Focus on Pitavastatin

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Abstract: Currently, different statins are available for the treatment of dyslipidemia: Atorvastatin, Simvastatin, Rosuvastatin, Lovastatin, Pravastatin, and Fluvastatin; the newest entry in this class of drugs is Pitavastatin.

The purpose of the present study was to examine the latest evidences on Pitavastatin, more than 10 years after its first marketing and focuses on the most recent evidence regarding its differences with other available statins. A literature review of the last 3 years (January 2013 - January 2016) has been carried out via Pub Med. 193 obtained items were analysed.

Pitavastatin has been studied against other drugs in its class and has demonstrated high potency in reducing LDL-Cholesterol levels and increasing HDL-Cholesterol. Pitavastatin has demonstrated a significant reduction in atherosclerotic plaque volumes and several pleiotropic effects, which suggest its potential benefits in reducing cardiovascular risk.

At present, Pitavastatin don't seem to have adverse effects on glucose metabolism; it has no adverse effects on renal function and currently there is no clinical evidence of Pitavastatin-induced hepatotoxicity. Pitavastatin has favorable pharmacokinetic and safety profiles and its characteristic structure provides significant efficacy at low doses.

Keyword: Pitavastatin, HMG-CoA reductase inhibitors, Statin therapy, Hyperlipidemia, Cardiovascular risk.

INTRODUCTION

Hyperlipidemia has a significant impact on public health, because this condition is a relevant risk factor for cardiovascular disease [1].

Several guidelines recommend that Low Density Lipoprotein-Cholesterol (LDL-C) plasma level is the primary target of lipid lowering therapy, because it is most often associated with the risk for developing cardiovascular disease. Other secondary targets of therapy include reduction of serum triglycerides (TGs) and increase of High Density Lipoprotein-Cholesterol (HDL-C).

Statins are frequently prescribed for the treatment of hyperlipidemia, especially for their ability to lower LDL-C plasma levels [2-4].

Statins act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-determining enzyme in hepatic cholesterol synthesis; consequently, LDL-C receptors in the liver are raised thereby increasing the removal of LDL-C from the blood.

Statins have also proved highly effective in reducing the risk of cardiovascular events in both primary and secondary prevention studies. These results are also due to proven pleiotropic effects of this class of drugs, such as anti-inflammatory effects, antioxidant effects, anti-proliferative and immunomodulatory effects, plaque stability, normalization of sympathetic outflow, and prevention of platelet aggregation [5-7].

Long since, different statins are available for the treatment of dyslipidemia: Atorvastatin, Simvastatin, Rosuvastatin, Lovastatin, Pravastatin, and Fluvastatin [5]. The newest entry in this class of drugs is Pitavastatin; it was first introduced in Japan in 2003 [8] and subsequently approved in many other countries, including United States of America, by the Food and Drug Administration in August 2009, and United Kingdom, by the Medicines and Healthcare products Regulatory Agency in August 2010. Pitavastatin has also been authorized in Italy in July 2012. However, Pitavastatin has not yet been worldwide introduced on a large scale.

The purpose of the present study was to examine the latest evidences on Pitavastatin, more than 10 years after its first marketing.

MATERIAL AND METHODS

A review of literature has been carried out via Pub Med, using the search term Pitavastatin. Search was not limited by language or human subjects. All the found items, published in the last 3 years (from January

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E-ISSN: 2410-2822/16

2013 to January 2016), were analysed. Additional articles were selected from the bibliographies of the quoted references.

RESULTS

193 items were obtained: 40 clinical trials (34 randomized controlled clinical trials), 26 multicenter studies, 25 comparative studies, 2 observational studies, 25 reviews (9 systematic review), 2 meta-analysis, 2 case reports, 2 editorials, 2 comments, 5 letters; the remaining items were prevalently other journal articles, research supports or other publication types. No guidelines or consensus were found. Most of the data were deduced from retrospective analysis and by careful assessment of the obtained items.

The analysis of data obtained showed that Pitavastatin, the newest HMG-CoA reductase inhibitor approved for treating dyslipidemia, has demonstrated high efficacy in lowering serum concentrations of LDL-C. The dose range for Pitavastatin is 1 to 4 mg orally once daily; results from a dose-finding trial indicate that the 1-mg dose decreases LDL-C concentrations by 33.6% and the 4-mg dose decreases LDL-C levels by 47.2% [9].

Like other statins, Pitavastatin has also been shown to have various pleiotropic effects that help to prevent cardiovascular risk. Moreover, Pitavastatin has a unique metabolic profile that may offer therapeutic advantages and benefits. Pitavastatin also shows favorable and promising safety profile [10, 11]

DISCUSSION AND CONCLUSION

This review focuses on the most recent evidence regarding Pitavastatin and its differences compared to other available statins.

Physicochemical Properties.

Pitavastatin is a fully synthetic lipophilic statin which belongs to the class of organic compounds known as phenylquinolines; these are heterocyclic compounds containing a quinoline moiety substituted with a phenyl group. Pitavastatin is a lipid-lowering agent that competitively inhibits HMG-CoA reductase, the enzyme that catalyses the first step of cholesterol synthesis in the liver. Unlike other statins, Pitavastatin has a unique cyclopropyl group in its base structure and this chemical group contributes to a more effective inhibition of the HMG-CoA reductase enzyme in decreasing cholesterol production [9, 12].

Pharmacodynamics and Pharmacokinetics

Pitavastatin, usually as a calcium salt, is available in strengths of 1 mg, 2 mg, and 4 mg; this drug is 51-60% bioavailable and achieves its peak plasma concentration (Cmax) approximately one hour after oral administration; plasma levels increase proportionally to the dose. Pitavastatin is more than 99% protein-bound in human plasma, mainly to albumin and $alpha_1$-acid glycoprotein, and it is selectively distributed to the liver; after oral administration, most of the bioavailable Pitavastatin is excreted unchanged in the bile and it is reabsorbed by the intestine and recirculates to the liver making itself available for enterohepatic recirculation.

Pitavastatin is mainly metabolized in the liver by glucuronidation; the cytochrome P450 system is only slightly involved in the metabolism of Pitavastatin; there is some metabolism by CYP2C9 and, to a lesser extent, CYP2C8, whereas Pitavastatin don't appears to be a substrate of cytochrome P3A4. As opposed to other statins, it's likely that the cyclopropyl group of Pitavastatin diverts the drug away from metabolism by cytochrome P450 system. As a result, Pitavastatin is minimally metabolized and these processes probably increase the bioavailability of Pitavastatin contributing to its prolonged duration of action; the mean plasma concentration half-life is 12 hours. Most of Pitavastatin is eventually excreted in the feces and approximately 15% of dose in the urine.

Taking Pitavastatin with fat meals decreases Cmax by 43%, whereas the area-under-the curve (AUC) concentration remains relatively unchanged. Cmax and AUC concentration don't differ when Pitavastatin is taken in the morning or evening. Moreover, the pharmacokinetic of Pitavastatin has been explored in a variety of patient groups with overlapping results, suggesting that dosage adjustments of this statin are not required for gender, age or race.

According to the results of several pharmacokinetic studies, Pitavastatin shows favorable and promising safety profile; moreover its unique metabolism reduces the likelihood of clinically significant drug-drug interactions. [9, 13-17].

Hypolipidemic Effect

Pitavastatin has been studied against other drugs in its class and has demonstrated high potency in reducing both total and LDL cholesterol levels; it was observed that Pitavastatin also significantly decreases the serum levels of TGs [9].

Mean percentage of LDL-C and total cholesterol (TC) reductions from baseline were significantly greater with Pitavastatin 2 mg daily compared to Pravastatin 10 mg daily [18].

Pitavastatin 2 mg once daily was also compared with Simvastatin 20 mg dilay. Pitavastatin was non-inferior to Simvastatin in terms of reducing LDL-C levels; there was no significant difference between two groups in changes in TC, TGs, or HDL-C levels [19].

Several comparative studies showed that Pitavastatin and Atorvastatin didn't differ significantly in terms of reductions in LDL-C, TC, and TGs or increases in HDL-C [20,21]. A recent meta-analysis of seven trials involving 1.529 patients, revealed that Pitavastatin was as effective as Atorvastatin in lowering LDL-C, TC and TGs levels; moreover Pitavastatin was significantly superior to Atorvastatin in increasing HDL-C levels [22].

In the PATROL trial was compared the safety and efficacy of Pitavastatin 2 mg daily, Atorvastatin 10 mg daily and Rosuvastatin 2.5 mg daily, for 16 weeks, in 302 patients with hypercholesterolemia; in this first prospective randomized multi-center trial Pitavastatin was non-inferior to the other two statins in lowering LDL-C levels [23].

No comparative studies have been found between Pitavastatin and Lovastatin nor between Pitavastatin and Fluvastatin regarding their effectiveness in lipid-lowering therapy. A comparison of the efficacy of available statins in lowering HDL-C is summarized in Table **1**.

Effect on Atherosclerosis

Several studies have demonstrated that Pitavastatin has stronger effects on the regression and stabilization of atherosclerotic plaque in the thoracic aorta, carotid and coronary arteries [27-29]. In many studies the administration of Pitavastatin resulted in a significant regression of the carotid intima-media thickness [30, 31]; moreover Pitavastatin not only improved the atherosis as measured by intima-media thickness and integrated backscatter values, but also attenuated inflammation of plaques as measured by maximum standard uptake values by PET/CT in the thoracic aorta and carotid artery [27]. These antiatherogenic effects of Pitavastatin were non-inferior to other statins administered in comparative studies, as Pravastatin [27, 28, 30] and Atorvastatin [29].

Ancillary Benefits

As other statins [32, 33], several experimental and clinical evidence suggest that Pitavastatin also has beneficial pleiotropic effects beyond its cholesterol-lowering properties. These cholesterol-independent effects play an important part in reducing cardiovascular mortality and morbidity [34] and they include improving endothelial function and reducing oxidative stress [35-41], attenuating vascular and myocardial remodeling [42, 43], decreasing in smooth muscle proliferation [44, 45], inhibiting vascular inflammation [46-48], antiplatelet [49, 50] and antithrombotic actions [51].

As Atorvastatin [52], Pitavastatin improves endothelial function even in chronic smokers through its anti-oxidative properties. Pitavastatin has been shown to restore significantly the endothelial function in chronic smokers with mild hypercholesterolemia, after treatment for 4 weeks, suggesting a possible role in reducing cardiovascular events not only by lowering LDL-C levels but also by improving endothelial function [53].

Table 1: Comparison of the Efficacy in Lowering HDL-C between Available Statins [24-26, 9, 14]

Statin	1 mg	2 mg	4 mg	5 mg	10 mg	20 mg	40 mg	80 mg
Simvastatin	n.a.(*)	n.a.(*)	n.a.(*)	n.a.(*)	-27%	-32%	-37%	-42%
Lovastatin	n.a.(*)	n.a.(*)	n.a.(*)	n.a.(*)	-21%	-29%	-37%	-45%
Fluvastatin	n.a.(*)	n.a.(*)	n.a.(*)	n.a.(*)	n.a.(*)	-21%	-27%	-36%
Pravastatin	n.a.(*)	n.a.(*)	n.a.(*)	n.a.(*)	-20%	-24%	-29%	n.a.(*)
Atorvastatin	n.a.(*)	n.a.(*)	n.a.(*)	n.a.(*)	-37%	-43%	-49%	-55%
Rosuvastatin	n.a.(*)	n.a.(*)	n.a.(*)	-38%	-43%	-48%	-53%	n.a.(*)
Pivastatin	-33%	-37%	-47%	n.a.(*)	n.a.(*)	n.a.(*)	n.a.(*)	n.a.(*)
HDL-C reduction (%)								

(*) n.a. = not available

Effect in Reducing Cardiovascular Risk

There is a lot of evidence that the statin therapy reduces the cardiovascular risk and several studies have demonstrated the efficacy of treatment with HMG-CoA reductase inhibitors in primary [54-58] and secondary prevention [58-60]. The efficacy in reducing cardiovascular diseases has been shown with many statins [54-60] but, regarding the efficacy of Pitavastatin in preventing cardiovascular diseases, in our research we have not found significant studies having a cardiovascular event as either a primary or secondary end-point. We have found only a comparative study designed to evaluate the preventive effect of Pitavastatin and other statins on cardiovascular events in Japanese patients who underwent percutaneous coronary intervention [61]. This is a retrospective, single-center observational study carried out, for seven years, on 743 patients receiving Pitavastatin, Atorvastatin, Pravastatin, or no statin. This study has shown that each statin treatment significantly decreased recurrent cardiac events compared with no statin and Pitavastatin resulted more effective than other statin treatments. The main limitation of this study is that cardiac events predominantly consisted of repeted percutaneous coronary intervention, a relatively "soft" end-point. The main mechanisms by which Pitavastatin might reduce cardiovascular risk are summarized in Table **2**. There is no doubt that the efficacy of Pitavastatin in reducing HDL-C and improving lipid profile, added to pleiotropic effects of this statin and its strong effects on the regression and stabilization of atherosclerotic plaque, may represent sufficient data to state that Pitavastatin is also effective in reducing cardiovascular risk. However, we believe that further studies will be needed to irrefutably confirm the efficacy of Pitavastatin in the prevention of cardiovascular risk.

Table 2: Potential Mechanisms of Pitavastatin in Cardiovascular Risk Prevention [9, 27-31, 34-53]

• LDL- and Total-Cholesterol reduction
• HDL-Cholesterol increase
• Triglycerides reduction
• Regression and stabilization of atherosclerotic plaque
• Regression of carotid intima-media thickness
• Improvement of endothelial function
• Oxidative stress reduction
• Attenuation of vascular and myocardial remodeling
• Reduction of smooth muscle cells proliferation
• Inhibition of vascular inflammation
• Antiplatelet and antithrombotic actions

Safety and Drug Interactions

Pitavastatin has pharmacodynamic and pharmacokinetic properties that are distinct from those of other statins, and may contribute to its favorable profile of safety [9-17].

The safety of Pitavastatin was assessed in the LIVES Study, a Japanese long-term prospective post-marketing surveillance study, designed to follow approximately 20.000 hypercholesterolemic patients treated with Pitavastatin [62].

During a 2-year follow-up period, no significant problems concerning safety were observed [63]; after 104 weeks, only 10.4% of pitavastatin-treated patients experienced adverse events, of which approximately 84% were mild and around 1% was severe. The most common adverse effects were myalgia (1.1%) and increases in blood creatine phosphokinase (2.7%), alanine aminotransferase (1.8%), aspartate aminotransferase (1.5%) and gamma-glutamyltransferase (1.0%); only 7.4% of patients were forced to discontinue Pitavastatin [64]. This study revealed no unexpected negative side effects of Pitavastatin treatment, confirming the general long-term safety and tolerability of this statin, as observed for Atorvastatin, Simvastatin and Rosuvastatin administered for extended periods in previous studies [65, 66]. Moreover, comparisons between Pitavastatin and other statins, as Atorvastatin, Rosuvastatin and Simvastatin, have shown that these statins have similar adverse event profiles [23, 67].

Recent evidence have suggested that statin therapy could be associated with an increased risk of developing type 2 diabetes mellitus [68-70]. A meta-analysis of 13 clinical trials (n = 91.140 patients without type 2 diabetes mellitus) indicates that standard doses of Atorvastatin, Pravastatin, Simvastatin, or Rosuvastatin were associated with a 9% increased risk for type 2 diabetes mellitus over 4 years. However this meta-analysis included trials with more than 1.000 patients, with identical follow-up in both groups and duration of more than 1 year [70].

More recently, a meta-analysis of 17 randomized controlled trials, including 113.394 patients without preexisting type 2 diabetes mellitus, showed that, when compared with placebo, Pravastatin 40 mg daily was

associated with the lowest risk for new-onset diabetes while Rosuvastatin 20 mg daily was associated with 25% increased risk for diabetes; the impact on diabetes appeared to be intermediate with Atorvastatin 80 mg daily [71]. These findings confirm that different types and doses of statins show different potential to increase the incidence of new-onset diabetes.

The efficacy and safety of Pitavastatin have also been assessed in patients with hyperlipidemia and concomitant glucose intolerance [72] or type 2 diabetes [73]; in these studies Pitavastatin has not caused adverse effect on glycemic control. Subsequently, a sub-analysis of LIVES Study [64] has shown an improvement in glycated hemoglobin in patients with type 2 diabetes after long-term Pitavastatin treatment.

Recently, neutral effects of Pitavastatin on glucose homeostasis were observed in two cohorts of patients with metabolic syndrome; however small number of patients and short follow-up represent limitations of this study [74].

In a more recent meta-analysis including 15 studies, Pitavastatin did not adversely affect glucose metabolism or diabetes development compared with placebo or other statins [75]. At present, Pitavastatin does not seem to have effects on the incidence of diabetes; the considerable increase in plasma adiponectin, documented in clinical studies, might be related to its favorable effect on glucose metabolism [76]. However, more studies are needed in well-controlled trials.

In the LIVES Study the treatment with Pitavastatin has allowed to obtain a significant increase in estimated glomerular filtration rate in patients with chronic kidney disease [77]. In a recent randomized trial [78] the renal effects of Pitavastatin, compared with Rosuvastatin, were assessed in dyslipidemic patients with chronic renal disease. The results of this study suggest that neither of these statins has adverse effects on renal function; however, in intra-group comparisons, the glomerular filtration rate was significantly increased in the Rosuvastatin group but not in the Pitavastatin group and showed no tendency to worsen in either groups.

Finally, in a recent observational study [79], Pitavastatin resulted to be inferior to Pravastatin, Rosuvastatin and Atorvastatin in preserving the kidney function in patients with type 2 diabetes.

It is reasonable that patients with moderate renal impairment and those receiving hemodialysis should begin with a starting dose of 1 mg and a maximum dose of 2 mg once daily. Patients with severe renal impairment who are not receiving hemodialysis have not been studied, and the use of Pitavastatin in this population is not recommended.

In contrast to other lipophilic statins, Pitavastatin undergoes limited metabolism by cytochrome P450 enzymes, particularly CYP3A4 which is a common source of drug interactions in other statins [80]. Clinical evidence suggests that concomitant therapy with drugs that are involved with the cytochrome P450 system has no effect on the pharmacokinetics of Pitavastatin [81, 82].

Although in literature [83, 84] are reported cases of hepatotoxicity due to statins, in our research we have not found clinical evidence of Pitavastatin-induced hepatotoxicity; however, patients with acute liver disease, including unexplained and persistent increases in transaminases, should not receive Pitavastatin [85].

In conclusion, the newest HMG-CoA reductase inhibitor Pitavastatin has been studied against other drugs in its class and has demonstrated high potency in reducing both total and LDL cholesterol levels; moreover, Pitavastatin has been shown to be effective in increasing HDL-C and reducing TGs. Pitavastatin treatment has demonstrated a significant reduction in atherosclerotic plaque volumes and several pleiotropic effects, which suggest its potential benefits in reducing cardiovascular risk. In particular, Pitavastatin improves endothelial function and reduces oxidative stress; this effect has also been demonstrated in chronic smokers.

At present, Pitavastatin don't seem to have adverse effects on glucose metabolism; moreover this statin has no adverse effects on renal function and currently there is no clinical evidence of Pitavastatin-induced hepatotoxicity.

Pitavastatin has favorable pharmacokinetic and safety profiles and its characteristic structure provides significant efficacy at low doses compared to other statins.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

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Received on 18-02-2016 Accepted on 01-03-2016 Published on 11-03-2016

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