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# Rosuvastatin

Updated: August 5, 2017.

# OVERVIEW

## Introduction

Rosuvastatin 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

Rosuvastatin (roe soo" va stat' in) is a potent, orally available inhibitor of hepatic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase the major rate-limiting enzyme in cholesterol synthesis. Like other members of its class (the "statins"), rosuvastatin lowers total serum cholesterol and low density lipoprotein (LDL) concentrations, thereby reducing the risk of atherosclerosis and its complications – myocardial infarction and stroke. Rosuvastatin was approved for use in the United States in 2003 and currently several million prescriptions are filled yearly. Rosuvastatin is indicated for treatment of hypercholesterolemia in persons at high risk for coronary, cerebrovascular and peripheral artery disease. Rosuvastatin is available in tablets of 5, 10, 20 and 40 mg generically and under the trade name Crestor. Rosuvastatin is one of the more potent statins available and is typically used in a comparably lower dose. The recommended dose in adults is 5 to 40 mg once daily, based upon tolerability and lipid levels. Common side effects include muscle cramps, joint aches, headache and weakness.

## Hepatotoxicity

Rosuvastatin therapy is associated with mild, asymptomatic and usually transient serum aminotransferase elevations in 1% to 3% of patients, but levels above 3 times the upper limit of normal (ULN) occur no more frequently among rosuvastatin treated [0.2%] as placebo [0.3%] recipients. Serum enzyme elevations are more common with higher doses of rosuvastatin, being 2.2% with 40 mg daily. Most of these elevations are self-limited and do not require dose modification. Rosuvastatin is also associated with frank, clinically apparent hepatic injury but this is rare, occurring in less than 1:10,000 patients. The onset is typically after 2 to 4 months and the pattern of serum enzyme elevations is usually hepatocellular, although cholestatic cases have also been reported. Rash, fever and eosinophilia are uncommon. Several of the statins including rosuvastatin have been linked to hepatitis with autoimmune features including elevated immunoglobulin levels, ANA positivity and a clinical response to corticosteroids. Such features are not, however, invariable (Case 1).

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

## Mechanism of Injury

The cause of hepatic injury from rosuvastatin is unknown. Rosuvastatin is minimally (~10%) metabolized in the liver (via CYP 2C9). The mild, self-limited ALT elevations may be 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 rosuvastatin is often accompanied by autoimmune features and may, therefore, be caused by immune mechanisms.

## Outcome and Management

The mild ALT elevations associated with rosuvastatin therapy are usually self-limited and do not require dose modification; rosuvastatin should be stopped if ALT levels rise above 10-fold the ULN, or persist in being above 5-fold elevated or are associated with symptoms. In the clinically apparent liver injury attributed to rosuvastatin, recovery is usually complete within 1 to 2 months. Recurrence of injury with rechallenge has been reported and should be avoided. Cases of chronic hepatitis, but no instances of acute liver failure or vanishing bile duct syndrome, attributable to rosuvastatin have been reported. In cases of autoimmune hepatitis-like injury, corticosteroids have been used when recovery does not occur promptly. If corticosteroids are used, the dose and duration of treatment should be kept to a minimum, and careful followed up after stopping is essential. Switching therapy to another statin after rosuvastatin 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, Lovastatin, Pitavastatin, Pravastatin, Simvastatin

# CASE REPORT

## Case 1. Acute self-limited hepatitis during rosuvastatin therapy.

[Modified from: Famularo G, Miele L, Minisola G, Grieco A. Liver toxicity of rosuvastatin therapy. World J Gastroenterol 2007; 13: 1286-8. PubMed Citation]

A 64 year old man developed jaundice approximately 15 weeks after starting rosuvastatin (10 mg daily) for hypercholesterolemia. He had a history of acute myocardial infarction four months previously, which was treated with angioplasty and stenting. Discharge medications included clopidogrel, aspirin, metoprolol, ramipril and atorvastatin. One week later, rosuvastatin was substituted for atorvastatin because of skin rash and minor ALT elevations (55 U/L). Subsequently, he felt well until he developed malaise, anorexia and upper abdominal discomfort followed by jaundice slightly over 3 months later. On examination, he had no fever, rash or signs of chronic liver disease. Laboratory results showed elevations in serum bilirubin and aminotransferase levels, but normal alkaline phosphatase and GGT (Table). Tests for hepatitis A, B, C, and E were negative as were routine autoantibodies. Ultrasonography of the liver and biliary tree was normal. Rosuvastatin was stopped while blood pressure and antiplatelet medications were continued. Liver test abnormalities improved promptly and were normal two weeks later.

### Key Points

| | |
|---|---|
| Medication: | Rosuvastatin (10 mg daily) |
| Pattern: | Hepatocellular (aminotransferase elevations only) |
| Severity: | 3+ (jaundice, hospitalization) |
| Latency: | 15 weeks |

*Table continued from previous page.*

| | |
|---|---|
| Recovery: | 2 weeks |
| Other medications: | Clopidogrel, aspirin, metoprolol, ramipril, atorvastatin |

## Laboratory Values

| Time After Starting | Time After Stopping | ALT* (U/L) | Alk P* (U/L) | Bilirubin (mg/dL) | Other |
|---|---|---|---|---|---|
| Pre | | 20 | Normal | Normal | Discharge after heart attack |
| Pre | | 55 | | | Atorvastatin stopped |
| Atorvastatin stopped and rosuvastatin started | | | | | |
| 2 days | | 40 | | | |
| 3 days | | 35 | | | |
| 15 weeks | 0 | 775 | Normal | 2.6 | Admission: rosuvastatin stopped |
| 15 weeks | 3 days | 198 | | 1.8 | INR Normal |
| 16 weeks | 1 week | 40 | | Normal | |
| 17 weeks | 2 weeks | 30 | Normal | Normal | |
| **Normal Values** | | **<36** | **<117** | **<1.2** | |

* Some values estimated from Figure 1.

## Comment

The onset of injury approximately 3 months after starting rosuvastatin and the rapid recovery with stopping therapy makes the diagnosis of rosuvastatin induced acute hepatitis highly likely. Other diagnoses were approximately ruled out and there was documentation of normal liver tests before starting statin therapy. Acute, clinically apparent liver injury is rare with rosuvastatin therapy (~1:10,000 patients treated) and is rapidly reversible with prompt discontinuation of therapy. Rechallenge with rosuvastatin is inadvisable, but other statins might be initiated with careful monitoring of serum enzymes.

# PRODUCT INFORMATION

**REPRESENTATIVE TRADE NAMES**

Rosuvastain – Crestor®

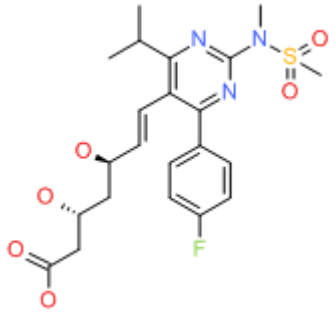
**DRUG CLASS**

Antilipemic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

## CHEMICAL FORMULA AND STRUCTURE

| DRUG | CAS REGISTRY NUMBER | MOLECULAR FORMULA | STRUCTURE |
|---|---|---|---|
| Rosuvastatin | 287714-41-4 | C22-H28-F-N3-O6-S |  |

## 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; 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).*

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).*

Brewer HB Jr. Benefit-risk assessment of rosuvastatin 10 to 40 milligrams. Am J Cardiol 2003; 92 (Suppl): 23K-29K. PubMed PMID: 12948873.

*(Review of efficacy and safety of rosuvastatin in doses of up to 80 mg daily in 12,569 patients [14,231 patient years]: ALT elevations >3 times ULN occurred in 0.2% and similar rate in comparators: atorvastatin, simvastatin, and pravastatin).*

Shepherd J, Hunninghake DB, Stein EA, Kastelein JJ, Harris S, Pears J, Hutchinson HG. Safety of rosuvastatin. Am J Cardiol 2004; 94: 882-8. PubMed PMID: 15464670.

*(Overview of safety of rosuvastatin based upon data from 12,400 patients in clinical trials using 5-40 mg daily; rates of adverse events similar to those with placebo, rates of ALT elevations >3 times ULN were 0.5% with 5, 0.1% with 10, 0.1% with 20 and 0.3% with 40 mg, with overall rates 0.2% similar to comparator statins).*

Wolters LMM, Van Buuren HR. Rosuvastatin-associated hepatitis with autoimmune features (letter). Eur J Gastroenterol Hepatol 2005; 17: 589-90. PubMed PMID: 15827453.

*(46 year old developed jaundice 9 weeks after starting rosuvastatin [bilirubin 7.9 mg/dL, ALT 2539 U/L, Alk P 151 U/L, IgG 2.4 g/dL, SMA1:160], improved upon stopping rosuvastatin, but eventually required long term corticosteroid therapy [during follow up for more than 4 years after this publication]).*

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

*(Review of MedWatch adverse event reports on rosuvastatin over first year of marketing; rates of liver related reports were 25 per million prescriptions for rosuvastatin compared to 4-5 for simvastatin, pravastatin and atorvastatin and rates also higher for comparable marketing period of the other statins).*

McKenney JM. An assessment of statin safety. Am J Manag Care 2006; 12: S310-7. PubMed PMID: 17042673.

*(Review of the safety of the statins; liver failure reported at a rate of 1 per million, which is similar to nonstatin-taking population, recommends monitoring based upon symptoms rather than blood test abnormalities).*

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]).*

Zipes DP, Zvaifler NJ, Glassock RJ, Gilman S, Muñoz A, Gogolak V, Gordis L, et al. Rosuvastatin: an independent analysis of risks and benefits. MedGenMed 2006; 8: 73. PubMed PMID: 16926812.

*(Expert review of the literature concludes that safety and tolerability of rosuvastatin is similar to other statins, and rates of liver injury are very low).*

McAfee AT, Ming EE, Seeger JD, Quinn SG, Ng EW, Danielson JD, Cutone JA, et al. The comparative safety of rosuvastatin: a retrospective matched cohort study in over 48,000 initiators of statin therapy. Pharmacoepidemiol Drug Saf 2006; 15: 444-53. PubMed PMID: 16761308.

*(Analysis of electronic records on 11,249 patients starting rosuvastatin compared to 37,282 starting another statin; over the first 6 months of treatment, hepatic dysfunction reported in 2 [0.020%] starting rosuvastatin vs 8 [0.024%] starting other statins).*

Goettsch WG, Heintjes EM, Kastelein JJ, Rabelink TJ, Johansson S, Herings RM. Results from a rosuvastatin historical cohort study in more than 45,000 Dutch statin users, a PHARMO study. Pharmacoepidemiol Drug Saf 2006; 15: 435-43. PubMed PMID: 16761304.

*(Analysis of electronic database on more than 2 million Dutch residents comparing those on rosuvastatin [10,147], other statins [37,396] and non-users [99,935]; hepatic impairment identified in none on rosuvastatin, 4 [0.011%] on statins and 7 [0.006%] controls).*

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

Antonopoulos S, Mikros S, Mylonopoulou M, Kokkoris S, Giannoulis G. Rosuvastatin as a novel treatment of non-alcoholic fatty liver disease in hyperlipidemic patients. Atherosclerosis 2006; 184: 233-4. PubMed PMID: 16168995.

*(Open label study of rosuvastatin [10 mg/day] for 8 months in 23 patients with nonalcoholic fatty liver disease; ALT levels fell to normal in all patients and no instance of hepatotoxicity).*

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

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

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).*

Guthrie RM, Martin DR. The safety of rosuvastatin: effects on renal and hepatic function. Expert Opin Drug Saf 2007; 6: 573-81. PubMed PMID: 17877444.

*(Review of hepatic adverse events due to rosuvastatin without new information; ALT elevations occur at a similar rate during rosuvastatin as with other statins and average ~0.4%; acute liver failure has not been definitely linked to statins, estimated rate being ~1 per million patient years, similar to background rate; authors argue against routine monitoring of liver enzymes during rosuvastatin therapy).*

Kasliwal R, Wilton LV, Cornelius V, Aurich-Barrera B, Shakir SA. Safety profile of rosuvastatin: results of a prescription-event monitoring study of 11,680 patients. Drug Saf 2007; 30: 157-70. PubMed PMID: 17253880.

*(Postmarketing study of 11,680 patients on rosuvastatin; therapy stopped in 17.5% because of adverse events, myalgias being most frequent reason; ALT or AST elevations in 101 patients [~1%], but only 9 [~0.1%] had confirmed ALT values >3 times ULN, one patient developed an autoimmune hepatitis-like syndrome 4 months after starting rosuvastatin, resolving spontaneously with stopping, another patient had cholestatic jaundice).*

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).*

Stein EA, Amerena J, Ballantyne CM, Brice E, Farnier M, Guthrie RM, Harats D, et al. Long-term efficacy and safety of rosuvastatin 40 mg in patients with severe hypercholesterolemia. Am J Cardiol 2007; 100: 1387-96. PubMed PMID: 17950795.

*(Open label, extension study of rosuvastatin [40 mg daily] for 2 years in 1,380 patients with severe hypercholesterolemia; confirmed ALT elevations >3 times ULN occurred in 0.8%, half resolved despite continuing therapy, no clinically apparent hepatitis or jaundice and no deaths from liver disease).*

Merz T, Fuller SH. Elevated serum transaminase levels resulting from concomitant use of rosuvastatin and amiodarone. Am J Health Syst Pharm 2007; 64: 1818-21. PubMed PMID: 17724362.

*(73 year old developed minimal ALT elevations on rosuvastatin which worsened two weeks after starting amiodarone [ALT 13→91→336 U/L], improving with stopping rosuvastatin despite continuing amiodarone, possibly demonstrating interaction between the two agents).*

Famularo G, Miele L, Minisola G, Grieco A. Liver toxicity of rosuvastatin therapy. World J Gastroenterol 2007; 13: 1286-8. PubMed PMID: 17451217.

*(64 year old man developed jaundice ~3 months after starting rosuvastatin [bilirubin 2.6 mg/dL, ALT 775 U/L, normal GGT, ANA negative], resolving within 2 weeks of stopping: case 1).*

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 clearly attributable to the statin therapy; none related to rosuvastatin).*

Oteri A, Catania MA, Russo A, Salvo F, Giacci L, Caputi AP, Polimeni G. Reversible acute hepatitis induced by rosuvastatin. South Med J 2008; 101: 768. PubMed PMID: 19209117.

*(62 year old man developed jaundice 2 months after switching from simvastatin to rosuvastatin [10 mg daily] [bilirubin 6.1 mg/dL, ALT 2317 U/L, Alk P levels and ANA not reported], resolving within 3 weeks of stopping drug).*

García-Rodríguez LA, Massó-González EL, Wallander MA, Johansson S. The safety of rosuvastatin in comparison with other statins in over 100,000 statin users in UK primary care. Pharmacoepidemiol Drug Saf 2008; 17: 943-52. PubMed PMID: 18425988.

*(Analysis of electronic records on 10,289 patients starting rosuvastatin and 117,102 starting other statins [mostly simvastatin and atorvastatin] for adverse events; 4 cases [0.003%] of myopathy, 4 [0.003%] of rhabdomyolysis and 6 [0.05%] of acute liver injury identified, but none in rosuvastatin users).*

García-Rodríguez LA, González-Pérez A, Stang MR, Wallander MA, Johansson S. The safety of rosuvastatin in comparison with other statins in over 25,000 statin users in the Saskatchewan Health Databases. Pharmacoepidemiol Drug Saf 2008; 17: 953-61. PubMed PMID: 18425987.

*(Analysis of electronic medical records on 25,238 first time statin users, 10,384 starting rosuvastatin; 2 cases each of myopathy, rhabdomyolysis and acute liver injury [all 0.008%], but both liver related adverse events occurred in atorvastatin treated patients).*

Rubba P, Marotta G, Gentile M. Efficacy and safety of rosuvastatin in the management of dyslipidemia. Vasc Health Risk Manag 2009; 5: 343-52. PubMed PMID: 19436657.

*(Review of mechanism of action, pharmacology, safety and efficacy of rosuvastatin; elevations of ALT levels >3 times ULN during rosuvastatin therapy are uncommon [<0.2%]).*

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], and intermediate for rosuvastatin [1.31 to 1.46]).*

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 rosuvastatin).*

Saku K, Zhang B, Noda K; The PATROL Trial Investigators. Randomized head-to-head comparison of pitavastatin, atorvastatin, and rosuvastatin for safety and efficacy (quantity and quality of LDL). Circ J 2011; 75: 1493-1505. PubMed PMID: 21498906.

*(Controlled trial comparing 3 potent statins in 302 patients for 16 weeks; ALT elevations above 3 times ULN occurred in 2 on atorvastatin, 2 on rosuvastatin and 1 on pitavastatin, but none developed clinically apparent liver injury).*

Toth PP, Dayspring TD. Drug safety evaluation of rosuvastatin. Expert Opin Drug Saf 2011; 10: 969-86. PubMed PMID: 21999163.

*(Review of pharmacology, safety and efficacy of rosuvastastin; "compared to other statins, it has no excess signal for liver, skeletal muscle or renal toxicity").*

Kato JD, Wang CT. Cardiac rehabilitation participant with sickle cell trait and statin-related hepatotoxicity: a case report. J Cardiopulm Rehabil Prev 2012; 32: 182-6. PubMed PMID: 22595892.

*(51 year old man developed marked aminotransferase elevations [ALT 2498 U/L, AST 1452 U/L; Alk P and bilirubin not given] 75 days after starting rosuvastatin, which fell to normal within 3 months of stopping, but rose again 1 month after restarting).*

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

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

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, but none to rosuvastatin).*

Vaverkova H, Farnier M, Averna M, Missault L, Viigimaa M, Dong Q, Shah A, et al. Lipid-altering efficacy of ezetimibe/simvastatin 10/20 mg compared to rosuvastatin 10 mg in high-risk patients with and without type 2 diabetes mellitus inadequately controlled despite prior statin monotherapy. Cardiovasc Ther 2012; 30: 61-74. PubMed PMID: 20626402.

*(In a randomized trial in patients with hypercholesterolemia, ALT or AST elevations >3 times ULN occurred in none of 303 patients receiving rosuvastatin versus 0.7% of 312 on the combination of simvastatin and ezetimibe).*

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

*(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, including 2 cases due to atorvastatin and 1 to simvastatin, but none to rosuvastatin).*

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 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]).*

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

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

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

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

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]).*

Hwang NK, Park JS, Cha KS, Kang JS. Hepatotoxicity associated with a short course of rosuvastatin. Chin Med J (Engl) 2015; 128: 1693-4. PubMed PMID: 26063377.

*(76 year old Korean man with coronary artery disease developed abdominal pain and jaundice 12 days after a percutaneous intervention and starting rosuvastatin [bilirubin 10.3 mg/dL, ALT 612 U/L, Alk P 174 U/L], which resolved rapidly [< 1 week] upon stopping).*

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