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Original Article

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Half Dose Once-Daily Pemafibrate Effectively Improved Hypertriglyceridemia in Real Practice

Chie Iitake[a, b], Kazuhiro Iitake[a]

Abstract

Background: Hyperlipidemia is a worldwide problem related to cardiovascular disease (CVD) and sudden death. Low-density lipoprotein cholesterol (LDL-C) has been treated well by the use of statins, but hypertriglyceridemia was not the case. Previous fibrates have been shown a certain effect of preventing CVD events, but some remain not enough or even could cause adverse events. Pemafibrate is a selective peroxisome proliferator-activated receptor α modulator (SPPARMα) with the potential to reduce high triglycerides. To evaluate the clinical effectiveness and safety profile of Pemafibrate, we have started with half dose once-daily administration.

Methods: Thirty-three patients with hypertriglyceridemia, triglyceride (TG) levels > 150 mg/dL, were treated with Pemafibrate (0.1 mg, once daily) from July 2018 to February 2019. Changes in TG (non-fasting) and LDL-C, high-density lipoprotein cholesterol (HDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), creatinine (Cre), blood glucose (PBG) (postprandial), hemoglobin A1c (HbA1c), and body weight (BW) levels were investigated, compared to the baseline levels of the previous visit.

Results: Of the 33 patients, 11 were using other fibrates before. Nine were given statins along with. Baseline TG was 285.0 (210.5 - 423.0) mg/dL, LDL-C 116.4 ± 33.4 mg/dL, and HDL-C 46.5 ± 12.5 mg/dL. TG changes were statistically significant (-20.8 ± 47.6%; $P < 0.01$). Patients with TG > 200 mg/dL, who used fibrates for the first time, experienced the most significant changes in TG levels (-34.5 ± 37.2%; $P < 0.01$). In patients using statins already, TG reduction was relatively less, compared to those not using statins (-25.4 ± 36.1%; $P < 0.01$). HDL-C increased by 3.9 ± 10.2 mg/dL ($P < 0.05$). LDL-C increased by 16.6 ± 23.7 mg/dL ($P < 0.001$) in patients not using statins, while patients using statins did not show such significant change. AST, ALT, CK, Cre, PBG, HbA1c and BW did not significantly change.

Conclusions: A selective PPARα modulator, Pemafibrate, effectively improved hypertriglyceridemia without major adverse events in real practice, with half dose once-daily administration. Combined use of statins might be a potent therapeutic maneuver for dyslipidemia.

Keywords: SPPARMα; Pemafibrate; Hypertriglyceridemia; Statins

Introduction

Dyslipidemia is currently a worldwide public health concern, since it leads to cardiovascular disease (CVD) and sudden death. It is often caused by excessive high-fat diet and lack of exercise. This lifestyle is often associated with hypertriglyceridemia and hypercholesterolemia, obesity and visceral fat accumulation. Especially for Japanese patients with type 2 diabetes, hypertriglyceridemia is one of the highest risk factors for CVD. According to the 2011 Japan Diabetes Complications Study [1], the strongest risk factor for CVD events in men was high low-density lipoprotein cholesterol (LDL-C) ($P < 0.001$), followed by hypertriglyceridemia ($P < 0.01$). In female patients, hypertriglyceridemia was the most important risk factor ($P < 0.01$). Other studies showed that around half of the Japanese patients at risk for CVD events had higher levels of triglycerides (TGs) than ideal [2]. Therefore, targeting TG levels is the next important challenge for preventing the onset of atherosclerosis and CVD events.

Pemafibrate is a selective peroxisome proliferator-activated receptor α modulator (SPPARMα) with the potential to reduce high TG levels. Peroxisome proliferator-activated receptor (PPAR) is a nuclear receptor which regulates transcriptions of many targeting genes on lipid and glucose metabolism. For this character, it is difficult to be selectively targeted for treatment. However since SPPARMα has been designed with much higher PPARα agonistic activity and selectivity than ever, it could become the most reliable agent for lowering TG levels and normalizing low high-density lipoprotein cholesterol (HDL-C), small LDL-C, and apolipoprotein A-1 concentrations. There are other fibrates currently used in Japan, and some studies have shown their efficacies in preventing CVD events, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid study [3]. On the other hand, for some patients, treatments with previous fibrates are still not very effective and could even cause adverse events, such as liver dysfunction. To solve these problems, a targeted treatment with SPPARMα may be an ideal and appropriate means of reducing high TG levels. A large ongoing global study,

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[a]Iitake Clinic for Internal Medicine, 2131-1976 Migawacho, Mito City, Ibaraki Prefecture, 310-0913, Japan
[b]Corresponding Author: Chie Iitake, Iitake Clinic for Internal Medicine, 2131-1976 Migawacho, Mito City, Ibaraki Prefecture, 310-0913, Japan.
Email: chieiitake@gmail.com

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called the PROMINENT study, is attempting to demonstrate the effects of Pemafibrate on type 2 diabetic patients [4]. However, before these results are published, it is necessary to know the effectiveness and safety earlier in the real world. Indeed, currently no reports discussing this are available, especially in a small clinic. Thus, the aim of our study was to evaluate the effectiveness and safety of this new compound.

Our clinic is located in Mito City, Ibaraki Prefecture, Japan, 100 km from central Tokyo. The city, which is in the suburb area, is middle-sized, with 0.24 million habitants. Our clinic is a general family clinic of an average size, receiving approximately 2,000 patients per month. The general patient population suffer from common diseases, including hypertension, diabetes, hyperlipidemia, and infections. We currently have around 2,100 patients with hyperlipidemia.

Materials and Methods

Subjects

After following the inclusion and exclusion criteria for participation in the study, 33 patients were selected, including those who were already using fibrates. Inclusion criteria were the following condition: patients who have hypertriglyceridemia (non-fasting TG levels ≥ 150 mg/dL), regularly visiting our clinic and not conflicting with the exclusion criteria. Each patient visit was every 35 - 50 days, an average interval for a general clinic visit. Exclusion criteria was the following conditions: patients who have stopped taking Pemafibrate on their own decisions, who have been admitted to other hospital or went under surgery, who have been pregnant or on breastfeeding, who have started a new diet and exercise therapy, and others whom the researcher thought inappropriate to be included in this study.

Dose

Pemafibrate (0.1 mg, once daily) was administered from July 2018 to February 2019. To study the safety of long-term administration of the drug, we provided a low, half dose compared to the recommended one. This study was approved by the Ethics Committee of the Japan Physicians Association, Tokyo, Japan (Approved ID: 022-1906-001) on August 7, 2019.

Laboratory findings and statistical analysis

Data of age and gender were collected.

Changes in TG (non-fasting, mg/dL) from the baseline to the last visit were investigated (from 1 to 6 months). The Wilcoxon signed rank test (a non-parametric method) was used to evaluate the difference between the values before and after the treatment, due to a broad range of TG affected by the individual lipid consumption. Values are expressed by median and interquartile range.

Changes in LDL-C (mg/dL), HDL-C (mg/dL), aspartate aminotransferase (AST) (U/L), alanine aminotransferase (ALT) (U/L), creatine kinase (CK) (U/L), creatinine (Cre) (mg/dL), postprandial blood glucose (PBG) (mg/dL), hemoglobin A1c (HbA1c) (%, National Glycohemoglobin Standardization Program (NGSP)), and body weight (BW) (kg) from the baseline to the last visit were investigated (from 1 to 6 months). LDL-C was measured directly. The paired-*t* test was used to evaluate the difference between the values before and after treatment. Statistical analysis was performed using JMP version 5.1. Values presented are mean ± SD.

Non-fasting TG was selected rather than fasting TG, due to recent supportive evidence of adapting non-fasting lipid measurement as a reliable indication of the occurrence of CVD events [5]. Samia et al reported that non-fasting lipid levels were similar to fasting lipid levels in association with incident CVD events overall and by randomized statin therapy [6]. Also some reports show that it is difficult to collect a pure fasting TG, since a fasting state occurs for only a short period of the day in a condition of a usual three-times-day meal [7]. And when patients have diabetes or other metabolic dysfunction, the peak of lipid is delayed and high TG levels are sustained for a long time [8], so that would not meet the condition of at least 10 h fasting period [9], which is believed to be a "fasting" state. Another thing, it is difficult to ask all patients to visit without having breakfast in the clinical settings. All together, adapting non-fasting TG is reasonable, as being collectable anytime, patient-friendly and scientifically evident.

Other parameters

Smoking and alcohol consumption have not been changed during the study. So this factor may not affect the results. However smoking patients were 7 (five men, two women) and alcohol habitat patients were 13 (10 men, three women) out of 33 patients. Also, exercise and diet have not been changed during the study, which was in the inclusion criteria.

Results

Baseline clinical and demographic characteristics of the patients are shown in Table 1. Among the 33 cases, 24 were men (72.7%) and nine women (27.3%) with an average age of 60.2 ± 12.8 years. The Pemafibrate dose was 0.1 mg, once daily for all the cases, for an average administrative period of 3.5 ± 1.7 months. Twenty-two cases (66.7%) were given fibrates for the first time. Eleven cases (33.3%) were using fibrates already, seven (21.2%) were given fenofibrates, and four (12.1%) were given bezafibrates. Statins had been used in nine cases (27.2%). The number of diabetic patients was 15 (45.4%). Baseline TG levels were 285.0 (210.5 - 423.0) mg/dL, HDL-C 46.5 ± 12.5 mg/dL, LDL-C 116.4 ± 33.4 g/dL, AST 32.2 ± 16.5 U/L, ALT 36.4 ± 29.0 U/L, CK 180.1 ± 162.8 U/L, Cre 0.8 ± 0.2 mg/dL, PBG 120.0 ± 27.0 mg/dL (n = 29), fasting BG 121.3 ± 13.9 mg/dL (n = 3), HbA1c 6.2 ± 0.7% (n = 26), and BW 76.6 ± 15.6 kg (n = 26). Lipid values after treatment are shown in Tables 2, 3 and 4.

Table 1. Background of Patients

Parameters	
Case number	Men: 24, women: 9
Average age	60.2 ± 12.8 years old
Average administration period	3.5 ± 1.7 months
Administration dose	0.1 mg, once daily
Other fibrates	None: 22 cases
	Fenofibrates: seven cases; bezafibrates: four cases
Use of statins	None: 24 cases
	Statins: nine cases
Baseline TG (non-fasting, mg/dL)	285.0 (210.5 - 423.0) (33)
HDL-C (mg/dL)	46.5 ± 12.5 (32)
LDL-C (mg/dL)	116.4 ± 33.4 (32)
AST (U/L)	32.2 ± 16.5 (33)
ALT (U/L)	36.4 ± 29.0 (33)
CK (U/L)	180.1 ± 162.8 (25)
Cre (mg/dL)	0.8 ± 0.2 (33)
PBG (mg/dL)	120.0 ± 27.0 (29)
FBG (mg/dL)	121.3 ± 13.9 (3)
HbA1c (%)	6.2 ± 0.7 (6)
BW (kg)	76.6 ± 15.6 (26)

Values are n (case numbers) or mean ± SD, and TG is in median and interquartile range. TG: triglyceride; PBG: postprandial blood glucose; FBG: fasting blood glucose; BW: body weight; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CK: creatine kinase; Cre: creatinine; HbA1c: hemoglobin A1c.

After Pemafibrate treatment, average TG levels were significantly reduced by -20.8 ± 47.6% (n = 31, P = 0.006) (Table 2). For those with baseline TG levels ≥ 150 mg/dL, the average TG levels were 299.0 (214.0 - 423.5) mg/dL (n = 32) before treatment, and TG levels significantly reduced by -21.6 ± 48.2% (n = 30, P = 0.006) (Table 3). Similarly, for those with

Table 2. Results

Parameters	Baseline	Post data	Changes	P value
Baseline TG (non-fasting, mg/dL)	285.0 (210.5 - 423.0) (33)	209.0 (137.0 - 273.0) (31)	-20.8 ± 47.6% (rates)	0.006**
HDL-C (mg/dL)	46.5 ± 12.5 (32)	49.8 ± 12.9 (30)	3.9 ± 10.2 (29)	0.0465*
			10.9 ± 20.8% (rates)	0.0091**
LDL-C (mg/dL)	116.4 ± 33.4 (32)	136.1 ± 37.0 (30)	16.6 ± 23.7 (29)	0.0008***
			15.8 ± 22.6% (rates)	0.0008***
AST (U/L)	32.2 ± 16.5 (33)	31.9 ± 14.0 (27)	-2.0 ± 13.5 (27)	0.4390
ALT (U/L)	36.4 ± 29.0 (33)	36.3 ± 30.1 (27)	-1.5 ± 18.3 (27)	0.6701
CK (U/L)	180.1 ± 162.8 (25)	135.4 ± 77.4 (16)	-42.3 ± 95.4 (15)	0.1083
Cre (mg/dL)	0.8 ± 0.2 (33)	0.8 ± 0.3 (21)	0.0 ± 0.1 (21)	0.6894
PBG (mg/dL)	120.0 ± 27.0 (29)	123.3 ± 31.7 (22)	0.0 ± 28.1 (22)	0.9940
FBG (mg/dL)	121.3 ± 13.9 (3)	113.3 ± 11.5 (3)	-8.0 ± 4.4 (3)	0.0863
HbA1c (%)	6.2 ± 0.7 (26)	6.4 ± 0.7 (18)	-0.1 ± 0.2 (16)	0.1984
BW (kg)	76.6 ± 15.6 (26)	77.4 ± 15.6 (22)	0.2 ± 1.5 (19)	0.5326

Values are n (case numbers) or mean ± SD, and TG is in median and interquartile range. TG: triglyceride; PBG: postprandial blood glucose; FBG: fasting blood glucose; BW: body weight; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CK: creatine kinase; Cre: creatinine; HbA1c: hemoglobin A1c. *P < 0.05, **P < 0.01, and ***P < 0.001.

Table 3. TG on Conditions

	Baseline	Post data	Changes	P value
TG ≥ 150 (mg/dL)	299.0 (214.0 - 423.5) (32)	218.5 (147.5 - 277.3) (30)	-21.6 ± 48.2% (rates)	0.006**
TG ≥ 200 (mg/dL)	354.5 (240.0 - 452.5) (28)	236.5 (155.8 - 292.0) (26)	-26.5 ± 48.3% (rates)	0.002**
TG (using fibrates for the first time) (mg/dL)	372.0 (211.0 - 433.5) (22)	208.5 (153.8 - 285.8) (20)	-28.4 ± 37.4% (rates)	0.006**
TG (changing from other fibrates) (mg/dL)	254.0 (208.0 - 366.0) (11)	236.0 (119.0 - 268.0) (11)	-7.0 ± 61.7% (rates)	0.465
TG ≥ 200 and using fibrates for the first time (mg/dL)	411.0 (237.0 - 462.0) (19)	209.0 (172.5 - 294.0) (17)	-34.5 ± 37.2% (rates)	0.006**
TG (mg/dL) with none use of statins	299.0 (205.8 - 466.3) (24)	218.5 (135.8 - 269.3) (24)	-25.4 ± 36.1% (rates)	0.003**
TG (mg/dL) with use of statins	267.0 (215.0 - 412.5) (9)	206.0 (130.5 - 317.5) (9)	-9.5 ± 69.7% (rates)	0.570

Values are n (case numbers) or mean ± SD, and TG is in median and interquartile range. TG: triglyceride. *P < 0.05, **P < 0.01, and ***P < 0.001.

baseline TG levels ≥ 200 mg/dL (n = 28), the average TG levels were 354.5 (240.0 - 452.5) mg/dL (n = 28), and TG levels significantly reduced by -26.5 ± 48.3% (n = 26, P = 0.002) (Table 3). For those who started fibrates for the first time, the average TG levels were 372.0 (211.0 - 433.5) mg/dL (n = 22), and TG levels significantly reduced by -28.4 ± 37.4% (n = 20, P = 0.006). On the other hand, those who changed from other fibrates to Pemafibrate showed a trend of decrease without significance. The average TG levels were initially 254.0 (208.0 - 366.0) mg/dL (n = 11), and reduced by -7.0 ± 61.7% (n = 11, P = 0.465). Patients with TG levels over 200 mg/dL and receiving fibrates for the first time showed a significant decrease in TG levels, by -34.5 ± 37.2% (n = 17, P = 0.003). Therefore, even at a small dose, Pemafibrate effectively decreased TG levels, especially in those who had never used fibrates before and had higher TG levels, and also equivalently to those who were pretreated with average dosage of former other fibrates.

When statins were used, TG results had somewhat different tendency (Table 3). Specifically, patients who were already using statins showed a relatively small decrease in TG levels by -9.5 ± 69.7% (n = 9, P = 0.570), compared to those who were not by -25.4 ± 36.1% (n = 24, P = 0.003), which was a significant decrease. Therefore, the use of statins seemed to affect the changes in TG levels.

Other lipid parameters also varied on conditions. HDL-C levels were significantly increased by 3.9 ± 10.2 mg/dL (n = 29, P = 0.0465), with a change in percentage of 10.9 ± 20.8% (n = 29, P = 0.0091), in agreement to a previous clinical trial [10] (Table 2). Even though the LDL-C changes varied in a broad range from -23 to 65 mg/dL, the mean post levels were not that high (136.1 ± 37.0 mg/dL; n = 30). However, the LDL-C levels significantly increased by 16.6 ± 23.7 mg/dL (n = 29, P = 0.0008). Conversely, different results were obtained when analyzing LDL-C levels in patients with use of statins (Table 4). Patients who were not treated with statins, average LDL-C was 119.7 ± 36 mg/dL (n = 23), but showed a significant increase by 23.2 ± 23.7 mg/dL (n = 21, P = 0.003). While patients who were treated with statins along, average LDL-C was 107.9 ± 25.4 mg/dL (n = 9), and changes were trivial with 1.9 ± 16.6 mg/dL (n = 9, P = 0.7414), without any significance. Only two cases stopped receiving statins when they started treatment with Pemafibrate. Therefore, the use of statins seemed to influence the changes in LDL-C levels.

Liver dysfunction was not observed in any case. Post-treatment levels of AST and ALT were 31.9 ± 14.0 U/L (with a change of -2.0 ± 13.5 U/L; n = 27; P = 0.4390) and 36.3 ± 30.1 U/L (with a change of -1.5 ± 18.3 U/L; n = 27; P = 0.6701), respectively. The increase of CK levels, which often occurs in the use of statins, was not observed. Post-treatment CK levels and changes were 135.4 ± 77.6 U/L (n = 16) and -42.3 ± 95.4 U/L (n = 15, P = 0.1083), respectively. In addition, levels of Cre, PBG, and HbA1c did not significantly change. Levels of Cre were 0.8 ± 0.3 mg/dL (n = 21), with changes of 0.0 ± 0.1 mg/dL (n = 21, P = 0.6894). Levels of PBG were 12.3 ± 31.7 mg/dL (n = 22), with changes of 0.0 ± 28.1 mg/dL (n = 22, P = 0.9940). Levels of HbA1c were 6.4 ± 0.7% (n = 18), with changes of -0.1 ± 0.2% (n = 16, P = 0.1984). BW remained unchanged; levels after treatment were 774 ± 15.6 mg/dL (n = 22), and changes were 0.2 ± 1.5 mg/dL (n = 19, P = 0.5326). Taken together, these results suggested that the half dose of Pemafibrate was safe, with no major adverse events, either with or without combination with statin treatment.

Discussion

From the results obtained in this study, we concluded that the administration of a half dose once-daily Pemafibrate sig-

Table 4. LDL-C on Conditions

	Baseline	Post data	Changes	P value
LDL (mg/dL) with no use of statins	119.7 ± 36.0 (23)	147.4 ± 34.3 (21)	23.2 ± 23.7 (21)	0.003**
	TG: 285.0 (205.0 - 481.0)		22.1 ± 22.9% (rates)	0.0004***
LDL (mg/dL) with use of statins	107.9 ± 25.4 (9)	109.8 ± 30.2 (9)	1.9 ± 16.6 (9)	0.7414
	TG: 267.0 (215.0 - 412.5)		1.9 ± 15.0% (rates)	0.7115

Values are n (case numbers) or mean ± SD, and TG is in median and interquartile range. TG: triglyceride. *P < 0.05, **P < 0.01, and ***P < 0.001.

nificantly decreased TG levels and increased HDL values to descent levels. On the other hand, LDL-C increased by 23.2 ± 23.7 mg/dL ($P < 0.01$) in patients not using statins, while patients using statins did not show such significant change. Therefore, the use of statins may impact the Pemafibrate mechanism for LDL-C values. Statins, which are 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, stimulate LDL-receptors in the liver, thus reducing the absolute concentration of LDL-C. As Pemafibrate stimulates the lipoprotein lipase, one of its target genes, it enhances the catabolic flow of lipoproteins from very low-density lipoprotein (VLDL)/chylomicron and remnant VLDL/chylomicron to LDL. Under such a stimulated catabolic status, both atherogenic remnant and small dense LDL particles should not be accumulated. However, there might be a small increase of LDL-C in non-statin treated patients, due to reaching the saturated capacity of physiological LDL receptors. In consistence with this notion, LDL levels did not increase in statin-treated patients whose LDL-receptors were up-regulated. For these points, further analysis evaluating the size and contents of each lipoprotein is needed to confirm this proposed mechanism of action for Pemafibrate.

The use of statins also seemed to affect the Pemafibrate efficacy of lowering TG concentrations, as changes in TG levels were relatively smaller when using statins than those not using statins. This may be because statins enhance the catabolism of LDL-C, which is associated with the decrease in VLDL/chylomicron particles. Subsequently, those patients who were already using statins might have already had a substantial decrease of TG.

The values of TG have been collected as non-fasting rather than fasting. And it is obvious that it would reflect the similar indications of future occurrence of CVD events and scientifically be reliable as the fasting TG. But on the other hand, non-fasting TG values would differ in a broad range affected by patients' consumption of food, especially quantity and quality of lipids. In this study, we were not using any test meal nor instructing meal to regulate the values of TG. Patients ate and drank whatever and whenever they wanted during the study. This difference might affect the results which could be the limitation of this study carried out in the real practice.

Our study used only half dose from the recommended dose of Pemafibrate. As the phase 2 trial reported [11], fasting TG levels decreased in a dose-dependent manner. Administration of 0.05, 0.1, 0.2, and 0.4 mg of twice daily (BID) induced changes in TG levels by 30.8%, -36.1%, -42.4%, and -42.5%, respectively, which suggested that if the 0.1 mg/day dose of the Pemafibrate is increased, TG levels may reach lower values than the ones obtained in our study. However, because the analyzed TG values in our study were postprandial, their values were affected by the diet. As a matter of fact, the long-term results of phase 3 trial [12] evidenced a -50% decrease when using 0.2 mg BID for fasting TG, while our study, which provided half the dose to the patients, elicited around less than half of the effect, -20.8 ± 47.6% ($n = 31$, $P = 0.006$). Importantly, for this investigation the administered dose was BID, while in our investigation was once daily. This implies that using half dose once daily may result in half the effect, but still with statistically significant effectiveness to lower TG. Therefore, if patients do not tolerate or cannot follow 0.2 mg BID of Pemafibrate, 0.1 mg once-daily therapy could be confidently suggested in real practice.

Moreover, a phase 2 study showed improvement of liver dysfunction in patients with dyslipidemia. Other study reported that Pemafibrate stimulated lipid turnover and upregulated uncoupling protein 3 expression in the liver, which might be related to improved conditions in the presence of non-alcoholic steatohepatitis and nonalcoholic fatty liver diseases [13]. On the contrary, normal liver function was observed before providing Pemafibrate in our case, so could explain that there were no changes.

There is also a report of a significant decrease in serum Cre levels when using Pemafibrate in aged patients with hypertriglyceridemia [14]. In our case, we used half the dose than the one recommended in the previous study. That could explain why we did not obtain statistically significant differences in Cre levels.

Conclusions

This clinical study demonstrated that Pemafibrate could decrease plasma TG and increase HDL-C levels even with a half dose. Furthermore, the treatment did not change LDL-C in statin-treated patients, while induced small increase in non-statin-treated subjects. Thus, we conclude that administration of Pemafibrate together with statins may be a more powerful therapy to effectively treat hypertriglyceridemia and cholesterloremia, without major adverse events, for the prevention of atherosclerosis.

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Financial Disclosure

None to declare.

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

Not applicable.

Author Contributions

CI developed the conceptual framework, collected data, per-

formed statistical analysis and wrote the manuscript in a collaborative fashion with KI.

References

1. Yamada N. Ministry of Health, Labor and Welfare Sciences Research Grant, Prospective study for improving the quality of life, vascular complication and long term prognosis of type 2 diabetic patients, Japan Diabetes Complication Study, Summary research report Fiscal Year 2007 (MHLW GRANTS SYSTEM). http://mhlw-grants.niph.go.jp/niph/search/NIDD00.do?resrchNum=200722056A.
2. Teramoto T, Sakuma T, Nakao K, Yamamoto O, ALWAYS study group. Atorvastatin Lipid lowering Assessment survey in patients with hypercholesterolemia(ALWAYS), Final Report: investigation according to Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012. Ther Res. 2013;34(4):455-483.
3. The ACCORD study group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR, 3rd, Leiter LA, Linz P, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1563-1574.
4. Pradhan AD, Paynter NP, Everett BM, Glynn RJ, Amarenco P, Elam M, Ginsberg H, et al. Rationale and design of the pemafibrate to reduce cardiovascular outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) study. Am Heart J. 2018;206:80-93.
5. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet. 2014;384(9943):626-635.
6. Mora S, Chang CL, Moorthy MV, Sever PS. Association of nonfasting vs fasting lipid levels with risk of major coronary events in the Anglo-Scandinavian cardiac outcomes trial-lipid lowering arm. JAMA Intern Med. 2019;179(7):898-905.
7. Nakamura K, Miyoshi T, Yunoki K, Ito H. Postprandial hyperlipidemia as a potential residual risk factor. J Cardiol. 2016;67(4):335-339.
8. Tanaka A, Tomie N, Nakano T, Nakajima K, Yui K, Tamura M, Numano F. Measurement of postprandial remnant-like particles (RLPs) following a fat-loading test. Clin Chim Acta. 1998;275(1):43-52.
9. Kinoshita M, Yokote K, Arai H, Iida M, Ishigaki Y, Ishibashi S, Umemoto S, et al. Japan Atherosclerosis Society: Comprehensive risk management. In: Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017. J Atheroscler Thromb. 2018;25;846-984.
10. Ishibashi S, Yamashita S, Arai H, Araki E, Yokote K, Suganami H, Jean-Charles F. K-877-04 Study Group: Effects of K-877, a novel selective PPARα modulator (SPPARMα), in dyslipidaemic patients: A randomized, double blind, active- and placebo-controlled, phase 2 trial. Atherosclerosis. 2016;249:36-43.
11. Hennuyer N, Duplan I, Paquet C, Vanhoutte J, Woitrain E, Touche V, Colin S, et al. The novel selective PPARalpha modulator (SPPARMalpha) pemafibrate improves dyslipidemia, enhances reverse cholesterol transport and decreases inflammation and atherosclerosis. Atherosclerosis. 2016;249:200-208.
12. Arai H, Yamashita S, Yokote K, Araki E, Suganami H, Ishibashi S, on behalf of the K-877 Study Group. Efficacy and safety of K-877, a novel selective peroxisome proliferator-activated receptor α modulator (SPPARMα), in combination with statin treatment: Two randomized, double-blind, placebo-controlled clinical trials in patients with dyslipidaemia. Atherosclerosis. 2017;261:144-152.
13. Honda Y, Kessoku T, Ogawa Y, Tomeno W, Imajo K, Fujita K, Yoneda M, et al. Pemafibrate, a novel selective peroxisome proliferator-activated receptor alpha modulator, improves the pathogenesis in a rodent model of nonalcoholic steatohepatitis. Sci Rep. 2017;7:42477.
14. Saito M, Kumagai F, Eto M. Effects of Pemafibrate on plasma lipids and renal function in aged patients with hypertriglyceridemia and renal dysfunction. Jpn Pharmacol Ther. 2018;46:12:1979-1983.