Beneficial Effects of Pitavastatin, a 3-Hydroxy-3-Methylglutaryl Coenzyme a Reductase Inhibitor, on Cardiac Function in Ischemic and Nonischemic Heart Failure

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SUMMARY

HMG-CoA reductase inhibitors (statins) have recently been reported to improve cardiac function, and decrease the incidence of heart failure (HF) in hyperlipidemic patients. However, evidence for statin treatment in patients with HF remains a subject of debate. Thus, a study was initiated to examine the effects of pitavastatin on cardiac function evaluated by echocardiographic findings and plasma brain natriuretic peptide (BNP) levels in patients with HF. Twenty-three patients with HF were treated with pitavastatin 1-2 mg/day in addition to standard therapy for 7.5 ± 3.8 months. Left ventricular end-diastolic dimension (LVDd) and left ventricular end-systolic dimension (LVDs) were determined by echocardiography. Left ventricular ejection fraction (LVEF) was calculated using Teichholz’s formula. Serum lipid and plasma BNP levels were also measured. During the follow-up period, LVEF was increased from 42 ± 11 to 48 ± 13% (P = 0.002). LVDs was reduced from 43 ± 10 to 40 ± 10 mm (P < 0.001), while there was no change in LVDd. E/A (n = 10) and deceleration time (n = 7), obtained in some patients, did not change significantly (0.89 ± 0.33 to 0.77 ± 0.17%, and 215 ± 46 to 227 ± 72 msec, respectively). In addition, the plasma BNP level was moderately, but significantly decreased from 94 ± 78 to 70 ± 56 pg/mL (P = 0.005). In subgroup analysis, LVEF was improved in both patients with ischemic and nonischemic HF. There was no significant correlation between the percent change in serum total cholesterol and the percent change in LVEF by pitavastatin treatment. Serum total cholesterol, LDL-cholesterol, and triglycerides decreased by 21%, 30%, and 15%, respectively, and HDL-cholesterol increased by 12%. Pitavastatin improved cardiac function in patients with HF, which generally worsens with time. The results suggest that pitavastatin may be beneficial for treatment of HF. (Int Heart J 2008; 49: 49-58)

Key words: Statins, Ejection fraction, Brain natriuretic peptide
ADMINISTRATION of angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), β-blockers, and aldosterone blockers is now a hallmark of therapy in patients with heart failure (HF). Despite advances in pharmacological therapy, morbidity and mortality due to HF remain high. It is therefore of critical importance to develop therapeutic strategies that will effectively inhibit the development and progression of HF.

HMG-CoA reductase inhibitors (statins) have many pleiotropic effects beyond lipid-lowering that provide a potential therapeutic pathway for patients with HF by downregulating inflammatory cytokines, improving endothelial function, reversing myocardial remodeling, and normalizing sympathetic activation.1-5

Statin therapy lowers morbidity and mortality in a broad range of patient populations with and without cardiovascular disease.6-10 Statin therapy may also reduce the risk of HF, although patients with symptomatic and severe HF generally have been excluded from these studies. A few studies have suggested that statin therapy improves cardiac function in patients with HF11,12 and prevents the development of HF,13,14 but the significance of these findings remains a subject of debate.

Pitavastatin is a potent HMG-CoA reductase inhibitor developed in Japan, and is minimally metabolized by the cytochrome P450 system, which may avoid adverse events caused by interactions with commonly used drugs.15 Considering its characteristics, pitavastatin has additional clinical benefits for patients receiving many drugs, such as patients with HF.

This study was therefore initiated to examine the effects of pitavastatin on cardiac function evaluated by echocardiographic findings and plasma brain natriuretic peptide (BNP) levels in patients with HF.

METHODS

Participants: Twenty-three patients with ischemic or nonischemic HF were studied. Men and women aged 20 years or older were eligible for enrollment if they: 1) had clinical evidence of HF including a history at more advanced stages; 2) had a left ventricular ejection fraction (LVEF) < 50% or BNP > 20 pg/mL; 3) had a New York Heart Association (NYHA) functional classification of I to III; and 4) needed cholesterol-lowering therapy. Exclusion criteria included chronic obstructive pulmonary disease and myocarditis.

Study design: All patients received some or all of the following standard HF therapy: digoxin, diuretics, nitrates, calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers. All treatment decisions were made by the attending physicians, and the doses of HF medications were not adjusted for the duration of this study and the prior 3
months. After a screening visit, they were treated with pitavastatin 1-2 mg/day (Kowa, Nagoya, Japan) for a 6-month period, and echocardiographic findings and biochemical markers were measured before and after the course of treatment. The dose of pitavastatin was at the discretion of the treating physician. Informed consent was obtained from all patients before participation in this study.

**Echocardiography:** M-mode echocardiography was performed, and left ventricular end-diastolic dimension (LVDd) and left ventricular end-systolic dimension (LVDs) were measured before and after treatment. Left ventricular volumes were calculated using Teichholtz’s formula and used to determine LVEF. The transmural peak E and A wave velocities were recorded, and the E/A ratio and deceleration time were assessed by pulse wave Doppler echocardiography in some patients.

**Biochemical markers:** Blood samples were collected before and after the course of treatment. Total cholesterol, HDL-cholesterol, and triglycerides were measured with standard techniques. LDL-cholesterol was measured by direct assay using commercially available kits (LDL-EX; Denka Seiken Co.). Safety parameters including alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl-transpeptidase (γ-GTP), and creatine phosphokinase (CPK) were measured with standard techniques. Plasma BNP level was measured using a specific immunoradiometric assay.16)

**Statistical analysis:** All data shown are the mean ± SD or as indicated. Student’s paired t-test was used to determine statistical differences before and after treatment. Pearson’s correlation coefficient was used to determine the relation between measurements. Significance was accepted at the 95% confidence interval (P < 0.05).

**RESULTS**

**Baseline characteristics and procedural data:** A total of 23 patients (17 men and 6 women, mean age, 68 years, range, 49-83 years) met all of our inclusion criteria and none of the exclusion criteria. No patients had received any lipid-lowering agents except one receiving simvastatin 5 mg/day. Table I shows the baseline characteristics of the patients. The mean follow-up period of pitavastatin treatment was 7.5 ± 3.8 months. Nineteen patients received pitavastatin 2 mg/day, and the others received 1 mg/day.

**Changes in lipid parameters and safety during the follow-up period:** Serum lipid parameters are shown in Table II. After pitavastatin treatment, total cholesterol, LDL-cholesterol, and triglycerides were decreased by 21 ± 13% (P < 0.001), 30 ± 14% (P < 0.001), and 15 ± 37% (P = 0.071), respectively, and HDL-cholesterol was increased by 12 ± 18% (P = 0.040). All patients were clinically stable, and
adverse events including ALT, AST, γ-GTP, and CPK were not observed during the follow-up period.

**Changes in hemodynamic parameters during the follow-up period:** Systolic and diastolic blood pressure did not significantly change between baseline and after pitavastatin treatment (139 ± 17 to 138 ± 14 mmHg, and 83 ± 13 to 78 ± 9 mmHg, respectively), nor did heart rate (67 ± 8 to 65 ± 11 beats/min). Echocardiographic findings are shown in Table III and Figure 1A. LVDs was reduced from 43 ± 10 to 40 ± 10 mm (P < 0.001), with no significant change in LVDd. LVEF was increased from 42 ± 11 to 48 ± 13% (P = 0.002). E/A (n = 10) and deceleration
Table III. Changes in Hemodynamic Parameters at Baseline and After Pitavastatin Treatment

<table>
<thead>
<tr>
<th></th>
<th>(n)</th>
<th>Baseline</th>
<th>After treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA functional class</td>
<td>23</td>
<td>1.4 ± 0.6</td>
<td>1.3 ± 0.6</td>
<td>0.083</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>23</td>
<td>42 ± 11</td>
<td>48 ± 13</td>
<td>0.002</td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>23</td>
<td>56 ± 8</td>
<td>55 ± 8</td>
<td>0.116</td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>23</td>
<td>43 ± 10</td>
<td>40 ± 10</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD or as indicated. Statistical analysis was performed to compare at baseline and after treatment. P < 0.05 was considered statistically significant.

Figure 1. Changes in LVEF at baseline and after pitavastatin treatment. Changes in LVEF were evaluated in entire patient population (A) and in subgroups of ischemic and nonischemic HF (B). Statistical analysis was performed to compare baseline and after treatment. P < 0.05 was considered statistically significant.

time (n = 7), obtained in some patients, did not change significantly (0.89 ± 0.33 to 0.77 ± 0.17%, and 215 ± 46 to 227 ± 72 msec, respectively). NYHA functional class improved in 3 patients, while it remained unchanged in the others. In subgroup analysis in the etiologies of HF (Figure 1B), LVEF was improved in both patients with ischemic (P = 0.036) and nonischemic (P = 0.017) HF.

Changes in BNP during the follow-up period: Plasma BNP level was moderately, but significantly decreased from 94 ± 78 to 70 ± 56 pg/mL (P = 0.005) after pitavastatin treatment (Figure 2A). In subgroup analysis in the etiologies of HF (Fig-
Figure 2. Changes in the plasma BNP level at baseline and after pitavastatin treatment. Changes in plasma BNP level were evaluated in entire patient population (A) and subgroups of ischemic and nonischemic HF (B). Statistical analysis was performed to compare baseline and after treatment. P < 0.05 was considered statistically significant.

Correlation between changes in total cholesterol and LVEF during the follow-up period: There was no significant correlation between the percent change in total cholesterol and percent change in LVEF ($r = 0.016, P = 0.944$) with pitavastatin treatment. Similarly, the percent changes in the other lipid parameters were not correlated with the percent changes in the LVEF (LDL-cholesterol: $r = 0.404, P = 0.108$; HDL-cholesterol: $r = -0.041, P = 0.900$; triglycerides: $r = -0.060, P = 0.787$).

**DISCUSSION**

The aim of this study was to evaluate the effects of pitavastatin on cardiac function and plasma BNP level in patients with HF. In the present study, pitavastatin treatment in addition to standard therapy was safe and well tolerated, and improved LVEF as well as the plasma BNP level in patients with HF in agreement with recent studies.11,12) The increase in LVEF was due to decreased LVDs,
indicating that pitavastatin may improve LV systolic function rather than diastolic function. Furthermore, it is worth emphasizing that the improvement of LVEF by pitavastatin was found in both the ischemic and nonischemic HF patient subgroups. This is the first report to show that pitavastatin improves cardiac function with a decrease in plasma BNP level in patients with HF.

In large randomized trials of statins, patients with symptomatic and severe HF generally have been excluded,\textsuperscript{6-10} and whether or not statin therapy is beneficial for patients with HF remains a subject of debate. A few observational studies have reported a significant association of statin therapy with lower mortality in patients with ischemic and nonischemic HF.\textsuperscript{17-19}

With respect to nonischemic HF, Node, \textit{et al} reported that statin therapy improved cardiac function and symptoms in patients with idiopathic dilated cardiomyopathy during a 3-month follow-up period.\textsuperscript{11} Similarly, Wojnicz, \textit{et al} reported that statin therapy improved cardiac function in patients with HF due to inflammatory dilated cardiomyopathy during 6 months follow-up.\textsuperscript{12} We obtained similar results, in other words, that pitavastatin improved LVEF as well as the plasma BNP level in nonischemic HF. The mean values of LVEF, E/A, and deceleration time in these subjects before treatment were 47\%, 0.84\%, and 246 msec, respectively, which indicated that most of the patients may have had diastolic dysfunction. The study by Serpil, \textit{et al} revealed that plasma BNP levels provided an indication about the cardiac functional capacity in patients admitted with diastolic dysfunction.\textsuperscript{20} Considering these results, we speculate that pitavastatin may improve signs and symptoms of HF.

On the other hand, little is known about the effect of statins on cardiac function in ischemic HF. In the present study, pitavastatin significantly increased LVEF in ischemic HF, but LVEF decreased in 4 patients, 3 of whom had LVEF < 35\% before treatment. Moreover, the plasma BNP level was not decreased significantly. Agnieszka, \textit{et al} reported that the plasma BNP level was elevated in the early stage of acute myocardial infarction,\textsuperscript{21} but we did not enroll such patients, and no patients developed any major adverse coronary events during the follow-up period. We expect that pitavastatin is effective on cardiac function in both ischemic and nonischemic HF. Because ischemic patients, especially those with LVEF < 35\%, have severe LV asynergy, the values of LVEF and plasma BNP in ischemic HF may vary widely compared with nonischemic HF.

Various studies support the validity of “the lower, the better” approach for cholesterol lowering,\textsuperscript{22} and it has recently been reported in subgroup analysis of the Treating to New Targets (TNT) Study that intensive statin therapy in patients with preexisting HF prevents hospitalizations for HF.\textsuperscript{13} In the present study, pitavastatin treatment lowered cholesterol levels and increased LVEF, but we could not find any correlations between cholesterol reduction and LVEF increase.
Thus, the improvement of LVEF by pitavastatin treatment may be independent of its cholesterol-lowering effect.

Recent experimental and clinical studies suggest that statins may improve cardiac function by cholesterol-independent mechanisms. These proposed pathways include potential pleiotropic actions of statins, such as decreases in Rho, Rac, and Ras via blockade of the mevalonate pathway. Inhibition of Rho geranylgeranylation leads to increased endothelial nitric oxide production and decreased endothelin-1 expression. In two studies investigating forearm blood flow in humans, improvement of endothelial function was observed within days after initiation of statin therapy without a significant reduction of cholesterol levels. In addition, treatment with a single dose of 40 mg pravastatin rapidly improved acetylcholine-mediated epicardial coronary vasomotion in patients with stable angina pectoris. These vasodilatory effects by statins may decrease left ventricular afterload and increase coronary perfusion, thereby improving LV relaxation and cardiac function. Inhibition of Rac by statins decreases vascular and myocardial oxidative stress by inhibiting Rac-induced NADPH oxidase activity. Failing myocardium in patients with HF is characterized by upregulation of NADPH oxidase-mediated reactive oxygen species release associated with increased Rac1 activity, and oral statin treatment inhibits myocardial Rac1-GTPase activity. Elevated inflammatory markers are associated with worse symptoms and poor survival in HF, and it has been reported that statin therapy improves cardiac function and symptoms by reducing plasma IL-6 and TNF-α levels. Other potential beneficial effects of statins include inhibition of the remodeling and interstitial fibrosis in experimental animal models.

This study has several limitations. The major limitation was the lack of a placebo control group. In addition, the duration and sample size of this study was not sufficient to evaluate the effects of pitavastatin on cardiac function or mortality in patients with HF. Because of these limitations, the results of the present study must be considered to be preliminary.

In conclusion, treatment with pitavastatin in addition to standard therapy, not only decreases the plasma BNP level but also increases LVEF in patients with HF. The present findings suggest that pitavastatin may be beneficial for treatment of HF. Large-scale, randomized clinical trials will be needed to evaluate the clinical benefits of statin therapy in patients with HF.

REFERENCES


