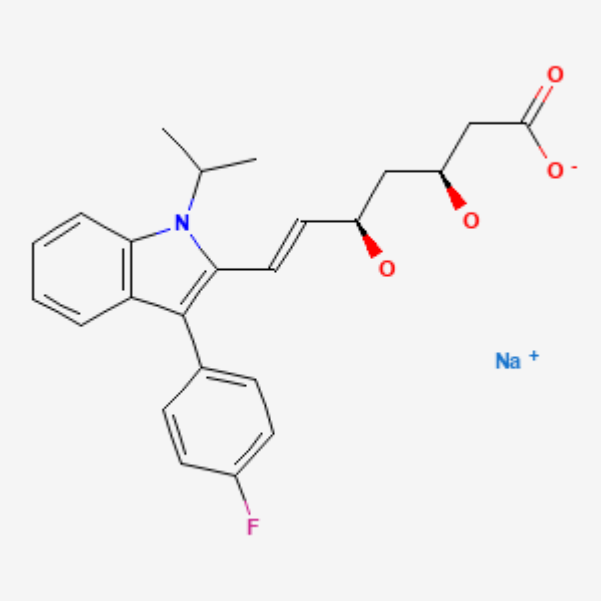
DRUG CLASS

Antilipemic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Fluvastatin	93957-55-2	C24-H26-F-N-O4.Na	

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, mentions that 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 drugs. Lipid regulating agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 526-7.

(Review of hepatotoxicity of lipid lowering agents; elevations in serum enzymes occur in up to 3% of patients, usually within first 3 months of therapy, apparently a class effect).

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).

Jokubaitis LA. Updated clinical safety experience with fluvastatin. Am J Cardiol. 1994;73:18D–24D. PubMed PMID: 8198019.

(Review of safety of fluvastatin from studies of 1881 patients and 747 controls treated for an average of 61 weeks; rates of ALT elevations greater than 3 times ULN were 1.3% with fluvastatin vs 0.5% with placebo).

Jacobson TA, Amorosa LF. Combination therapy with fluvastatin and niacin in hypercholesterolemia: a preliminary report on safety. Am J Cardiol. 1994;73:25D–29D. PubMed PMID: 8198020.

(Controlled trial of fluvastatin vs placebo followed by addition of niacin in 74 patients; ALT elevations occurred in 5.3% on fluvastatin and niacin compared to 6.5% of niacin alone; no case of clinically apparent liver injury).

Gascon A, Zabala S, Iglesuas E. Acute cholestasis during long-term treatment with fluvastatin in a nephrotic patient. Nephrol Dial Transplant. 1999;14:1038. PubMed PMID: 10328507.

(71 year old man developed elevations in ALT [210 U/L], GGT [1818 U/L] and Alk P [472 U/L], without symptoms or jaundice 7 months after starting fluvastatin and 2 months after increasing the dose; serum enzymes returned to normal 2 weeks after stopping and recurred upon restarting [GGT 532 U/L] fluvastatin, but remaining normal after switching to simvastatin).

Lawrence JM, Reckless JP. Fluvastatin. Expert Opin Pharmacother. 2002;3:1631–41. PubMed PMID: 12437496.

(Review of chemistry, pharmacology, metabolism, clinical efficacy and safety of fluvastatin; "All statins may cause elevations in liver function tests, which are usually dose-dependent, and fluvastatin is no exception." Confirmed ALT elevations >3 times ULN occur in 0.2% of patients on 20 mg, 1.5% on 40 mg, and 2.7% on 80 mg of fluvastatin daily).

Hartleb M, Biernat L, Kochel A. Drug-induced liver damage – a three-year study of patients from one gastroenterological department. Med Sci Monit. 2002;8:CR292–6. PubMed PMID: 11951073.

(14 patients with drug induced liver injury seen in one hospital [Silesian Medical University] over 3 year period; amoxicillin/clavulanate in 3, antituberculosis agents in 2, pravastatin in 2, fluvastatin in 1 and 6 other agents in 1 each; fluvastatin case was a 49 year old with onset after 3 weeks of therapy [bilirubin 1.4 mg/dL, ALT 10.5 times and Alk P 5.0 times ULN], ultimately resolving).

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

(Review and discussion of individual lipid lowering agents; little information on fluvastatin).

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, the 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).

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

(Systematic review of 13 large controlled trials of statins with at least 48 weeks of therapy in 43,390 patients; overall odds ratio for liver test abnormalities with statins versus placebo was 1.26; lovastatin 1.78; simvastatin 1.06; pravastatin 1.00, and fluvastatin, 3.54).

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 patients with elevations at baseline).

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 reported between 1984 to 2004 in a Spanish Registry; 11 cases were attributed to "statins", but no specific agent mentioned and none caused more than 4 cases).

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 statin [6.6% vs 1.2%]).

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 greater than 3 times ULN in 1.7% of statin vs 1.4% placebo recipients; event rates highest with atorvastatin, lowest with fluvastatin).

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 attributed to statins were submitted to MedWatch by end of 1999, which gave an estimated rate of 1 per million person years of use; rate of confirmed ALT elevations above 3 times ULN was 0.1% with statins and 0.04% with placebo).

Chen YW, Lai HW, Wang TD. Marked elevation of liver transaminases after high-dose fluvastatin unmasks chronic hepatitis C: safety and rechallenge. Acta Neurol Taiwan. 2007;16:163–7. PubMed PMID: 17966956.

(85 year old woman developed elevations in ALT [409 U/L] 6 weeks after starting fluvastatin [80 mg daily] and was found to have hepatitis C, but restarting fluvastatin and switching to simvastatin also led to ALT elevations; eventually, long term fluvastatin was tolerated and ALT levels returned to normal).

Castiella A, Fernanzez J, Zapata E. Autoimmune hepatitis after treatment with fluvastatin. Liver Int. 2007;27:592. PubMed PMID: 17403199.

(67 year old man developed anicteric hepatitis [ALT 791 U/L, Alk P 1661 U/L, ANA 1:160, HLA-DR3], ultimately requiring prednisone and azathioprine).

Akoglu H, Yilmaz K, Kirkpantur A, Arici M, Altun B, Turgan C. Combined organ failure with combination antihyperlipidemic treatment: a case of hepatic injury and acute renal failure. Ann Pharmacother. 2007;41:143–7. PubMed PMID: 17148651.

(56 year old developed rhabdomyolysis 1 month after starting fluvastatin [bilirubin and Alk P normal, ALT 2100 U/L, LDH 45,758], resolving within 15 days).

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 above 3 times ULN are atorvastatin 0.7%, fluvastatin 1.2%, lovastatin 0.6%, pravastatin 1.4%, rosuvastatin 0% and simvastatin 1.8%; elevations were 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).

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 in the US collected from 2004 to 2008, 3 cases were attributed to atorvastatin, 3 to simvastatin/ezetimibe, and one each to pravastatin, fluvastatin, and simvastatin, but most cases were mild or not always 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).

Neuvonen PJ, Backman JT, Niemi M. Pharmacokinetic comparison of the potential over-the-counter statins simvastatin, lovastatin, fluvastatin and pravastatin. Clin Pharmacokinet. 2008;47:463–74. PubMed PMID: 18563955.

(Review of literature on pharmacokinetics of statins; simvastatin and lovastatin are metabolized extensively by the P450 system and levels are affected by inhibitors or inducers of CYP 3A4 [itraconazole, erythromycin, verapamil, diltiazem, cyclosporine], whereas fluvastatin and pravastatin are minimally, if at all, affected).

Bader T, Fazili J, Madhoun M, Aston C, Hughes D, Rizvi S, Seres K, et al. Fluvastatin inhibits hepatitis C replication in humans. Am J Gastroenterol. 2008;103:1383–9. PubMed PMID: 18410471.

(Open labeled study in 31 men with chronic hepatitis C given fluvastatin at doses of 80 to 320 mg daily for 2-12 weeks; no worsening of serum ALT levels and slight decrease in HCV RNA levels during therapy).

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

(Case reports and review of literature; 52 year old woman who developed fatigue 12 weeks after starting fluvastatin [bilirubin 1.2 mg/dL, ALT 850 U/L, Alk P 215 U/L, ANA negative], resolving on stopping fluvastatin but recurring within 11 weeks of starting atorvastatin [bilirubin 1.0 rising to 12.5 mg/dL, ALT 1750 U/L, Alk P 285 U/L, ANA 1:160], responding to prednisone and azathioprine therapy).

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 225,922 new users of statins in a UK health care database, there was an increased risk of moderate or severe liver dysfunction [ALT above 3 times ULN], usually within first 6 months and associated with higher doses of statins; relative risks were highest with fluvastatin [2.53 in women, 1.97 in men] and lowest with pravastatin [0.93 to 1.58]).

Nakayama S, Murashima N. Overlap syndrome of autoimmune hepatitis and primary biliary cirrhosis triggered by fluvastatin. Indian J Gastroenterol. 2011;30(2):97–9. PubMed PMID: 21503830.

(59 year old man developed serum enzyme elevations 1 month after starting fluvastatin [bilirubin 1.1 rising to 3.1 mg/dL, ALT 1010 U/L, Alk P 303 U/L, ANA 1:1280, AMA positive, IgG 2031 mg/dL], liver biopsy showing changes of autoimmune hepatitis and bile duct loss, subsequently liver tests fell to normal on prednisone).

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 were attributed to drug induced liver injury including 2 due to atorvastatin, 2 simvastatin and 2 cerivastatin, but none to fluvastatin).

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 to 248 days; fluvastatin had the highest estimated rate per daily dose of 17/10,000 person years compared to 1.6 overall).

Sirtori CR, Mombelli G, Triolo M, Laaksonen R. Clinical response to statins: mechanism(s) of variable activity and adverse effects. Ann Med. 2012;44:419–32. PubMed PMID: 21623698.

(Review of the possible mechanisms for the beneficial and adverse effects of statins including genetic variations in CYP enzymes, ABC transporters and HLA genes in causing adverse events, focused mostly upon myopathy and myalgias).

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 and 1 to simvastatin, but none to fluvastatin).

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 injury).

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 due to atorvastatin 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]).

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).

Li L, Ma Y, Geng XB, Song YX, Tan Z, Shang XM, Zhao GY, et al. Drug-induced acute liver injury within 12 hours after fluvastatin therapy. Am J Ther. 2016;23:e318–20. PubMed PMID: 24451297.

(52 year old Chinese man on rosuvastatin started fluvastatin [80 mg/day] and developed fever, nausea and weakness after the first dose [bilirubin 3.2 mg/dL, ALT 421 U/L, Alk P 115 U/L], with return of tests to normal within 1 week, only to have a recurrence of the same symptoms, blood test abnormalities, and outcome on rechallenge with a single 80 mg dose one year later).

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).

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]).

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).

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 28 cases of fluvastatin associated liver injury have been published including examples of positive rechallenge and autoimmune phenotype, but no case has been fatal and chronicity is rare).

Giugliano RP, Wiviott SD, Blazing MA, De Ferrari GM, Park JG, Murphy SA, White JA, et al. Long-term safety and efficacy of achieving very low levels of low-density lipoprotein cholesterol: a prespecified analysis of the IMPROVE-IT Trial. JAMA Cardiol. 2017;2:547–555. PubMed PMID: 28291866.

(Among 15,281 patients recovering from an acute cardiac syndrome treated with simvastatin [40 mg daily] with or without ezetimibe for up to 6 years, 6.4% achieved very low LDL-cholesterol levels [<30 mg/dL] and subsequently had low rates of cardiovascular events but also no increase in rates of adverse events from statins such including ALT elevations above 3 times ULN [2.2% vs 1.8-2.1%]).

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).

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).

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").

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 fluvastatin] 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%).

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).

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).

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 rosuvastatin] with specific recommendations for the most common inhibitors).

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).

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).

Alanazi NS, Alenazi TS, Alenzi KA. Hepatotoxicity induced by fluvastatin: a reversible acute cholestatic liver injury. Am J Case Rep. 2021;22:e931418. PubMed PMID: 34383728.

(69 year old man with hyperlipidemia and diabetes was switched from simvastatin [20 mg] to Fluvastatin [40 mg] once daily and developed fatigue, itching, dark urine and jaundice 6-7 weeks later [bilirubin 18.5 mg/dL, ALT 108 U/L, Alk P 1200 U/L, CPK 4200 U/L, INR 1.1], with worsening for a week and then slow resolution after stopping fluvastatin).