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REVIEW

Pitavastatin: a New 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitor for the Treatment of Hyperlipidemia

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ABSTRACT

Statins have proven beneficial for reducing both primary and secondary events in patients with coronary heart disease. Tight control of serum lipid parameters in these patients is recommended by the most recent clinical guidelines. Although numerous lipid-lowering treatments are available, only a small percentage of eligible patients receive therapy and fewer achieve their lipid-lowering goals. Thus it is clear that new treatment strategies to manage patients with lipid abnormalities are warranted. Pitavastatin (Livalo®; Kowa Pharmaceuticals America, Montgomery, AL, USA) has been recently approved for the treatment of hypercholesterolemia and combined dyslipidemia. Pitavastatin 1-4 mg/day has shown similar low-density lipoprotein-reducing activity to other commercially available statins, including simvastatin and atorvastatin. Adverse events occurred at similar rates to other statins in clinical trials with favorable effects seen in patients with dyslipidemia and metabolic syndrome. Pharmacokinetic drug-drug interactions are minimized due to the lack of significant metabolism of pitavastatin by the cytochrome P450 enzyme system, although some drugs affect its uptake into hepatocytes and should be avoided. In addition to its higher acquisition cost, pitavastatin has not been shown to improve clinical outcomes in high-risk patient populations and thus may not be the agent of choice in many patients at this time in lieu of cheaper, clinically proven alternatives.

Keywords: HMG-CoA reductase inhibitor; hypercholesterolemia; hyperlipidemia; pitavastatin; statin

BACKGROUND

Numerous recent trials have demonstrated the beneficial effects of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors in both the primary and secondary prevention of events in patients with coronary heart disease (CHD).[1-7] In fact, a linear relationship between reductions in both low-density lipoprotein (LDL) cholesterol and nonhigh-density lipoprotein (non-HDL) cholesterol and a lower risk for

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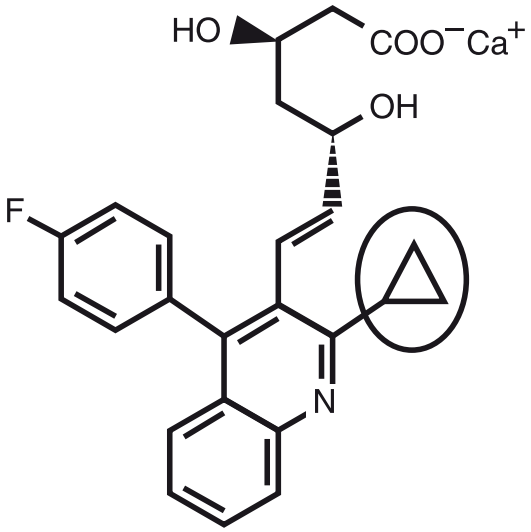
CHD events has been suggested.[8,9] The current clinical guidelines recommend an LDL goal of <100 mg/dL in patients at high risk for a CHD event or <70 mg/dL for those at very high risk, and a non-HDL goal of <100 mg mg/dL for all CHD patients and diabetic patients with one other cardiovascular risk factor.[10-12] Despite this robust evidence base, concerns over safety with the use of high-dose HMG-CoA therapy have been raised.[13,14] Moreover, observational research has shown that only 50% of patients being treated with cholesterol-lowering agents achieved their goals.[15] Therefore, the availability of new lipid-lowering therapies in the armamentarium available to clinicians has the potential to improve these numbers.

In August 2009, the US Food and Drug Administration (FDA) approved pitavastatin (Livalo®; Kowa Pharmaceuticals America, Montgomery, AL, USA) for the treatment of hypercholesterolemia and combined dyslipidemia.[16] It has been available for clinical use in Japan since 2003 and was launched in the USA in 2010. The present review will examine the potential benefits of this new HMG-CoA reductase inhibitor with respect to its pharmacology, pharmacokinetics, and available clinical evidence, as well as its role in management of patients with dyslipidemia.

CHEMISTRY AND PHARMACOLOGY

Pitavastatin, (+)-monocalcium bis(3R,5S,6E)-7-(2-cyclopropyl-4-[4-fluorophenyl]-3-quinolyl)-3,5-dihydroxy-6-heptenoate, is a fully synthetic statin with a molecular weight of 880.98.[17] The chemical structure of pitavastatin is shown in Figure 1. In contrast with other statins, pitavastatin contains a cyclopropyl group that fits within the hydrophobic areas of the HMG-CoA reductase enzyme, partially explaining its potent inhibitory activities.[18,19]

Figure 1. Chemical structure of pitavastatin.



Pitavastatin has been shown to inhibit HMG-CoA reductase in a concentration-dependent manner. Initial studies suggested its potency to be 2.4-fold and 6.8-fold greater than simvastatin and pravastatin, respectively.[17] Pitavastatin has also been shown to inhibit cholesterol synthesis to a greater degree than simvastatin (2.9-fold) and atorvastatin (5.7-fold).[20] In addition, its inhibitory effects on sterol synthesis appear to be liver selective and significantly stronger than simvastatin.[21] Appreciable increases in LDL receptor mRNA have been seen with pitavastatin as well as LDL internalization into the cells and degradation of apolipoprotein B.[19,22] The expression of LDL receptor mRNA was significantly higher with pitavastatin as compared with either simvastatin or atorvastatin.[20]

Statins as a class have been shown to have beneficial pleiotropic effects beyond their LDL-lowering ability, which may be responsible for much of their clinical event reductions. Numerous investigations have demonstrated that pitavastatin attenuates the inflammatory response,[23,24] improves endothelial function,[24,25]

increases nitric oxide production,[26] decreases reactive oxygen species production,[27] reduces foam cell formation,[28] and prevents thrombosis formation.[29,30]

PHARMACOKINETICS

Pharmacokinetic animal studies have demonstrated that pitavastatin has high bioavailability (80%) with peak plasma concentrations achieved approximately 1 hour following oral administration.[16,31] The prescribing information for pitavastatin reports the bioavailability of an oral solution in humans to be 51%.[16] It is more than 99% protein bound, primarily to albumin and alpha-1 acid glycoprotein with a volume of distribution of nearly 150 L. It is rapidly taken up into the liver through organic anion transporter proteins (OATP), including OATP1B1 and OATP2.[32,33] The 24-hour area under the curve (AUC_{0-24}) of pitavastatin was increased 4.6-fold when it was concurrently administered with a potent OATP2 inhibitor (cyclosporine).[34] Unlike most other currently available statins, pitavastatin undergoes minimal metabolism by the cytochrome P450 (CYP450) enzyme system including CYP2C9 and to a lesser extent CYP2C8 (Table 1).[16,35-40] Alternatively, it is rapidly glucuronized by uridine diphosphate-glucuronyltransferase (UGT) in the liver to its major inactive lactone metabolite.[31] As a result, it is primarily contained within the enterohepatic circulation and excreted mainly in the feces with approximately 15% excreted in the urine. Its elimination half-life is approximately 12 hours, longer than many of the currently available agents.[16]

Pharmacokinetic studies have not demonstrated clinically significant differences based either on sex (men vs. women) or age (younger vs. older; age >65 years).[16] A study by Hui and colleagues evaluated the properties of pitavastatin in 12 male patients with liver cirrhosis, six of whom had Child-Pugh grade A and six had Child-Pugh grade B disease, and compared them with six healthy male volunteers.[41] Significant increases in both maximum plasma concentration of drug (C_{max}) and AUC were seen in both cirrhotic groups compared with the healthy subjects. Similarly, the elimination half-life was 7.0 hours in the healthy subject group as compared with 8.3 hours and 14.4 hours in the Child-Pugh A and Child-Pugh B groups, respectively (P=0.06 using analysis of variance [ANOVA]). Therefore, caution may be warranted when pitavastatin is used in patients with mild-to-moderate liver impairment.[41] Similar results were seen in studies of patients with moderate renal impairment or undergoing hemodialysis with significant increases in various pharmacokinetic parameters, including C_{max} and AUC, when compared with healthy controls.[16] Specific dosage recommendations in these patient populations can be found in the dosing section later in this review.

CLINICAL TRIAL EVIDENCE

Noncomparative Lipid-Lowering Studies

A prospective, single-group study by Kajinami and colleagues studied 30 Japanese patients with heterozygous familial hypercholesterolemia with a primary objective of evaluating the impact of pitavastatin therapy on various lipid parameters including total cholesterol (TC) and LDL.[42] Included patients had a mean age of 51±13 years, 50% were men, 30% had coronary artery disease, 17% had impaired glucose tolerance, and baseline lipid parameters included a mean TC of 340±53 mg/dL and LDL of 263±59 mg/dL. In addition to a National Cholesterol

Table 1. Characteristics of currently available 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors.

Drug	Absolute bioavailability (%)	Molecular weight	Metabolism	Elimination after oral administration	Production of lipid-lowering metabolite	Administration with food and time of day	T_{max} after oral administration	$t_{1/2}$, hours	Percentage bound to plasma proteins
Lovastatin	<5	404.55	CYP3A4	Urine (10%) feces (83%)	Yes: beta-hydroxy acid	Take in the evening with meal	2-4 hours	1-2	>95
Atorvastatin	14	1209.42	CYP3A4	Biliary, <2% in urine	Yes: orthohydroxy-lated and parahydroxylated metabolites	Any time of day with or without food	1-2 hours	20-30	>98
Rosuvastatin	20	1001.14	CYP2C9, CYP3A4	Feces (90%)	Yes, mainly : inactive *N*-desmethyl rosuvastatin	Any time of day with or without food	3-5 hours	19	88
Pitavistatin	51	880.98	Minimally by CYP2C9, CYP2C8 Extensively by UDP, UGT1A3, UGT2B7	Urine (79%), feces (15%)	No	Any time of day with or without food	1 hour	12	>99
Simvastatin	<5	418.57	CYP3A4	Urine (13%), feces (60%)	Yes: beta-hydroxy acid	Take in the evening with or without food	1.3-2.4 hours	N/A	95
Pravasatain	17	446.52	Bio-transformation	Urine (20%), feces (70%)	No	Any time of day with or without food	1-1.5 hours	77	50
Fluvastatin	24	433.46	CYP2C9, CYP2C8, CYP3A4	Urine (5%), feces (90%)	No	Any time of day with or without food	<1 hour	<3	98

CYP=cytochrome P450; N/A=not available; $t_{1/2}$=half-life; T_{max}=time when maximum plasma concentration is reached.

Education Program (NCEP) step 2 diet, patients underwent a 4-week placebo run-in phase followed by 8 weeks of pitavastatin 2 mg/day, which was then increased to 4 mg/day for an additional 8 weeks. Mean TC levels decreased by 31% (P<0.01 vs. baseline) with pitavastatin 2 mg/day with a further reduction (37% from baseline, P=0.0002) when the dose was increased to 4 mg/day. Similar reductions in LDL (–40%, –48%) and non-HDL (–36%, –45%) were seen during the 2 mg/day and 4 mg/day phases, respectively, as compared with baseline (P<0.05 for all). Significant reductions in triglycerides (TG) from baseline were not seen in the 2 mg/day phase (–15%, P=0.17), although this change was significant in the 4 mg/day phase (–23%, P<0.0001).[42] When the 4 mg/day phase was extended for up to 104 weeks, significant reductions from baseline in TC (33%) and LDL (44%) were maintained while slight improvements in HDL (+6%) and TG (–9%) were seen.[43]

Saito and colleagues conducted a 12-week multicenter, double-blind, dose-finding study of pitavastatin in 273 patients aged 25-75 years with hypercholesterolemia and baseline TC levels ≥230 mg/dL.[44] A total of 80 (29%) of patients were men, the mean body mass index (BMI) was 23.9 kg/m^2, and 8% had familial hypercholesterolemia. Following a 4-week placebo run-in period, patients were randomized to receive pitavastatin 1 mg, 2 mg, or 4 mg for a total of 12 weeks with doses given once daily after dinner. The primary endpoint was the change from baseline in lipid parameters, including TC, LDL, and TG, at week 12. Dose-dependent improvements in both TC and LDL from baseline were seen with the dosage of 4 mg/day showing the highest efficacy. Similar relationships were not seen with either TG or HDL levels, although improvements in both parameters from baseline were seen.

A more recent prospective, open-label study by Koshiyama and colleagues was conducted in 178 Japanese with hypercholesterolemia including TC ≥220 mg/dL and TC <400 mg/dL.[45] Patients were provided pitavastatin at a dose of either 1 (n=44) or 2 (n=134) mg/day for a total of 12 months. The mean age of the population was 62.0±0.9 years, 47% were men, the mean BMI was 24.5 kg/m^2, and 58% of patients had type 2 diabetes. The main aims of the study included changes in various lipid parameters as well as inflammatory biomarkers from baseline to 12 months. Statistically significant reductions in TC (–21%; P<0.01) and LDL (–30.3%; P<0.01), as well as improvements in HDL (+2.6%; P<0.01) from baseline were seen over the entire follow-up period. In addition, serum high-sensitivity C-reactive protein (hs-CRP) (–34.8%; P<0.01) and remnant-like particle cholesterol levels (–22.8%, P<0.01) were significantly reduced when compared with baseline.

These comparative studies have a number of limitations. First, two of the studies are of short duration (8-12 weeks) making extrapolation of their results to chronic therapy challenging. The populations of these studies were also limited to those of Asian descent. Whether the effects seen in these studies could be expected in populations outside of this area is unknown. Lastly, the patients studied were relatively healthy with few patients having hypertension, diabetes, or coronary heart disease. Thus, the results from the above-described noncomparative studies cannot be consistently applied to these populations.

Comparative Lipid-Lowering Studies

A number of published studies have evaluated the comparative efficacy of pitavastatin with other commercially available statins on lipid parameters (Table 2).[46-53] One trial each evaluated pravastatin[46] and simvastatin[47] as the

Table 2. Results of comparative lipid-lowering clinical trials.

Reference (year)	Design	Study duration, weeks	Dose/day	*n*	Change from baseline (%)				Comment
					TC	LDL	TG	HDL	
Saito et al (2002)[46]	R, DB, AC	12	Pravastatin 10 mg	111	−13.8	−18.4	−23.3	+9.8	Japanese patients with primary hyperlipidemia (TC ≥220 mg/dL)
			Pitavastatin 2 mg	125	−28.0*	−37.6*	−20.2†	+8.9	
Park et al (2005)[47]	R, OL, AC	8	Simvastatin 20 mg	46	−28.5	−39.4	−17.4	+3.6	Korean patients with fasting TG <600 mg/dL and LDL >130 mg/dL after a 4-week dietary lead-in period
			Pitavastatin 2 mg	49	−26.9	−38.2	−29.8	+8.3	
Yoshitomi et al (2006)[48]	NR, OL, AC	12	Atorvastatin 10 mg	67	−29	−41	−21‡	+7	Japanese patients with LDL >140 mg/dL and TG <400 mg/dL
			Pitavastatin 1 mg	70	−28	−38	−11	+3	
Lee et al (2007)[49]	R, OL, AC	8	Atorvastatin 10 mg	112	−29.6	−44.1	−11	+6.7	Korean patients with fasting LDL >130 mg/dL and TG <400 mg/dL after a 4-week dietary lead-in period. Those not meeting goals at week 4 received a doubling of their dose.
			Pitavastatin 2 mg	110	−28.2	−42.9	−9.9	+7.1	
Yokote et al (2008)[50]	R, OL, AC	12	Atorvastatin 10 mg	103	−31.1	−44.1	−10.7	+1.7	Japanese patients with TC ≥220 mg/dL and TG <400 mg/dL after a 4-week dietary lead-in period
			Pitavastatin 2 mg	101	−29.7	−42.6	−17.3	+3.2	
Sasaki et al (2008)[51]	R, OL, AC	52	Atorvastatin 10 mg	85	N/A	−40.1‡	−14.6‡	+2.9	Japanese patients with LDL ≥140 mg/dL HDL <80 mg/dL, TG <500 mg/dL, and glucose intolerance[§]
			Pitavastatin 2 mg	88		−33.0	−7.1	+8.2	
Budinski et al (2009)[52]	R, DB, AC	18-20	Atorvastatin						European patients with LDL 160-220 mg/dL and TG ≤400 mg/dL after a 6-8- week lead-in period
			10 mg	102	−28.1	N/A	−17.7	+3	
			20 mg	102	−32.7		−22.3	+2.5	
			Pitavastatin						
			2 mg	315	−27.7		−14.1	+4	
			4 mg	298	−32.4		−19	+5	
Sansanayudh et al (2010)[53]	R, OL, AC	8	Atorvastatin 10 mg	50	−32.3	−45.8‡	−7.1	−0.4	Thai patients with hypercholesterolemia and an indication for statin therapy according to NCEP-ATP III guidelines[10]
			Pitavastatin 1 mg	48	−27.6	−37.4	−10.4	+2.8	

*P<0.05 for pitavastatin versus the comparator.†Data for TG reductions were only reported for those patients (pitavastatin=50, pravastatin=44) who had baseline TG values ≥150 mg/dL. ‡P<0.05 for atorvastatin versus pitavastatin. §Glucose intolerance was defined as receipt of an antidiabetic medication or fasting blood glucose ≥110 mg/dL, 1-hour blood glucose ≥180 mg/dL, or 2-hour blood glucose ≥140 mg/dL after a 75 g oral glucose challenge, or casual blood glucose ≥140 mg/dL. AC=active control; DB=double-blind; HDL=high-density lipoprotein cholesterol; LDL=low-density lipoprotein cholesterol; N/A=not available; NR=nonrandomized; OL=open-label; R=randomized; TC=total cholesterol; TG=triglycerides.

comparator while the rest used atorvastatin.[48-53] Each comparison will be discussed in brief below.

A single trial compared the lipid-lowering potential of pitavastatin to pravastatin.[46] Following a 4-week run-in period, Saito and colleagues randomized 240 Japanese patients with primary hyperlipidemia (TC ≥220 mg/dL and TG <400 mg/dL) to receive either pravastatin 10 mg/day or pitavastatin 2 mg/day for a total of 12 weeks.[46] The primary endpoint of the study was the percentage change in TC at the last follow-up assessment time point. The authors aimed to establish the noninferiority of pitavastatin to pravastatin therapy. A noninferiority trial is appropriate for evaluation of the efficacy of an experimental treatment (pitavastatin) versus an active control (pravastatin) when it is hypothesized that the experimental treatment may not be superior to a proven effective treatment, but is clinically and statistically not inferior in effectiveness. At the end of the follow-up period, patients receiving pitavastatin had greater reductions from baseline in both TC (P<0.001) and LDL (P=0.001) values as compared with pravastatin. In patients who had a baseline TG level 150 mg/dL, pitavastatin was shown to be noninferior to pravastatin (P=0.024) in observed reductions from baseline. No significant differences between the groups in other lipid parameters, including changes from baseline in HDL and various apolipoprotein measurements, were seen. However, significantly more patients receiving pitavastatin achieved their TC goal of <220 mg/dL (72% vs. 36%) and LDL target of <140 mg/dL (75% vs. 36%) as compared with pravastatin.

The comparative effectiveness of pitavastatin and simvastatin was evaluated in a prospective, randomized, open-label trial by Park and colleagues.[47] A total of 104 Korean patients between the ages of 20 and 75 years who had a fasting TG <600 mg/dL and LDL >130 mg/dL following a 4-week dietary run-in period were randomized to receive either pitavastatin 2 mg/day or simvastatin 20 mg/day for a total of 8 weeks. A total of 36 (34.6%) of the patients were men. The mean age of the pitavastatin group (59.9±7.8) was higher than that of the simvastatin group (56.4±9.5) although this difference was not statistically significant. The primary endpoint of the study was the change in LDL from baseline to week 8. At the end of this time, no significant differences in the percentage change from baseline in any of the measured lipid parameters were seen between the groups (Table 2). Similarly, although a high proportion of patients achieved NCEP Adult Treatment Panel (ATP) III treatment goals[10] (pitavastatin = 93.9%, simvastatin = 91.3%), no significant differences between the groups were seen (P=0.709).

A total of six trials have evaluated the impact of pitavastatin versus atorvastatin on serum lipid levels and cholesterol control rates (Table 2).[48-53] One study was a randomized, double-blind trial[52] while another was a nonrandomized, open-label comparator trial.[48] The remainder are randomized, open-label, parallel-group trials.[49-51,53] Two studies compared pitavastatin 1 mg/day to atorvastatin 10 mg/day,[48,53] three studies compared pitavastatin 2 mg/day to atorvastatin 10 mg/day,[49-51] and one study compared two pitavastatin doses (2-4 mg/day) to two atorvastatin doses (10-20 mg/day).[52] Four studies evaluated Japanese populations,[46,48,50,51] two evaluated Korean populations,[47,49] and one each evaluated European[52] and Thai patients.[53]

Results from these studies varied from one to the next. Yoshitomi and colleagues, using a nonrandomized, open-label design, showed that pitavastatin 1 mg/day and atorvastatin 10 mg/day resulted in similar improvements in TC, LDL, and HDL while atorvastatin was superior in TG lowering.[47] A more recent study

by Sansanayudh and colleagues showed that atorvastatin 10 mg/day had superior efficacy for TC and LDL-lowering than pitavastatin 1 mg/day, with similar effects on TG and HDL.[53] Saito and colleagues showed that pitavastatin 2 mg/day resulted in significantly greater reductions in TC, LDL, and TG from baseline when compared with atorvastatin 10 mg/day in a population of Japanese patients with primary hyperlipidemia.[46] Alternatively, studies by Lee and colleagues[49] as well as Yokote and colleagues,[50] both using the same dosing, showed similar lipid-lowering abilities with pitavastatin 2 mg/day and atorvastatin 10 mg/day. Sasaki and colleagues showed that atorvastatin 10 mg/day had greater LDL and TG lowering potency than pitavastatin 2 mg/day.

Many of these studies had relatively short follow-up periods of 8-12 weeks. Whether the differences seen between statins would continue to be significant in longer-duration studies is unclear. In addition, the relative homogeneity of the patient populations (mostly Asian with one European study) from these studies potentially limits extrapolation to many clinical practices in the USA. Although differential cholesterol-lowering abilities among patients with varying ethnic backgrounds would not be expected, definitive evidence of benefit in heterogeneous populations is required before its true role in management can be elucidated. Taken together, these studies suggest that use of pitavastatin 1-2 mg/day results in similar improvements in lipid parameters when compared with simvastatin 20 mg/day and atorvastatin 10-20 mg/day, whereas pitavastatin 2 mg/day has greater potency than pravastatin 10 mg/day. However, some differences between study results do exist as noted above.

Acute Coronary Syndromes

A variety of studies have evaluated the impact of pitavastatin therapy on regression of coronary atherosclerotic plaque in patients with active coronary disease.[54-58] Takashima and colleagues retrospectively studied whether pitavastatin 2 mg/day (n=41) or a matched dietary control group (n=41) had an effect on regression of coronary artery plaque as measured by three-dimensional intravascular ultrasound (3D-IVUS) in patients undergoing a percutaneous coronary intervention (PCI) for treatment of an acute coronary syndrome.[54] Plaque volume index (PVI), as measured by volumetric IVUS 6 months after the initial procedure, was significantly reduced in the pitavastatin group (–10.6% from baseline) versus the control group (+8.1%; P<0.001). A positive correlation between changes in PVI and follow-up LDL levels (P<0.001) were seen. A similar study by Nakamura and colleagues showed improvements in carotid artery plaque volume with 1 month of pitavastatin 4 mg/day versus placebo in 65 patients with ACS.[55]

A more recent prospective trial by Toi and colleagues randomized patients with ACS resulting from significant stenosis of a coronary artery to receive either pitavastatin 2 mg/day (n=80) or atorvastatin 10 mg/day (n=80) for a total of 2-3 weeks following PCI of the causative arteries.[56] Male patients comprised 75.6% of the population that had a mean age of 62.0±10.6 years, 40.6% had hypertension, 53.1% had diabetes, and 33.1% were smokers. The primary endpoints included changes in lipid parameters and IVUS before and after statin treatment. No significant differences in PVI or luminal volume index (LVI), as measured using serial IVUS compared with baseline were seen between the groups although the pitavastatin group saw significant reductions

in PVI versus baseline (–2.6%; $P<0.05$), whereas no change was seen with atorvastatin.

The larger Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome (JAPAN-ACS) study randomized 307 patients with ACS undergoing IVUS-guided PCI who were randomized to receive either pitavastatin 4 mg/day or atorvastatin 20 mg/day for a total of 8-12 months.[57,58] This all-Japanese population consisted of mostly men (82%), with 29% of patients having diabetes. Approximately two of three patients had ST-segment elevation myocardial infarctions, and drug-eluting stents were used in one of three and bare-metal stents in two of three patients. The primary endpoint of the study was the percentage change in nonculprit coronary plaque volume (PV) from baseline between the groups. No significant differences in lipid parameters, including TC, LDL, or HDL, were seen between the groups. The percentage change in coronary PV was significantly reduced from baseline in both the pitavastatin (–16.9±13.9%) and atorvastatin (–18.1±14.2%) groups, although no differences between the groups were seen ($P=0.5$). These studies support the use of statins, such as pitavastatin and atorvastatin, in patients immediately following an ACS for achieving aggressive lipid lowering as well as regression of coronary PV and negative vessel remodeling, although no differences between agents were seen.

Diabetes Mellitus

Clinical evidence has shown that use of pitavastatin, either alone[59-62] or in combination with eicosapentaenoic acid,[63] significantly improves serum lipid parameters as well as reduces remnant-like particle cholesterol and regresses PV[61] in patients with diabetes mellitus (DM). Motomura and colleagues showed significant reductions in TC ($P<0.001$), LDL ($P<0.001$), and TG ($P<0.05$) from baseline when pitavastatin 2 mg/day was used in 65 Japanese patients with type 2 DM and hypercholesterolemia (LDL ≥120 mg/dL and TG <400 mg/dL).[60] Significant reductions in hs-CRP were also seen after 6 months of pitavastatin therapy as compared with baseline ($P<0.05$). A substudy of the JAPAN-ACS trial also showed significant regression of coronary plaque with both pitavastatin as well as atorvastatin use, although this effect was weaker in patients with DM than their nondiabetic counterparts.[61]

Chronic Kidney Disease

Two recent studies evaluated pitavastatin use in patients with chronic kidney disease (CKD).[64,65] Kimura and colleagues reported on the use of pitavastatin 1-4 mg/day in a 104-week, large-scale, prospective postmarketing surveillance study of 20,279 patients with hypercholesterolemia and CKD (estimated glomerular filtration rate [eGFR] <60 mL/min/2.73 m^2).[64] The primary aims of the study were to evaluate the impact of pitavastatin on serum lipids as well as eGFR in this high-risk population. In addition to the expected improvements in lipid parameters, patients saw significant increases in eGFR from a baseline of 47.8±11.5 mL/min/2.73 m^2 to 53.2±18.6 mL/min/2.73 m^2 ($P<0.001$) over the follow-up period. Patients not receiving either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker saw less improvement in eGFR (3.2 mL/min/2.73 m^2) than those receiving this therapy (7.5 mL/min/2.73 m^2) ($P<0.001$).

Nakamura and colleagues recently examined the benefits of pitavastatin (2 mg/day; $n=10$) alone or coadministered with ezetimibe (10 mg/day; $n=10$) on renal function and urine protein levels in patients with nondiabetic CKD

and dyslipidemia.[65] The purpose of the study was to determine if adding ezetimibe to pitavastatin therapy resulted in additive improvements in renal function in a CKD population. In this small study, combination therapy was associated with greater improvements in LDL ($P<0.05$) and TG ($P<0.01$) than pitavastatin alone. In addition, the combination of pitavastatin and ezetimibe resulted in significant reductions in proteinuria versus pitavastatin alone ($P<0.05$).

ADVERSE EVENTS

The most common general tolerance adverse events associated with use of pitavastatin include back pain, constipation, diarrhea, abdominal pain, and dizziness with incidences ranging from 2% to 4%, similarly to other currently available statins.[16] Elevations of blood creatinine kinase (CK), the most commonly reported adverse event in clinical trials, occurred in 5.8% of patients receiving pitavastatin.[66] No differences in the incidence of CK elevations were noted in clinical trials compared with atorvastatin.[49,51] The manufacturer's literature recommends discontinuation of pitavastatin therapy if CK levels markedly increase or are associated with myopathy.[16] Kobayashi and colleagues examined the mechanism involved with muscle cytotoxicity associated with statins and provided the following rank order for the class: cerivastatin > simvastatin > fluvastatin > atorvastatin > lovastatin > pitavastatin >> rosuvastatin, pravastatin.[67] Another concerning adverse event with the statin class is elevations in liver function tests (LFTs). Clinical trials have shown that increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) greater than three times the upper limit of normal have been seen in 0.5% of patients receiving the pitavastatin 4 mg/day dose. Abnormalities in AST and ALT have not been routinely seen with lower doses, although the manufacturer recommends that LFTs be monitored before, at 12 weeks, and periodically after the initiation of pitavastatin therapy.[16]

Evidence has suggested that statins may have adverse effects on markers of insulin sensitivity, including the homeostasis model assessment for insulin resistance (HOMA-IR), although differences between agents in the class may exist.[68] Clinical studies have shown that no significant differences exist between pitavastatin and atorvastatin regarding their impact on fasting glucose, hemoglobin A_{1c}, or HOMA-IR.[51,69]

DRUG INTERACTIONS

Various clinically relevant drug-drug interactions have been demonstrated with pitavastatin as a result of inhibition of the OATP enzyme that is responsible for uptake of pitavastatin into human hepatocytes.[70] Several drugs have been found to interact with OATP1B1-mediated pitavastatin uptake including cyclosporine, rifampin, clarithromycin, and indinavir.[70,71] As a result, the concomitant use of pitavastatin with cyclosporine is contraindicated, with lower dosing recommendations required with erythromycin and rifampin coadministration.[16]

Coadministration of statins with fibric acid derivatives, including gemfibrozil, has historically been avoided due to a proposed increased risk for myopathy as a result of a pharmacokinetic drug-drug interaction. Various studies have demonstrated that plasma levels of pitavastatin are not appreciably affected by either gemfibrozil or fenofibrate in vitro and in healthy volunteers.[72-74] Similarly, concomitant ingestion of grapefruit juice with pitavastatin did not demonstrate clinically significant alterations to its pharmacokinetics, although

significant increases in mean AUC_{0-24} were seen with atorvastatin.[75,76]

DOSING

Pitavastatin is available as 1, 2, and 4 mg film-coated tablets. The recommended initial dose is 2 mg/day, which can be titrated to a maximum of 4 mg/day, based on tolerability and desired therapeutic goals. A reduction to 1 mg/day (with a maximum of 2 mg/day) is recommended for patients with moderate renal insufficiency (GFR 30-60 mL/min/2.73 m^2), and those with end-stage renal disease receiving hemodialysis. Additionally, patients receiving concomitant therapy with erythromycin or rifampin should receive no more than pitavastatin 1 or 2 mg/day, respectively.[16]

CONCLUSIONS

Pitavastatin is a new HMG-CoA reductase inhibitor that has been studied primarily in Asian populations with similar lipid-lowering potency as initial doses of atorvastatin. The fact that most of the current information is in Asian populations is a potential concern. The only non-Asian study conducted by Budinski and colleagues[52] enrolled a mixed European population and showed similar overall effects to other studies. Whether these data can be translated to American populations is unclear and deserves further investigation. Similarly, all of the currently available studies compare pitavastatin with initial starting doses of statins such as simvastatin and atorvastatin. Given the data that support higher doses of these drugs (eg, 80 mg/day of each), particularly in patients following an acute coronary syndrome, the comparative role of pitavastatin is unclear.[5,6] Comparative studies with pitavastatin to these higher-dosed statins as well as other more potent statins (eg, rosuvastatin) is required before the definitive role of pitavastatin can be clarified.

Pitavastatin is FDA approved to improve the lipid profile of patients with primary hyperlipidemia or mixed dyslipidemia, in addition to a diet restricted in saturated fat and cholesterol. Given the pharmacokinetic profile of pitavastatin, its relative lack of drug-drug interactions, particularly those that are CYP450 mediated, and similar safety profile to other statins, it may be an alternative to currently available statins. Patients receiving multiple medications who are prone to drug-drug interactions may particularly benefit from pitavastatin therapy. In addition, the effect of pitavastatin on clinical events in certain high-risk patient populations, including those with coronary heart disease, remains to be elucidated. This is in contrast to a majority of the currently available statins with proven event reduction in a variety of populations such as stroke, myocardial infarctions, revascularization, and mortality. Moreover, many of these agents are available in generic form or will be in the near future. As an example, the average wholesale price of pitavastatin 1 mg/day is $3.96 as compared with simvastatin 5 mg/day ($1.82), pravastatin 10 mg/day ($2.72), and atorvastatin 10 mg/day ($3.61). This ultimately suggests that the role of this newer agent may be limited versus other statins that have demonstrated reduced outcomes and are currently generically available.

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