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Pitavastatin

Updated: December 1, 2021.

OVERVIEW

Introduction

Pitavastatin is a relatively newly developed cholesterol lowering agent (statin) that is associated with mild, asymptomatic and self-limited serum aminotransferase elevations during therapy, but has had limited use and has yet to be linked with clinically apparent acute liver injury.

Background

Pitavastatin (pi ta" 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"), pitavastatin lowers total serum cholesterol and low density lipoprotein (LDL) concentrations, thereby reducing the risk of atherosclerosis and its complications – myocardial infarction and stroke. Pitavastatin was approved for use in the United States in 2009 but experience with its use is limited. Pitavastatin is indicated for treatment of hypercholesterolemia in persons at high risk for coronary, cerebrovascular and peripheral artery disease. It has not been shown to have an effect on mortality. Pitavastatin is available in tablets of 1, 2 and 4 mg under the trade names Livalo and Zypitamag. Pitavastatin is one of the more potent statins and is typically used in a comparably lower dose. The recommended dose is 2 to 4 mg once daily based upon tolerability and lipid levels. Common side effects include muscle cramps, joint aches, abdominal pain, nausea, headache and weakness, symptoms that occur with all of the currently available statins. Rare but potentially severe adverse events include liver injury, myopathy, rhabdomyolysis, and immune-mediated necrotizing myopathy.

Hepatotoxicity

Less information is available on the potential hepatotoxicity of pitavastatin in comparison to other more widely used statins. In large clinical trials, pitavastatin therapy was associated with mild, asymptomatic and usually transient serum aminotransferase elevations in approximately 1% of patients, but levels above 3 times the upper limit of normal (ULN) were infrequent and no cases of clinically apparent hepatitis were reported from the preregistration clinical trials. Since marketing of pitavastatin, however, the sponsor has received reports of jaundice, hepatitis and hepatic failure including fatal cases. However, the clinical features and typical course of the liver injury associated with pitavastatin have not been defined in the published literature. On the other hand, the other statins have all been implicated in cases of clinically apparent acute liver injury that typically arise after 1 to 6 months of therapy with either a cholestatic or hepatocellular pattern of serum enzyme elevations. Rash, fever and eosinophilia are uncommon, but some cases have been marked by autoimmune features including

autoantibodies, chronic hepatitis on liver biopsy and a clinical response to corticosteroid therapy. This pattern has yet to be shown to apply to pitavastatin.

Likelihood score: D (possible rare cause of clinically apparent liver injury).

Mechanism of Injury

The cause of hepatic injury from pitavastatin is unknown. Pitavastatin 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 many statins is often accompanied by autoimmune features and may, therefore, be caused by immune mechanisms. The apparent lower rate of liver injury associated with pitavastatin may be due to the low doses used (<10 mg daily) which is characteristic of medications that do not cause liver injury.

Outcome and Management

The product label for pitavastatin recommends screening for liver test abnormalities before starting therapy and repeating tests as clinically indicated. The mild ALT elevations associated with pitavastatin therapy are usually self-limited and do not require dose modification. Pitavastatin 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 statins, recovery is usually complete within 1 to 2 months. Recurrence of injury with rechallenge has been reported and should be avoided. Whether there is cross relativity to hepatic injury with other statins is unknown.

Drug Class: Antilipemic Agents

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

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Pitavastatin – Livalo®

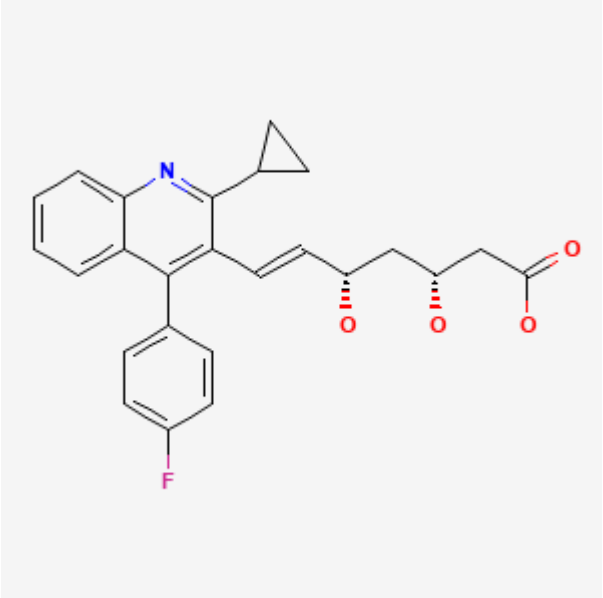
DRUG CLASS

Antilipemic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Pitavastatin	147511-69-1	C25-H24-F-N-O4	

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; no mention of pitavastatin).

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 states that 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).

Pitavastatin (Livalo) – the seventh statin. Med Lett Drugs Ther. 2010;52:57–8. PubMed PMID: 20651638.

(Brief summary of the safety and efficacy of pitavastatin shortly after its approval in the US; no mention of hepatotoxicity).

Wensel TM, Waldrop BA, Wensel B. Pitavastatin: a new HMG-CoA reductase inhibitor. Ann Pharmacother. 2010;44:507–14. PubMed PMID: 20179258.

(Literature review and summary of pharmacology, mechanism of action, clinical efficacy and side effects; ALT elevations reported in 1% of pitavastatin and 2% of atorvastatin recipients).

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, and none developed clinically apparent liver injury).

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

(Between 1988 and 2010, the Swedish registry received 217 adverse event reports possibly related to statins, 124 [57%] being liver related, 73 of which could be evaluated; 2 were fatal and one led to liver transplant; 3 had positive rechallenge; 43 [59%] were hepatocellular, 22 [30%] cholestatic and 8 [11%] mixed; 30 were due to atorvastatin, 28 simvastatin, 11 fluvastatin, 2 pravastatin and 2 rosuvastatin, arising after 30 to 248 days; pitavastatin was not mentioned).

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; pitavastatin was not mentioned).

Saito Y. Pitavastatin: an overview. Atheroscler Suppl. 2011;12:271–6. PubMed PMID: 22152281.

(Review of the mechanisms of action, efficacy and tolerability of pitavastatin; no mention of ALT elevations or hepatotoxicity).

Han KH, Rha SW, Kang HJ, Bae JW, Choi BJ, Choi SY, Gwon HC, et al. Evaluation of short-term safety and efficacy of HMG-CoA reductase inhibitors in hypercholesterolemic patients with elevated serum alanine transaminase concentrations: PITCH study (PITavastatin versus atorvastatin to evaluate the effect on patients with hypercholesterolemia and mild to moderate hepatic damage). J Clin Lipidol. 2012;6:340–51. PubMed PMID: 22836071.

(Among 189 Korean patients with hypercholesterolemia and mild ALT elevations [not due to alcohol, HBV or HCV] treated with statins for 12 weeks, 5.2% on pitavastatin and 5.4% on atorvastatin had rises of ALT above 100 U/L [range 102-218 U/L], although average values decreased and hepatic steatosis was reduced [as assessed by computerized tomography).

Berkelhammer C, Lerma EV. Statin treatment in patients with elevated liver enzymes: pitch to proceed. J Clin Lipidol. 2012;6:310–1. PubMed PMID: 22836066.

(Editorial in response to article by Han [2012] suggesting that "the benefits of statin therapy outweigh the risk of transaminitis").

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

(Concise recommendations for management of hyperlipidemia mentions that, unlike for other statins, there are no data on the effects of pitavastatin therapy on clinical outcomes such as coronary artery disease events, stroke and all-cause mortality).

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], but none due to pitavastatin).

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).

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; no mention of pitavastatin).

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, but none due to pitavastatin).

Mora-Cuadrado N, Santana-Lora R, Fernández-Salazar L, González-Hernández JM. Pitavastatin: other statin to be used and monitored. Rev Esp Enferm Dig. 2015;107:578–9. PubMed PMID: 26334470.

(48 year old man developed weakness, diarrhea and a "cholestatic pattern" of liver test abnormalities 4 months after starting pitavastatin [bilirubin and ALT not given, GGT 496 U/L, Alk P 382 U/L], which declined rapidly on switching to simvastatin).

Gosho M, Tanahashi M, Hounslow N, Teramoto T. Pitavastatin therapy in polymedicated patients is associated with a low risk of drug-drug interactions: analysis of real-world and phase 3 clinical trial data. Int J Clin Pharmacol Ther. 2015;53:635–46. PubMed PMID: 26104032.

(Analysis of postmarketing surveillance system on pitavastatin found no increase in adverse event reports in patients taking pitavastatin in combination with agents that interact with CYP 2C9).

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]).

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 represent 5% of cases of drug induced liver injury published in large case series or from registries and discusses atorvastatin, simvastatin, fluvastatin, lovastatin and pravastatin, but not pitavastatin).

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 [ator-, sim- and lo-vastatin] as well as by inhibitors of P glycoprotein and OATP1B1 [most statins including rosuvastatin], with specific recommendations for the most common inhibitors).

Sung S, Al-Karaghouli M, Kalainy S, Cabrera Garcia L, Abraldes JG. A systematic review on pharmacokinetics, cardiovascular outcomes and safety profiles of statins in cirrhosis. BMC Gastroenterol. 2021;21:120. PubMed PMID: 33726685.

(Systematic review of literature suggests that rosuvastatin and pitavastatin pharmacokinetics are unchanged in patients with Child's Class A cirrhosis as opposed to atorvastatin and pravastatin, although unlike rosuvastatin, simvastatin, atorvastatin and pravastatin have been assessed in clinical trials in cirrhotic patients).

Lu B, Sun L, Seraydarian M, Hoffmann TJ, Medina MW, Risch N, Iribarren C, et al. Effect of SLCO1B1 T521C on statin-related myotoxicity with use of lovastatin and atorvastatin. Clin Pharmacol Ther. 2021;110:733–740. PubMed PMID: 34114646.

(Among 233 patients with statin associated myopathy and 2342 controls selected from an aging cohort with genetic testing, the allele frequency of c.521T>C in SLCO1B1 [rs4149056] was higher in those with myopathy, C allele frequency being 14-15% of controls compared to 17% of atorvastatin [p=0.4], 19% of lovastatin [p<0.001], and 25% of simvastatin [p<0.001] myopathy cases).

Cai T, Abel L, Langford O, Monaghan G, Aronson JK, Stevens RJ, Lay-Flurrie S, et al. Associations between statins and adverse events in primary prevention of cardiovascular disease: systematic review with pairwise, network, and dose-response meta-analyses. BMJ. 2021;374(n1537) PubMed PMID: 34261627.

(Systematic review of placebo controlled trials of statins for cardiovascular disease prevention identified 62 publications with 120,456 patients and found an increased risk of muscle symptoms, liver test abnormalities, renal insufficiency and eye conditions for all 7 statins, but not muscle disorders or diabetes; rosuvastatin having relatively high risk for muscle symptoms and renal abnormalities and also was also associated with eye conditions and diabetes, while atorvastatin and lovastatin had highest risk for liver abnormalities).