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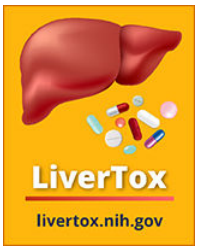

Statins

Updated: December 1, 2021.

OVERVIEW

The hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, are the most potent, best tolerated and most widely used oral cholesterol lowering agents and represent some of the most commonly prescribed medications in the United States. HMG-CoA reductase is the rate limiting step in cholesterol synthesis by the liver, and inhibition of its activity causes a significant decrease in total and LDL cholesterol levels. The statins also have minor effects on triglyceride and HDL levels. Seven statins are available in the United States (year of approval and brand name in parentheses): lovastatin (1987: Mevacor), pravastatin (1991: Pravachol), simvastatin (1991: Zocor), fluvastatin (1993: Lescol), atorvastatin (1996: Lipitor), rosuvastatin (2003: Crestor) and pitavastatin (2009: Livalo). All 7 statins have been associated with mild-to-moderate serum aminotransferase elevations during therapy that are typically transient, asymptomatic and may resolve even with continuation without dose adjustment. All have also been associated rare instances of clinically apparent acute liver injury and the frequency of reports reflects, in some part, the frequency of their use. Nevertheless, the most reports have been with atorvastatin and simvastatin and the fewest with pravastatin and pitavastatin. The latency to onset variables considerably and can be more than 6 months or even several years after starting. The majority of cases are hepatocellular but cholestatic hepatitis is also well described for most statins. Cases with autoimmune features have been reported with atorvastatin, simvastatin, rosuvastatin and fluvastatin, as well as with combinations of these agents with ezetimibe, an inhibitor of cholesterol absorption. The following medications are discussed individually:

- Atorvastatin
- Ezetimibe [used in combination]
- Fluvastatin
- Lovastatin
- Pitavastatin
- Pravastatin
- Rosuvastatin
- Simvastatin

Drug Class: Antilipemic Agents

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 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).

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 the statins were 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).

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, 4690 reports of drug induced liver fatality: none of the statins were in the top 20 suspected causes of acute liver failure due to medications).

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, statins represented 3% of cases overall including 3 cases attributed to atorvastatin, 3 simvastatin/ezetimibe, and one each to pravastatin, fluvastatin, and simvastatin).

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

(Report of two cases of hepatotoxicity attributed to statins, accompanied by a review of the literature. Most cases demonstrate a hepatocellular pattern of injury, and some manifest features of autoimmunity).

Calderon RM, Cubeddu LX, Goldberg RB, Schiff ER. Statins in the treatment of dyslipidemia in the presence of elevated liver aminotransferase levels: a therapeutic dilemma. Mayo Clin Proc. 2010;85:349–56. PubMed PMID: 20360293.

(Review of published articles and studies of statin use in patients with liver disease; the authors conclude that statins can be used in patients with elevated transaminase levels and/or stable liver disease).

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 followed in a large UK healthcare database, the risk of moderate-to-severe liver dysfunction [ALT >3 times ULN] was increased in statin users compared to controls, relative risk ranging from 1.31-2.53 in women and 1.21-1.97 in men being highest with fluvastatin and lowest with pravastatin, more common with higher doses and usually arising within 6 months of starting).

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 they can cause, including silent aminotransferase elevations, cholestatic and hepatocellular hepatitis and autoimmune hepatitis-like syndromes, all of which are rare).

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 other statins).

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).

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).

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).

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).

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).

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 statins account for approximately 5% of cases of clinically apparent liver injury, atorvastatin has been the most frequently implicated statin [accounting for 30-40% of cases] followed by simvastatin and fluvastatin; chronic injury lasting more than 6 months occurs in 18% of cases and fatalities are uncommon, usually the result of acute injury occurring in a patient with preexisting cirrhosis).

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").

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 [atorva-, simva- and lova-statin] as well as by inhibitors of P glycoprotein and OATP1B1 [most statins including rosuvastatin], with specific recommendations for the most common inhibitors).

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).