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 1,4,10. 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 then 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 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

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 rosuvastatin (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 hypoglycemic 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 TOHJUP 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 CIRCLE23 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 138. 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.

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