



Pitavastatin (Livalo) for Hyperlipidemia And Mixed Dyslipidemia

A Novel Therapeutic Agent, or a 'Me-Too' Drug?

Timothy Reilly, PharmD, BCPS; George King; Jee Hye Park; and Amanda Tracy

INTRODUCTION

Hyperlipidemia is extremely prevalent in both men and women today. Total cholesterol (TC) levels, as well as low-density lipoprotein-cholesterol (LDL-C) levels, usually increase throughout our lives. Nearly half of all Americans older than 20 years of age have TC levels exceeding 200 mg/dL. Only 50% of adults who qualify for lipid-lowering therapy receive it, and only one-third of treated patients are at their cholesterol goals. In addition to a high prevalence, hyperlipidemia has a significant impact on public health, as this condition is a risk factor for many types of cardiovascular disease (CVD), including coronary heart disease (CHD).¹

The National Cholesterol Education Program's Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults (ATP III) describes the approach to the management of hyperlipidemia. These guidelines recommend that LDL-C be the initial target of lipid-lowering therapy, because it is most often associated with the risk for developing CHD. Other secondary targets of lipid-lowering therapy include serum triglycerides (TGs) and non-high density lipoprotein-cholesterol (non-HDL-C). Although the goal is to decrease most lipid markers, HDL-C levels should be

increased, because this lipoprotein may aid in removing cholesterol from atherogenic lesions. The guidelines further describe general goals for optimal lipid levels: TC below 200 mg/dL, LDL-C below 100 mg/dL, HDL-C above 40 mg/dL, and TG below 150 mg/dL. Patient-specific goals are further defined based on CHD risk factors.²

Statins are frequently prescribed for the treatment of hyperlipidemia, largely as a result of their efficacy and side-effect profile.² Despite their overall safety, a possible link to diabetes has recently been proposed.³ Table 1 compares statins currently on the market in terms of their effect on the lipid panel.⁴⁻⁶

The newest entry in this class on the U.S. market is pitavastatin (Livalo, Kowa).⁷ It has been approved in Asia, where it has been used for many years. In this article, we review the available data from clinical trials as well as other information relevant to clinical practice.

CHEMICAL AND PHYSICAL PROPERTIES⁷

Pitavastatin, an oral tablet, is available in strengths of 1 mg, 2 mg, and 4 mg. Each tablet is white and round, with the letters KC on one side and the strength on the opposing side.

MECHANISM OF ACTION⁷

Pitavastatin completely inhibits HMG CoA reductase, the rate-determining enzyme in hepatic cholesterol synthesis. Consequently, LDL-C receptors in the liver are increased, thereby increasing the removal of LDL-C from the blood.

PHARMACOKINETICS⁷

Absorption and Distribution. Pitavastatin is 51% bioavailable and reaches its peak plasma concentration (C_{max}) approximately one hour after oral administration; plasma levels increase proportionally to the dose. Taking pitavastatin

with a high-fat meal decreases the drug's C_{max} by 43%, whereas the area-under-the-curve (AUC) concentration remains relatively unchanged. Neither the C_{max} nor the AUC concentration differed when pitavastatin was taken in the morning or evening. Pitavastatin is more than 99% protein-bound in human plasma, mainly to albumin and alpha₁-acid glycoprotein.

Metabolism and Excretion. The primary route of metabolism is hepatic glucuronidation with minimal metabolism by cytochrome P450 2C9 (CYP 2C9) and CYP 2C8. Most of the dose is excreted in the feces, but approximately 15% of the dose is excreted in the urine. The mean plasma concentration half-life is 12 hours.

INDICATIONS⁷

The FDA approved pitavastatin as part of a multidimensional treatment plan to reduce levels of TC; LDL-C; apolipoprotein B (Apo B), a component of LDL-C; and TG and to raise HDL-C levels in adults with primary hyperlipidemia or mixed dyslipidemia.

CLINICAL EFFICACY

Cholesterol Reduction with Pitavastatin and Other Statins

Saito et al.⁸ A multicenter, randomized, double-blind, controlled study was conducted in Japan to compare the efficacy and safety of 12 weeks of treatment with pitavastatin against pravastatin (Pravachol, Bristol-Myers Squibb). The primary endpoint of the trial was a reduction of TC, TG, and LDL-C levels at week 12. Safety endpoints included drug-related adverse events (AEs) and laboratory parameters.

Patients were enrolled in the trial if they were between 20 and 75 years of age and had primary hyperlipidemia (TC, 220 mg/dL or higher; TG, below 400 mg/dL). Patients were excluded if

Dr. Reilly is Clinical Assistant Professor at the Ernest Mario School of Pharmacy—Rutgers, The State University of New Jersey, in Piscataway, New Jersey, and Clinical Pharmacist at University Medical Center at Princeton in Princeton, New Jersey. George King, Jee Hye Park, and Amanda Tracy are pharmacy students at the Ernest Mario School of Pharmacy, Rutgers.

Disclosure: The authors report no financial or commercial relationships in regard to this article.

they were pregnant or breast-feeding, had taken pitavastatin, or had participated in other studies within four months of enrollment. Patients were also ineligible if they had uncontrolled diabetes mellitus, severe hypertension, a cerebrovascular disorder, or myocardial infarction (MI) within three months of study enrollment, heart failure, hepatic or renal dysfunction, or a drug allergy.

After enrollment, patients were assigned to receive pitavastatin 2 mg and pravastatin-matched placebo or pravastatin 10 mg and pitavastatin-matched placebo. They were instructed to take both tablets in the evening for 12 weeks.

The trial also included a 4-week run-in period. After 12 weeks of treatment, placebo was given for another four weeks. Fasting blood samples were collected at the baseline examination (week -4 and week 0); at treatment weeks 4, 8, and 12; and during the follow-up period (week +4). (Week -4 is the beginning of the run-in period; week 0 is the end of the run-in period, just before the start of therapy; and week +4 is the 4th week of placebo at the end of the trial.)

The study was designed to evaluate the superiority of pitavastatin for TC and LDL-C reduction and the non-inferiority of pitavastatin for reducing TG levels in patients with hypertriglyceridemia. Safety was evaluated based on the incidence of AEs, laboratory abnormalities, and changes in blood pressure, pulse rate, and weight.

At the end of the trial, 281 patients were screened and 240 patients were assigned as follows: 127 received pitavastatin and 113 received pravastatin. Fifteen of the 240 patients were excluded from the efficacy analysis for various reasons (seven in the pitavastatin group and eight in the pravastatin group). The two

treatment groups were well balanced in terms of their baseline characteristics, except for a lower mean HDL-C value in the pravastatin group (52.9 mg/dL vs. 56.8 mg/dL, respectively; $P = 0.031$).

For the primary endpoint, mean percentage of TC and LDL-C reductions from baseline were significantly greater with pitavastatin than with pravastatin (28.2% vs. 14% for TC and 37.6% vs. 18.4% for LDL-C, respectively; $P < 0.001$ for both comparisons).

For patients with a baseline TG level of 150 mg/dL or higher, the mean percentage of TG reduction in the pitavastatin group was non-inferior to that of the pravastatin group (23.3% vs. 20.2%, respectively; $P = 0.024$).

In the safety analysis, three pitavastatin patients withdrew because of drug-related AEs (headache and abdominal pain, exacerbation of chronic hepatitis C, and somnolence). Two patients in the pravastatin group withdrew because of drug-related AEs (muscle convulsion and vertigo). There were no serious, drug-related AEs reported, and most AEs were mild-to-moderate clinical laboratory abnormalities. Two pitavastatin patients and one pravastatin patient experienced elevated alanine aminotransferase (ALT) levels of more than three times the upper limit of normal (ULN). None of the patients experienced creatinine kinase (CK) elevations in conjunction with muscle pain, and only one patient in the pravastatin group experienced a CK elevation of more than 1,000 units/L.

In this trial, pitavastatin 2 mg/day showed a larger decrease in LDL-C levels compared with pravastatin 10 mg/day in patients with hyperlipidemia. The safety analysis also indicated that this dose of pitavastatin was well tolerated.

Park et al.⁹

In addition to the evaluation of pitavastatin and pravastatin by Saito et al.,⁸ pitavastatin was also compared with simvastatin (Zocor, Merck). Park et al. conducted a prospective, randomized, open-label trial to compare the efficacy and safety of these two agents in Korean patients with hyperlipidemia. The primary endpoint was the mean change in LDL-C levels at eight weeks compared with the baseline level (evaluated for non-inferiority). Secondary endpoints included the mean change from baseline in TC, TG, and HDL-C values and the rate of achieving cholesterol goals, as defined by ATP III guidelines.

Eligible patients included men and women between 20 and 75 years of age who had fasting TG levels below 600 mg/dL and LDL-C levels above 130 mg/dL after four weeks of a dietary lead-in period that was similar to the Therapeutic Lifetime Changes (TLC) diet.

Significant exclusion criteria included pregnancy, breast-feeding, participation in other studies three months prior to enrollment, current antihyperlipidemic therapy, CK levels greater than twice the ULN, aspartate transaminase (AST) or ALT levels greater than 2.5 times the ULN, and serum creatinine levels greater than 2.5 times the ULN. Patients who had uncontrolled diabetes, thyroid dysfunction, uncontrolled hypertension, symptomatic cerebrovascular disease, or an MI within three months of enrollment were also ineligible to enter the study.

At the conclusion of the dietary run-in period, patients were randomly assigned to receive pitavastatin 2 mg orally once daily or simvastatin 20 mg orally once daily for eight weeks. Patients participated in follow-up visits at the fourth and eighth weeks of treatment. At each visit,

Table 1 Efficacy of Currently Available HMG CoA Reductase Inhibitors (Statins)

Agent	TC Change (%)	LDL Change (%)	TG Change (%)	HDL Change (%)
Atorvastatin (Lipitor) 10 mg	-27	-37	-20	+6
Fluvastatin (Lescol) 20 mg	-17	-22	-12	+3
Lovastatin (Mevacor) 10 mg	-16	-21	-10	+5
Pravastatin (Pravachol) 10 mg	-15	-20	-8	+3
Rosuvastatin (Crestor) 10 mg	-33	-46	-20	+8
Simvastatin (Zocor) 10 mg	-20	-28	-12	+5

HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol; TG = triglycerides.

Data from Jones PH, et al. *Am J Cardiol* 2003;92:152-160;⁴ lovastatin, package insert;⁵ and fluvastatin, package insert.⁶

continued on page 204

continued from page 198

a complete medical history, physical examination, laboratory analysis, and assessment of drug compliance (as determined by a pill count) were performed.

At the end of the trial, 104 patients were enrolled and 95 patients completed the study (49 receiving pitavastatin, 46 receiving simvastatin). There were no significant differences in the baseline characteristics of the treatment groups.

For the primary endpoint, there was no significant difference in the percentage of decrease in LDL-C levels: mean (standard deviation [SD]), 38.2% (11.6%) for pitavastatin and 39.4% (12.9%) for simvastatin ($P = 0.648$). The 95% confidence interval (CI) for the treatment difference was -6.1 to 3.8 , which was within the pre-specified parameters for non-inferiority.

No statistically significant differences were found between groups in changes in TC, TG, or HDL-C levels from the baseline to the study's end, and no significant differences were noted in the proportion of patients who achieved ATP III treatment targets.

For the safety portion, 103 patients were evaluated according to the intent-to-treat analysis. A significantly larger rate of AEs was experienced in the simvastatin group (37.3%) compared with the pitavastatin group (15.4%) ($P = 0.015$). At least one clinical AE was observed in 25% of the pitavastatin patients and in 37.3% of the simvastatin patients.

Of these two arms, 11.5% of patients in the pitavastatin group and 23.5% in the simvastatin group experienced an AE that was drug-related. The number of patients experiencing at least one AE or one drug-related AE did not differ significantly between groups.

One patient receiving pitavastatin discontinued therapy because of stomach discomfort, and four simvastatin patients discontinued therapy because of eye pain, edema, vomiting, anxiety, myalgia, and dizziness.

The results of this trial indicated that pitavastatin 2 mg/day was non-inferior to simvastatin 20 mg/day in terms of reducing LDL-C levels and attaining cholesterol goals, as defined in ATP III. In addition, this trial did not demonstrate a significant difference between the two treatments in reducing TC and TG levels or in raising HDL-C levels.

Pitavastatin in Diabetic Patients

Sasaki et al.¹⁰

In addition to studies of hyperlipidemia in patients without specific comorbidities, the effects of pitavastatin on both the lipid panel and glucose control have been assessed in patients with hyperlipidemia and concomitant glucose intolerance. Sasaki and associates conducted a multicenter, open-label, parallel-group trial that compared the efficacy and safety of pitavastatin and atorvastatin (Lipitor, Pfizer) in terms of changes in lipid goals and glucose tolerance. The primary efficacy endpoint was the difference in the percentage of change in HDL-C levels between the study groups. Secondary efficacy endpoints included the percentage of change in other lipid parameters. Tolerability endpoints included glucose tolerance, AEs, physical findings, and clinical laboratory test results.

Men or postmenopausal women had to have LDL-C levels of 140 mg/dL or higher, HDL-C levels below 80 mg/dL, TG levels below 500 mg/dL, and glucose intolerance. For this trial, glucose intolerance was defined as having received an antidiabetic agent (excluding insulin) or having a glucose measurement in the past three months that indicated glucose intolerance.

Patients were excluded from enrollment if they had:

- contraindications to the use of or a history of severe reaction to statins.
- a serum creatinine level of 2 mg/dL or higher.
- secondary hyperlipidemia.
- cardiovascular disease, such as severe hypertension, recent MI, recent coronary artery procedure, or New York Heart Association (NYHA) class 3 heart failure or greater.
- recent cerebrovascular disease.
- poorly controlled type-2 diabetes.
- type-1 diabetes.

The current use of any steroids (including topical and nasal preparations) also disqualified patients from eligibility.

Patients were prohibited from using other lipid-lowering drugs, immunosuppressants,azole antifungal agents, erythromycin, and insulin throughout the course of the study. Participants were permitted to continue taking oral diabetic

medications, but they had to maintain the same dose for the entire study period.

Upon entry into the study, patients underwent a two- to four-week drug-free, run-in period. Patients who were taking antihyperlipidemic agents prior to entry into the study underwent a four-week, drug-free washout period before the run-in period. At the end of the run-in period, patients received either pitavastatin 2 mg orally daily or atorvastatin 10 mg orally daily for 52 weeks.

During the study, fasting blood samples were drawn at baseline and at treatment weeks 8, 26, and 52 to measure lipid panels, plasma insulin levels, glucose, and glycosylated hemoglobin (HbA_{1c}). The homeostasis model (HOMA-IR) was then used to calculate insulin resistance on all samples when blood glucose levels were 140 mg/dL or lower. In addition to the laboratory analysis, patients underwent physical examinations and were assessed for AEs and adherence to the study drug.

At the end of the study period, 207 patients were enrolled in the trial; 18 patients never returned to the clinic, and 189 patients were therefore included in the safety analysis. Sixteen patients discontinued treatment prior to six months, and efficacy was evaluated in 173 patients (88 receiving pitavastatin, 85 receiving atorvastatin). Women accounted for 62% of the evaluable population, with a mean age of 63.3 years and a mean weight of 63 kg (about 139 pounds); 89% had diabetes mellitus. There were no significant differences between the treatment groups in terms of baseline characteristics or adherence to the study drug during the trial.

There was a significantly greater percentage of increase in HDL-C levels with pitavastatin (8.2%) than with atorvastatin (2.9%) ($P = 0.031$). A significantly larger increase was also seen in Apo A-I, a component of HDL-C (5.1 with pitavastatin vs. 0.6 with atorvastatin; $P = 0.019$).

The percentage of change in LDL-C levels was significantly greater with atorvastatin (-40.1%) than with pitavastatin (-33.0%) ($P = 0.002$), as was the percentage of change in non-HDL-C (-37.4 vs. -31.1 ; $P = 0.004$); Apo B, a component of LDL-C (-35.1% vs. -28.2% ; $P < 0.001$); and Apo E (-28.1% v. -17.8% ; $P < 0.001$). Apo E is a protein that binds the LDL receptor, as it is a component of several

lipoproteins. The significance of these results was unchanged when all 189 subjects who received one or more doses of the study medication were included in the analysis.^{8,9}

For glucose metabolism, no significant differences were observed between treatments in fasting plasma insulin, fasting plasma glucose, HbA_{1c}, or HOMA-IR. There was also no significant difference between the groups in terms of deterioration in glucose metabolism (a composite of the number of patients who needed to begin antidiabetic therapy, increased doses of antidiabetic agents, or increased HbA_{1c}).

AEs were experienced by 9% of the pitavastatin patients (9/96) and by 14% of the atorvastatin group (13/93); the *P* value was nonsignificant. Two patients in the pitavastatin group and none in the atorvastatin group had an ALT value of more than three times the ULN; *P* was nonsignificant.

In this trial, 52 weeks of treatment with pitavastatin 2 mg/day was associated with significantly greater increases in HDL-C and Apo A-I levels when compared with atorvastatin 10 mg/day. However, the effect of pitavastatin in lowering LDL-C values was less than that of atorvastatin. Both treatments were also well tolerated, resulting in similar rates of AEs, including deterioration of glucose control.

Yamakawa et al.¹²

A retrospective study was conducted to evaluate the effects of pravastatin, atorvastatin, and pitavastatin on Japanese patients with type-2 diabetes complicated by hyperlipidemia. Patients were selected for the trial if they were receiving treatment with a statin.

Participants were divided into three groups according to the statin that the physician had chosen for them: atorvastatin (group A), pravastatin (group Pr), and pitavastatin (group Pi). Patients were ineligible to enroll if their antidiabetic medication (insulin or oral agent) had been adjusted during the three months before or after initiation with their statin therapy. Patients who experienced events that would be expected to alter their glycemic control, including changes in medications or enrollment in a diabetes education program, were also excluded.

There were 99 patients in the atorva-

statin group (45 men and 54 women; mean age, 59.4 years); 85 patients in the pravastatin group (38 men and 47 women; mean age 65.9 years); and 95 patients in the pitavastatin group (46 men and 49 women; mean age, 63 years). There were no significant differences between the groups in age, body weight, history of coronary artery disease, or diabetic medication adjustments. Notably, prior treatment with other antihyperlipidemic drugs was more common in the atorvastatin and pitavastatin patients, and insulin treatment was significantly more common with the pitavastatin group (*P* < 0.01 for both comparisons).

There were no changes in antidiabetic drug doses for 75% of patients in the atorvastatin group, 82% of patients in the pravastatin group, and 80% of patients in the pitavastatin group. Specific values for glucose and lipid parameters are detailed in Table 2.

Only the atorvastatin arm experienced a significant elevation in both arbitrary blood glucose and HbA_{1c} levels, and these changes were significantly larger than those experienced in the pravastatin and pitavastatin arms (*P* < 0.01). All of the patients experienced a significant decrease in TC and LDL-C levels, but lipid

levels improved more with atorvastatin than with pravastatin and pitavastatin. No significant changes in HDL-C or TG levels were noted in any of the groups.

The authors of this study concluded that pitavastatin showed a potent cholesterol-lowering effect when compared with atorvastatin and that glycemic parameters increased significantly only in the atorvastatin group. These findings suggested that pitavastatin and pravastatin did not have an adverse effect on glycemic control in patients with type-2 diabetes. Although these observations are true, the study authors did not analyze the dose of each agent used. In addition, arbitrary glucose levels rather than standardized levels were used, and the study groups had different levels of pretreatment with antihyperlipidemic drugs.

Effect of Pitavastatin on Atherosclerosis

Kastelin et al.¹³ and Taylor et al.¹⁴

All of the trials described previously have measured the ability of pitavastatin to alter serum lipid markers. For many years, this effect has been considered a reasonable measure of the performance of an antihyperlipidemic agent. Some more recent trials, however, such as ENHANCE (Ezetimibe and Simvastatin

Table 2 Changes in Glycemic and Lipid Parameters with the Use Of Three Statins

Level	Pitavastatin	Atorvastatin	Pravastatin
Random glucose (mg/dL)*			
Baseline	155 ± 53	147 ± 51	136 ± 31
End of study	154 ± 51	176 ± 69†	134 ± 32
HbA_{1c} (%)*			
Baseline	7.3 ± 1.0	7.0 ± 1.1	6.9 ± 0.9
End of study	7.2 ± 1.0	7.4 ± 1.2‡	6.9 ± 1.0
TC (mg/dL)*			
Baseline	225 ± 47	254 ± 40	226 ± 36
End of study	198 ± 34‡	200 ± 52‡	202 ± 34‡
LDL-C (mg/dL)*			
Baseline	137 ± 36	155 ± 33	143 ± 31
End of study	113 ± 28	111 ± 27‡	120 ± 27‡
HDL-C (mg/dL)*			
Baseline	55 ± 14	55 ± 11	56 ± 12
End of study	56 ± 15	56 ± 18	58 ± 31

HbA_{1c} = glycosylated hemoglobin; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; TC = total cholesterol.

* Unless otherwise specified, all *P* values are not significant.

† *P* < 0.001.

‡ *P* < 0.0001.

Adapted from Yamakawa T, et al. *J Atheroscler Thromb* 2008;15:269–327.¹²

in Hypercholesterolemia Enhances Atherosclerosis Regression)¹³ and ARBITER 6-HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: HDL and LDL Treatment Strategies),¹⁴ have called into question the relationship of LDL-C reduction and atherosclerotic plaque regression.

Hiro et al.¹⁵

Hiro et al. conducted a non-inferiority study, JAPAN-ACS (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome) to compare the efficacy of pitavastatin and atorvastatin in reducing coronary plaque volume following ACS. Patients were enrolled if they had ACS, which was defined as unstable angina or MI.

Treatment consisted of either atorvastatin 20 mg orally daily or pitavastatin 4 mg orally daily in addition to standard antiplatelet therapy and other ACS therapy. Patients were stratified according to the presence of diabetes, sex, and TC levels. Lipid panels, inflammatory marker assays, and intravascular ultrasound (IVUS) were performed at the baseline evaluation and at 8 and 12 months to measure coronary plaque volume. Blinded evaluators performed the IVUS in a centralized location.

At the end of the study period, 307 patients (153 receiving pitavastatin and 154 receiving atorvastatin) were enrolled at 33 centers. Of these patients, 82% of each group completed all IVUS studies. The treatment groups were well matched at baseline.

After 8 to 12 months of follow-up, no significant differences between treatments were noted in the lipid panel or in inflammatory markers. Both groups showed a significant regression in plaque volume, but there was no significant difference between the groups: a mean percentage reduction \pm SD, -16.9 ± 13.9 for pitavastatin and -18.1 ± 14.2 for atorvastatin ($P < 0.001$ for the comparison of each group to baseline and $P = 0.5$ for the comparison between groups).

The mean difference of drug effects was 1.11% (95% CI, -2.27% to 4.48%), which met the prespecified requirement for non-inferiority. Additional results from the trial included a significant reduction in the percentage of plaque volume and normalized plaque volume, compared

with baseline, with no difference noted between groups. Moreover, no significant differences in AEs between study groups were observed.

The authors concluded that any difference in the reduction of plaque volume with pitavastatin 4 mg daily or with atorvastatin 20 mg daily was insignificant. The data are promising; however, caution must be exercised in interpreting the findings because the dose of atorvastatin that has been demonstrated to decrease mortality in ACS is 80 mg daily.¹⁶

DOSAGE⁷

Adults. The dose range for pitavastatin is 1 to 4 mg orally once daily at any time of the day without regard to meals. The recommended starting dose is 2 mg, and the maximum dose is 4 mg.⁵ Results from a dose-finding trial by Saito et al. indicated that the 1-mg dose decreased LDL-C concentrations by 33.6% and the 4-mg dose decreased LDL-C levels by 47.2%.¹⁷

Special Populations. In pharmacokinetic studies, pitavastatin C_{max} and AUC were 21% and 5% lower, respectively, in African-American healthy volunteers than in Caucasian healthy volunteers. There was no difference in drug levels between Caucasian and Japanese volunteers. Pitavastatin C_{max} and AUC were 10% higher in elderly subjects and 30% higher in young, healthy volunteers. This difference appears to have no effect on the efficacy or safety of pitavastatin.

Organ Dysfunction. Patients with moderate renal impairment and those receiving hemodialysis should begin with a starting dose of 1 mg once daily 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.

Patients with acute liver disease, including unexplained, persistent increases in ALT or AST, should not receive pitavastatin. The ratios of pitavastatin C_{max} and AUC between patients with moderate hepatic impairment (Child-Pugh B disease) and healthy volunteers were 2.7 and 3.8, respectively.

DRUG INTERACTIONS⁷

Because enzyme inhibitors, including erythromycin and rifampin, increase pitavastatin exposure, smaller pitavastatin doses should be used. The concomitant use of cyclosporine or lopinavir/ritonavir (Kaletra, Abbott) should be avoided. The additional use of fibric acid derivatives or niacin may increase the risk of myopathy, and the dose of pitavastatin should be reduced in these situations.

CONCLUSION

Pitavastatin, a new HMG CoA reductase inhibitor (statin), has been studied against other drugs in its class and has demonstrated high potency. In diabetic patients, the drug does not seem to have an effect on the incidence of diabetes, although more studies are needed in well-controlled trials.

Pitavastatin has demonstrated a significant reduction in atherosclerotic plaque volumes; however, because the 20-mg dose of atorvastatin was a poor comparator, pitavastatin should not replace standard therapy after ACS. (A 20-mg dose of atorvastatin was used in the Hiro trial, but 80 mg is the dose that has proved to be the most beneficial in reducing mortality in clinical trials.)

REFERENCES

1. American Heart Association. *Heart Disease and Stroke Statistics—2010 Update*. Dallas, Tex: American Heart Association; 2010.
2. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143–3421.
3. Sattar N, Preiss D, Murray HM, et al. Statins and the risk of diabetes: A collaborative meta-analysis of randomised statin trials. *Lancet* 2010;375:735–742.
4. Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol* 2003; 92:152–160.
5. Mevacor (lovastatin), package insert. Whitehouse Station, N.J.: Merck & Co., Inc., October 2009.
6. Lescol (fluvastatin), package insert. East Hanover, NJ: Novartis; April 2006.
7. Livalo (pitavastatin), package insert.

- Montgomery, AL: Kowa Pharmaceuticals America; 2009.
8. Saito Y, Yamada N, Teramoto T, et al. A randomized, double-blind trial comparing the efficacy and safety of pitavastatin versus pravastatin in patients with primary hypercholesterolemia. *Atherosclerosis* 2002;162:373–379.
 9. Park SH, Kang HJ, Rim SJ, et al. A randomized, open-label study to evaluate the efficacy and safety of pitavastatin compared with simvastatin in Korean patients with hypercholesterolemia. *Clin Ther* 2005;27:1074–1082.
 10. Sasaki J, Ikeda Y, Kuribayashi T, et al. A 52-week, randomized open-label, parallel-group comparison of the tolerability and effects of pitavastatin and atorvastatin on high-density lipoprotein cholesterol levels and glucose metabolism in Japanese patients with elevated levels of low-density lipoprotein cholesterol and glucose intolerance. *Clin Ther* 2008;30:1089–1101.
 11. Talbert RL. Hyperlipidemia. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*, 7th ed. New York: McGraw-Hill; 2008:385–408.
 12. Yamakawa T, Takano T, Tanaka S, et al. Influence of pitavastatin on glucose tolerance in patients with type 2 diabetes mellitus. *J Atheroscler Thromb* 2008;15:269–275.
 13. Kastelin JJP, Akdim F, Stroes ESG, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008;358:1431–1443.
 14. Taylor AJ, Villines TC, Stanek EJ, et al. Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med* 2009;361:2113–2122.
 15. Hiro T, Kimura T, Morimoto T, et al. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome. *J Am Coll Cardiol* 2009;54:293–302.
 16. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495–1504.
 17. Saito Y, Yamada N, Teramoto T, et al. Clinical efficacy of pitavastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, in patients with hyperlipidemia. *Drug Res* 2002;45:251–255. ■