Comparative Efficacy and Safety of Pravastatin and Fenofibrate on Primary Hypercholesterolemia in A Taiwanese Community

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Summary

To assess both the efficacy and safety of pravastatin and fenofibrate in patients with primary hypercholesterolemia, we evaluated changes of the lipid profiles and side effects among patients with hypercholesterolemia in a community. The patients were randomized either to receive pravastatin 5 mg twice a day or fenofibrate 100 mg 3 times daily. Among the 69 patients recruited to the study, 55 patients (28 on pravastatin and 27 on fenofibrate) completed in this study. At the end of 3-month treatment, both groups showed significantly similar and comparable reduction in cholesterol (18.3% on pravastatin and 18.1% on fenofibrate) and low-density lipoprotein cholesterol (LDL-C) levels (28.2% and 29.8%, respectively). A concomitant noticeable increase in high-density lipoprotein cholesterol (HDL-C) level in both groups was also noted. In addition, there were apparent reductions in the serum level of triglyceride (TG) to a greater extent in those patients on fenofibrate than on pravastatin (30.2% vs. 21.5%, P＝0.034). However, a few minor drug-related side effects were noted in both groups. In conclusion, we believe that dosing 10 mg of pravastatin and 300 mg of fenofibrate daily would provide adequate lipid-lowering effect and excellent safety for patients with primary hypercholesterolemia in Taiwan.

Key words：Hypercholesterolemia, Efficacy, Safety, Pravastatin, Fenofibrate.

Introduction

Hypercholesterolemia has long been recognized as one of the major risk factors for coronary heart disease.[1-5] Lipid-lowering therapy has been widely used in both primary and secondary prevention studies to reduce the incidence of cardiovascular disease and cerebrovascular disease.[6-11] Controlling hypercholesterolemia has shown reduction in disease progression and induction in regression of atherosclerosis in both coronary arteries and carotid arteries.[12-15] In Taiwan, cerebrovascular disease and cardiovascular disease have been ranked as the second and fourth leading causes of death, respectively, for two decades.[16] The epidemiological studies in Taiwan have already revealed the increasing prevalence of hypercholesterolemia, from 5.5% (cholesterol ≥ 250 mg/dl) in 1974 [17] to 16.9% in 1991.[18]

The interaction between hypercholesterolemia and atherosclerosis is observing evidence in Taiwan. The Chin-Shan Community Cardiovascular (CCC) Study has been established to define the impact of classic and new emerging risk factors leading of cerebrovascular disease and cardiovascular disease in Taiwan and thereby to propose for effective medical strategies for the prevention of cerebrovascular disease and cardiovascular disease.[19-21] The CCC Study had included 3602 adults, age 35 and above, in a suburban community, approximately 35 kilometers from metropolitan Taipei since 1990. This study has well designed on a basis of biennial check-up with the response rate at 82.5%. Taking the advantage of well organization and high level of cooperative effort from the public, we chose those with primary hypercholesterolemia for comparative study. The clinical approach used has been to have patients with the diagnosis to be on a strict dietary therapy before any initiation of lipid-lowering agents. Only lipid-lowering medication, either pravastatin or fenofibrate, in this trial would follow those who fail the dietary therapy. We have decided to treat patients in this community in which they share with the similar living environment rather than the patients from hospital clinics whose environmental background are diversified and heterogeneous. This article documents the efficacy and safety of pravastatin and fenofibrate for patients with hypercholesterolemia after the failure of dietary therapy in the CCC Study cohort participants in 1994.

Pravastatin, a lipid-lowering agent, has a well-established profile of efficacy and safety.[9,11,14,15] It is a potent inhibitor of 3-hydroxyl-3-methylglutaryl coenzyme A reductase. Pravastatin works though its ability to inhibit 3-hydroxyl-3-methylglutaryl coenzyme A reductase, which catalyzes the conversion of hydroxymethyl glutarate to mevalonate, a rate-limiting step in the biosynthesis of cholesterol. Fenofibrate, a second-generation fibrate, is another important class of cholesterol-lowering drug, the efficacy and safety of which also have been documented well for Caucasian.[22,23] But, to the best of our knowledge, the efficacy and safety of these regimens have not been analyzed based on Chinese patients with hypercholesterolemia. It is important to conduct a well-designed strict quality controlled study for Chinese patients to assess the effectiveness and safety of these being widely prescribed drugs in Taiwan.

Patients and Methods

Patients：In the CCC Study cohort, 347 patients with cholesterol levels met the clinical trial inclusion criteria of American National Cholesterol Educational Program (NCEP) Adult Treatment Panel II had received a dietary education program (American Heart Association step I diet) from March to August 1994.[19] Three months after the dietary regimen control, 81 patients still showed higher serum lipid levels and then were advised to follow the NCEP guideline for hypolipidemic drug therapy.[24] Of the screened candidates for this study, twelve did not participate and a total of 69 patients enrolled in this intervention study. Informed consents were obtained before the study.

Inclusion criteria：Patients who were eligible have one of any of the following conditions：1.) LDL-C level is 190 mg/dl and above, 2.) LDL-C level in the range of 160 and 189 mg/dl associated with two or more cardiovascular risk factors, 3.) LDL-C level of 130 mg/dl or above with the concomitant cardiovascular disease or another atherosclerotic disease.[24]

Patients with hypothyroidism, poor-controlled diabetes mellitus, pancreatitis, cholestasis, nephrotic syndrome, renal or hepatic dysfunction, and women in pregnancy, lactation or with oral contraceptive uses were excluded from the trial. No enrollees had medical history of myocardial infarction, unstable angina pectoris, or stroke in recent 6 months. Patient with major operation in recent 6 months also was excluded. Previous use of other lipid-lowering drugs should be discontinued for at least 8 weeks prior to the enrollment.

Study group enrollment：Simple randomization study design with open-labeled controlled trial was adopted in this study. Sixty-nine subjects were randomized into two parallel treatment groups. 34 patients received fenofibrate (F group) 100 mg after meal three times daily and 35 patients received pravastatin (P group) 5 mg twice daily. Each patient received a weekly follow-up visit in Chin-Shan community health center by one cardiologist and the drug compliance and adverse reaction of medications were thoroughly examined and recorded.

Among 69 enrolled patients (intention-to-treat), 55 patients completed the trial and 14 patients were excluded due to

poor compliance or drug-related side effects. There are seven dropout cases in both groups. Of these dropout cases, 3 in P group and 4 in F group were ascribed to drug-related side effect and 4 in P group and 3 in F group were due to poor compliance.

Among 55 patients completed treatment course, 28 received pravastatin and 27 received fenofibrate. One week before the inclusion visit, blood samples of 9-12 hours overnight fasting for lipid determination were drawn from antecubital vein with patient in a seated position as baseline data. The final blood sample was drawn immediately after three months of treatment, to compare the efficacy of the drug treatment. Lipid profile assays were performed on the same day.

Lipid and lipoprotein assays：Serum levels of lipid profiles (cholesterol, LDL-C, HDL-C, TG, apolipoprotein (apo) A1, and B), uric acid, liver function profiles (aspartate transaminase, alanine transaminase, γ -glutamyl transpeptidase), and muscle enzyme (creatine phosphokinase) were analyzed in a central laboratory of National Taiwan University Hospital. The certified technicians were blinded to treatment status throughout the whole trial. Cholesterol and TG were assayed with enzymatic kits (Merck：14366 and 14354, respectively) by Eppendorf Epose 5060 autoanalyzer.[25,26.] The HDL-C was determined by measuring cholesterol in the supernatant after very low-density lipoprotein cholesterol (VLDL-C) and LDL-C precipitated by Mg^{2+}/phosphotungstate reagent (Merck：14993). LDL-C was precipitated by heparin/citrate reagent (Merck：14992) while VLDL-C and HDL-C were in the supernatant after LDL-C was precipitated out；so the concentration of LDL-C was equivalent to the "total cholesterol – cholesterol in the supernatant" [27]. Apolipoproteins were determined by turbidimetric immunoassay in commercial kits (Sigma) [28].

Safety evaluation：The following laboratory tests were performed at the baseline and at the 3 months follow-up：serum alanine aminotransferase, aspartate aminotransferase, γ -glutamyl transpeptidase, uric acid, and creatine phosphokinase. The drug related adverse effects were assessed for patients during their weekly visits.

Statistical analysis：This study adopted the paired-samples design, the main data analyses consisted of simple paired t-tests within each treatment for the mean of each paired difference of the lipid levels assessed between the end of the 3-month treatment and at the corresponding baseline levels for each lipid profiles. A t-test was conducted to test difference of each lipid profiles between pravastatin and fenofibrate groups. After treatment, percent changes of lipid profiles from baseline were also calculated.

Adverse events were counted and presented by contingency table, and the χ^2 test was used to test the significance level of percentage of adverse events between both groups. Difference were considered as statistically significant if $P<0.05$. All statistical analysis was done by SAS version 6.12 system.

Results

Population description：The sociodemographic characteristics of the participants completed the trial on pravastatin and on fenofibrate were similar in sex, age, marital status, occupation, and years of education (Table I). Table 2 presents the baseline cardiovascular characteristics of participants; no significant differences for all variables, including lipid profiles, were found prior to the trial between participants on pravastatin and participants on fenofibrate.

Efficacy：Table 3 shows the average paired changes in serum lipid profiles between the levels at the end of the 3-month trial and the baseline for the trial participants both on pravastatin and fenofibrate. Both drugs significantly lowered levels of cholesterol, LDL-C, TG and apo B after treatment, such as lowering 50.5 mg/dl for LDL-C level in P group ($P<0.001$) and 56.7 mg/dl in F group ($P<0.001$). HDL-C level was significantly increased in both groups, an average increase of 7.7 mg/dl in P group ($P<0.01$)；and 8.3 mg/dl in F group ($P<0.01$). There were also significant elevation in apo A1 level in both groups.

Figure 1 shows the relative changes in lipids by the drugs after the trial. Both drugs showed comparable reduction in cholesterol (18.3% in P group, 18.1% in F group), and LDL-C (28.2 % in P group, 29.8% in F group), and relative increment in HDL-C (18% in P group and 19.4% in F group). The relative reductions in apo B level were even greater, 46.5 % on pravastatin and 42.9% on fenofibrate. Furthermore, the reduction in TG was greater in F group than in P group (30.2% vs. 21.5%, $P= 0.034$). A significant drop in serum uric acid level was also noted in F group as compared with P group, -1.9 mg/dl (-30%) and –0.4 mg/dl (-7.2%), respectively ($P<0.01$).

Drug-related adverse effects：We followed up all cases in the Chin-Shan community health center every week. Home-visit or telephone contacted all dropouts. We found no significant change in serum creatine phosphokinase level or liver enzymes after treatment (Table 4). Both groups showed similar incidence of a few minor possible drug-related side effects, such as myalgia (8.6% in P group vs. 8.8% in F group, $P > 0.05$) and gastrointestinal disturbance (5.7% vs. 5.9%, $P > 0.05$). Mild skin rash with itching was found in two patients on fenofibrate (5.9%), which was resolved spontaneously in two weeks after antihistamine and calamine lotion were given.

Discussion

This is the first report demonstrating that low dose pravastatin and regular fenofibrate achieve a similar and significant lowering effect of cholesterol and LDL-C in a Taiwanese community. Previously, there were no reports documenting a comparative study between pravastatin and fenofibrate in such a community. Studies in Japanese show a similar lipid-lowering effect at the same low dose of pravastatin.[29,30] However, the cholesterol, LDL-C, TG and apo B lowering effects of pravastatin and fenofibrate in our study were greater than those in previous studies conducted in the U.S. and by the European Study Group at the same low dose.[31-36] (Table 5) Compared with those studies, our study demonstrates a greater increase in HDL-C and apo A1 levels than other studies.[29-36] The difference in lipid-lowering effect may be due to the difference in genetic metabolic traits or receptor-competition for enzymes, or body size between Caucasian and Chinese, and between Caucasian and Japanese. Lower level of HDL-C was attributed as an independent risk factor for patients with acute myocardial infarction in Taiwanese in a hospital-based study.[37] An elevated HDL-C level for patients on pravastatin or fenofibrate may have better clinical implication in the treatment of Chinese with hypercholesterolemia in the future.

The unique therapeutic benefit of fenofibrate, compared with pravastatin, in terms of triglyceride-lowering effect, was similar to previous trials and revealed the different mechanisms of lipid-lowering effect between fibric acid derivatives and statins.[22,23,35,36]

The uricosuric effect of fenofibrate was equal to or greater in the current study compared with previous study：a 30 % decrease in uric acid in this study and 10-28 % decrease in the European experience.[36] Because hyperuricemia is considered as one of the most common problems in health examination, the uricosuric effect of fenofibrate may achieve an additional advantageous indication in clinical practice.

Though the drug-related side effects associated with fenofibrate therapy in this study were similar to those of European clinical experience, only 6.3% in average (2-15%).[36] Adverse drug-related effects associated with pravastatin therapy in this study were similar to those in previous trials, 2.9-8.0%.[31-34] As the major strategy of primary and

secondary prevention of coronary heart diseases in hypercholesterolemic patients, hypolipidemic treatment was proved useful in large-scale, double-blinded and placebo controlled trials in recent five years.[9-11] American College of Cardiology/American Heart Association recommended patients with low-density lipoprotein cholesterol level above 125 mg/dl to receive lipid-lowing therapy as an important secondary prevention strategy of patients with acute myocardial infarction.[38] A meta-analysis of statins in lipid-lowering therapy documented by Hebert et al. revealed 30% reduction in LDL-C could substantially reduce by 29% risk for stroke, 28% risk for cardiovascular disease death, and 22% risk for total mortality.[39] The result of the West Scotland Coronary Prevention Study revealed that 24% reduction in LDL-C level was sufficient to produce the full benefit for patients using pravastatin.[40] The LDL-C reduction in current study presented a slightly greater than 24% in such a low dose of pravastatin.

In conclusion, 10 mg of pravastatin daily or 300 mg of fenofibrate daily can achieve significant lipid-lowering effect without exerting clinically severe drug-related side effects for patients with primary hypercholesterolemia in our study. Some mild clinical complaints are transient and tolerable through the study period. On the basis of the cost-effectiveness approach toward drug therapies, these two drugs are recommended as good choices among all other hypolipidemic agents being used in clinical practice in Taiwanese. Furthermore, for patients with elevated TG level or hyperuricemia, fenofibrate can be considered as the front-line agent if its side effects are tolerable.

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比較在一台灣社區中使用 Pravastatin 和 Fenofibrate 治療原發性高膽固醇血症患者的效果及安全性

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摘要

背景：欲對原發性高膽固醇血症患者，評估使用 Pravastatin 和 Fenofibrate 治療的效果及安全性，我們評估在金山社區中高膽固醇血症病患治療後膽固醇的改變及副作用。
方法與結果：病人被隨機分成兩組，一組接受 Pravastatin 5 毫克一天兩次或 Fenofibrate 100 毫克一天三次。在 69 位接受邀請參加者中，有 55 位（28 位用 Pravastatin，27 位用 Fenofibrate）完成。三個月療程結束，兩組皆呈明顯相類似的膽固醇值降低；總膽固醇（Pravastatin 組降 18.3%，Fenofibrate 組降 18.1%），而低密度膽固醇值（分別是降 28.2%及 29.8%），同時亦可見兩組其高密度膽固醇值增加。使用 Fenofibrate 治療組，其三酸甘油酯降低比 Pravastatin 組來得明顯（分別是 30.2%及 21.5%，P 值＝0.034）。然而，兩組皆可發現些微的小副作用。
結果：總之，我們相信使用每天 Pravastatin 10 毫克或 Fenofibrate 300 毫克，來治療台灣原發性高膽固醇血症患者，皆可提供足夠的降低膽固醇療效，而且有相當好的安全性。

Table I. Sociodemographic characteristics of participants.

Characteristics (%)	Pravastatin (N = 28)	Fenofibrate (N = 27)	P
Male	59.1	51.9	0.18
Age, years (mean)	58.6	56.4	0.48
Currently Married			
Yes	77.8	81.8	0.76
Education, years			
≦6	37.0	22.7	
7~9	48.2	72.7	
10+	14.8	4.6	0.07
Occupation			
None	51.9	54.6	
White Collar	22.1	18.2	
Blue Collar	25.9	27.3	0.23

Table 2. Average baseline cardiovascular characteristics and lipid profiles

Characteristics	Pravastatin (N = 28)	Fenofibrate (N = 27)	P
Body weight (kg)	67.7±10.2	65.0±11.5	0.39
Body mass index (kg/m$^{2)}$	26.2±3.2	24.7±3.4	0.14
Hypertension (%)	66.7	59.1	0.58
Diabetes (%)	7.4	4.6	0.68
Current smoking (%)	29.6	36.4	0.62
Cholesterol, mg/dl	247.1±27.9	256.4±39.8	0.35
LDL-C, mg/dl	179.3±27.2	190.0±35.7	0.24
HDL-C, mg/dl	43.1±9.1	42.7±8.6	0.89
Triglyceride, mg/dl	158.8±68.4	145.6±63.8	0.49
LDL-C/HDL-C	4.3±1.1	4.6±1.2	0.40
Apo A1, g/l	1.4±0.2	1.3±0.2	0.34
Apo B, g/l	1.3±0.4	1.3±0.4	0.87

Abbreviations：LDL-C, low-density lipoprotein cholesterol；HDL-C, high-density lipoprotein cholesterol；Apo A1and B, apolipoprotein A1 and B.

Table 3. Average paired change of lipid profiles after treatment between pravastatin and fenofibrate groups

Lipid profiles	Pravastatin [a] Mean ±S.D.	Fenofibrate [a] Mean ±S.D.	P [b]
Cholesterol, mg/dl	-45.2 ±33.3***	-46.3 ±32.6***	0.91
LDL-C, mg/dl	-50.5 ±35.9***	-56.7 ±31.7***	0.53
HDL-C, mg/dl	7.7 ±10.0**	8.3 ±11.3**	0.86
Triglyceride, mg/dl	-34.1 ±64.5*	-43.9 ±63.8**	0.034 *
LDL-C/ HDL-C	-1.6 ±1.1***	-1.7 ±1.1***	0.76
Apo A1, g/l	0.2 ±0.3**	0.3 ±0.3***	0.65
Apo B, g/l	-0.6 ±0.3***	-0.6 ±0.5***	0.86

[a]：represent average paired difference measured using post-treatment value minus baseline value of each participants in the group.
[b]：significance level of t-test between pravastatin and fenofibrate groups.
● P< 0.05, ** P<0.01, *** P<0.001

Table 4. Possible or probable drug-related side effects

Side effects	Liver enzymes			Muscle enzyme	Clinical complaints		
	AST ↑	ALT ↑	γ-GT ↑	CPK ↑	Myalgia	GI disturbance	Skin rash
Pravastatin	0	0	0	0	3/35 (8.6%)	2/35 (5.7%)	0
Fenofibrate	0	0	0	0	3/34 (8.8%)	2/34 (5.9%)	2/34 (5.9%)

Abbreviations：AST, aspartate aminotrasferase；ALT, alanine aminotransferase；γ-GT, γ-glutamyl transpeptidase；CPK, creatine phosphokinase；GI, gastrointestinal.
↑：1.5 times elevation than the values of upper normal limit.

Table 5. Summary of clinical trials comparing the lipid-lowering efficacy of 10 mg of pravastatin daily in patients with primary hypercholesterolemia

References	No.	Design	Duration	Percentage change in mean values from baseline					
				TC	LDL-C	HDL-C	TG	Apo A-I	Apo B
Goto et al. (29)	89	Db, pg, mc	4 months	-19*	-27*	+5*	-1		
Yoshino et al. (30)	25	Nb, pg	3 months	-17*	-29*	+12*	-13		
This Study	28	Nb, r, pg	3 months	-18*	-28*	+18*	-22*	+17*	-47*
Jones et al. (31)	18	Db, r, pg, mc	8 weeks	-16*	-22*	+7*	-15*		
Lovastatin Pravastatin Study Group (32)	333	Db, r, pg, mc	6 weeks	-13*	-19*	+12*	-9*	+3*	-14*
European Study Group (33)	146	Nb, r, pg, mc	6 weeks	-16*	-22*	+5*	-6*		
Steinhagen-Thiessen et al. (34)	138	Db, r, pg, mc	12 weeks	-11*	-17*	+8*	-4*	+5*	-11*

Abbreviations：db, double-blind；nb, nonblind；r, randomised; pg, parallel group；mc, multi-center；TC, total cholesterol；TG, triglyceride.
*P<0.05, post treatment vs baseline.

Legends for figures

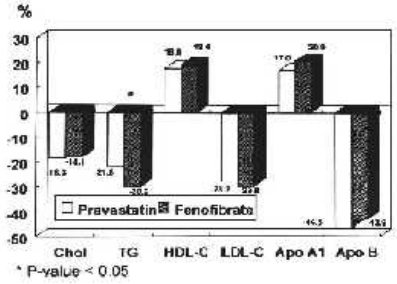

Figure 1. Percentage change in lipid levels after drug treatment