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Letter to Editor

All About Pitavastatin: Ten Questions And Answers

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Introduction

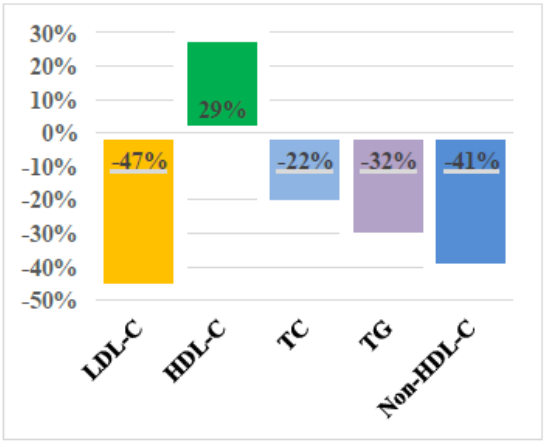
Pitavastatin, a new-generation moderate lipophilic statin, is indicated for the treatment of primary and mixed dyslipidemia.While dyslipidemia is the leading cause of cardiovascular mortality and morbidity, reduction of lipids, particularly low- density lipoprotein cholesterol (LDL-C) with statins, significantly decreases the risk of cardiovascular events. Among different statins pitavastatin exhibits a peculiar pharmacokinetic and pharmacological profile.

What are the most important pharmacological properties of pitavastatin?

The pharmacological mechanism is similar to that of other statins, that is inhibition of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, with subsequent reduction of cholesterol synthesis. After oral administration, pitavastatin is largely absorbed (80%) with an absolute bioavailability 80%, higher than that of other lipophilic statins [1,40]. The peak plasma level is achieved after 0.5-1.2 h without difference between single and multiple doses [1,2] and the steady state is reached after 4 days without drug accumulation [1,2]. The elimination half-life after single and multiple dose is 9-13 hours respectively. Pitavastatin is excreted unchanged in the bile and then reabsorbed through the enterohepatic circulation. This finding explains the long elimination half-life. The drug is minimally metabolized at hepatic level where through a process of glucuronidation. Pitavastatin is converted to its the main inactive metabolite called pitavastatin lactone and than reversibly reconverted in pitavastatin acid [1,2]. The excretion is in large part with the feces, while a very low amount (<5%) is eliminated with urine. Pharmacokinetic properties are not affected by food, does not differ between Caucasian and Asian, young and elderly subjects [1,3].

What is the evidence of pitavastatin efficacy on lipids ?

The lipid lowering of pitavastatin has been reported in several clinical trials, observational studies and summarized in in some reviews [4-7]. Pitavastatin is equally effective in elderly, in subjects with type 2 diabetes or metabolic syndrome and in people at high cardiovascular risk or with coronary artery disease [8-12].



LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides

(From Tokgozoglu L, Zamorano JL. Current perspectives on the use of statins in the treatment of dyslipidaemic patients: Focus on pitavastatin. Drugs Context. 2020; 12:2020-4)

Are the lipids lowering efficacy different or similar to that of other statins?

Compared to other statins, pitavastatin is about 6-fold more potent than atorvastatin, 1.7-fold more potent than rosuvastatin in reducing LDL-C [4].

What is the effect of pitavastatin on plasma HDL-C ?

Pitavastatin, differently from other statins (atorvastatin, pravastatin, fluvastatin, simvastatin, rosuvastatin), significantly increases the plasma levels of HDL by 13.4%-29.0%. This effect is more evident in subjects with low HDL (<40 mg/dl in men and < 50 mg/dl in women) at baseline [5,13-15].

What is the impact of pitavastatin on glucose homeostasis?

Statins are associated with variable incidence (12.0%-61.7%) of new-onset diabetes [16,17]. Observational and comparative randomized clinical trials, have shown that pitavastatin, at variance of other statins, has a neutral, or even a favourable effect on glucose metabolism [18, 19]. A meta-analysis, involving non-diabetic patients shown that pitavastatin, compared with placebo or other statins, did not adversely affect glucose metabolism and decreased the risk of new onset diabetes [20,21]. A recent study [22] performed in patients with dyslipidemia and type 2 diabetes, under stable therapy with hypoglycemic drugs, has shown that moderate doses of rosuvatatin (10 mg/daily), atorvastatin (20 mg/daily) and pitavastatin (2 mg/daily) have a different effect on glucose homeostasis. Indeed, in patients who treated with hypoglicemic drugs and concomitant rosuvastatin or atorvastatin use, fasting plasma glucose levels decreased less (-3.5 mg/dl and -6.5 mg/dl, respectively) when compared with pitavastatin (-19 mg/dl, p<0.001).

Is pitavastatin effective on atherosclerotic plaque volume/composition?

Different studies and reviews [10,12,23,24] have shown the effectiveness of pitavastatin in primary and secondary cardiovascular prevention, in patients with hypercholesterolemia and concomitant high cardiovascular risk factors (advanced age, diabetes, hypertension) and in subjects with coronary artery disease. In the TOHOLIP study [12] the cumulative incidence of the primary endpoint (composite of cardiovascular death, sudden death, acute myocardial infarction, ischemic stroke, ischemic attack, or heart failure) was significantly lower with pitavastatin than with atorvastatin (2.9% vs 8.1%, p = 0.006). Similar results have been obtained in the REAL-CAD [10], in the CIRCLE[23] and LAMIS trials [11], comparing pitavastatin with other statins. Overall these findings clearly demonstrate a significant benefit of pitavastatin (2–4 mg/day), in reducing the rate of major cardiovascular events, in patients at high risk of atherosclerotic disease and in those with stable CAD or recent AMI. In addition to these studies which are carried out in subjects with acute coronary syndrome [25-27] or stable coronary artery disease [28, 29], have evaluated the changes induced by pitavastatin on quantitative and qualitative aspects of coronary atherosclerotic plaque. These studies showing that pitavastatin, differently from other statins, significantly lowered plaque volume index and composition, increasing the fibrous cap thickness which is a marker of plaque vulnerability [30].

What is the benefit of pitavastatin administration before percutaneous coronary intervention (PCI)?

There is evidence that statins, administered before PCI, improve cardiovascular outcomes [31, 32] and the risk of PCI-related peri-procedural complications [33,34]. The effect of early statin therapy on the atheroma components has been highlighted by the ESCORT study [35], that shown that after a short period of pitavastatin use the fibrous-cap thickness increases, thus lowering plaque vulnerability, while after long period of use it also decreases plaque volume.

What are the most frequent adverse events of pitavastatin ?

The most frequent adverse events (AEs) induced by statins are related to myopathy (in rare cases rhabdomyolysis) and liver injury. Pitavastatin is associated with a very low rate of adverse events (AEs), also with high doses and during prolonged treatment. [10, 36]. The most common AEs, mild in severity, are myalgia, muscle spasm or weakness, experienced by a low percentage of patients. Pitavastatin treatment is generally not associated with abnormal liver function.

Are these adverse events (AEs) similar or different from those of other statins?

The incidence of AEs during pitavastatin treatment is lower than that observed with other statins [7,37]. Moreover pitavastatin is poorly metabolized by CYP isoenzymes, therefore differently from other statins, has a very low incidence of drug-drug interactions [1,38]. This aspect has important clinical implications, such as to avoid the risk of high plasma level when pitavastatin is co-administered with other cardiovascular drugs [39].

What is the optimal dosage of pitavastatin?

The starting dose is 2 mg and the maximum dose of 4 mg/daily, taken at any time of the day, with or without food [24].

Conflicts of interest:

Gokhan Faikoglu and Kubra Saygisever-Faikoglu are employees of Recordati.

References

1 Catapano AL. Pitavastatin - pharmacological profile from early phase studies. Atherosclerosis Supplements, 2010; 11:3-7 https://doi.org/10.1016/S1567-5688(10)71063-1 PMid:21193152

2 Luo Z, Zhang Y, Gu J, Feng P, Wang Y. Pharmacokinetic properties of single- and multiple-dose pitavastatin calcium tablets in healthy chinese volunteers. Ther Res Clin Exp, 2015; 77:52-57 https://doi.org/10.1016/j.curtheres.2015.02.001 PMid:26082816 PMCid:PMC4460194

3 Baker W, Chamberlin K. Benefit\risk assessment of pitavastatin for the treatment of hypercholesterolemia in older patients. Clin Interv Aging, 2015; 10:733 https://doi.org/10.2147/CIA.S67532 PMid:25931816 PMCid:PMC4404990

4 Adams SP, Alaeiilkhchi N, Wright JM Pitavastatin for lowering lipids Cochrane Database Syst Rev. 2020; 6 https://doi.org/10.1002/14651858.CD013673 PMCid:PMC7387836

5,Tokgözoglu L, Zamorano JL Current perspectives on the use of statins in the treatment of dyslipidaemic patients: focus on pitavastatin. Drugs Context. 2020; 9:2020-4-4 https://doi.org/10.7573/dic.2020-4-4 PMid:32587627 PMCid:PMC7295107

6 Jeong IK, Kim SR Efficacy and Safety of Pitavastatin in a Real-World Setting: Observational Study Evaluating SaFety in Patient Treated with Pitavastatin in Korea (PROOF Study). Endocrinol Metab (Seoul). 2020 Dec; 35(4):882-891 https://doi.org/10.3803/EnM.2020.723 PMid:33261312 PMCid:PMC7803594

7 Fici F, Tarim B A, Faikoglu G et al Review article: Pitavastatin: Similarities And Differences Compared With Other Statins Acta Pharm. Sci. 2021; 59:(4). https://doi.org/10.23893/1307-2080.APS.05935

8 Stender S, Budinski D, Gosho M, Hounslow N. Pitavastatin shows greater lipid lowering efficacy over 12 weeks than pravastatin in elderly patients with primary hypercholesterolaemia or combined (mixed) dyslipidaemia. Eur J Prev Cardiol, 2013; 20:40-53 https://doi.org/10.1177/2047487312451251 PMid:22679249

9 Gumprecht J, Gosho M, Budinski D, Hounslow N. Comparative long-term efficacy and tolerability of pitavastatin 4 mg and atorvastatin 20-40 mg in patients with type 2 diabetes mellitus and combined (mixed) dyslipidaemia. Diabetes, Obesity and Metabolism, 2011; 13:1047-1055, https://doi.org/10.1111/j.1463-1326.2011.01477.x PMid:21812889

10 Taguchi I, Iimuro S, Iwata H, et al. High-dose versus low-dose pitavastatin in Japanese patients with stable coronary artery disease (REAL-CAD) a randomized superiority trial. Circ, 2018; 137:1997-2009 https://doi.org/10.1161/CIRCULATIONAHA.117.032615 PMid:29735587 PMCid:PMC5959207

11Suh SY, Rha SW, Ahn TH et al. Long-term safety and efficacy of pitavastatin in patients with acute myocardial infarction (from the Livalo acute myocardial infarction study LAMIS). Am J Cardiol, 2011; 108:1530-1535 https://doi.org/10.1016/j.amjcard.2011.07.009 PMid:21890083

12 Moroi M, Nagayama D, Hara F, et al. Outcome of pitavastatin versus atorvastatin therapy in patients with hypercholesterolemia at high risk for atherosclerotic cardiovascular disease. Int J Cardiol, 2020; 305:139-146 https://doi.org/10.1016/j.ijcard.2020.01.006 PMid:31987664

13 Teramoto T, Shimano H, Yokote K, Urashima M. New evidence on pitavastatin: Efficacy and safety in clinical studies, Expert Opin Pharmacother, 2010; 11: 817-828, 14 Pirillo A, Catapano AL. Pitavastatin and HDL: Effects on plasma levels and function(s). Atheroscler Suppl, 2017; 27:e1-9 https://doi.org/10.1517/14656561003641990 PMid:20201733

15 Kurogi K, Sugiyama S, Sakamoto K, et al. Comparison of pitavastatin with atorvastatin in increasing HDL-cholesterol and adiponectin in patients with dyslipidemia and coronary artery disease: The COMPACT-CAD study. J Cardiol, 2013; 62:87-94. https://doi.org/10.1016/j.jjcc.2013.03.008 PMid:23672789

16 Thakker D, Nair S, Pagada A, et al. Statin use and the risk of developing diabetes: a network meta-analysis. Pharmacoepidemiol Drug Saf, 2016; 25:1131-1149 https://doi.org/10.1002/pds.4020 PMid:27277934

17 Casula M, Mozzanica F, Scotti L, et al Statin use and risk of new-onset diabetes: A meta-analysis of observational studies. Nutr Metab Cardiovasc Dis, 2017; 27:396-406 https://doi.org/10.1016/j.numecd.2017.03.001 PMid:28416099

18 Arnaboldi L, Corsini A. Could changes in adiponectin drive the effect of statins on the risk of new-onset diabetes? The case of pitavastatin. Atherosclerosis Supplements, 2015; 16: 1-27 https://doi.org/10.1016/S1567-5688(14)70002-9 PMid:25575403

19 Chapman MJ, Orsoni A, Robillard P et al Effect of high-dose pitavastatin on glucose homeostasis in patients at elevated risk of new-onset diabetes: Insights from the CAPITAIN and PREVAIL-US studies. Curr Med Res Opin, 2014; 30:775-784 https://doi.org/10.1185/03007995.2013.874989 PMid:24328357

20 Vallejo-Vaz AJa. Effect of pitavastatin on glucose, HbA1c and incident diabetes: A meta-analysis of randomized controlled clinical trials in individuals without diabetes. Atherosclerosis, 2015; 241:409-418 https://doi.org/10.1016/j.atherosclerosis.2015.06.001 PMid:26074315

21 Cui JY, Zhou RR, Han S, et al Statin therapy on glycemic control in type 2 diabetic patients: A network meta-analysis. J Clin Pharm Ther, 2018; 43:556-570 https://doi.org/10.1111/jcpt.12690 PMid:29733433

22 Bahar Arican Tarim, Francesco Fici, Istemihan Tengiz et al Do statins counteract the effect of antidiabetic drugs? Results of the SCEAD study Yonsei Med J 2023; 64:175-180 https://doi.org/10.3349/ymj.2022.0287 PMid:36825343 PMCid:PMC9971433

23 Maruyama T, Takada M, Nishibori Y, et al. Comparison of preventive effect on cardiovascular events with different statins- The CIRCLE Study. Circ J. 2011; 75:1951-9 https://doi.org/10.1253/circj.CJ-10-1163 PMid:21673458

24 Francesco Fici, Gokhan Faikoglu, Bahar Arican Tarim et al Pitavastatin: Coronary Atherosclerotic Plaques Changes and Cardiovascular Prevention High Blood Pressure and Cardiovascular Prevention 2022; 29:137-144 https://doi.org/10.1007/s40292-021-00496-0 PMid:35064911

25 Hiro T, Kimura T. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: a multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN-ACS [Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome] study). J Am Coll Cardiol. 2009; 54:293-302 https://doi.org/10.1016/j.jacc.2009.04.033 PMid:19608026

26 Matsushita K, Hibi K, Komura N, et al. Effects of 4 statins on regression of coronary plaque in acute coronary syndrome. Circ J. 2016; 80:1634-43. https://doi.org/10.1253/circj.CJ-15-1379 PMid:27264413

27 Toi T, Taguchi I, Yoneda S, et al. Early effect of lipid-lowering therapy with pitavastatin on regression of coronary atherosclerotic plaque-comparison with atorvastatin. Circ J. 2009; 73:1466-72, https://doi.org/10.1253/circj.CJ-08-1051 PMid:19531899

28 Kodama K, Komatsu S, Ueda Y, et al. Stabilization and regression of coronary plaques treated with pitavastatin proven by angioscopy and intravascular ultrasound: The TOGETHAR trial. Circ J. 2010; 74:1922-8 https://doi.org/10.1253/circj.CJ-10-0038 PMid:20625215

29 Hattori K, Ozaki Y, Ismail TF, et al. Impact of statin therapy on plaque characteristics as assessed by serial OCT, grayscale and integrated backscatter-IVUS. Am Coll Cardiol Imaging. 2012; 5:169-77 https://doi.org/10.1016/j.jcmg.2011.11.012 PMid:22340823

30 Kubo T, Imanishi T, Takarada S, et al. Implication of plaque color classification for assessing plaque vulnerability: a coronary angioscopy and optical coherence tomography investigation. JACC Cardiovasc Interv. 2008; 1:74-80 https://doi.org/10.1016/j.jcin.2007.11.001 PMid:19393149

31Navarese EP, Kowalewski M, Andreotti F, et al. Meta-analysis of time-related benefits of statin therapy in patients with acute coronary syndrome undergoing percutaneous coronary intervention. Am J Cardiol. 2014; 113:1753-6 https://doi.org/10.1016/j.amjcard.2014.02.034 PMid:24792742

32 Gili S, Iannaccone M, Colombo F, et al. Effects of statins on plaque rupture assessed by optical coherence tomography in patients presenting with acute coronary syndromes: insights from the optical coherence tomography (OCT)-FORMIDABLE registry. Eur Heart J Cardiovasc Imaging. 2018; 19:524-31 https://doi.org/10.1093/ehjci/jex102 PMid:28605473

33 Goliasch G, Winter MP, Ayoub M, et al. A contemporary definition of periprocedural myocardial injury after percutaneous coronary intervention of chronic total occlusions. JACC Cardiovasc Interv. 2019; 12:1915-23 https://doi.org/10.1016/j.jcin.2019.06.053 PMid:31601387

34 Lampropoulos K, Megalou A, Bazoukis G et al Pre-loading therapy with statins in patients with angina and acute coronary syndromes undergoing PCI J Interv Cardiol 2017; 30:507-51 https://doi.org/10.1111/joic.12421 PMid:28786142

35 Nishiguchi T, Kubo T, Tanimoto T, et al. Effect of early pitavastatin therapy on coronary fibrous-cap thickness assessed by optical coherence tomography in patients with acute coronary syndrome. The ESCORT study. JACC Cardiovasc Imaging. 2018; 11:829-38 https://doi.org/10.1016/j.jcmg.2017.07.011 PMid:28917689

36 Kurihara Y, Douzono T, Kawakita K, er al A Large–scale, Long–term, Prospective Post–marketing Surveillance of Pitavastatin 2008; 36: 709-731

37 Saito Y Critical appraisal of the role of pitavastatin in treating dyslipidemia and achieving lipid goals Vascular Health and Risk Management 2009:5 921-936 https://doi.org/10.2147/VHRM.S5551 PMid:19997573 PMCid:PMC2788597

38 Corsini A, Ceska R. Drug-drug interactions with statins: will pitavastatin overcome the statins' Achilles' heel?. Curr Med Res Opin, 2011; 27:1551-1562 https://doi.org/10.1185/03007995.2011.589433 PMid:21682551

39 Gosho M, Tanahashi M, Hounslow N, et al. 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 https://doi.org/10.5414/CP202195 PMid:26104032

40 Michael Schachter. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol. 2005 Feb; 19(1):117-25. https://doi.org/10.1111/j.1472-8206.2004.00299.x PMid:15660968