Clinical SCIENCE

www.clinsci.org

Clinical Science (2009) 116, 497–505 (Printed in Great Britain) doi:10.1042/CS20080241

comment

Effects of pravastatin on functional capacity in patients with chronic obstructive pulmonary disease and pulmonary hypertension

Tsung-Ming LEE*, Chien-Chang CHEN†, Hsiu-Nien SHEN‡ and Nen-Chung CHANG§

*Cardiology Section, Department of Medicine, Taipei Medical University and Chi-Mei Medical Center, Tainan, Taiwan, †Cardiology Section, Department of Surgery, Chi-Mei Medical Center, Tainan, Taiwan, ‡Department of Intensive Care Medicine, Chi-Mei Medical Center, Tainan, Taiwan, and §Department of Medicine, Cardiology Section, Taipei Medical University and Hospital, Taipei, Taiwan

ABSTRACT

PH (pulmonary hypertension) often complicates the disease course of patients with COPD (chronic obstructive pulmonary disease) and is an indication of a worse prognosis. In the present study, we assessed whether pravastatin administration was effective in improving PH and exercise capacity in COPD patients with PH, and whether the pulmonary protection was mediated by inhibiting ET-1 (endothelin-1) production. In a double-blind parallel design, 53 COPD patients with PH were randomly assigned to receive either placebo or pravastatin (40 mg/day) over a period of 6 months at a medical centre. Baseline characteristics were similar in both groups. The exercise time remained stable throughout the study in the placebo group. After 6 months, the exercise time significantly increased 52% from 660 ± 352 to 1006 ± 316 s ($P < 0.0001$) in pravastatin-treated patients. With pravastatin, echocardiographically derived systolic PAP (pulmonary artery pressure) decreased significantly from 47 ± 8 to 40 ± 6 mmHg. There was significant improvement in the Borg dyspnoea score after administering pravastatin. Despite unchanged plasma ET-1 levels throughout the study, urinary excretion of the peptide was decreased and significantly correlated with an improvement in exercise time in pravastatin-treated patients ($r = -0.47$, $P = 0.01$). In conclusion, pravastatin significantly improved exercise tolerance, and decreased PH and dyspnoea during exercise in COPD patients with PH, probably by inhibiting ET-1 synthesis.

INTRODUCTION

PH (pulmonary hypertension) often complicates the disease course of patients with COPD (chronic obstructive pulmonary disease), and is an indication of a worse prognosis [1]. An increase in the mean pressure of 10 mmHg was associated with a greater than 4-fold increase in mortality [2]. Attempts to use vasodilator therapy to reverse PH in COPD patients have included the calcium channel blockers dipyridamole and hydralazine [3]. These drugs lower both pulmonary and systemic vascular resistance causing systemic hypotension. Therefore the response is variable with considerable morbidity and mortality despite therapy [3]. Clearly, there is an urgent need for new therapies.

Key words: chronic obstructive pulmonary disease (COPD), dyspnoea, endothelin-1 (ET-1), exercise capacity, pulmonary hypertension, statin.

Abbreviations: BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; *E*, early diastolic peak filling velocity; ET, endothelin; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Pa_{O_2}, arterial partial pressure of oxygen; PAP, pulmonary artery pressure; PH, pulmonary hypertension; TDI, tissue Doppler imaging; *E*′, TDI-derived peak early diastolic filling velocity.

Correspondence: Professor Nen-Chung Chang (email ncchang@tmu.edu.tw).

ET (endothelin)-1, a potent pulmonary vasoconstrictor, has been shown to be involved in COPD patients with PH [4]. Immunohistochemical analysis of lung tissue demonstrated increased levels of ET-1 protein and mRNA predominantly in endothelial cells of vessels of patients with PH secondary to COPD [5]. Furthermore, there is a significant correlation between pulmonary ET-1 concentration and pulmonary vascular resistance [6]. This evidence suggests that increased local production of ET-1 may contribute to the vascular abnormalities of PH. Statins appear to be potent drugs with a variety of pleiotropic effects including vasculoprotective activity [7]. We have demonstrated previously that statins can reduce the synthesis of ET-1 at the transcriptional level [8]; however, whether pravastatin can improve PH in COPD patients via the attenuation of ET-1 levels remains unclear. Although a previous study in rats has shown that statins attenuated PH induced by chronic cigarette smoking [9], there are no clinical studies available investigating the effect of statins on COPD with PH. Given the high coincidence of coronary artery disease and COPD [10], this group may represent a segment of the population for whom statins are prescribed. Therefore the aim of the present study was to investigate whether pravastatin administration was effective in improving PH and exercise capacity when given to patients with stable COPD, and whether pulmonary protection was mediated by inhibiting ET-1 production. The primary end point was the change in exercise time on a treadmill test using the Naughton protocol. Secondary end points were changes in cardiac index and systolic PAP (pulmonary artery pressure), as assessed by Doppler echocardiography, a pulmonary function test, and the Borg dyspnoea score during exercise test.

MATERIALS AND METHODS

Patients

COPD patients of either gender from a tertiary care medical centre in whom a routine echocardiogram showed PH were invited to participate in the study, provided conditions were stable for at least 3 months and that they were between 40 and 80 years of age. The criteria for diagnosis of COPD was based on American Thoracic Society standards [11], with an FEV_1 (forced expiratory volume in 1 s) $< 80\%$ of the predicted values, and an FEV_1/FVC (forced vital capacity) ratio $< 70\%$. None of the patients had suffered from acute exacerbations of COPD, any active infection, or renal disease (serum creatinine concentration $\geqslant 1.5$ mg/dl or 133 μmol/l) for at least 3 months before entering the study. Subjects with one or more of the following conditions were excluded from the study: asthma, periodic wheezing, pulmonary embolism, a history of perennial allergic rhinitis and an improvement in $FEV_1 > 15\%$ from the predicted values after inhalation of a bronchodilator. None of the patients had received cholesterol-lowering agents before they were enrolled in the study. In order to evaluate the add-on effect of pravastatin, all medication for COPD was kept constant throughout the study. Other concomitant medication considered necessary for the well-being of each patient could be given at the investigator's discretion. The patients were not given specific risk-factor-modification instructions, such as exercise training or smoking cessation. Each patient received a randomized code number, according to which the study assistant supplied the study drug. Special drug packaging was used to maintain the blindness of the treatment. A sealed envelope, with information on the treatment allocated, was kept in the clinical file of each patient. At recruitment, the daily respiratory symptoms of the patients, smoking history and drug history were recorded. Height (± 0.5 cm) and weight (± 0.1 kg) were measured and the BMI (body mass index) was calculated (weight/height^2).

The study protocol was approved by ChiMei Institutional Ethics Committee (No. IRB9406-002), and all subjects provided informed written consent before participation.

After a run-in period of 2 weeks, during which the entry criteria were evaluated, COPD patients were randomized to receive either 40 mg of pravastatin or placebo for 6 months. All patients were assessed at the outpatient clinic every 4 weeks. At 6 months of therapy, patients were re-evaluated with a physical examination, pulmonary function test, echocardiogram, blood test and exercise test with a symptom score. The patients were advised not to use β_2-agonists and to avoid strenuous activity for 6 h before the assessments. The patients were also instructed not to smoke for 1 h before the clinic visit, and smoking was not allowed during the visits. Tolerability was assessed by using spontaneously reported adverse events at each visit.

Pulmonary function tests

Pulmonary function indices at baseline and at the end of the study were performed according to American Thoracic Society standards [11]. We used an FEV_1/FVC ratio of < 0.70 to define airflow obstruction.

Exercise testing

To assess the functional capacity more objectively, we performed a symptom-limited Naughton exercise stress test at baseline and 6 months. Exercise time was monitored on a treadmill (Centra of Marquette Medical Systems) using the Naughton protocol. Exercise was discontinued when the imposed workload could not be maintained. At peak exercise, a rating of dyspnoea using the Borg scale was obtained. The Borg scale is a well-validated scoring

system (on a 0–10 point scale) to gauge the perceived effort of exertion and the degree of fatigue experienced (where 0 = nothing at all, and 10 = maximum) [12].

Echocardiography

Echocardiography was performed using conventional clinical echocardiographic equipment (Hewlett-Packard 5500 model) with a 2.5 MHz transducer. Tricuspid regurgitation flow was identified by colour flow Doppler techniques, and the maximal jet velocity was recorded from the parasternal or apical window with the continuous-wave Doppler echocardiographic probe. Systolic PAP was calculated using the modified Bernoulli equation: systolic PAP = 4 × (tricuspid jet velocity)^2 + estimated right atrial pressure [13]. Estimated right atrial pressure [14] was defined to be 5, 10 and 15 mmHg based on the variation in the size of the inferior vena cava with inspiration as follows: complete collapse, 5 mmHg; partial collapse, 10 mmHg; and no collapse, 15 mmHg. PH was defined as a systolic pulmonary pressure $\geqslant$35 mmHg [15]. Stroke volume (litre per beat/min) was calculated as described previously [16] as follows: velocity time integral (cm) × cross-sectional area (cm^2)/1000, where velocity time integral was obtained in the left ventricular outlet tract and the cross-sectional area was averaged over three parasternal long-axis frames frozen in early systole from the left ventricular outlet tract. The cardiac index was computed as cardiac output/body surface area.

To evaluate left ventricular preload, we measured mitral annulus velocity by TDI (tissue Doppler imaging), as described previously [17]. Sample volume was located at the septal side of the mitral annulus and E' (TDI-derived peak early diastolic filling velocity) was obtained. The leading edge of the transmitral Doppler flow pattern was traced to derive E (early diastolic peak filling velocity). All measurements were averaged over five cycles. The E/E' ratio was used as preload conditions. The patient, clinical investigator, echocardiographer and the person supervising the exercise were all blinded to the patient's treatment regimen.

Analysis of blood and urinary samples

Plasma from a peripheral vein and 24-h urinary samples for ET-1 measurements were collected on the same day and extracted as described previously [18]. Samples were immediately centrifuged at 3000 *g* for 10 min, and the samples were stored at −70 °C until further analysis. ET-1 was measured by immunoassay (R&D Systems). Results are expressed as pg/ml for plasma and ng/g of urinary creatinine for urine. Plasma concentrations of total cholesterol, HDL (high-density lipoprotein)-cholesterol and triacylglycerols (triglycerides) were measured by enzymatic methods, as described previously [19]. LDL (low-density lipoprotein)-cholesterol was calculated using the Friedewald equation.

Statistics

All statistical analyses were performed using Excel software (Microsoft) loaded with SPSS. Continuous variables are expressed as means ± S.D. The primary end point of the study was a change in treadmill time from baseline to the 6-month visit. Secondary end points included changes in the pulmonary function test, pulmonary pressure and dyspnoea score from baseline to the 6-month visit. The sample size computation for the normal control subjects was based on a power calculation using a two-sided Student's t test at $\alpha = 0.05$ and $\beta = 0.20$ (power = 0.80). A group of at least 16 COPD patients per treatment group was required to detect an expected difference in exercise time of at least 200 s between placebo- and pravastatin-treated patients. The differences in continuous parameters between groups were compared by unpaired Student's t tests. For the categorical parameters, the differences were compared using χ^2 test or Fisher exact test if $n < 5$. Relationships between the changes were determined using Spearman's correlation and multiple linear regression analysis. P values < 0.05 were considered statistically significant.

RESULTS

Of the 65 patients enrolled in the present study, 12 patients had incomplete data at the end of the study (Figure 1). Thus there were a total of 53 patients available for evaluation (26 in the placebo group and 27 in the pravastatin group). Table 1 shows the baseline and demographic characteristics of the patients in each group. Pravastatin was very well-tolerated by all patients, and none had any significant subjective side effects, such as abnormal levels of liver and muscle enzymes. Patient compliance with the treatment was confirmed by the significant effects on blood lipids (Table 2). Standard COPD therapy was similar in the two groups. There were no significant changes in systemic BP (blood pressure) after administering pravastatin.

Lipid profiles

The levels of total cholesterol, LDL-cholesterol, HDL-cholesterol and triacylglycerols at baseline and after 6 months are shown in Table 2. Compared with the placebo group, pravastatin administration caused significant reductions in plasma total cholesterol (14 %) and LDL-cholesterol (24 %) levels, as well as increased HDL-cholesterol (11 %) (all $P < 0.05$).

Primary outcome

All of the 53 patients performed the exercise test without chest pain or ST-segment depression. Changes in exercise

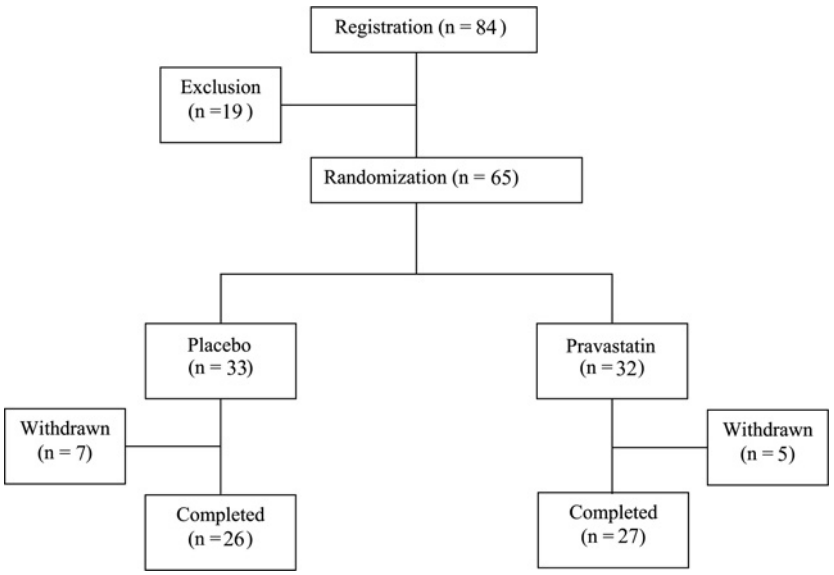

Figure 1 Randomization protocol of the patients enrolled in the present study

For exclusion criteria, see text. With regard to withdrawn patients, in the pravastatin group, two patients withdrew consent, three were lost to follow-up and two discontinued treatment. In the placebo group, three patients withdrew consent and two were lost to follow-up.

Table 1 Clinical characteristics of the patients at baseline

Values are means ± S.D. No significant differences were observed between placebo- and pravastatin-treated subjects.

Parameter	Pravastatin	Placebo
n	27	26
Gender (*n*) (male/female)	20/7	19/7
Age (years)	71 ± 8	72 ± 6
Current smoker at study entry (*n*)	22 (81 %)	21 (81 %)
BMI (kg/m^2)	22 ± 2	23 ± 1
Medication		
Steroid-dependent (*n*)	16 (59 %)	14 (54 %)
Theophylline (*n*)	25 (93 %)	26 (96 %)
β_2-Adrenoreceptor agonist (*n*)	20 (74 %)	21 (81 %)
Anticholinergics (*n*)	10 (37 %)	8 (31 %)
Nocturnal oxygen supplementation (*n*)	1 (4 %)	1 (4 %)

time are shown in Table 3. The exercise time did not differ between the two groups at baseline, and the exercise time remained stable throughout the study in the placebo group. In pravastatin-treated patients, the exercise time increased significantly 52 % (from 660 ± 352 to 1006 ± 316 s; $P < 0.0001$) compared with baseline values. Target heart rate was significantly increased in the pravastatin-treated patients.

Secondary outcomes

After 6 months of therapy, there were significant differences in dyspnoea scores between the two groups (Table 3). The patients treated with pravastatin experienced a lower degree of dyspnoea after exercise compared with those receiving the placebo.

In the pravastatin-treated group, systolic PAP decreased significantly from 47 ± 8 mmHg at baseline to 40 ± 6 mmHg at the end of the study (Table 3). The cardiac index remained stable throughout the study.

The patients in both groups did not differ in terms of pulmonary function parameters (Table 3), with no significant differences in FEV_1, total lung capacity or inspiratory capacity before and after 6 months of treatment.

ET-1 levels

Baseline urinary ET-1 levels were similar in the two groups (Table 2 and Figure 2). Urinary ET-1 levels were significantly reduced in pravastatin-treated patients, whereas plasma ET-1 levels remained stable throughout the study.

Correlation analysis

The linear regression models in the pravastatin-treated group showed that changes in urinary ET-1 correlated with changes in exercise time ($r = -0.47$, $P = 0.01$; Figure 3). Changes in total cholesterol, LDL-cholesterol, HDL-cholesterol or triacylglycerols were not predictors of a change in exercise time ($P = 0.47$, 0.94, 0.69 and 0.35 respectively). These results suggests a non-lipid effect of pravastatin on exercise time. Additionally, no significant correlations were observed between changes in exercise

Table 2 Haemodynamics, biochemistry and haemoglobin at baseline and at follow-up after 6 months of therapy

Values are means ± S.D. *$P < 0.05$ compared with baseline; †$P < 0.05$ compared with pravastatin-treated patients at follow-up.

	Pravastatin ($n = 27$)		Placebo ($n = 26$)	
Parameter	Baseline	Follow-up	Baseline	Follow-up
Haemodynamics				
Systolic BP (mmHg)	133 ± 16	130 ± 18	134 ± 15	132 ± 14
Diastolic BP (mmHg)	76 ± 10	79 ± 8	75 ± 9	79 ± 8
Pulse pressure (mmHg)	56 ± 14	51 ± 16	59 ± 13	53 ± 15
Heart rate (beats/min)	86 ± 14	85 ± 10	86 ± 11	88 ± 8
Biochemistry				
Total cholesterol (mg/dl)	240 ± 43	206 ± 42*	245 ± 39	248 ± 27†
HDL-cholesterol (mg/dl)	65 ± 15	72 ± 19*	61 ± 13	64 ± 10†
LDL-cholesterol (mg/dl)	145 ± 46	110 ± 42*	148 ± 50	145 ± 32†
Triacylglycerols (mg/dl)	146 ± 70	118 ± 52*	180 ± 66	197 ± 62†
Plasma ET-1 (pg/ml)	2.03 ± 1.18	1.72 ± 0.80	2.15 ± 0.94	2.23 ± 0.92
Urinary ET-1 (ng/g of urinary creatinine)	32.6 ± 9.7	27.9 ± 10.1*	33.0 ± 7.8	33.1 ± 9.1†
Haemoglobin (g/dl)	14.4 ± 1.3	14.3 ± 1.2	14.8 ± 1.4	14.5 ± 1.2

Table 3 Comparison of efficacy of pravastatin with placebo at baseline and at follow-up after 6 months of therapy

Values are means ± S.D. *$P < 0.05$ compared with baseline; †$P < 0.05$ compared with pravastatin-treated patients at follow-up. IC, inspiratory capacity; TLC, total lung capacity.

	Pravastatin ($n = 27$)		Placebo ($n = 26$)	
Parameter	Baseline	Follow-up	Baseline	Follow-up
Treadmill test				
Exercise time (s)	660 ± 352	1006 ± 316*	653 ± 274	629 ± 181†
Target heart rate (%)	74 ± 10	83 ± 9*	77 ± 10	77 ± 12
Echocardiogram				
Cardiac index (l/m^2)	4.09 ± 0.49	4.23 ± 0.33	4.33 ± 0.55	4.26 ± 0.38
Systolic PAP (mmHg)	47 ± 8	40 ± 6*	47 ± 7	46 ± 7†
E/E'	10.6 ± 2.5	9.8 ± 2.6	10.2 ± 2.9	9.2 ± 2.1
Pulmonary function test				
FEV_1 (%)	55.9 ± 21.0	60.5 ± 20.4	57.4 ± 12.5	57.3 ± 13.0
FEV_1/FVC (%)	55.5 ± 10.8	58.5 ± 13.1	55.1 ± 8.6	54.5 ± 8.5
TLC (litres)	4.96 ± 1.29	4.87 ± 1.16	5.00 ± 0.85	4.91 ± 1.27
IC (litres)	1.26 ± 0.60	1.32 ± 0.72	1.10 ± 0.78	1.21 ± 0.54
Borg dyspnoea score	6.7 ± 1.0	3.86 ± 0.7*	6.9 ± 0.9	6.8 ± 1.2†

time and haemodynamics (systolic BP, diastolic BP and mean BP) (results not shown).

DISCUSSION

To our knowledge, this is the first randomized controlled trial to demonstrate that, in PH due to COPD, treatment for 6 months with pravastatin is associated with a significant improvement in exercise tolerance together with pulmonary haemodynamics, quality of life and chemical markers, independent of a lipid profile change and systemic BP reduction. Because of the significant correlation between the changes in exercise time and urinary ET-1 levels in patients treated with pravastatin, it is possible that the mechanism involved could be via the direct inhibition of ET-1 synthesis. These findings suggest that COPD patients with PH may not only benefit from a reduction in vascular events with pravastatin, but also have an improvement in functional capacity.

Our conclusions are supported by three lines of evidence. First pravastatin improved the primary outcome (exercise capacity) in patients already treated with standard therapy. To our knowledge, there are no other studies addressing the effect of statins in addition to standard therapy on exercise tolerance in stable COPD

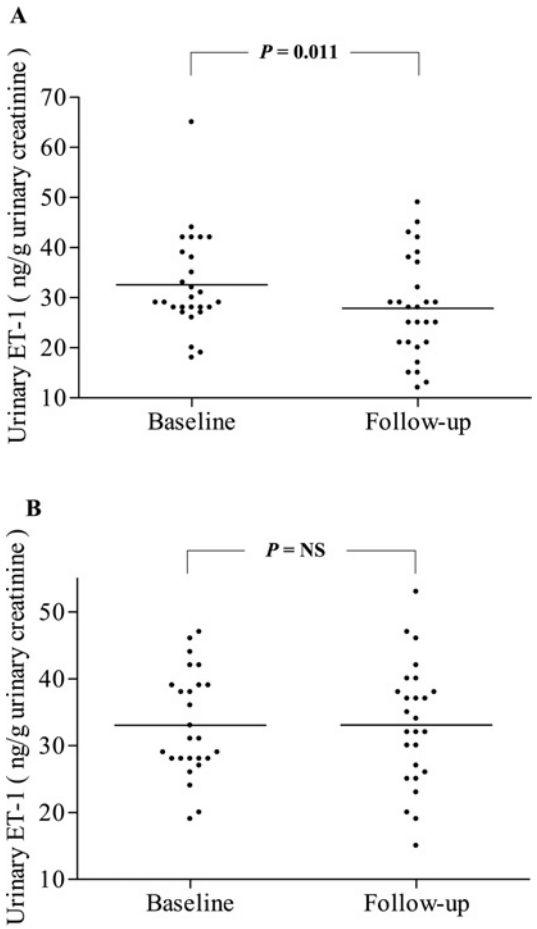

Figure 2 Distribution of urinary ET-1 at baseline and during follow-up in pravastatin- (A) and placebo- (B) treated groups

Horizontal lines represent median urinary ET-1. NS, not significant.

patients with PH. The addition of pravastatin on the background of standard therapy led to a further striking improvement in exercise tolerance. Thus it is of great importance to consider adjunctive therapy to improve exercise tolerance. Secondly, pravastatin improved secondary outcomes, including PH and dyspnoea after exercise. PH may result from increased pulmonary venous pressure, enhanced resistance, elevated cardiac output or a combination of these. There were similar left ventricular diastolic pressure, as assessed by the E/E' ratio, and cardiac output in patients treated with pravastatin at baseline and during follow-up. Therefore a decrease in pulmonary vascular resistance may account for most of the decrease in PH. It should be noted that, despite the haemodynamic improvement after pravastatin administration, in the majority of the patients pulmonary pressure values recorded in the follow-up study did not return to normal levels. Thirdly, because of the significant correlation between changes in exercise time and urinary ET-1 levels, it is possible that the mechanism involved could be related to the inhibition of renal ET-1 synthesis by pravastatin, denoting the reversibility of ET-1 after drug administration. However, our present study was cross-sectional and, therefore, we cannot comment on a causal relationship and this needs to be assessed in longitudinal studies. Nevertheless, the results of the present study provide a foundation for the use of pravastatin in improving exercise tolerance by inhibiting renal ET-1 formation.

A variety of mechanisms have been suggested to explain the impaired exercise tolerance that ensues in COPD patients, including the role of ET-1. ET-1 is involved in the inhibition of both calcium-activated and ATP-dependent potassium channels, contributing to the hypoxic response of pulmonary vascular cells [20,21]. In the present study, although pravastatin did not reduce plasma ET-1 levels, renal ET-1 production, as assessed by urinary ET-1 excretion, was significantly decreased, implying the importance of local ET-1 effects. Urinary and plasma ET-1 are produced by two distinct functional systems, each of which is regulated by its own control mechanisms. Because plasma ET-1 is produced by a large variety of normal cell types, including endothelial, tracheal, bronchial and alveolar epithelial cells, and by tissue macrophages, plasma ET-1 levels may be affected in pulmonary or non-pulmonary diseases. However, urinary ET-1 appears to be mainly derived from the kidney [22]. Urinary ET-1 correlated significantly with overall ET-1 endogenous production [23], and increased urine ET excretion has been reported in COPD [24]. Previous studies have shown that 24-h urinary excretion detects changes in endogenous ET production more sensitively than single blood measurements [25]. Thus circulating venous ET concentrations may not be an accurate index of either ET release or its local activity [26].

In addition to the reduction in ET-1 levels, pravastatin may have altered other mechanisms involved in lung protection. On the basis of the correlation shown in Figure 3, urinary ET-1 levels only explain 22 % of the variation in exercise time. Therefore other potential mechanisms need to be studied, such as antioxidation [27] and vasodilation [28]. With regard to antioxidation, we have shown previously that statins attenuated free radical generation [27]. Given that oxidative stress is increased in COPD patients and that free radicals contribute to its pathophysiology [29], this mechanism could contribute to the effects of pravastatin on pulmonary vascular remodelling. Antioxidant treatment offers a potential new therapeutic approach to the treatment of COPD in animal models [28]. With regard to vasodilation, statins may have direct vasodilatory properties. One of the downstream effectors of Rho-A is Rho-associated kinase, which leads to increased phosphorylation of myosin light chains [29], an important determinant of vascular smooth muscle tone. Statins acting as Rho-associated-kinase inhibitors effectively abolished hypoxic

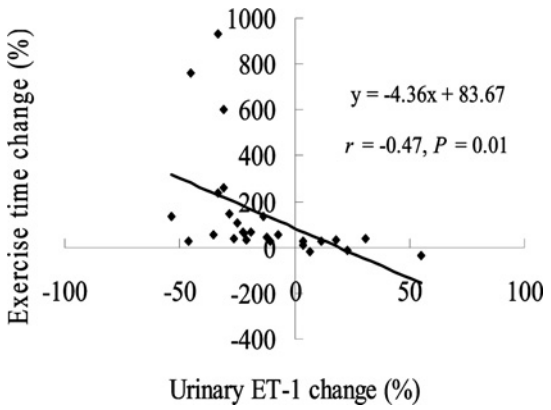

Figure 3 Correlation between the change in exercise time and the change in urinary ET-1 in pravastatin-treated patients

A greater increase in urinary ET-1 release was associated with a decrease in exercise time. The correlation given in the Figure is for all of the pravastatin-treated patients (i.e. $n = 27$). With the three outliers excluded, the correlation was $r = -0.60$, $P = 0.002$ ($n = 24$) (results not shown).

pulmonary vasoconstriction in isolated perfused rat lungs [30].

There are some limitations of the present study. First, this was a short-term study that was not designed to comment on survival advantage. The duration of the study may be considered too short, but it was associated with haemodynamic and clinical benefit. Given a correlation between dyspnoea, exercise capacity and mortality in COPD [31], it is not unrealistic to anticipate in our present population that there would be a beneficial effect on clinical events. Secondly, we did not measure PaO_2 (arterial partial pressure of oxygen) in the present study. Hypoxia alone is not the primary driver of PH, and PaO_2 has not been identified as an independent predictor of mean PAP [32]. Clinical and animal experimental findings have shown that PH probably occurs as a result of the direct effect of mediators that control vasoconstriction, vasodilatation and vascular cell proliferation, ultimately leading to aberrant vascular remodelling and aberrant vascular physiology. Thirdly, there are controversies regarding the use of different statins for cardiovascular effects. There are many kinds of statins used clinically which have differences in pharmacological lipophilicity, structure and solubility. Thus, although pravastatin, a hydrophilic statin, has been shown to exert beneficial effects in COPD patients, the effects cannot necessarily be extrapolated to lipophilic statins. Previous studies have shown that pravastatin, but not simvastatin, reduced the progression of PH [33]. Thus this intermolecular difference within the class of statins deserves to be investigated further. Fourthly, an exercise test has been used to assess the effectiveness of the therapeutic intervention. Exercise functional capacity is a powerful independent predictor of all-cause and cardiovascular mortality [34]. Exercise capacity of COPD patients has been studied using walking tests, such as the 6- or 12-min walking test. These tests are dependent on motivation and encouragement, and are therefore difficult to standardize. Thus time-limited walking tests have been shown to be limited in detecting a clinically significant change in patients with non-advanced diseases [35]. The Naughton walking test used in the present study is externally paced and is less dependent on encouragement from the test leader. It is incremental, pushing the patient to a symptom-limited maximum performance. Thus the Naughton protocol may represent a more precise and reproducible exercise test, and previous studies have shown that the Naughton test appears to be a more sensitive measure in detecting changes in exercise capacity compared with the 6-min walking test in less sick patients with PH [36]. However, some elderly patients find treadmill assessments stressful or perform poorly due to restricting factors in more severe cardiovascular co-morbidities [37]. The use of the Naughton test can be problematic, as the test is terminated when the patient is unable to maintain the imposed workload. One alternative modality to treadmill walking is a shuttle walk test. In shuttle walk tests, patients walk back and forth at a pace that is controlled by audiotape bleeps. Walking speed can be increased incrementally, which gradually stresses the cardiorespiratory system to a symptom-limited maximum [38], potentially making it safer for patients with respiratory conditions. Previous studies have shown that the test–retest coefficient of variation in the walking distance for shuttle walks was better than that for the treadmill [39]. This might explain, in part, why there was a large variation in exercise time in response to pravastatin treatment in the present study. Shuttle walking could be considered as a complementary testing modality. Finally, patients in the placebo group also received active treatment for COPD. In the present study, we investigated the potential effects of pravastatin plus standard treatment compared with placebo plus standard treatment, which could have reduced the potential effects of pravastatin, rather pravastatin compared with placebo in the absence of standard COPD treatment. Because an active treatment washout period was believed to be unethical, the study including medicated patients reflects the practical clinical setting.

Conclusions

This prospective randomized controlled study has shown that pravastatin administration to COPD patients with PH was associated with an amelioration in exercise limitation, PH and dyspnoea and was mediated by reducing urinary ET-1 levels. The improvement was independent of BP and lipid changes. Thus pravastatin may be a useful adjunct to currently available therapies for PH and may be of particular importance for the

future design of combination drugs. Further larger studies are needed to determine the effect of long-term treatment of pravastatin on mortality in patients with COPD.

ACKNOWLEDGEMENTS

Pravastatin was, in part, a generous gift from Sankyo Co. Ltd (Tokyo, Japan). Special thanks are given to the participants for their co-operation and commitment to the trial.

FUNDING

This work was supported by the Chi-Mei Medical Center [grant numbers CMFHT9501; CMFHR9702; 97CM-TMU01]; and by the Department of Health, Taiwan, Republic of China [DOH97-TD-I-111-TM001].

REFERENCES

1 Incalzi, R. A., Fuso, L., De Rosa, M. et al. (1999) Electrocardiographic signs of chronic cor pulmonale: a negative prognostic finding in chronic obstructive pulmonary disease. Circulation **99**, 1600–1605
2 Cooper, R., Ghali, J., Simmons, B. E. and Castaner, A. (1991) Elevated pulmonary artery pressure. An independent predictor of mortality. Chest **99**, 112–120
3 Weitzenblum, E., Kessler, R., Oswald, M. and Fraisse, P. (1994) Medical treatment of pulmonary hypertension in chronic lung disease. Eur. Respir. J. **7**, 148–152
4 Wright, J. L., Levy, R. D. and Churg, A. (2005) Pulmonary hypertension in chronic obstructive pulmonary disease: current theories of pathogenesis and their implications for treatment. Thorax **60**, 605–609
5 Giaid, A., Yanagisawa, M., Langleben, D. et al. (1993) Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N. Engl. J. Med. **328**, 1732–1739
6 Cacoub, P., Dorent, R., Nataf, P. et al. (1997) Endothelin-1 in the lungs of patients with pulmonary hypertension. Cardiovasc. Res. **33**, 196–200
7 Ridker, P. M., Rifai, N., Pfeffer, M. A. et al. (1998) Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Circulation **98**, 839–844
8 Lee, T. M., Chou, T. F. and Tsai, C. H. (2003) Effect of pravastatin on cardiomyocyte hypertrophy and ventricular vulnerability in normolipidemic rats after myocardial infarction. J. Mol. Cell. Cardiol. **35**, 1449–1459
9 Lee, J. H., Lee, D. S., Kim, E. K. et al. (2005) Simvastatin inhibits cigarette smoking-induced emphysema and pulmonary hypertension in rat lungs. Am. J. Respir. Crit. Care Med. **172**, 987–993
10 Sin, D. D. and Man, S. F. (2003) Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation **107**, 1514–1519
11 Pauwels, R. A., Buist, A. S., Calverley, P. M., Jenkins, C. R. and Hurd, S. S. (2001) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am. J. Respir. Crit. Care Med. **163**, 1256–1276
12 Wilson, R. C. and Jones, P. W. (1989) A comparison of the visual analogue scale and modified Borg scale for the measurement of dyspnea during exercise. Clin. Sci. **76**, 277–282
13 Berger, M., Haimowitz, A., Van Tosh, A., Berdoff, R. L. and Goldberg, E. (1985) Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. J. Am. Coll. Cardiol. **6**, 359–365
14 Bredikis, A. J. and Liebson, P. R. (1998) The echocardiogram in COPD: estimating right heart pressures. J. Respir. Dis. **19**, 191–198
15 Barst, R. J., McGoon, M., Torbicki, A. et al. (2004) Diagnosis and differential assessment of pulmonary arterial hypertension. J. Am. Coll. Cardiol. **43** (Suppl.), 40S–47S
16 Tsai, C. H., Lee, T. M., Wang, C. H. et al. (1997) Effects of dobutamine on aortic valve indexes in asymptomatic patients with bileaflet mechanical prostheses in the aortic valve position. Am. J. Cardiol. **79**, 1546–1549
17 Pan, N. H., Lee, T. M., Lin, M. S., Huang, C. L. and Chang, N. C. (2006) Association of gliclazide and left ventricular mass in type 2 diabetic patients. Diabetes Res. Clin. Pract. **74**, 121–128
18 Lee, T. M., Su, S. F. and Tsai, C. H. (2002) Effect of pravastatin on proteinuria in patients with well-controlled hypertension. Hypertension **40**, 67–73
19 Allain, C. C., Poon, L. S., Chan, C. S., Richmond, W. and Fu, P. C. (1974) Enzymatic determination of total serum cholesterol. Clin. Chem. **20**, 470–475
20 Peng, W., Michael, J. R., Hoidal, J. R., Karwande, S. V. and Farrukh, I. S. (1998) ET-1 modulates KCa-channel activity and arterial tension in normoxic and hypoxic human pulmonary vasculature. Am. J. Physiol. **275**, L729–L739
21 Sato, K., Morio, Y., Morris, K. G., Rodman, D. M. and McMurtry, I. F. (2000) Mechanism of hypoxic pulmonary vasoconstriction involves ET_A receptor-mediated inhibition of K_{ATP} channel. Am. J. Physiol. Lung Cell. Mol. Physiol. **278**, L432–L442
22 Kohan, D. E. (1993) Endothelins in the normal and diseased kidney. Am. J. Kidney Dis. **29**, 2–26
23 Battistini, B., D'Orleans-Juste, P. and Sirois, P. (1993) Endothelins: circulating plasma levels and presence in other biologic fluids. Lab. Invest. **68**, 600–627
24 Sofia, M., Mormile, M., Faraone, S. et al. (1994) Increased 24-hour endothelin-1 urinary excretion in patients with chronic obstructive pulmonary disease. Respiration **61**, 263–268
25 Berbinschi, A. and Ketelslegers, J. M. (1989) Endothelin in urine. Lancet **ii**, 46
26 Cody, R. J., Haas, G. J., Binkley, P. F., Capers, Q. and Kelley, R. (1992) Plasma endothelin correlates with the extent of pulmonary hypertension in patients with chronic congestive heart failure. Circulation **85**, 504–509
27 Lee, T. M., Chou, T. F. and Tsai, C. H. (2002) Association of pravastatin and left ventricular mass in hypercholesterolemic patients: role of 8-iso-prostaglandin $F_{2\alpha}$ formation. J. Cardiovasc. Pharmacol. **40**, 868–874
28 Santus, P., Sola, A., Carlucci, P. et al. (2005) Lipid peroxidation and 5-lipoxygenase activity in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **171**, 838–843
29 Repine, J. E., Bast, A. and Lankhorst, I. (1997) Oxidative stress in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **156**, 341–357
30 Robertson, T. P., Dipp, M., Ward, J. P., Aaronson, P. I. and Evans, A. M. (2000) Inhibition of sustained hypoxic vasoconstriction by Y-27632 in isolated intrapulmonary arteries and perfused lung of the rat. Br. J. Pharmacol. **131**, 5–9
31 Jeffery, T. K. and Morrell, N. W. (2002) Molecular and cellular basis of pulmonary vascular remodeling in pulmonary hypertension. Prog. Cardiovasc. Dis. **45**, 173–202
32 Scharf, S. M., Iqbal, M., Keller, C., Criner, G., Lee, S. and Fessler, H. E. (2002) Hemodynamic characterization of patients with severe emphysema. Am. J. Respir. Crit. Care Med. **166**, 314–322
33 Rakotoniaina, Z., Guerard, P., Lirussi, F. et al. (2006) The protective effect of HMG-CoA reductase inhibitors against monocrotaline-induced pulmonary hypertension in the rat might not be a class effect: comparison of pravastatin and atorvastatin. Naunyn Schmiedebergs Arch. Pharmacol. **374**, 195–206

34 Gulati, M., Black, H. R., Shaw, L. J. et al. (2005) The prognostic value of a nomogram for exercise capacity in women. N. Engl. J. Med. **353**, 468–475
35 Frost, A. E., Langleben, D., Oudiz, R. et al. (2005) The 6-min walk test (6MW) as an efficacy endpoint in pulmonary arterial hypertension clinical trials: demonstration of a ceiling effect. Vasc. Pharmacol. **43**, 36–39
36 Gomberg-Maitland, M., Huo, D., Benza, R. L., McLaughlin, V. V., Tapson, V. F. and Barst, R. J. (2007) Creation of a model comparing 6-minute walk test to metabolic equivalent in evaluating treatment effects in pulmonary arterial hypertension. J. Heart Lung Transplant. **26**, 732–738
37 Amirhamzeh, M. M., Chant, H. J., Rees, J. L., Hands, L. J., Powell, R. J. and Campbell, W. B. (1997) A comparative study of treadmill tests and heel raising exercise for peripheral arterial disease. Eur. J. Vasc. Endovasc. Surg. **13**, 301–305
38 Singh, S. J., Morgan, M. D., Scott, S., Walters, D. and Hardman, A. E. (1992) Development of a shuttle walking test of disability in patients with chronic airways obstruction. Thorax **47**, 1019–1024
39 Zwierska, I., Nawaz, S., Walker, R. D., Wood, R. F., Pockley, A. G. and Saxton, J. M. (2004) Treadmill versus shuttle walk tests of walking ability in intermittent claudication. Med. Sci. Sports Exercise **36**, 1835–1840

Received 18 June 2008/2 October 2008; accepted 3 October 2008
Published as Immediate Publication 3 October 2008, doi:10.1042/CS20080241