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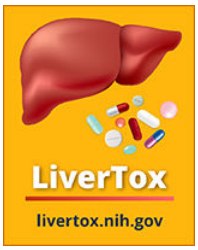


Lovastatin

Updated: December 1, 2021.

OVERVIEW

Introduction

Lovastatin 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

Lovastatin (loe" 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"), lovastatin lowers total serum cholesterol and low density lipoprotein (LDL) concentrations, thereby reducing the risk of atherosclerosis and its complications – myocardial infarction and stroke. Lovastatin is indicated for treatment of hypercholesterolemia in persons at high risk for coronary, cerebrovascular and peripheral artery disease. It is also indicated for prevention of cardiovascular disease and to decrease the risk of progression in patients with known coronary artery disease. Lovastatin is available in tablets of 10, 20, and 40 mg in generic forms and under the brand name Mevacor. Extended release forms (Altoprev) and fixed combinations with niacin (Advicor) are also available. The recommended adult dose is 10 to 80 mg daily in single or two divided doses based upon tolerability and lipid levels. Lovastatin was approved for use in the United States in 1987, the first of this class of drugs to be commercially available. Lovastatin is a widely prescribed drug with more than 7 million prescriptions filled yearly. 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

Lovastatin therapy is associated with mild, asymptomatic and usually transient serum aminotransferase elevations. In summary analyses of large scale studies with prospective monitoring, ALT elevations above normal occurred in 3% to 5% of patients, but were above 3 times the upper limit of normal (ULN) in only 0.4% compared to 0.1% of placebo recipients. These elevations were more common with higher doses of lovastatin, being greater than 3 times ULN in 0.1% of patients receiving 20 mg daily, 0.9% with 40 mg and 1.5% with 80 mg daily. Most of these elevations were self-limited and did not require dose modification, although discontinuation is recommended for any elevation above 10 times and for persistent elevations above 5 times the ULN. Lovastatin is also associated with frank, clinically apparent hepatic injury, but cases are rare. The onset of clinical injury ranges from a few weeks to several years. The pattern of injury is typically cholestatic, but can be

hepatocellular. Rash, fever and eosinophilia are uncommon as are autoimmune features. The injury usually resolves rapidly upon stopping lovastatin, but instances of fatal acute liver failure and of prolonged cholestasis have been reported (Case 1).

The traditional Chinese medication known as red yeast rice which is used to treat hyperlipidemia has been shown to contain monacolin K, a natural component that is chemically identical to lovastatin, perhaps explaining its efficacy in reducing cholesterol levels. Red yeast rice has also been implicated in cases of acute liver injury and myopathies that are similar to those linked to lovastatin. In some instances cross-sensitivity to hepatic injury has been shown between red yeast rice products and lovastatin.

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

Mechanism of Injury

The cause of hepatic injury from lovastatin is unknown. Lovastatin is largely metabolized in the liver (via CYP 3A4) and metabolites are excreted in bile. Lovastatin is susceptible to drug-drug interactions and strong inhibitors of CYP 3A4 can result in higher plasma lovastatin levels which increases the risk of muscle and liver injury. 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 lovastatin is probably immunologically mediated.

Outcome and Management

The product label for lovastatin recommends screening for liver test abnormalities before starting therapy and repeating tests as clinically indicated. The ALT elevations that occur with lovastatin therapy usually resolve spontaneously within a few weeks even without discontinuation. The product label for lovastatin mentions rare cases of acute liver failure due to lovastatin, some of which were fatal. There have not been fatal instances of acute liver injury attributable to lovastatin in the published literature. In the average case, recovery is expected within 1 to 2 months of stopping lovastatin, but instances of prolonged cholestasis and some degree of vanishing bile duct syndrome have been reported. In view of the wide scale use of lovastatin, 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 lovastatin 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], Fluvastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin

CASE REPORT

Case 1. Cholestatic hepatitis due to lovastatin therapy.(1)

A 40 year old man developed fatigue, dark urine, jaundice and itching approximately 11 weeks after starting lovastatin (20 mg daily). He had no previous history of liver disease and drank little alcohol. He had a past history of kidney stones, hyperlipidemia and hypertension, and his other medications included allopurinol (100 mg daily) and the combination of hydrochlorothiazide and amiloride. Liver tests had been normal in the past. When he was finally seen and evaluated, 17 weeks after starting therapy, laboratory tests showed a mixed pattern of serum enzyme elevations. Tests for hepatitis A and B and for autoantibodies were negative. An ultrasound of the abdomen showed evidence suggestive of bile duct dilatation, but ERCP was normal. Lovastatin was stopped and he improved symptomatically. Liver tests had improved but were not completely normal six months later.

Key Points

Medication:	Lovastatin (20 mg daily)
Pattern:	Mixed (R=4.7)
Severity:	3+ (jaundice, hospitalization)
Latency:	11 weeks to symptoms
Recovery:	6 months
Other medications:	Allopurinol, hydrochlorothiazide, amiloride

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
0		25	77		Lovastatin started
7 weeks		38	64		
17 weeks	0	381	277		Lovastatin stopped
19 weeks	10 days	337	381		
21 weeks	4 weeks	205		6.5	
6 months	2 months	229	133	1.9	
10 months	6 months	65	112		
Normal Values		**<35**	**<120**	**<1.2**	

* Some values estimated from Figure 1.

Comment

The patient had symptoms of a cholestatic hepatitis with prominence of jaundice and itching. There was a delay in stopping lovastatin and the cholestatic hepatitis was prolonged. At the time of this report, lovastatin had been available for only approximately a year, and 3 cases of jaundice possibly related to lovastatin had already been reported to the Food and Drug Administration (MedWatch).

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Lovastatin – Generic, Altoprev®, Mevacor®

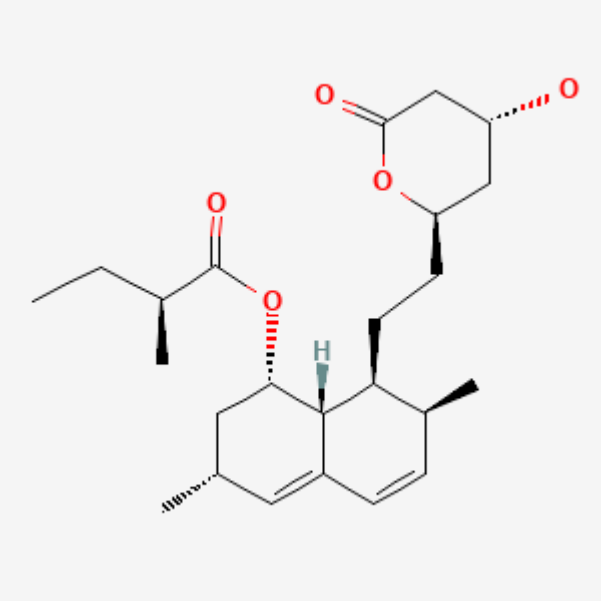
DRUG CLASS

Antilipemic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Lovastatin	75330-75-5	C24-H36-O5	

CITED REFERENCE

1. McQueen MJ. Cholestatic jaundice associated with lovastatin (Mevacor) therapy. Can Med Assoc J. 1990;142:841–2. PubMed PMID: 2322916.

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).

Stein EA, Lamkin GE, Bewley DZ. Lovastatin alone and in combination for treatment of primary hypercholesterolemia. Prog Clin Biol Res. 1988;255:281–93. PubMed PMID: 3340642.

(Controlled trial comparing lovastatin to niacin in 80 patients, one lovastatin treated patient had transient ALT elevation >3 times ULN).

The Lovastatin Study Group III. A multicenter comparison of lovastatin and cholestyramine therapy for severe primary hypercholesterolemia. JAMA. 1988;260:359–66. PubMed PMID: 2898027.

(Controlled trial of lovastatin [20 or 40 mg/day] vs cholestyramine [16 g/day] for 12 weeks in 264 patients with hypercholesterolemia; ALT levels increased more frequently in cholestyramine treated patients, and ALT levels >2 times ULN occurred in 9% of cholestyramine vs 1% of lovastatin treated patients).

Tobert JA. Efficacy and long-term adverse effect pattern of lovastatin. Am J Cardiol. 1988;63:28J–34J. PubMed PMID: 3055921.

(Long term safety study of 744 patients receiving lovastatin, 9 [1.2%] developed raised serum enzymes).

Mantell G, Burke MT, Staggers J. Extended clinical safety profile of lovastatin. Am J Cardiol. 1990;66:11B–15B. PubMed PMID: 2206031.

(Review of safety data on lovastatin from extensions of prelicensure clinical trials and the first year of postmarketing adverse event reporting; in clinical trials in 744 patients, rates of ALT elevations >3 times ULN were 0.1% on placebo vs 0.1% on 20 mg, 0.7% on 40 mg, and 1.5% on 80 mg of lovastatin daily; 49 cases of liver toxicity reported to MedWatch, but most could not be verified and most resolved spontaneously, but two positive rechallenges and two deaths from liver disease, although they were considered not drug related).

Bilheimer DW. Long-term clinical tolerance of lovastatin and simvastatin. Cardiology. 1990;77 Suppl 4:58–65. PubMed PMID: 2073673.

(Review; serum enzyme elevations occur in 1.3% of lovastatin treated patients, reversible upon discontinuation of drug).

McQueen MJ. Cholestatic jaundice associated with lovastatin (Mevacor) therapy. Can Med Assoc J. 1990;142:841–2. PubMed PMID: 2322916.

(40 year old man developed jaundice 11 weeks after starting lovastatin [peak bilirubin 6.5 mg/dL, ALT 381 U/L, Alk P 381 U/L], resolving, but not completely, within 6 months of stopping: Case 1).

Geddes JA. Cholestatic jaundice associated with lovastatin (Mevacor) therapy. Can Med Assoc J. 1990;143:13–14. PubMed PMID: 2357675.

(72 year old woman developed jaundice 13 months after starting lovastatin [bilirubin 1.8 mg/dL, AST 177 U/L, Alk P 351 U/L], resolving within 4 weeks of stopping, but also exposed to cloxacillin 2 weeks before onset of jaundice).

Spreckelsen U, Kirchoff R, Haake H. [Cholestatic jaundice during lovastatin medication] (German). Dtsch Med Wochenschr. 1991;116:739–40. PubMed PMID: 2026107.

(48 year old man developed jaundice 8 weeks after starting lovastatin [bilirubin 6.2 mg/dL, ALT 341 U/L, Alk P 389 U/L], resolving within 2 weeks of stopping).

Bradford RH, Shear RL, Chremos AN, Dujovne C, Downton M, Franklin FA, Gould AL, et al. Expanded clinical evaluation of lovastatin (EXCEL) study results. I. Efficacy in modifying lipoproteins and adverse events

profile of 8245 patients with moderate hypercholesterolemia. Arch Intern Med. 1991;151:43–9. PubMed PMID: 1985608.

(Large, randomized controlled trial of 3 doses of lovastatin vs placebo in 8245 patients; serum ALT or AST elevations >3 times ULN occurred in 0.1% on placebo, 0.1% on 20 mg, 0.9% on 40 mg, and 1.5% on 80 mg of lovastatin daily).

Raveh D, Arnon R, Israeli A, Eisenberg S. Lovastatin-induced hepatitis. Isr J Med Sci. 1992;28:101–2. PubMed PMID: 1559791.

(50 year old woman developed enzyme elevations and marked pruritus 7 months after starting lovastatin [bilirubin 0.7 mg/dL, ALT 296 U/L, Alk P 626 U/L], with prompt disappearance of symptoms, but slow improvement in abnormal liver tests upon stopping lovastatin).

The Lovastatin Pravastatin Study Group. A multicenter comparative trial of lovastatin and pravastatin in the treatment of hypercholesterolemia. Am J Cardiol. 1993;71:810–5. PubMed PMID: 8456759.

(Controlled trial of lovastatin [20 to 80 mg] vs pravastatin [10 to 40 mg] daily for 18 weeks in 672 hypercholesterolemic patients; ALT elevations >3 times ULN occurred in 1 lovastatin and 2 pravastatin treated patients; no clinically apparent liver injury mentioned).

Grimbert S, Pessayre D, Degott C, Benhamou JP. Acute hepatitis induced by HMG-CoA reductase inhibitor, lovastatin. Dig Dis Sci. 1994;39:2032–3. PubMed PMID: 8082513.

(64 year old man developed jaundice 12 weeks after starting lovastatin [bilirubin 11.7 mg/dL, ALT 8 times and Alk P 1.5 times ULN], resolving within 2 months of stopping).

LaRosa JC, Applegate W, Crouse JR 3rd, Hunninghake DB, Grimm R, Knopp R, Eckfeldt JH, et al. Cholesterol lowering in the elderly: results of the cholesterol reduction in seniors program (CRISP) pilot study. Arch Intern Med. 1994;154:529–39. PubMed PMID: 8122946.

(Controlled trial of lovastatin vs placebo in 431 patients; average ALT levels were identical and constant in all 3 groups during treatment).

Furberg CD, Adams HP Jr, Applegate WB, Byington RP, Espeland MA, Hartwell T, Hunninghake DB, et al. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic carotid artery progression study (ACAPS) research group. Circulation. 1994;90:1679–87. PubMed PMID: 7734010.

(No comment on liver injury in this double blind randomized controlled clinical trial).

Bradford RH, Shear RL, Chremos AN, Cujovne CA, Franklin FA, Grillo RB, Higgins J, et al. Expanded clinical evaluation of lovastatin (EXCEL) study results. Two year efficacy and safety follow up. Am J Cardiol. 1994;74:667–73. PubMed PMID: 7942524.

(Controlled trial of lovastatin [20 mg daily] vs placebo in 8245 patients with hypercholesterolemia; confirmed ALT elevations >3 times ULN occurred in only 1 patient on lovastatin during year 2, and no episodes of clinically apparent liver disease; rates of ALT elevations >3 times ULN were 0.1% for placebo and 20 mg, 0.9% for 40 mg, and 1.9% for 80 mg daily).

Huchzermeyer H, Munzenmaier R. Dtsch Med Wochenschr. 1995;120:252–6. [Lovastatin-induced acute cholestatic hepatitis] [German]. German. PubMed PMID: 7867482.

(58 year old man and 54 year old woman developed cholestatic hepatitis 3 years and 2 months after starting lovastatin [peak bilirubin 15.0 and 9.2 mg/dL, ALT 276 and 384 U/L, Alk P 1227 and 595 U/L], both cases resolving slowly after stopping).

Gavilán Carrasco JC, Bermúdez Recio F, Salgado Ordóñez F, González Santos P. Med Clin (Barc). 1996;107:557–8. [Hepatitis due to lovastatin]. PubMed PMID: 8999220.

(51 year old with epilepsy on long term phenytoin, phenobarbital and valproate therapy developed jaundice 6 weeks after starting lovastatin [bilirubin 15 mg/dL, ALT 4000 U/L, Alk P 662 U/L], resolving within 2 months of stopping; restarted on phenobarbital and carbamazepine without recurrence).

Bruguera M, Joya P, Rodés J. Gastroenterol Hepatol. 1998;21:127–8. [Hepatitis associated with treatment with lovastatin. Presentation of 2 cases]. PubMed PMID: 9607293.

(Two women, ages 57 and 59 years, developed symptomatic but anicteric hepatitis 9 months and 3 years after starting lovastatin [bilirubin 0.8 and 1.3 mg/dL, ALT 244 and 273 U/L, Alk P 845 and 306 U/L], resolving rapidly on stopping).

Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TexCAPS. JAMA. 1998;279:1615–22. PubMed PMID: 9613910.

(Controlled trial of lovastatin in 9905 patients; AST or ALT elevations >3 times ULN occurred in 0.7% on 20 mg and 0.4% on 40 mg of lovastatin, and 0.3% on placebo).

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).

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 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 2-8 weeks, except one death; 3 of 7 recurred on rechallenge, 5 of 6 tolerated switching to another statin).

Tolman KG. The liver and lovastatin. Am J Cardiol. 2002;89:1374–80. PubMed PMID: 12062731.

(In premarketing controlled trials of lovastatin, 21% of patients had ALT elevations, but only 1.9% had ALT >3 times ULN and rates were similar to comparator statins).

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

(Review and discussion of individual agents; lovastatin available since 1990 and linked to several case reports of hepatotoxicity).

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).

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 1984 to 2004 in Spanish Registry; 11 cases [2%] were attributed to "statins", but no specific agent 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 statins [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 >3 times ULN in 1.7% of statin vs 1.4% placebo recipients; event rates highest with atorvastatin, lowest with fluvastatin).

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 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).

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]).

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 prescription 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).

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).

Stein CA, Goel S, Ghavamian R. Hepatitis and rhabdomyolysis in a patient with hormone refractory prostate cancer on ketoconazole and concurrent lovastatin therapy. Invest New Drugs. 2007;25:277–8. PubMed PMID: 17216557.

(84 year old man on long term lovastatin developed muscle weakness 4 weeks after starting ketoconazole [bilirubin and Alk P normal, ALT 829 U/L, CPK 47,250 U/L], suspected to be rhabdomyolysis caused by effects of ketoconazole on lovastatin pharmacokinetics, resolving in 3 weeks after stopping both).

Alsheikh-Ali A, Karas RH. Safety of lovastatin/extended release niacin compared with lovastatin alone, atorvastatin alone, pravastatin alone, and simvastatin alone. Am J Cardiol. 2007;99:379–81. PubMed PMID: 17261402.

(Review of MedWatch data base for serious adverse events: rates per million prescriptions were 11.2 for lovastatin/ niacin ER; 11.6 niacin ER; 7.7 lovastatin; 19.6 atorvastatin; 22.6 simvastatin; 14.8 pravastatin. Hepatotoxicity [undefined] per million occurred in: 3.6 for lovastatin/ niacin ER; 2.4 niacin ER; 2.2 lovastatin; 4.2 atorvastatin; 5.9 simvastatin; 5.0 pravastatin).

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).

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 [none attributed to lovastatin], but most cases were mild or not clearly attributable to the statin therapy).

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).

Avins AL, Manos MM, Ackerson L, Zhao W, Murphy R, Levin TR, Watson DJ, et al. Hepatic effects of lovastatin exposure in patients with liver disease: a retrospective cohort study. Drug Saf. 2008;31:325–34. PubMed PMID: 18366243.

(Analysis of electronic medical records on 93,106 patients, 14% of whom had received lovastatin; compared to controls, patients receiving lovastatin had lower rates of moderate ALT elevations and diagnosis of cirrhosis or liver failure compared to controls who did not receive lovastatin).

Roselle H, Ekatan A, Tzeng J, Sapienza M, Kocher J. Symptomatic hepatitis associated with the use of herbal red yeast rice. Ann Intern Med. 2008;149:516–7. PubMed PMID: 18838736.

(62 year old woman developed fever, nausea and fatigue 4 months after starting red yeast rice extract [ALT 211 U/L, bilirubin and Alk P not given], resolving within several months of stopping).

Grieco A, Miele L, Pompili M, Biolato M, Vecchio FM, Grattagliano I, Gasbarrini G. Acute hepatitis caused by a natural lipid-lowering product: when "alternative" medicine is no "alternative" at all. J Hepatol. 2009;50:1273–7. PubMed PMID: 19398239.

(63 year old woman with ALT elevations after 6 months of lovastatin use, developed fatigue 6 months after starting a cholesterol lowering herbal preparation containing red yeast rice extract [bilirubin 1.9 mg/dL, ALT 1760 U/L, Alk P 722 U/L], resolving over the next 6 months, but with persistence of ALT elevations).

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 linked to fluvastatin and atorvastatin and review of literature on statin related hepatotoxicity).

Becker DJ, Gordon RY, Halbert SC, French B, Morris PB, Rader DJ. Red yeast rice for dyslipidemia in statin-intolerant patients: a randomized trial. Ann Intern Med. 2009;150:830–9. PubMed PMID: 19528562.

(Controlled trial of red yeast rice extract vs placebo in 62 patients who had stopped statin therapy because of myalgias, found similar rates of myalgias [7% vs 3%] and no change in ALT or AST levels in both groups).

Halbert SC, French B, Gordon RY, Farrar JT, Schmitz K, Morris PB, Thompson PD, et al. Tolerability of red yeast rice (2,400 mg twice daily) versus pravastatin (20 mg twice daily) in patients with previous statin intolerance. Am J Cardiol. 2010;105:198–204. PubMed PMID: 20102918.

(43 patients with myalgias due to statin use were treated with pravastatin or red rice extract for 24 weeks; discontinuation due to myalgias occurred in 5% on red yeast rice extract and 9% on pravastatin, and mean ALT levels were similar between the 2 groups).

Gordon RY, Cooperman T, Obermeyer W, Becker DJ. Marked variability of monacolin levels in commercial red yeast rice products: buyer beware! Arch Intern Med. 2010;170:1722–7. PubMed PMID: 20975018.

(Among 12 red yeast rice extracts commercially available in the US, total monacolin concentrations varied from 0.3-11.1 mg/capsule, monacolin K by 0.1-10.1 mg/capsule, and citrinin [which is nephrotoxic] was present in 4).

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 >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]; there were too few persons treated with lovastatin for separate analysis).

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 were attributed to statins: 2 atorvastatin, 2 simvastatin [one with ezetimibe] and 2 cerivastatin).

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; no mention of lovastatin).

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 lovastatin).

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).

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).

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 rosuvastatin], and there were no differences in disease features or peak enzyme or bilirubin levels between HBsAg positive vs negative subjects [n=16 vs 92]).

Mazzanti G, Moro PA, Raschi E, Da Cas R, Menniti-Ippolito F. Adverse reactions to dietary supplements containing red yeast rice: assessment of cases from the Italian surveillance system. Br J Clin Pharmacol. 2017;83:894–908. PubMed PMID: 28093797.

(Among 1261 spontaneous adverse event reports made to an Italian surveillance system for natural health products between 2002 and 2015, 55 were for red yeast rice, including 10 for liver injury of which 6 were described as "hepatitis" and required hospitalization, ALT elevations 315 to 3566 U/L, bilirubin normal or minimally elevated, all resolving upon stopping supplements).

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 12 cases of lovastatin induced liver injury have been published, but none were fatal or had a positive rechallenge).

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").

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 [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).

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).

Karampoor S, Hesamizadeh K, Shams Z, Ghafari Novin A, Farahmand M, Zahednasab H, Mirzaei R, et al. The role of lovastatin in the attenuation of COVID-19. Int Immunopharmacol. 2021;101(Pt A):108192.

(Among 284 patients with COVID-19 admitted to the intensive care unit, mortality rates were lower in those receiving 20 mg [n=99] or 40 mg [n=93] of lovastatin daily [0% and 2%] than in 92 controls [4%] while changes in serum aminotransferase levels were similar in all three groups).