

Pitavastatin subacutely improves endothelial function and reduces inflammatory cytokines and chemokines in patients with hypercholesterolaemia

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Received 19 June 2013

Revised 5 August 2013

Accepted 26 August 2013

ABSTRACT

Background Pitavastatin is a statin with strong pleiotropic effects, but the effects of pitavastatin on endothelial cell function (ECF) and both inflammatory cytokines and chemokines have not been fully investigated.

Material and methods We simultaneously measured brachial artery (BA) flow-mediated vasodilatation (FMD) and nitroglycerin-mediated vasodilatation (NMD), as well as plasma biomarkers of inflammatory cytokines and chemokines, in patients with hypercholesterolaemia and other atherosclerotic risk factors who were treated with pitavastatin. Sixty-five hypercholesterolaemic patients (age, 66±11 years) with conventional coronary risk factors were enrolled. BA FMD, BA NMD and serum biomarkers (tumour necrosis factor, interleukin (IL)-6, IL-10, monocyte chemoattractant protein-1, IL-8, P-selectin, E-selectin, soluble intercellular cell adhesion molecule-1 (s-ICAM1)) were measured before and after 4 weeks of treatment with pitavastatin (2 mg/day).

Results Pitavastatin treatment resulted in an increase from baseline to post-treatment in FMD (3.22±1.72 vs 3.97±2.18%, $p<0.05$) but not in NMD. Furthermore, pitavastatin treatment led to a decrease from baseline to post-treatment in E-selectin (51±27 vs 46±29 pg/mL, $p<0.05$) and s-ICAM1 (276±86 vs 258±91 pg/mL, $p<0.05$). Changes in FMD in response to pitavastatin treatment did not correlate with those of E-selectin or s-ICAM1.

Conclusions Pitavastatin treatment resulted in a subacute improvement in ECF and a decrease in chemokine levels. These results suggest that pitavastatin might improve long-term outcomes in patients with atherosclerotic disorders.

effect of different statins on endothelial function has been widely evaluated. Endothelial function can be investigated by assessment of brachial artery flow-mediated vasodilatation (FMD) or plethysmography with acetylcholine infusion in forearm vessels.^{7–9}

Inflammation and inflammatory mediators, including cytokines, chemokine leucocyte function and oxidative stress, are also involved in the pathophysiology of atherosclerosis. Cytokines and chemokines also play a part in the pathogenesis of plaque destabilisation that leads to acute coronary syndrome or other serious conditions. Studies have investigated whether plasma markers of either cytokines or chemokines might serve as non-invasive indices of atherosclerotic disorders.⁷ Thus, it is important to understand the action of statins on cytokines and chemokines.^{10–12}

Although the effects of pitavastatin on endothelial function and cytokines and/or chemokines have been previously studied, simultaneous assessment of the effect of pitavastatin on these important parameters in humans has not been fully investigated. In this study, the subacute effect of pitavastatin on endothelial function was investigated via assessment of brachial artery FMD and nitroglycerin-mediated vasodilatation (NMD). Additionally, the effect of pitavastatin on various peripheral blood biomarkers of cytokines and chemokines, including tumour necrosis factor, interleukin (IL)-6, IL-10, monocyte chemoattractant protein-1, IL-8, P-selectin, E-selectin and soluble intercellular cell adhesion molecule-1 (s-ICAM1), was measured in patients with hypercholesterolaemia and other atherosclerotic risk factors.

INTRODUCTION

Statin therapy is a powerful strategy for the secondary prevention of acute coronary syndrome or other cardiovascular events. Statins reduce low-density lipoprotein cholesterol (LDL-C) and produce additional beneficial effects, including improvements in endothelial function, decreases in smooth muscle proliferation and vascular inflammation and antiplatelet actions.^{1–4} Pitavastatin may have the strongest pleiotropic properties of all the statins⁵ and relatively quickly benefits patients with hypercholesterolaemia.

Previous reports have shown that endothelial dysfunction is present in both the early and advanced/destabilised stages of atherosclerosis.⁶ Since endothelial function plays a central role in the pathogenesis of atherosclerotic progression, the

METHODS

Study population

The study population consisted of 65 patients with hypercholesterolaemia (51 men and 14 women; age 66.5±9.6 years) who were referred to our hospital. If LDL-C was >100 mg/dL despite already being prescribed lipid-lowering medication, including a statin other than pitavastatin, then these patients were included in this study. As shown in table 1, since around 45% of study patients had coronary artery disease, about one-third of study patients were receiving statin therapy other than pitavastatin before entering this study. In these cases, statins were withdrawn for at least five half-lives before pitavastatin was initiated. Exclusion criteria were as follows: (1) allergic reaction to statins, (2) diabetic acidosis, (3) advanced heart failure and

To cite: Takase B, Hattori H, Tanaka Y, et al. *Heart Asia* 2013;5:204–209. doi:10.1136/heartasia-2013-010368

arrhythmias, (4) thyroid disease, (5) severe disease of the liver and kidneys, (6) pregnancy or (7) any other acute disorder. Written informed consent was obtained from each patient and the study protocol was approved by our institutional review board.

Study protocol

This was a prospective open-labelled study. Each eligible patient was prescribed 4 weeks of pitavastatin (2 mg/day). After fasting overnight, venous blood samples were obtained from the antecubital vein for measurement of blood chemistries and indices of inflammatory cytokines and chemokines. Then, brachial artery endothelial function testing was performed. All measurements were repeated before and after pitavastatin treatment.

Ultrasound brachial artery FMD and NMD measurements

All ultrasound studies were conducted between 14:00 to 17:00 in a temperature-controlled room (25°C) with the subject in a fasting, resting and supine state. All studies were performed by the same technician who was blinded to any other clinical information, including the study protocol. Heavy meals, including a high fat diet and caffeine-containing beverages, were prohibited beginning on the night before the study. Patients were not allowed to have lunch on the day of the ultrasound study. Blood pressure and heart rate were recorded from the left arm every 3 min with an automatic sphygmomanometer (Nihon Korin, BP-203, Tokyo, Japan) during the ultrasound procedure. Vasodilatation responses of the brachial artery were determined by the ultrasound technique using a semiautomatic device (EF18G; UNEX, Nagoya, Japan). Briefly, the diameter of the brachial artery was measured from B-mode ultrasound images using a 10 MHz linear array transducer. Then, a blood pressure cuff was inflated to 50 mm Hg above the systolic blood pressure over the proximal portion of the right forearm for 5 min. The diastolic diameter of the brachial artery was determined semiautomatically using an instrument equipped with software for monitoring the brachial artery diameter. The changes in the diastolic diameter were continuously recorded.

FMD was determined as the maximum change in diameter after cuff release normalised to the baseline diameter (percentage of baseline diameter). NMD was obtained after a 15 min interval to obviate any effect of reactive hyperaemia on measurements. Baseline measurements of brachial artery diameter and flow velocity were again obtained and 0.3 mg of sublingual nitroglycerin was then given. Three minutes later, the brachial artery diameter was recorded. The NMD was defined as the percentage change of the brachial artery diameter relative to the baseline diameter. These measures were obtained using EF18G and calculations conducted using EF18G showed that the intraobserver and interobserver variabilities (coefficient of variation) for repeated measures of diameter before and after reactive hyperaemia in the brachial artery were <3%.^{8 13}

Biochemical analyses

All blood samples taken before and after pitavastatin treatment were obtained at the time of the FMD measurement after an overnight fast. Blood samples were centrifuged at 50 000 × *g* for 20 min at room temperature within an hour of collection. After centrifugation, the fresh serum was used for measurement of total cholesterol, triglycerides (TG), LDL-C, high-density lipoprotein cholesterol (HDL-C), serum alanine aminotransferase, serum aspartate aminotransferase, blood urea nitrogen, serum creatinine, fasting blood sugar and creatine phosphokinase. The residual serum samples were frozen and stored at −80°C until

Table 1 Clinical characteristics of the study population

| Characteristics | Value |
|---|----------|
| Number of patients | 65 |
| Age (years), mean±SD | 66.5±9.6 |
| Men/women | 51/14 |
| Body mass index (kg/m ²), mean±SD | 24±4 |
| Current smoker | 7 (11) |
| Complications* | |
| Hypertension | 40 (62) |
| Diabetes mellitus | 14 (22) |
| Coronary artery disease (CAD) | 29 (45) |
| Number of coronary diseased vessels in CAD | |
| 1 | 21 |
| 2 | 8 |
| 3 | 0 |
| Medical treatments | |
| ACEI or ARB | 24 (37) |
| β Blockers | 26 (40) |
| Calcium channel blockers | 19 (29) |
| Nitrates | 3 (5) |
| Antiplatelet agents | 43 (66) |
| Oral antidiabetic agents | 14 (22) |

Results are shown as number (%) unless stated otherwise.

*Hypertension, either systolic blood pressure >160 mm Hg or diastolic blood pressure >90 mm Hg; diabetes mellitus, fasting blood sugar >126 mg/dL; coronary artery disease, luminal stenosis >50% in the major branch of coronary artery by angiogram. ACEI, ACE inhibitor; ARB, angiotensin II receptor blocker.

later analysis of high-sensitivity C-reactive protein (hs-CRP), cytokines and chemokine levels. Total cholesterol, TG and HDL-C were measured using the enzymatic colorimetric method. LDL-C was calculated using the Friedewald formula: LDL-C=total cholesterol−(HDL-C+TG/5). The TG level was <400 mg/dL in all patients at the time of biomarker measurements in this study population. The concentrations of serum alanine aminotransferase, serum aspartate aminotransferase, blood urea nitrogen, serum creatinine, fasting blood sugar and creatine phosphokinase were measured by the standard methods used at our hospital. The stored serum samples were used for analyses of hs-CRP, tumour necrosis factor, IL-6, IL-10, monocyte chemoattractant protein-1, IL-8, P-selectin, E-selectin and s-ICAM1 by specific ELISA kits (Endogen, Woburn, Massachusetts, USA).

Statistical analysis

Data are expressed as the mean±SD. A paired Student *t* test was used to compare data before and after each treatment. Pearson product-moment correlation was performed to compare the changes of FMD and those of LDL-C or the indices for inflammatory cytokines and chemokines. Differences or statistical values were considered significant at *p*<0.05. Analyses were conducted using SPSS V.11 (SPSS, Inc, Chicago, Illinois, USA).

RESULTS

Patient profiles

Clinical characteristics of patients are summarised in table 1. Study patients had relatively high risks for atherosclerosis in addition to hypercholesterolaemia. About 45% of study patients had coronary artery disease, 62% had hypertension and one-fifth of patients were diabetic. One-third of the patients who had both hypercholesterolaemia and coronary artery disease had been prescribed statins other than pitavastatin. However, their

Table 2 Effect of pitavastatin on FMD and nitroglycerin-mediated vasodilatation in the brachial artery

| | Before treatment | After treatment |
|---|------------------|-----------------|
| Systolic BP (mm Hg) | 147±15 | 146±16 |
| Diastolic BP (mm Hg) | 80±8 | 82±9 |
| Heart rate (beats/min) | 67±11 | 66±12 |
| Brachial artery diameter at baseline (mm) | 4.30±0.45 | 4.37±0.43 |
| FMD (%) | 3.22±1.72 | 3.97±2.18* |
| NMD (%) | 9.92±5.37 | 10.32±5.77 |

Data are expressed as mean±SD.

*p<0.05 versus before treatment.

BP, blood pressure; FMD, flow-mediated vasodilatation; NMD, nitroglycerin-mediated vasodilatation.

LDL-C levels were ≥ 100 mg/dL, which met the inclusion criteria to receive pitavastatin in this study. More than 60% of the patients had been receiving antiplatelet agents and about 30–40% of patients were receiving antihypertensive drugs (table 1). As a result, the mean FMD, which reflects brachial artery endothelial dysfunction at baseline, was 3.22%. Almost all patients had abnormal baseline FMD values (<6%, which is the normal cut-off value of our laboratory)⁸ (table 2, figure 1A,B).

Effect of pitavastatin on brachial artery endothelial function

A 4-week course of pitavastatin resulted in a significant increase in FMD (table 2). In 55 of 65 patients, FMD increased in response to pitavastatin therapy (figure 1A,B), despite no significant change in NMD. Pitavastatin treatment did not affect blood pressure, heart rate or brachial artery diameter. A previous study reported that a change in artery diameter is a very strong confounding factor when assessing FMD as a proxy for endothelial function.¹⁴

Changes in blood chemistries, inflammatory cytokines and chemokines in response to pitavastatin treatment

Pitavastatin treatment resulted in a significant decrease in LDL-C (–37%; from 124 to 78 mg/dL), a significant decrease in serum levels of total cholesterol, a significant decrease in TG levels and a non-statistically significant increase in HDL-C (table 3). Pitavastatin treatment did not result in any detectable changes in most ordinary parameters of blood chemistries (table 3).

hs-CRP was not affected by pitavastatin treatment (table 4). Among the changes in the indices of cytokines and chemokines, only levels of adhesion-related molecules (ie, E-selectin and s-ICAM1) significantly decreased in response to pitavastatin treatment (table 4, figures 2 and 3). No significant relationship was seen between either E-selectin or s-ICAM1 and FMD (figures 4 and 5). Additionally, no significant relationship was found between changes in FMD, E-selectin or s-ICAM1 and changes in LDL-C ($r = -0.12$, -0.13 and -0.16 , respectively, NS) in response to pitavastatin treatment.

DISCUSSION

This study showed that pitavastatin produced subacute improvements in endothelial function and decreases in chemokine levels. Furthermore, these beneficial effects were not directly related to the LDL-C-lowering effect of pitavastatin. A 4-week course of pitavastatin resulted in significant improvement in brachial artery FMD and lower plasma levels of E-selectin and s-ICAM1 but had no significant effects on the other plasma

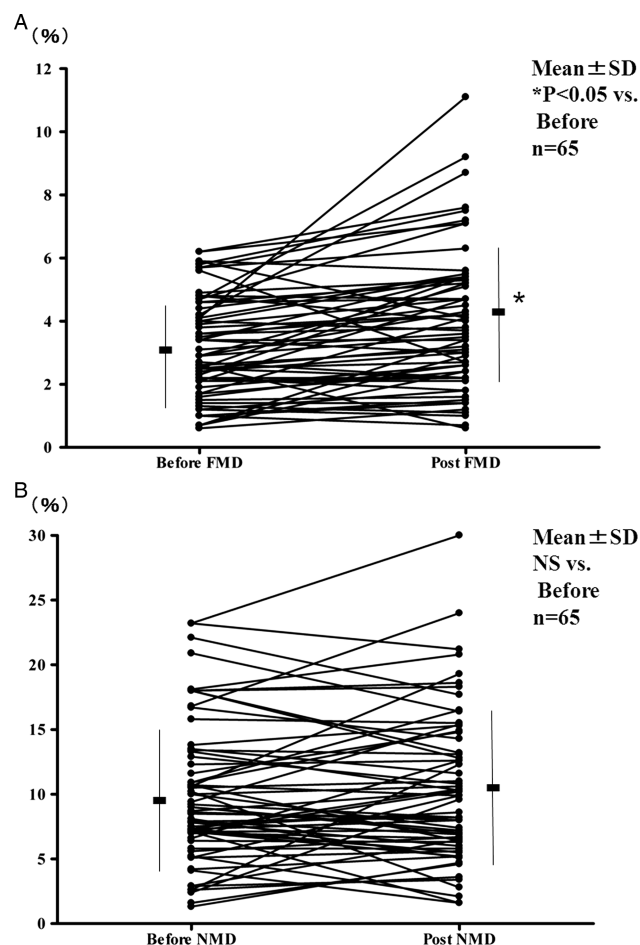


Figure 1 (A) Effect of pitavastatin on FMD. (B) Effect of pitavastatin on NMD. Changes in FMD and NMD in individual patients in response to a 4-week course of pitavastatin are shown. Fifty-five patients out of the total study population had an increase in FMD in response to pitavastatin treatment. *p<0.05 versus before pitavastatin treatment. FMD, flow-mediated vasodilatation; NMD, nitroglycerin-mediated vasodilatation.

Table 3 Effect of pitavastatin on lipid profiles and blood chemistry

| | Before treatment | After treatment |
|---------------------------|------------------|-----------------|
| Total cholesterol (mg/dL) | 202±34 | 156±24* |
| LDL-cholesterol (mg/dL) | 124±21 | 78±20* |
| HDL-cholesterol (mg/dL) | 48±15 | 49±14 |
| Triglyceride (mg/dL) | 196±150 | 149±73* |
| s-ALT (IU/L) | 26±10 | 26±9 |
| s-AST (IU/L) | 26±18 | 26±12 |
| BUN (mg/dL) | 15±4 | 15±4 |
| Cr (mg/dL) | 196±150 | 196±150 |
| FBS (mg/dL) | 0.88±0.33 | 0.97±0.31 |
| CPK (IU/L) | 78±32 | 73±25 |

Data are expressed as mean±SD.

*p<0.05 versus before treatment.

BUN, blood urea nitrogen; CPK, creatine phosphokinase; Cr, serum creatinine; FBS, fasting blood sugar; HDL, high-density lipoprotein; LDL, low-density lipoprotein; s-ALT, serum alanine aminotransferase; s-AST, serum aspartate aminotransferase.

Table 4 Effect of pitavastatin on hs-CRP, inflammatory cytokine and chemokine levels

| | Before treatment | Post treatment |
|--------------------|------------------|----------------|
| hs-CRP (mg/dL) | 0.0316±0.0512 | 0.0195±0.0204 |
| TNF (pg/mL) | 7.18±10.89 | 6.32±11.74 |
| IL-6 (pg/mL) | 8.76±25.26 | 8.87±26.64 |
| IL-10 (pg/mL) | 19.21±70.21 | 19.60±65.33 |
| MCP-1 (pg/mL) | 168±76 | 164±70 |
| IL-8 (pg/mL) | 50.60±60.92 | 47.65±63.33 |
| P-selectin (pg/mL) | 1788±587 | 1694±591 |
| E-selectin (pg/mL) | 51±27 | 46±29* |
| s-ICAM1 (pg/mL) | 276±86 | 258±91* |

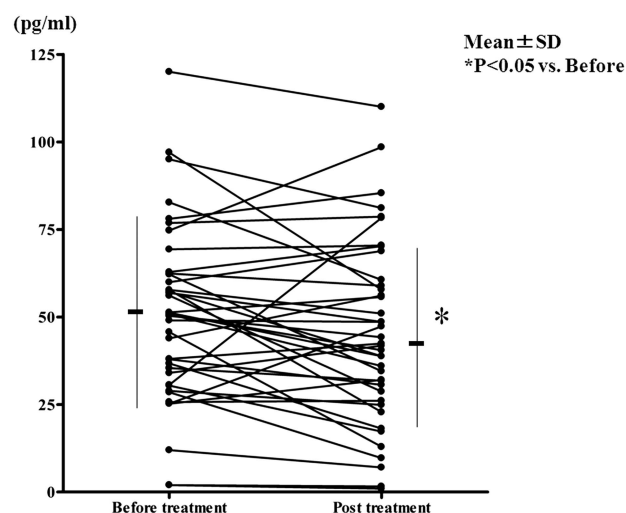
Data are expressed as mean±SD.

*p<0.05 versus before treatment.

hs-CRP, high-sensitive C-reactive protein; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; s-ICAM1, soluble intercellular cell adhesion molecule-1; TNF, tumour necrosis factor.

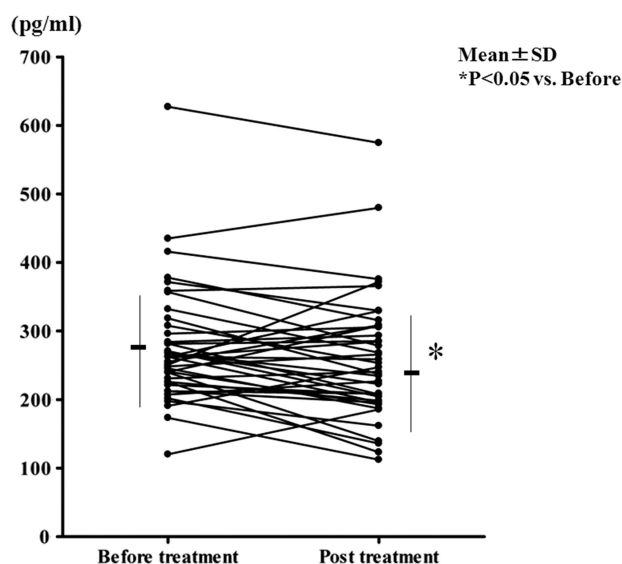
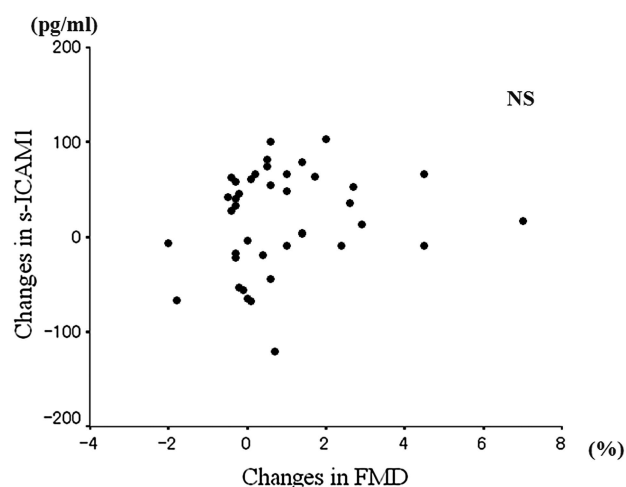
markers of cytokines and chemokines. Changes in FMD in response to pitavastatin treatment did not correlate with those of either E-selectin or s-ICAM1. In addition, the degree of change in LDL-C did not correlate with that of FMD or values of E-selectin and s-ICAM1.

This is the first study to simultaneously measure FMD and vascular adhesion molecules in order to characterise the subacute effects of pitavastatin in patients with hypercholesterolaemia and other atherosclerotic risk factors. These data suggest that pitavastatin may enhance outcomes in patients with acute coronary syndrome or ischaemic cerebral infarction. Previous reports demonstrated that the brachial artery FMD correlates with coronary artery endothelial function^{8 9 15} and that vascular adhesion molecules play an important role in the progression of atherosclerosis and the destabilisation of atherosclerotic plaque.^{6 16} Thus, the therapeutic effect of a 4-week course of pitavastatin, as shown in this study, might have an impact on clinical practice. Endothelial dysfunction combined with plaque destabilisation increases the

**Figure 3** Effect of pitavastatin on serum E-selectin levels. Changes in serum levels of E-selectin in individual patients in response to a 4-week course of pitavastatin are shown. *p<0.05 versus before pitavastatin treatment.

risk of cardiovascular events, such as acute coronary syndrome. The relatively quick action of pitavastatin treatment is another feature that might be particularly advantageous in clinical practice.

The efficacy of pitavastatin on endothelial function, cytokines and chemokines demonstrated in this study is consistent with observations from previous reports.^{17 18} In many reports on experimental^{19 20} and clinical populations, pitavastatin improved endothelial function through upregulated endothelial nitric oxide synthase activity. In addition, data from previous reports support the suggestion that pitavastatin treatment reduces the levels of cytokines and chemokines.^{5 21 22} The relatively quick pleiotropic action of pitavastatin seen in this study is also consistent with observations from a previous study, in which a 2-week course of pitavastatin resulted in improved FMD in patients with hypercholesterolaemia.^{21 23 24} Another report showed that a 4-week course of pitavastatin stabilised vulnerable carotid artery plaque in

**Figure 2** Effect of pitavastatin on serum s-ICAM1 levels. Changes in serum levels of s-ICAM1 in individual patients in response to a 4-week course of pitavastatin are shown. *p<0.05 versus before pitavastatin treatment. s-ICAM1, soluble intercellular cell adhesion molecule-1.**Figure 4** Relationship between changes in FMD and s-ICAM1 in response to pitavastatin treatment. The change in FMD in response to a 4-week course of pitavastatin did not significantly correlate with that of s-ICAM1. Data from each patient are plotted. FMD, flow-mediated vasodilatation; NS, not significant; s-ICAM1, soluble intercellular cell adhesion molecule-1.

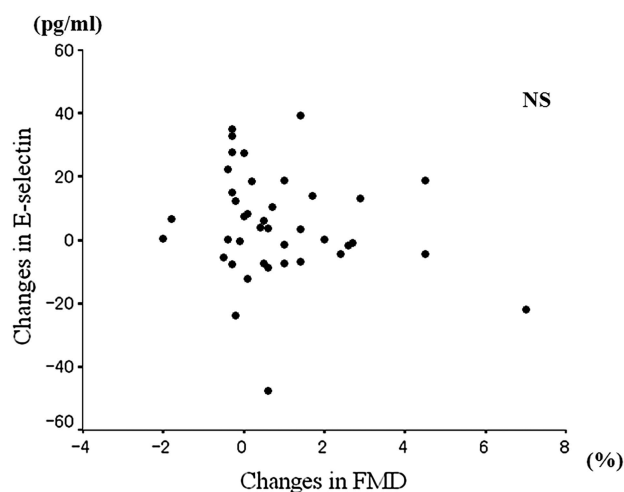


Figure 5 Relationship between changes in FMD and E-selectin in response to pitavastatin treatment. The change in FMD in response to a 4-week course of pitavastatin did not significantly correlate with that of E-selectin. Data from each patient are plotted. FMD, flow-mediated vasodilatation; NS, not significant.

patients with acute coronary syndrome and decreased the inflammatory biomarkers.²⁵ In these clinical studies,^{21–25} the results related to pleiotropic effects of pitavastatin were not directly associated with changes in LDL-C values, which is consistent with findings from our study.

This study has several limitations.

First, the number of the patients was small and the study was conducted in only two medical centres, including one academic medical school hospital. Thus, this study should be repeated with a multicentre randomised clinical trial design.

Second, this study lacks a control group. However, as mentioned earlier, since endothelial function and cytokine and chemokine levels were measured in the same patients at the same time, we believe that these results are valid.

Third, the mechanisms of each effect of pitavastatin were not investigated in this study. However, according to numerous previous experimental and clinical studies,^{5–26–29} the mechanisms of these effects were explained by the previously proposed anti-atherosclerotic pleiotropic effects. Pleiotropic effects include antiplatelet aggregation, anti-inflammation, inhibition of polynuclear monocyte migration and improvement of endothelial function. Endothelial function further includes the increased production of endothelium-derived substances such as nitric oxide, prostacyclin and endothelium-derived hyperpolarising factor.

Fourth, because the number of patients studied was small the absence of a significant effect of pitavastatin on inflammatory cytokines and the absence of a relationship between the pitavastatin efficacy on FMD and that on chemokine levels might be simply due to a lack of statistical powers. In particular, the lack of the latter relationship might show that pitavastatin has greater effect on endothelial dysfunction than on endothelial expression of adhesion molecules because statins have been reported to strongly increase vascular tone due to a decrease in nitric oxide³⁰ or production and proliferation of smooth muscle cells.^{31–32}

The pleiotropic effects of statins include anti-inflammatory and antioxidant actions.³⁰ Specifically, pitavastatin has been reported to have acute anti-inflammatory and anti-monocyte chemoattractant effects *in vitro*.³¹ In addition, lowering LDL-C might decrease sICAM1 and soluble endothelial leucocyte adhesion molecule-1.³² Lastly, the long-term effect of pitavastatin was not studied and would benefit from future investigation.

Large trials have already described the clinical efficacy of statins in patients with cardiovascular and/or atherosclerotic disorders.³³ The relatively new findings of the subacute effects of pitavastatin therapy provide useful information for the relatively common situation in which vulnerable patients, such as those with acute coronary syndrome, are treated in clinical settings. However, the best time to start pitavastatin for patients with acute coronary syndrome to achieve the best efficacy remains controversial. Our findings might promote the administration of statins, especially pitavastatin, in the very early phase of the treatment of acute coronary syndrome.

In conclusion, a 4-week course of pitavastatin improved endothelial function and reduced chemokine levels in patients with hypercholesterolaemia and other atherosclerotic risk factors. Pitavastatin may be a powerful drug, improving outcomes for patients with atherosclerotic disorders, but a large-scale randomised clinical trial is needed to confirm these conclusions.

Contributors HH: data measurement; YT, MI: manuscript review; MN: data collection and manuscript review; BT: organised and conducted study and wrote the manuscript.

Competing interests None.

Patient consent Obtained.

Ethics approval National Defense Medical College and Iruma Heart Hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

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