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Pitavastatin and HDL: Effects on plasma levels and function(s)

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Abstract

Low high density lipoprotein cholesterol (HDL-C) levels represent an independent risk factor for cardiovascular disease; in addition to the reduced HDL-C levels commonly observed in patients at cardiovascular risk, the presence of dysfunctional HDL, i.e. HDL with reduced atheroprotective properties, has been reported. Despite the established inverse correlation between HDL-C levels and cardiovascular risk, several clinical trials with HDL-C-increasing drugs (such as niacin, CETP inhibitors or fibrate) failed to demonstrate that a significant rise in HDL-C levels translate into a cardiovascular benefit. Statins, that are the most used lipid-lowering drugs, can also increase HDL-C levels, although this effect is highly variable among studies and statins; the most recent developed statin, pitavastatin, beside its role as LDL-C-lowering agent, increases HDL-C levels at a significantly higher extent and progressively upon treatment; such increase was observed also when patients where shifted from another statin to pitavastatin. The stratification by baseline HDL-C levels revealed that only pitavastatin significantly increased HDL-C levels in patients with baseline HDL-C $\leq$45 mg/dl, while no changes were observed in patients with higher baseline HDL-C levels. In the last years the hypothesis that functional properties of HDL may be more relevant than HDL-C levels has risen from several observations. The treatment with pitavastatin not only increased HDL-C levels, but also increased the phospholipid content of HDL, increased the HDL efflux capacity and their anti-oxidant properties. These observations suggest that, besides its high LDL-C-lowering effect, pitavastatin also exhibits a significantly higher ability to increase HDL-C levels and may also positively affect the quality and functionality of HDL particles.

Keywords: Statins; Cholesterol; High density lipoproteins

1. Introduction

The role of statins in the reduction of low density lipoprotein cholesterol (LDL-C) levels and in the prevention of cardiovascular disease has been largely established. However, despite large reduction of LDL-C plasma levels, patients still experience cardiovascular events, due to the "residual risk" related to factors other than LDL-C levels that include other lipid anomalies, such as low HDL-C and high triglyceride levels, or the presence of pathological conditions such as diabetes or metabolic syndrome [1]. Low HDL-C levels is a well-established independent risk factor for atherosclerosis-related disease [2,3], mainly due to the many atheroprotective properties of this class of lipoproteins, suggesting that increasing HDL-C levels should reduce the cardiovascular risk. However, the failure of some clinical trials to demonstrate that increasing HDL-C levels reduced the cardiovascular events [4–9], and data from genetic studies [10] challenged the "HDL hypothesis" and suggested that the improvement of HDL particle function would be more important than simply increase their plasma levels [11].

Statins are the most widely used LDL-C-lowering drugs and clinically increase also HDL-C levels, although a great

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variability has been reported [12]; among them, pitavastatin has a LDL-C-lowering effect similar or even superior to that of other statins, but a significantly higher ability to increase HDL-C levels [13−15] and may also positively affect the quality and functionality of HDL particles. In the present review we focus our attention on this peculiar effect of pitavastatin in comparison with other statins and discuss both the effect on HDL-C levels and HDL functionality.

2. Pitavastatin: a general overview

Pitavastatin is a synthetic lipophilic statin with a unique structure (Fig. 1), compared with other statins, that determines an increased oral absorption and systemic bioavailability [16], as well as an increased affinity for HMG-CoA reductase [17] and strong effects on plasma LDL-C and HDL-C levels [18]. Pitavastatin undergoes limited metabolism, as it is poorly metabolized by cytochrome P450 (CYP) 2C9 [19] (Fig. 1). This can explain the lack of increase in the incidence of muscle-related adverse events in patients treated with pitavastatin and drugs known to affect CYP isoenzymes, even when considering drugs interacting with CYP2C9 that is minimally involved in the metabolism of pitavastatin [20]. Furthermore, the P-glycoprotein transporter does not play a major role in pitavastatin disposition, and pitavastatin does not inhibit P-glycoprotein activity, thus it is unlikely that pitavastatin plasma levels may be affected by concomitant use of P-glycoprotein inhibitors [21]. Pitavastatin may, however, interact with other transporters systems, such as the organic anion transporting polypeptide OATP1B1, responsible for its uptake into hepatocytes [22]. This implies that pitavastatin may interact with various drugs through these transporters [23] (Fig. 1). However, the available data from clinical trials and post-marketing surveillance suggest that concomitant administration of pitavastatin with other drugs was associated with a low incidence of adverse events due to drug−drug interactions [20], in agreement with data obtained in healthy volunteers [24−27], indicating this drug as helpful for the treatment of high-risk patients who receive concomitant therapies Fig. 2.

Several clinical trials have suggested the possibility that statin therapy may increase the risk of incident type 2 diabetes (T2D) [28−30]. In this context, pitavastatin seems to have a neutral and possibly beneficial effect on glucose

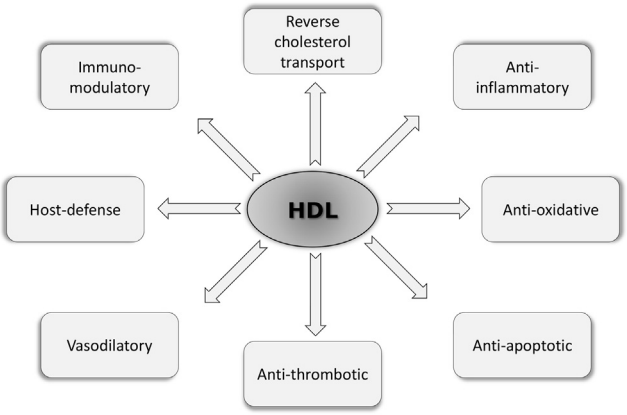

Fig. 2. Anti-atherogenic properties of HDL.

homeostasis, as it was not associated with significant changes in fasting plasma glucose, glycated haemoglobin, insulin or homeostasis model assessment index [31−33]. A recent meta-analysis of 15 randomized controlled clinical trials reported that pitavastatin therapy was not associated with increased fasting blood glucose, HbA1c or new-onset diabetes in non-diabetic patients [34]. Most trials (11 out of 15) included in this meta-analysis had a short follow-up (12 weeks), while it is known that the exposure time to a statin may influence the risk to have glucose-related anomalies; however no significant differences were observed between short-term and longer-term (32−120 weeks) treatments [34]. In fact the CAPITAIN study, performed in healthy subjects with metabolic syndrome showed that a 6-month treatment with the highest available dose of pitavastatin (4 mg/day) did not alter significantly parameters related to glucose or insulin metabolism [31] and a subanalysis of the LIVES study showed a significant 0.28% ($p < 0.001$) reduction of HbA1c in diabetic patients treated with pitavastatin for 104 weeks [35]. These results seem to suggest that the diabetogenic effect of statins is not a class effect and that pitavastatin may be specifically useful in patients at risk of developing diabetes, such as those with metabolic syndrome. The J-PREDICT (Japan Prevention Trial of Diabetes by Pitavastatin in Patients with Impaired Glucose Tolerance) study was designed to specifically address this issue, as it evaluated the cumulative incidence of new-onset diabetes in patients with impaired glucose tolerance treated with pitavastatin 1−2 mg/day in combination with lifestyle

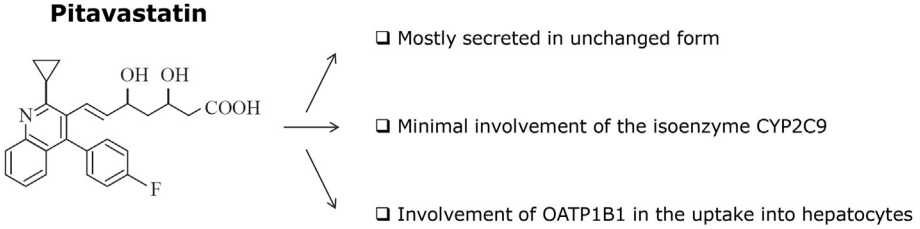

Fig. 1. Chemical structure and metabolic pathways of pitavastatin.

modification for 5 years (NCT00301392). The study has been completed in 2015 and we are waiting for final results. Preliminary data showed a lower diabetes incidence rate in the pitavastatin group compared with the only lifestyle modification group [36]. Pitavastatin is the only statin able to increase plasma levels of adiponectin, a protein possessing anti-atherosclerotic, anti-inflammatory and anti-diabetogenic properties, which might explain, at least in part, the neutral or even beneficial effect of pitavastatin on glucose metabolism [37], although other mechanisms cannot be excluded. These findings suggest that pitavastatin may be a useful treatment for patients with type 2 diabetes or at risk to develop diabetes, although a long-term evaluation of the diabetogenic effect of pitavastatin is still lacking.

3. HDL: role in cardiovascular disease and findings from clinical trials

HDL is believed to be protective toward the development of atherosclerosis possibly via the process of reverse cholesterol transport, i.e. the removal of excess cholesterol from peripheral tissues to the liver for excretion; both lipid-poor apolipoprotein A-I (the main apoprotein of HDL) and mature HDL contribute to this process [38]. In addition to this, HDL possesses several other functions, including anti-inflammatory and anti-oxidative activities, as well as immuno-modulatory and innate host defense properties [38–40] (Fig. 1). HDL is highly heterogeneous and comprises several subfractions having different size, composition and functions, and several lipolytic enzymes as well as lipid exchange proteins are involved in the remodelling of HDL particles [38].

HDL-C levels inversely correlate with the risk of coronary artery disease (CAD) [2,3], and low HDL-C levels, that are common in patients with high cardiovascular risk, remain significantly and independently associated with increased CAD risk also in statin-treated patients [41]. Despite this inverse relationship, and although several therapeutic options are available to increase HDL-C levels, most of the clinical trials failed to demonstrate that an increase of HDL-C results in a reduction of cardiovascular risk. This occurred in trials with either niacin [4,5], CETP inhibitors [6–8] or fenofibrate [9], although a reduction of CV events was observed in subgroups of patients with low baseline HDL-C levels and high TG when treated with fibrates [9,42]. A possible explanation for the failure in the remaining study population could be that these therapies, while increasing HDL-C levels, do not restore or improve the functionality of HDL particles that may become dysfunctional (which includes loss of physiological function and gain of pathological dysfunction) under acute and chronic inflammatory conditions, including dyslipidemia and atherosclerosis-related conditions [43]. On the other hand, despite the significant cardiovascular protection, patients treated with statins still experience cardiovascular events, referred to as “residual risk”, present also during intensive lipid-lowering treatments. Such residual risk is, at least in part, linked to several conditions other than LDL-C levels, including high levels of triglycerides, low levels of HDL-C, presence of diabetes, hypertension, and obesity, all of which are independent risk factors for CAD. It is known that statins can increase plasma concentrations of HDL-C, although modestly and with great variability among studies and different statins [44,45]. The extent of HDL increase seems to be mainly related to the baseline levels of HDL-C, being low HDL-C levels associated with a higher percent increase during statin therapy, while patients with higher HDL-C levels (~60 mg/dL) show no or marginal increase [46,47].

In contrast with the findings obtained in clinical studies with HDL-raising drugs, clinical trials evaluating the effects of increasing HDL-C levels during statin therapy have shown a reduction of cardiovascular events. A post hoc analysis of the Treating to New Target (TNT) study showed that HDL-C levels during statin treatment were predictive of major cardiovascular events, and even among subjects with LDL-C below 70 mg/dL, those in the highest quintile of HDL-C levels had a lower cardiovascular risk than those in the lowest quintile [1]. Similarly, in hypercholesterolemic patients treated with low dose simvastatin (5–10 mg/day), which induced a 4.5% average percent increase in HDL-C levels over a period of 6 years, the mortality rate was higher in patients with HDL-C levels below 40 mg/dl than in those with levels above 50 mg/dl [48]. In addition, statin therapy induced coronary artery atheroma regression when LDL-C was significantly reduced and HDL-C increased by more than 7.5% [49], suggesting that statin benefit may derive from both LDL-C reduction and HDL-C increase.

4. The clinical impact of pitavastatin: focus on HDL-C

Several clinical trials have demonstrated the ability of pitavastatin to improve the lipid profile in patients with primary hypercholesterolemia or combined dyslipidemia, with an efficacy comparable or even superior to that of other statins including atorvastatin, simvastatin or pravastatin [50–54]. However, although statins have generally only a modest and variable effect on HDL, pitavastatin has unique pharmacological features that result in a clinically significant reproducible increase of HDL-C levels (Table 1) [14,15,52]. Such an effect may be particularly relevant in some groups of patients, such as those with type 2 diabetes or metabolic syndrome, as they usually have low HDL-C levels in addition to high LDL-C and TG levels [55]. The J-LIT study showed, in fact, that an increase of 10 mg/dL (0.26 mmol/L) of HDL-C levels translated into a 34.9% reduction in the risk of coronary events in patients with both hypercholesterolemia and type 2 diabetes [56]. Clinical studies have also shown that increasing HDL-C levels by statins significantly decreases the progression of

Table 1
Effect of pitavastatin on HDL-C and apoA-I levels in different groups of patients.

Baseline characteristics of patients (Ref.)	Interventions	Duration	Effects on HDL-C levels (% change)
LDL-C≥140 mg/dl Glucose intolerance (Sasaki et al., 2008) [13]	Pitavastatin 2 mg/day Atorvastatin 10 mg/day	52 weeks	HDL-C: Pitavastatin +8.2%; p = 0.031 *vs* Atorvastatin Atorvastatin: +2.9% ApoA-I: Pitavastatin: +5.1%; p = 0.019 *vs* Atorvastatin Atorvastatin:+0.6%
Stable CAD; LDL-C>100 under statin or LDL-C>140 without LLT; HDL-C<40 mg/dl (Kurogi et al., 2013) [61]	Pitavastatin 2–4 mg/day Atorvastatin 10–20 mg/day	30 months	HDL-C: Pitavastatin: +20.1%; p = 0.013 *vs* Atorvastatin Atorvastatin: +6.3% ApoA-I: Pitavastatin: +20.84%; p = 0.034 *vs* Atorvastatin Atorvastatin: +11.36%
LDL-C >130, <220 mg/dl TG ≤ 400 mg/dl (Sponseller et al., 2014) [62]	Pitavastatin 4 mg Pravastatin 40 mg	12 weeks	HDL-C: Pitavastatin: +6.3%; p = 0.101 *vs* Pravastatin Pravastatin: +5.2%
Hypercholesterolemia or FH (Teramoto et al., 2009) [14]	Pitavastatin (1–4 mg) (*de novo* or switch from other statins or lipid-lowering drugs)	104 weeks	All patients: HDL-C, +5.9%; p < 0.0001 *vs* baseline Baseline HDL-C<40 mg/dl: HDL-C, +24.6%; p < 0.0001 *vs* baseline *De novo* pitavastatin: All patients: +6.5%; p < 0.01 *vs* baseline; Baseline HDL-C<40 mg/dl: +27.3%; p < 0.01 *vs* baseline Switch from other LLT: All patients: +3.8%; p < 0.01 vs baseline; Baseline HDL-C<40 mg/dl: +19.8%; p < 0.01 *vs* baseline Switch from: Pravastatin: All patients: +3.9%; p < 0.01 *vs* baseline Baseline HDL-C<40 mg/dl: +21.0%; p < 0.01 *vs* baseline Simvastatin: All patients: +5.5%; p < 0.01 *vs* baseline Baseline HDL-C<40 mg/dl: +11.8%; ns Fluvastatin: All patients: +5.3%; p < 0.01 vs baseline Baseline HDL-C<40 mg/dl: +20.1%; ns Atorvastatin: All patients: +2.9; p < 0.01 vs baseline; Baseline HDL-C<40 mg/dl: +15.8%; p < 0.01 *vs* baseline Other LLT: All patients: +3.5%; Baseline HDL-C<40 mg/dl: +9.2%
Dyslipidemic treated with Pitavastatin 2 mg/day or Atorvastatin 10 mg/day or Rosuvastatin 2.5 mg/day (Kakuda et al., 2014) [64]	Switch to another statin	3 months	ATO→PIT: HDL-C: +7.69%; p = 0.001 *vs* baseline ApoA-I: +6.69%; p = 0.0047 *vs* baseline PIT→ATO: HDL-C: −5.56%; p = 0.0290 *vs* baseline ApoA-I: −4.5%; p = 0.0342 *vs* baseline ROS→PIT: HDL-C: +7.53%, p = 0.0004 *vs* baseline ApoA-I: 4.85%, p = 0.0122 *vs* baseline
Hypercholesterolemic (Teramoto et al., 2011) [67]	Pitavastatin 1, 2 and 4 mg	5 years	All patients: +5.7%; p < 0.001 *vs* baseline Subgroup analysis: Low baseline HDL-C: +28.9%; p < 0.001 *vs* baseline Low baseline HDL-C + diabetes: +26.7%; p < 0.001 *vs* baseline Low baseline HDL-C + IHD: +22.5%; p < 0.001 *vs* baseline
Post-PCI patients (Maruyama et al., 2011) [15]	Statins		All patients: No statin: +5.3% Pravastatin: +5.4%; ns Atorvastatin: +7.0%; ns Pitavastatin: +13.4%; p = 0.01 *vs* no statin group Baseline HDL-C ≤45 mg/dl: No statin: +9.7% Pravastatin: +13.6% Atorvastatin: +14.5% Pitavastatin: +21.3%; p < 0.001 *vs* no statin group

CAD: coronary artery disease; LLT: lipid-lowering treatment; PCI: percutaneous coronary intervention. Only statistically significant p values were reported.

atherosclerosis and reduces both cardiovascular and cerebrovascular risk independently of LDL-C levels [49,57–60].

4.1. Comparison between pitavastatin and other statins

Patients with high baseline LDL-C levels and glucose intolerance were given pitavastatin (2 mg/day) or atorvastatin (10 mg/day) and followed for 52 weeks [13]. Pitavastatin increased HDL-C and apoA-I more than atorvastatin (difference in % change, pitavastatin *vs* atorvastatin: +5.3%, p = 0.031 and +4.5%, p = 0.019, respectively) [13]. Similar observations were reported in the COMPACT-CAD study in which patients with stable coronary artery disease, hypercholesterolemia and low HDL-C levels (<50 mg/mL) were treated with pitavastatin 2–4 mg/day or atorvastatin 10–20 mg/day for 30 months [61]. Despite similar reductions in LDL-C levels, percent changes in HDL-C levels were significantly greater with pitavastatin than with atorvastatin (+20.1 ± 25.7% and 6.3 ± 19.8%, respectively, p = 0.01), with similar results in apoA-I levels [61]. Contrarily to what was observed with atorvastatin, the increase of HDL-C levels induced by pitavastatin was progressive and continuous during the follow-up period [61]. When compared with pravastatin in patients with primary hypercholesterolemia or combined dyslipidemia, both treatments significantly (p < 0.001) increased HDL-C (pitavastatin 4 mg: +6.3%, pravastatin 40 mg: +5.2%) after 12 weeks without difference between the two statins [62]. A possible explanation for these disagreeing findings may be related to the time of treatment: in fact, in the study by Kurogi et al. [61] the difference between pitavastatin and atorvastatin on HDL-C levels started to become evident after 12 months treatment and were significantly different at 30 months. This may suggest that, due to the progressive and continuous increase of HDL over time following treatment with pitavastatin, a long-term therapy with pitavastatin may be required to observe its specific effect on HDL-C levels.

The LIVALO Effectiveness and Safety Study (LIVES Study) followed hypercholesterolemic patients treated with pitavastatin for 2 years, showing a significant 7.5% (p < 0.05) increase of HDL-C levels, with a 24.9% (p < 0.001) increase in the subgroup with low baseline HDL-C levels (<40 mg/dL) [14]. In contrast with LDL-C levels, that showed a dramatic decrease after 12 weeks and then remained constantly low, HDL-C levels gradually and continuously increased in the course of the follow-up period [14,63]. Although statin-naïve patients showed the highest increase, a significant rise of HDL-C levels was observed also in patients who had been taking cholesterol-lowering drugs other than pitavastatin, with increases after switch from atorvastatin or rosuvastatin to pitavastatin (+7.7%, p = 0.0010 and +7.5%, p = 0.0004, respectively) and reduction in patients switched from pitavastatin to atorvastatin (−5.6%, p = 0.029) [64], thus confirming the observations of previous studies [14,65,66]. The LIVES Study Extension, which followed patients for an additional 3 years, confirmed a 5.7% increase of HDL-C in the whole study population, with higher increases in subgroups of patients such as those with low baseline HDL-C levels (<40 mg/dL; +28.9% ± 38.1, p < 0.001) as well as in those with low HDL-C associated with either diabetes (+26.7% ± 27.5, p < 0.001) or history of ischemic heart disease (+22.5% ± 27.3, p < 0.001) [67]. Interestingly, the Kaplan–Meier curves showed that the cumulative incidence of total (cardiovascular + cerebrovascular) events was higher in patients who achieved only LDL-C or HDL-C treatment goals compared with those who achieved both treatment goals [67].

The CIRCLE study confirmed these findings, showing that pitavastatin and atorvastatin more efficiently decreased LDL-C levels in patients who underwent percutaneous coronary intervention compared with pravastatin [15]; however, the increment of HDL-C was much higher with pitavastatin than with the other statins, and the incidence of major adverse cardiac events were significantly lower in the pitavastatin group than in the other groups (8.3% with pitavastatin, 19.3% with atorvastatin, 27.2% with pravastatin and 35.1% in the placebo group) [15]. The analysis based on the baseline HDL-C values revealed that, despite similar reductions in LDL-C levels, only patients with baseline HDL-C levels ≤45 mg/dL experienced an increase in HDL-C levels, and that pitavastatin was the most effective statin [15]. The incidence of cardiac events in the various groups reflected this finding, being patients with baseline HDL-C levels ≤45 mg/dL treated with pitavastatin those with the lowest incidence of major adverse cardiovascular events [15]. This finding suggests that a therapeutic intervention focused on both LDL-C and HDL-C levels may be beneficial and that pitavastatin may play a special role, especially in patients with low baseline HDL-C levels.

5. Possible mechanisms of the pitavastatin-induced effects on HDL

Circulating levels of HDL are determined by the balance between production and catabolism. One mechanism by which pitavastatin increases HDL-C levels is by inducing the production and secretion of hepatic apoA-I [68] (Table 2); such induction was more marked with pitavastatin than with other statins (simvastatin or atorvastatin) [68]. Pitavastatin also increases ABCA1 expression [68,69] (Table 2); since ABCA1 plays a key role in the lipidation of apoA-I to generate HDL particles and in protecting apoA-I from catabolism, its induction by pitavastatin may contribute to the increased secretion of hepatic apoA-I [68]. The apoA-I induction by pitavastatin is related to the inhibition of cholesterol synthesis pathway, as suggested by the inhibitory effect of mevalonate addition [68];

Table 2
Possible mechanisms by which pitavastatin increases HDL quality and function.

Reference	System	Effects
Maejima et al., 2004 [68]	HepG2	↑apoA-I production and secretion
Maejima et al., 2011 [69]	HepG2	↑ABCA1 mRNA expression
Han et al., 2004 [71]	J774, mouse peritoneal macrophages, human monocyte-derived macrophages	↑SR-BI expression → ↑macrophage HDL binding ↑ cholesterol efflux ↑ cholesteryl ester influx
Kojima et al., 2010 [72]	HUVEC Mouse aorta and liver Patients with cardiovascular disease	↓EL expression ↓EL expression ↑HDL particle size ↓ plasma EL levels ↑HDL particle size
Miyamoto-Sasaki et al., 2013 [75]	Dyslipidemic subjects treated with pitavastatin 2 mg/day for 4 weeks	↑ HDL-C levels ↑PL content in HDL ↑large HDL particle number ↑HDL-mediated efflux ↑PON-1 activity
Kawano et al., 2008 [76]	Hypercholesterolemic patients treated with pitavastatin 2 mg/day for 4 weeks	↑HDL2-C ↓preβ-HDL levels; ↑preβ-HDL disappearance rate ↓LCAT activity ↓CETP mass
Orsoni et al., 2016 [78]	Insulin-resistant, HTG, hypertensive obese male patients treated with pitavastatin 4 mg/day for 6 months	↓TG content in HDL2 and HDL3 ↑CE content in HDL2 and HDL3 ↑PE plasmalogens and PUPC in HDL3
Igarashi et al., 2007 [81]	BAEC	↑S1P1 receptors ↑HDL-mediated eNOS stimulation

HUVEC: human umbilical vein endothelial cells; ABCA1: ATP-binding cassette transporter A1; SR-BI: scavenger receptor class B type I; EL: endothelial lipase; PL: phospholipids; PON1: paraoxonase 1; LCAT: lecithin-cholesterol acyltransferase; CETP: cholesteryl ester transfer protein; TG: triglyceride; CE: cholesteryl ester: PE: phosphatidylethanolamine; PUPC: polyunsaturated phosphatidylcholines; BAEC: bovine aortic endothelial cells; S1P1: sphingosine-1-phosphate subtype 1 receptor; eNOS: endothelial nitric oxide synthase.

pitavastatin inhibits HMG-CoA reductase 3 and 6 times more effectively than simvastatin and atorvastatin, respectively, which may explain the greater increase of apoA-I secretion compared with the other two statins [68]. Furthermore, pitavastatin increased the expression of macrophage scavenger receptor class B type I (SR-BI), a HDL receptor involved in the reverse cholesterol transport process [70], resulting in increased binding of HDL to macrophages and enhanced efflux of free cholesterol to HDL and uptake of cholesteryl ester/HDL by cells [71] (Table 2).

Another mechanism by which pitavastatin increases HDL-C levels is through the inhibition of endothelial lipase (EL) [72] (Table 2). EL, whose expression is increased by pro-inflammatory stimuli, is a negative regulator of HDL-C levels; in fact, by hydrolyzing phospholipids, EL destabilizes HDL particles thus resulting in an enhanced catabolism [73]; EL inhibition increases both HDL-C levels and HDL particle quality, as it generates HDL endowed with increased anti-inflammatory, antioxidative and cholesterol effluxing properties [74] (Fig. 1). Pitavastatin was shown to suppress basal and cytokine-induced expression of EL in cultured endothelial cells and decreased EL expression in mouse aorta and liver [72]. Moreover, pitavastatin reduced plasma EL in hypercholesterolemic patients by 14%, increased HDL-C levels by 11% and HDL particle size by 12% due to increase of phospholipid content [72], an effect that was independent of the changes in plasma LDL-C levels. This suggests that pitavastatin not only increases the quantity of HDL, but may also improve the quality, and thus function, of HDL. In fact, dyslipidemic patients treated with pitavastatin for 4 weeks showed a significant increase in HDL-C levels compared with baseline levels (55.3 ± 11.4 *vs* 50.7 ± 11.4, $p \leq 0.01$) as well as HDL-phospholipids levels (+7.8%, $p = 0.047$) [75]; the number of large HDL particles increased after pitavastatin treatment [75] (Table 2). Pitavastatin treatment also resulted in an increased capacity of cholesterol efflux of isolated HDL and in increased activity of the antioxidant HDL-associated enzyme paraoxonase-1 (PON-1) [75] (Table 2). The observations suggest that pitavastatin increases the serum levels of HDL-C but also increases the anti-atherogenic properties of HDL particles.

Some studies have also evaluated the effect of pitavastatin treatment on HDL subfractions. Hypercholesterolemic patients treated with 2 mg/day pitavastatin showed a 6% increase of HDL-C levels after 4 weeks and a 9% HDL2-C levels increase [76]. Preβ1-HDL is the main cholesterol acceptor during the initial step of reverse cholesterol transport, and thus its plasma concentration

reflects the efficiency by which cholesterol is removed from cells; thus high plasma levels of preβ1-HDL level may reflect an impaired ability of cells to efflux cholesterol and may represent a marker of cardiovascular risk [77]. Following treatment with pitavastatin, preβ1-HDL was significantly reduced (−8.7%, $p < 0.05$), possibly due to an increased disappearance rate, suggesting that pitavastatin may promote the early step of reverse cholesterol transport, thus possibly explaining also the increase of the largest HDL_2 particle [76]. Recently it was shown that in dyslipidemic patients with metabolic syndrome recruited for the CAPITAIN (An Open Label Study of the Chronic and Acute Effects of Pitavastatin on Monocyte Phenotype, Endothelial Dysfunction and HL Atheroprotective Function in Subjects with Metabolic Syndrome) study, pitavastatin, although without significant effects on total HDL levels (+4%) or HDL2 and HDL3 levels (−7% and +8%, respectively) after a 6-month treatment, had a positive impact on the antioxidant capacity of HDL [78]. In fact, pitavastatin treatment reduced the content of oxidizable polyunsaturated phosphatidylcholine (PC) species containing docosahexaenoic acid and linolenic acid in LDL, increased the content of PC and phosphatidylethanolamine plasmalogens containing arachidonic acid and docosahexaenoic acid in small dense HDL3 [78]; furthermore, it induced the formation of HDL3 with increased ability to inactivate redox-active phospholipid hydroperoxides PCOOH to redox-inactive PCOH [78]. This results in an attenuated propagation of lipid peroxidation and reduced formation of potentially atherogenic secondary oxidation products [78], suggesting a potential anti-inflammatory effect of pitavastatin treatment.

Statins also play a relevant role in establishing the normal endothelial function and increasing the bioavailability of nitric oxide (NO) [79]. Sphingosine-1-phosphate (S1P), a bioactive sphingolipid associated with HDL, plays a relevant role in the production of NO by endothelial NO synthase [80]; pitavastatin was shown to upregulate the expression of S1P1 receptor in cultured endothelial cells more than atorvastatin and pravastatin, and this resulted in an increased eNOS activation upon stimulation with HDL [81].

6. Possible implications and conclusions

Specific studies are required to establish whether pitavastatin-induced HDL-C level increase may result in a positive clinical impact. To date, some data seem to suggest that this could be the case. For example, it was shown that a 12-month pitavastatin treatment slightly but significantly reduced mean carotid intima–media thickness (IMT) in patients with coronary heart disease, an effect that was observed significantly more frequently in subjects with high on-treatment HDL-C levels than in those with low HDL-C levels ($P = 0.017$) and tended to be inversely correlated with increments in HDL-C and apoA-I [82]. A wave of skepticism has recently come into the HDL hypothesis, mainly based on the data from CETP inhibitors [6,7,83,84]. It should be reminded however that targeting CETP is one of the several mechanisms by which HDL-C could be increased, and these failures may not be extrapolated to targeting other mechanisms (as an example increase apoA-I production rate).

The effect of pitavastatin on HDL needs further evaluation and may prove ultimately beneficial, yet more data need to be gathered to support these promising findings.

Conflict of interest

AP: no conflict of interest. ALC has received honoraria, lecture fees, or research grants from: SigmaTau, Menarini, Kowa, Eli Lilly, Recordati, Pfizer, Sanofi, Mediolanum, Merck, Aegerion, Amgen, Genzyme, Bayer, Astrazeneca, ISIS, Regeneron.

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