A Retrospective Meta-Analysis of the Efficacy and Tolerability of Fenofibrate 300 mg/d on High-Density Lipoprotein Cholesterol Levels in Randomized, Double-Blind, Comparative Studies Conducted in Japan

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ABSTRACT

Background: Low levels of plasma high-density lipoprotein cholesterol (HDL-C) represent an important risk factor for coronary heart disease (CHD). Increasing HDL-C by 1 mg/dL decreases the incidence of CHD by 2% to 3%. Fenofibrate increases HDL-C by ~23%, to ≥ 40 mg/dL, and may be effective in preventing CHD.

Objective: The aim of this study was to assess the effects of fenofibrate on HDL-C in patients treated for 12 weeks in 3 randomized, double-blind, comparative studies conducted in Japan. Changes in total cholesterol (TC) and triglycerides (TG), effects on HDL-C and apolipoprotein (apo) A-I and A-II by TG level, and effects on serum lipid levels by type of hyperlipidemia were the secondary end points.

Methods: Changes in HDL-C levels, as well as TC and TG levels, were analyzed in patients who received fenofibrate 300 mg/d for 12 weeks. Patients aged 20 to 80 years with mean TC ≥ 220 mg/dL (hypercholesterolemia), TG ≥ 150 mg/dL (hypertriglyceridemia), or both (combined hyperlipidemia) were considered assessable.

Results: In this retrospective meta-analysis conducted at Grelan Pharmaceutical Co. Ltd. (Tokyo, Japan), data from 263 patients (137 women, 126 men; mean [SD] age, 56.0 [10.8] years; range, 25–79 years) were included. The mean (SD) HDL-C level increased significantly, from 46.1 (0.9) mg/dL to 55.9 (1.0) mg/dL after 12 weeks of treatment with fenofibrate ($P < 0.001$). Serum TC and TG decreased significantly (both $P < 0.001$). HDL-C elevation was greater in patients with TG ≥ 150 mg/dL than in patients with TG < 150 mg/dL, although apo A-I and A-II changes were the same in both groups. HDL-C increased in every type of hyperlipidemia, 14.9% in hypercholesterolemia, 22.0% in hypertriglyceridemia, and 33.5% in combined hyperlipidemia. Baseline HDL-C levels

were <40 mg/dL in 93 patients (group 1) and ≥ 40 mg/dL in 170 patients (group 2). Mean HDL-C levels increased significantly in both groups during the treatment period, from 32.6 (0.6) mg/dL to 42.6 (1.0) mg/dL in group 1 and from 53.5 (0.9) mg/dL to 63.1 (1.1) mg/dL in group 2 (both $P < 0.001$). One patient (0.3%) of the 331 included in the tolerability analysis experienced a serious adverse effect (jaundice).

Conclusion: In this study of patients with hypercholesterolemia, hypertriglyceridemia, or combined hyperlipidemia, 12-week treatment with fenofibrate 300 mg/d was effective and generally well tolerated, with the possible exception of transient changes in aminotransferases. HDL-C was increased in all patients to ~ 40 mg/dL, the target level. (*Curr Ther Res Clin Exp.* 2003;64:634–644) Copyright © 2003 Excerpta Medica, Inc.

Key words: fenofibrate, high-density lipoprotein cholesterol, apolipoprotein A-I, apolipoprotein A-II, double-blind comparative study.

INTRODUCTION

A negative relationship has been observed between the plasma level of high-density lipoprotein cholesterol (HDL-C) and the risk for coronary heart disease (CHD) in studies conducted in both the United States¹ and Europe.² Epidemiologic studies^{3,4} in Japanese people—whose total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels are generally lower than those reported in the United States and Europe—have demonstrated a negative relationship between HDL-C and CHD. Therefore, a low level of HDL-C (<40 mg/dL) is considered a risk factor for CHD in Japanese patients.⁵ In addition, a study⁶ that followed up 2733 Japanese patients with CHD for 2.9 years identified HDL-C as an important factor in predicting relapse of CHD.

Fibrate drugs, including fenofibrate, gemfibrozil, and bezafibrate, increase HDL-C and suppress the onset of CHD.^{7–9} These drugs activate peroxisome proliferator activated receptor- α (PPAR α), an intranuclear receptor that increases production of apolipoproteins (apo) A-I and A-II^{10,11}; ATP-binding cassette, transporter 1 (ABCA1)¹²; and scavenger receptor class B, type 1 (SR-B1).¹³

Increasing HDL-C by 1 mg/dL decreases the incidence of CHD by 2% to 3%. Fenofibrate increases HDL-C by 23%, to ≥ 40 mg/dL, and may be effective in preventing CHD. In a Western study,¹⁴ administration of micronized fenofibrate formulation at 200 mg/d for 12 weeks resulted in HDL-C levels increasing to ≥ 40 mg/dL, achieving treatment target level. Our study was conducted to determine whether fenofibrate produced similar results in a Japanese population. In this meta-analysis we examined the effect of fenofibrate on HDL-C levels in 3 studies conducted in Japanese patients. The effects on TC, triglycerides (TG), and apo A-I and A-II also were examined.

PATIENTS AND METHODS

Patients

Japanese patients aged 20 to 80 years with baseline TC ≥ 220 mg/dL (hypercholesterolemia), or TG ≥ 150 mg/dL (hypertriglyceridemia), or both (combined hyperlipidemia) were eligible for inclusion in this meta-analysis of 3 randomized, double-blind, comparative studies of fenofibrate.¹⁵⁻¹⁷ Patients who had serious liver, gallbladder, or kidney disease; drug sensitivity; serious or new (onset ≤ 3 months prior to enrollment) myocardial infarction or cerebrovascular disease; hyperlipidemia due to reduced thyroid function; poorly controlled diabetes mellitus; alcohol abuse and alcohol poisoning; pancreatitis; Cushing syndrome; or use of drugs such as steroids were excluded from all 3 studies. Women who were pregnant, possibly pregnant, or breastfeeding also were excluded. No changes in dietary or exercise therapy were allowed during the studies.

Studies

In all 3 studies, patients followed dietary and exercise therapy, after which a 4-week run-in period was used to determine baseline laboratory values for inclusion in the assessment of HDL-C elevation. All 3 studies also used the double-dummy method, in which fenofibrate* was administered orally at a dose of 300 mg/d (equivalent to 200 mg/d of the micronized preparation¹⁸) for 12 weeks.

Study 1¹⁵ was a dose-finding study, in which fenofibrate was administered at 100, 200, or 300 mg/d. The study comprised patients with hypercholesterolemia and/or hypertriglyceridemia and was conducted at 64 clinical research centers in Japan. A total of 340 patients were enrolled; 86 patients receiving 100 mg/d, 75 receiving 200 mg/d, and 86 receiving 300 mg/d were eligible for assessment of HDL-C elevation.

Study 2,¹⁶ which assessed fenofibrate 300 mg/d or ciprofibrate 600 mg/d, comprised patients with hypercholesterolemia and/or hypertriglyceridemia at 42 clinical research centers in Japan. A total of 236 patients were enrolled, and 88 patients treated with fenofibrate and 96 patients treated with ciprofibrate were eligible for assessment of HDL-C elevation.

Study 3¹⁷ examined fenofibrate 300 mg/d or bezafibrate 400 mg/d. This study of patients with hypercholesterolemia and/or hypertriglyceridemia was conducted at 36 clinical research centers in Japan. A total of 205 patients were enrolled; 89 patients treated with fenofibrate and 77 patients treated with bezafibrate were eligible for assessment of HDL-C elevation.

All protocols were prepared by the study committee at each study site and conducted in compliance with the Good Clinical Practice guidelines. After approval was received from the ethics committee at each institution, written informed consent was obtained from all patients in all 3 studies.

*Trademark: Lipantil® (Grelan Pharmaceutical Co., Tokyo, Japan).

Study Schedule

Fenofibrate 300 mg was administered orally after dinner for 12 weeks. During the observation period and every 4 weeks during the treatment period, a serum lipid profile, blood analysis, serum chemistry, and urinalysis were performed. Blood samples were collected early in the morning after at least a 14-hour fast. TC and TG levels were determined using enzymatic methods. HDL-C levels were determined using the heparin- Ca^{2+} - Ni^{2+} -precipitation method. Apolipoprotein levels were determined using the turbidimetry immunoassay method. Plasma lipoprotein and apolipoprotein levels were measured at a central laboratory (Special Reference Laboratory Co., Tokyo, Japan).

Statistical Analysis

Paired *t* tests were used to compare HDL-C, TC, and TG levels before and after fenofibrate treatment. Statistical significance was set at $P \leq 0.05$. SAS version 8.02 (SAS Institute Inc., Cary, North Carolina) was used to calculate the data.

RESULTS

Patient Characteristics

Data from 263 patients were analyzed (86, 88, and 89 patients from studies 1, 2, and 3, respectively; 137 women, 126 men; mean [SD] age, 56.0 [10.8] years; range, 25–79 years). Although the numbers of women and men were similar, men represented 67.7% of patients with HDL-C < 40 mg/dL. Although the mean (SD) body mass index (BMI) was 24.4 (3.1) kg/m^2 , 101 patients (38.4%) had a BMI ≥ 25 kg/m^2 and were considered overweight. Eighty-seven patients (33.1%) were hypertensive and 65 (24.7%) had diabetes mellitus (Table I).

Efficacy

Effects on High-Density Lipoprotein Cholesterol

Mean HDL-C increased significantly in patients who received fenofibrate. The mean increase was ~ 10 mg/dL, from a mean (SD) level of 46.1 (0.9) to 55.9 (1.0) mg/dL ($P < 0.001$). When patients were separated into 2 groups by pretreatment HDL-C level of < 40 mg/dL in 93 patients (group 1) and ≥ 40 mg/dL in 170 patients (group 2), both groups displayed similar statistically significant increases in mean HDL-C level, from 32.6 (0.6) mg/dL before treatment to 42.6 (1.0) mg/dL after treatment in group 1 and from 53.5 (0.9) mg/dL before treatment to 63.1 (1.1) mg/dL after treatment in group 2 (both $P < 0.001$) (Figure 1).

When group 1 was subdivided, fenofibrate increased mean HDL-C levels in all groups to ~ 40 mg/dL, which is the target level set by the Japan Atherosclerosis Society.⁵ As shown in Figure 1, subdivisions and corresponding changes in HDL-C levels were as follows: 20.5 (1.6) mg/dL to 40.1 (4.0) mg/dL in the < 25 mg/dL subgroup ($P = 0.001$); 28.2 (0.4) mg/dL to 36.9 (2.0) mg/dL in the 25 to < 30 mg/dL group ($P < 0.001$); 32.7 (0.3) mg/dL to 41.7 (1.5) mg/dL in the 30 to < 35

Table I. Characteristics of patients with high-density lipoprotein cholesterol (HDL-C) <40 mg/dL and the entire study population during the observation period.

Characteristic	Patients with HDL-C <40 mg/dL (n = 93)	Overall (N = 263)
Age, y		
Mean (SD)	53.3 (11.3)	56.0 (10.8)
Range	25–78	25–79
Sex, no. (%)		
Men	63 (67.7)	126 (47.9)
Women	30 (32.3)	137 (52.1)
BMI, kg/m ²		
Mean (SD)	24.8 (2.7)	24.4 (3.1)
Range	18.6–31.6	16.0–38.0
Other risk factors, no. (%) of patients*		
Overweight	38 (40.9)	101 (38.4)
Smoking	35 (37.6)	62 (23.6)
Hypertension	27 (29.0)	87 (33.1)
Diabetes mellitus	25 (26.9)	65 (24.7)
History of CHD	15 (16.1)	35 (13.3)

BMI = body mass index; CHD = coronary heart disease.

*Some patients had >1 risk factor.

mg/dL group ($P < 0.001$); and 37.8 (0.3) mg/dL to 46.9 (1.3) mg/dL in the 35 to <40 mg/dL group ($P < 0.001$).

Effects on High-Density Lipoprotein Cholesterol and Apolipoproteins A-I and A-II, by Baseline Triglyceride Level

The effects of fenofibrate on HDL-C and apo A-I and A-II were examined in patients with normal (<150 mg/dL) and abnormal (≥ 150 mg/dL) baseline TG levels in groups 1 and 2 (Figure 2). Fenofibrate produced greater increases in HDL-C level in group 1 than group 2 in patients with elevated TG levels (36.6% in group 1 and 24.7% in group 2). Corresponding values for patients with normal TG levels in groups 1 and 2 were 21.0% and 14.3%, respectively. Conversely, no significant differences in changes in apo A-I and A-II levels were found between patients with normal and abnormal TG values.

Effects on High-Density Lipoprotein Cholesterol Levels in Various Types of Hyperlipidemia

The effects of fenofibrate on serum lipid levels in patients with hypercholesterolemia, hypertriglyceridemia, and combined hyperlipidemia are shown in Figure 3. HDL-C levels increased by 14.9% in hypercholesterolemic patients, 22.0% in

Figure 1. Changes in high-density lipoprotein cholesterol (HDL-C) levels (stratified by pretreatment HDL-C levels) before and after administration of fenofibrate 300 mg/d for 12 weeks. * $P = 0.001$ versus pretreatment. † $P < 0.001$ versus pretreatment.

hypertriglyceridemic patients, and 33.5% in patients with combined hyperlipidemia (all $P < 0.001$).

Tolerability

All patients who were administered fenofibrate 300 mg/d in these double-blind studies were eligible for the tolerability analysis ($N = 331$). Fenofibrate administration was discontinued in 17 of 331 patients (5.1%) due to possible treatment-related adverse effects (AEs) (Table II). These effects included digestive tract symptoms and dermatologic symptoms. Only 1 patient (0.3%) experienced a serious AE (jaundice attributed to biliary congestion).

In terms of laboratory values, fenofibrate produced changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyltranspeptidase (γ -GTP), and creatine kinase (CK) in a large number of patients. AST and ALT exceeded 200 U/L in 9 of 331 patients (2.7%) (normal value, 5–40 U/L), and γ -GTP exceeded 300 U/L in 14 of these patients (4.2%) (normal value, 0–50 U/L). These values normalized during the course of treatment. In 1 patient, CK exceeded 5 times the upper limit of normal, but no clinical symptoms (eg,

Figure 2. Changes in high-density lipoprotein cholesterol (HDL-C) and apolipoprotein (apo) A-I and apo A-II levels (stratified by pretreatment HDL-C and triglyceride [TG] levels) before and after administration of fenofibrate 300 mg/d for 12 weeks.

muscle pain) were observed. CK levels normalized in all patients as treatment continued.

DISCUSSION

When 200 mg/d of micronized fenofibrate (a new formulation of fenofibrate with an improved pharmacokinetic profile) was taken orally for 12 weeks by 7098 German patients with hyperlipidemia, HDL-C increased to ≥ 40 mg/dL irrespective of pretreatment values.¹⁴ As reported in the German study, we observed that fenofibrate increased mean HDL-C by ~ 10 mg/dL, independent of pretreatment values. Thus, mean HDL-C was increased to ≥ 40 mg/dL with fenofibrate, achieving the target value set by the Japan Atherosclerosis Society.⁵

Because HDL-C may well have been secondarily increased by the potent TG-lowering effect of fenofibrate, the effects of fenofibrate on increased HDL-C and apo A-I and A-II were compared by separating patients according to normal

Figure 3. Effects of fenofibrate 300 mg/d on serum lipid levels by type of hyperlipidemia. TC = total cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol. * $P < 0.001$ versus baseline.

(<150 mg/dL) and abnormal (≥ 150 mg/dL) baseline TG levels. Patients with normal TG levels also displayed elevated HDL-C and apo A-I and A-II levels. Furthermore, no significant changes in apo A-I and A-II were found between patients with normal and abnormal TG levels, although the increases in HDL-C appeared to be lower among patients with normal TG than among those with abnormal TG. This finding suggests that the mechanism by which fenofibrate increases HDL-C might differ between patients with normal and abnormal TG levels.

Concerning the tolerability of fenofibrate, excluding the 1 patient with jaundice that appeared attributable to biliary congestion, no serious adverse effects were reported. In Japan, any deviation from the normal range is considered "abnormal," so abnormalities in laboratory values were frequently observed. Aminotransferases were ≥ 200 U/L in only 2.7% of cases, and γ -GTP was ≥ 300 U/L in only 4.2%. These values normalized as treatment continued. No clinical symptoms such as muscle pain were observed in patients with elevated CK. CK exceeded 5 times the upper limit of normal in only 1 patient. These results indicate that fenofibrate was generally well tolerated. According to the results of the Diabetes Atherosclerosis Intervention Study,⁷ fenofibrate was judged safe

Table II. No. (%) of patients experiencing ≥ 1 adverse effect (AE) in the patients eligible for the tolerability assessment (N = 331).

AE	No. (%) of Patients
Clinical (n = 24 AEs)	
Nausea/retching	4 (1.2)
Constipation	2 (0.6)
Diarrhea/loose stools	2 (0.6)
Rash/drug eruption	2 (0.6)
Stomachache/stomach discomfort	2 (0.6)
Vomiting	2 (0.6)
Anorexia	1 (0.3)
Dermatitis/skin roughness	1 (0.3)
Eczema	1 (0.3)
Epigastric discomfort/abdominal bloating	1 (0.3)
Generalized fatigue	1 (0.3)
Pruritus	1 (0.3)
Urticaria	1 (0.3)
Upper abdominal pain/symptoms	1 (0.3)
Epigastric pain	1 (0.3)
Jaundice	1 (0.3)*
Laboratory (n = 282 AEs)	
ALT elevated	83 (25.1)
AST elevated	81 (24.5)
γ -GTP elevated	77 (23.3)
CK elevated	18 (5.4)
γ -GTP ≥ 300 IU/L	14 (4.2)
AST or ALT ≥ 200 IU/L	9 (2.7)
No. (%) patients who withdrew due to AE(s)	17 (5.1)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; γ -GTP = γ -glutamyltranspeptidase; CK = creatine kinase.

*This AE was considered serious and was attributed to biliary congestion.

after 3 years of treatment, and it was suggested that increases in aminotransferases occurred via PPAR α mechanisms.^{19,20}

Low HDL-C represents an important risk factor for CHD, according to epidemiologic studies conducted in Japan^{3,4,6} and other countries.⁷⁻⁹ Our study demonstrated that fenofibrate exerts a beneficial effect on HDL-C and reduces TG, TC, and LDL-C levels. Therefore, fenofibrate may prove effective in preventing CHD, even among Japanese people, whose TC and LDL-C levels are generally lower than the levels reported in Europe and the United States.

Patients in our study were limited to those with hypercholesterolemia, hypertriglyceridemia, and combined hyperlipidemia, and the treatment period was only 12 weeks. Future studies should examine the effects of fenofibrate on low

HDL-C levels in a population with additional risk factors for CHD, such as hypertension and diabetes mellitus.

CONCLUSION

In this study of patients with hypercholesterolemia, hypertriglyceridemia, or combined hyperlipidemia, 12-week treatment with fenofibrate 300 mg/d was effective and generally well tolerated, with the possible exception of transient changes in aminotransferases. HDL-C was increased in all patients to ~40 mg/dL, the target level.

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