U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Fluvastatin. [Updated 2017 Aug 5].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Fluvastatin

Updated: August 5, 2017.

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. Fluvastatin is available in capsules of 20 and 40 mg and as extended release tablets of 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, headache and weakness.

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.

Likelihood score: B (likely 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 a toxic 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 hypersensivity or to a failure of adaptation.

Outcome and Management

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®

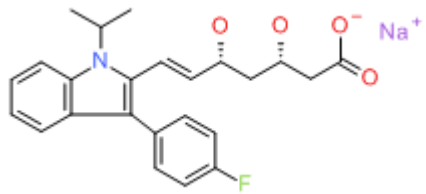
DRUG CLASS

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: 05 August 2017

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).

Bersot TP. Drug therapy for hypercholesterolemia and dyslipidemia. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 877-908.

(Textbook of pharmacology and therapeutics; "the statins are the most effective and best-tolerated agents for treating dyslipidemia." Act by inhibition of the rate-limiting step in hepatic cholesterol synthesis).

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 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.

(Meta analysis 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 Citation (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 rosu-vastatin).

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).

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: 4829162.

(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 diesase 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).

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).