

Clinical Applications of a Novel Selective PPAR α Modulator, Pemafibrate, in Dyslipidemia and Metabolic Diseases

Shizuya Yamashita^{1, 2, 3}, Daisaku Masuda¹ and Yuji Matsuzawa⁴

¹Department of Cardiology, Rinku General Medical Center, Osaka, Japan

²Department of Community Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

³Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

⁴Sumitomo Hospital, Osaka, Japan

Fasting and postprandial hypertriglyceridemia is a risk factor for atherosclerotic cardiovascular diseases (ASCVD). Fibrates have been used to treat dyslipidemia, particularly hypertriglyceridemia, and low HDL-cholesterol (HDL-C). However, conventional fibrates have low selectivity for peroxisome proliferator-activated receptor (PPAR) α . Fibrates' clinical use causes side effects such as worsening liver function and elevating the creatinine level. Large-scale clinical trials of fibrates have shown negative results for prevention of ASCVD. To overcome these issues, the concept of the selective PPAR α modulator (SPPARM α), with a superior balance of efficacy and safety, has been proposed. A SPPARM α , pemafibrate (K-877), was synthesized by Kowa Company, Ltd. for better efficacy and safety. Clinical trials conducted in Japan confirmed the superior effects of pemafibrate on triglyceride reduction and HDL-C elevation.

Conventional fibrates showed elevated liver function test values and worsened kidney function test values, while pemafibrate demonstrated improved liver function test values and was less likely to increase serum creatinine or decrease the estimated glomerular filtration rate. There were extremely few drug interactions even when it was used concomitantly with various statins. Furthermore, unlike many of the conventional fibrates that are renal excretory-type drugs, pemafibrate is excreted into the bile, so it can be safely used even in patients with impaired renal function and there is no increase in its blood concentration.

This novel SPPARM α , pemafibrate, has superior benefit-risk balance compared to conventional fibrates and can be used for patients for whom it was difficult to use existing fibrates, including those who are taking statins and those with renal dysfunction. A large-scale trial PROMINENT using pemafibrate for patients with type 2 diabetes is in progress. In the current review, the latest data on pemafibrate will be summarized.

Key words: Peroxisome proliferator-activated receptor alpha (PPAR α),
Selective PPAR alpha modulator (SPPARM α), Pemafibrate, Triglycerides, Dyslipidemia

1. Background to the Development of Pemafibrate as the First SPPARM α in the World

Fibrate development stemmed from the discovery of phenylethyl acetate, an ester that reduced lipids from agricultural chemical ingredients in the 1950s¹. Fibrates were subsequently developed, starting with clofibrate, which functioned as a lipid-lowering agent. However, fibrates' mechanisms of action remained elusive for a long time. Elucidating the structure of

peroxisome proliferator-activated receptor (PPAR)² and thereafter, PPAR subtype demonstrated that PPAR α was intimately involved in regulating lipid metabolism since it was associated with the transcription of genes involved in the reduction of serum triglycerides (TG) and increase in high-density lipoprotein (HDL) cholesterol (HDL-C). It was also clarified that fibrates act on PPAR α and elicit their biological effects^{3, 4}. However, while activation of PPAR α by fibrates exhibited improved lipid levels, various off-

Address for correspondence: Shizuya Yamashita, Department of Cardiology, Rinku General Medical Center, Izumisano, Osaka 598-8577, Japan
E-mail: shizu@imed2.med.osaka-u.ac.jp

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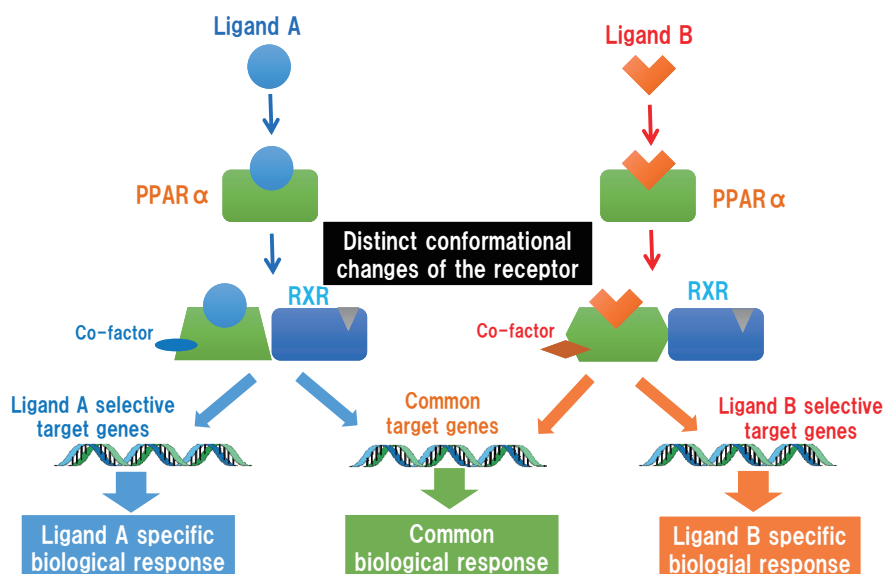


Fig. 1. The Concept of SPPARM α

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target effects, such as deterioration in liver and kidney function test values, were observed, which were difficult to attenuate.

Several large-scale clinical trials using fibrates have previously been conducted. In the Helsinki Heart Study⁵⁾ and VA-HIT study⁶⁾ for gemfibrozil, it was confirmed, for the first time, that fibrates have a significant inhibitory effect on cardiovascular (CV) events, which were the primary endpoints of the trials. However, a report indicated that drug-drug interactions between gemfibrozil and some statins (cerivastatin) caused a high incidence of rhabdomyolysis in patients⁷⁾. In subsequent trials, such as the BIP study (bezafibrate)⁸⁾, FIELD study (fenofibrate)⁹⁾, and the ACCORD-lipid study (fenofibrate on top of simvastatin)¹⁰⁾, primary endpoints could not be achieved, and the clinical efficacy of fibrates could not be reliably demonstrated. However, in a meta-analysis of fibrates¹¹⁾, fibrates' inhibitory effects on CV events were demonstrated, and the event inhibitory effect was shown for each test, particularly in analysis of the subclasses of patients with high TG and low HDL-C¹²⁾. On the other hand, the meta-analysis showed no significant reduction in the total mortality rate upon the administration of fibrates. Statin meta-analyses by the Cholesterol Treatment Trialists' (CTT) Collaboration¹³⁻¹⁵⁾ showed contrasting results, indicating that administration of statins significantly reduced the total mortality rate, but the aforementioned off-target effects of fibrates may have offset their efficacy.

In these circumstances, a novel notion of selective PPAR α modulator (SPPARM α) was proposed by

Fruchart^{16, 17)}. The principle of SPPARM α action is shown in **Fig. 1**. Multiple ligands with a variety of structures, including free fatty acids and fibrates, bind to PPAR α , inducing downstream, ligand-specific structural changes and responses upon association with ligand-specific cofactors. SPPARM α introduces the concept of a drug that selectively regulates transcription of genes involved in beneficial actions among the PPAR α target genes. Thus, it should have a better benefit-risk balance compared to the existing PPAR α agonists. Based on the concept of SPPARM α , Kowa Company, Ltd. developed pemafibrate (K-877, Parmodia[®] tablet), while screening for a compound with potent PPAR α activity and high PPAR α selectivity. A 2-aminobenzoxazole ring was inserted into an existing fibric acid skeleton, the length of the carbon chain was modified, and a phenoxyalkyl group was introduced to enable synthesis of this drug as a highly active and selective PPAR α agonist¹⁸⁾. The PPAR α activation by pemafibrate was reported to be >2,500 times stronger than fenofibric acid, the active form of fenofibrate, making it an extremely selective PPAR α agonist (subtype-selectivity >5,000-fold for PPAR γ , and >11,000-fold for PPAR δ , respectively)^{19, 20)} (**Table 1**).

Pemafibrate (R-36 form in the literature) showed an equivalent or better TG-lowering activity, compared to fenofibric acid in rats, without increasing the liver weight¹⁸⁾. Transcriptome analysis using rats and human liver cells, also suggested that the induced and suppressed gene groups differ between pemafibrate and fenofibrate²¹⁾. Pemafibrate has a Y-shaped structure, unlike conventional fibrates (**Fig. 2**). The ligand-

Table 1. Activity of PPAR Agonists in Cell-Based Transactivation Assays

Compound	Human receptor EC ₅₀ (μ M)		
	PPAR α	PPAR γ	PPAR δ
pemafibrate ¹⁾	0.00080	4.3	9.0
Wy-14643 ²⁾	5.0	60	35
clofibrate ^{2)*}	55	~500	Ia at 100
fenofibrate ^{2)*}	30	300	Ia at 100
bezafibrate ²⁾	50	60	20
GW 9578 ²⁾	0.05	1.0	1.4
troglitazone ²⁾	Ia	0.55	Ia
pioglitazone ²⁾	Ia	0.58	Ia
rosiglitazone ²⁾	Ia	0.043	Ia
KRP-297 ²⁾	0.85	0.083	9.1
JTT-501 ^{2)*}	1.9	0.083	Ia
SB 213068 ²⁾	0.74	0.066	Ia
GI 262570 ²⁾	0.45	0.00034	Ia
GW 1929 ²⁾	Ia	0.0062	Ia
GW 7845 ²⁾	3.5	0.00071	Ia
GW 0207 ²⁾	Ia	0.044	Ia
L-796449 ²⁾	0.0041	0.0052	0.0079
L-165041 ²⁾	10	5.5	0.53
GW 2433 ²⁾	0.17	2.5	0.19

Ia=Inactive at 10 μ M or the concentration indicated. *Data are presented for the active metabolites.

¹⁾Takizawa T, Inokuchi Y, Goto S, Yoshinaka Y, Abe K, Inoue K and Tanabe S: Abstract 12867: The Mechanism of K-877, a Highly Potent and Selective PPARalpha Modulator, on Regulation of Synthesis, Secretion and Metabolism of Triglycerides and Cholesterol. Circulation, 2013; 128: A12867 [AHA2013 Abstract]

²⁾Willson TM, Brown PJ, Sternbach DD and Henke BR: The PPARs: from orphan receptors to drug discovery. J Med Chem, 2000; 43: 527-550

Y-shaped structure with a potent PPAR α activity and high PPAR α selectivity

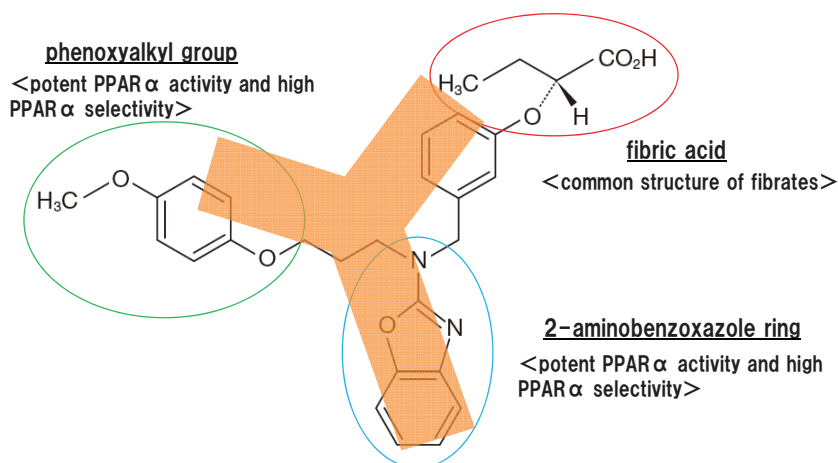


Fig. 2. Structural Conformation of Pemafibrate Favoring Better Selectivity for PPAR α

Table 2. Classification of Medications Used to Treat Dyslipidemia According to Their Efficacy

Category	LDL-C	Non-HDL-C	TG	HDL-C	Major drug name
Statin	↓↓~↓↓↓	↓↓~↓↓↓	↓	—~↑	Pravastatin, Simvastatin, Fluvastatin, Atorvastatin, Pitavastatin, Rosuvastatin
Intestinal cholesterol transporter inhibitor (Cholesterol absorption inhibitor)	↓↓	↓↓	↓	↑	Ezetimibe
Anion exchange resin	↓↓	↓↓	↑	↑	Colestimide, Cholestyramine
Probucol	↓	↓	—	↓↓	Probucol
PCSK9 inhibitor	↓↓↓	↓↓↓	↓~↓↓	—~↑	Evolocumab, Alirocumab
MTP inhibitor*	↓↓↓	↓↓↓	↓↓↓	↓	Lomitapide
Fibrate	↑~↓	↓	↓↓↓	↑↑	Bezafibrate, Fenofibrate, Clofibrate, Clofibrate
Selective peroxisome proliferator-activated receptor α modulator (SPPARM α)	↑~↓	↓	↓↓↓	↑↑	Pemafibrate
Nicotinic acid derivative	↓	↓	↓↓	↑	Niceritrol, Nicomol, Tocopheryl nicotinate
N-3 polyunsaturated fatty acid	—	—	↓	—	Ethyl icosapentate, Omega-3-acid ethyl ester

*Applicable only to patients with homozygous FH.

↓↓↓↓ : $\leq -50\%$, ↓↓↓ : $-30\% \sim -50\%$, ↓↓ : $-20\% \sim -30\%$, ↓ : $-10\% \sim -20\%$, ↑ : $10\% \sim 20\%$, ↑↑ : $20\% \sim 30\%$, — : $-10\% \sim 10\%$

binding domain in PPAR α is Y-shaped, and when the Y-shaped pemafibrate binds with the entire cavity area, like a key in a lock, the structure of PPAR α undergoes specific conformational changes due to the strong interaction, and a new region is exposed. This region is the PPAR α co-activator, which strongly activates PPAR α by binding with peroxisome proliferator-activated receptor- γ coactivator 1 α (PGC-1 α). Studies suggest that, in addition to fibric acid, which is common to the conventional fibrates, a Y-shaped structure with suitably arranged aminobenzoxazole and dimethoxybenzene is ideal for SPPARM α ²². Thus, pemafibrate has an ideal structure that corresponds to the concept of SPPARM α .

Pemafibrate was launched in Japan in June 2018, ahead of the rest of the world, and is expected to have a superior benefit-risk balance compared to the conventional fibrates. The Japan Atherosclerosis Society, along with overseas evaluations, has positioned pemafibrate as a drug classified into the SPPARM α category, which is completely different from the fibrates (Table 2)²³.

2. Results of Clinical Trials of Pemafibrate

2.1 Comparative Studies with Fenofibrate

The results of clinical studies on pemafibrate in Japan were reviewed. The results of three Japanese

clinical studies demonstrated the high efficacy of pemafibrate, compared to fenofibrate²⁴⁻²⁶. The TG-lowering action of 0.4 mg/day pemafibrate was greater than that of 100 mg/day (80 mg/day with tablet conversion), and 106.6 mg/day fenofibrate, respectively, and was equivalent to 200 mg/day fenofibrate (160 mg/day with tablet conversion) (Fig. 3). The incidence of adverse events observed with pemafibrate administration was equivalent to placebo and was markedly lower than fenofibrate, with a particularly low proportion of adverse events related to kidney and liver function (Table 3). Previous reports have indicated that existing fibrates worsened kidney function test values, such as serum creatinine, cystatin C, and estimated glomerular filtration rate (eGFR)²⁷⁻²⁹. Pemafibrate exhibited a relatively significant lower elevation in serum creatinine and cystatin C, and a comparatively lower reduction in eGFR than those seen with fenofibrate, and less exacerbation in test values related to kidney function. It is well known that administration of fenofibrate elevates liver function test values, and the mechanism of action includes PPAR α activation³⁰. The liver function test values for alanine aminotransferase (ALT) and gamma-glutamyl transferase (γ -GT) did not show an elevation with pemafibrate when compared to fenofibrate; conversely, these values tended to decrease. This may be a characteristic clinical effect of the SPPARM α , pemafibrate.

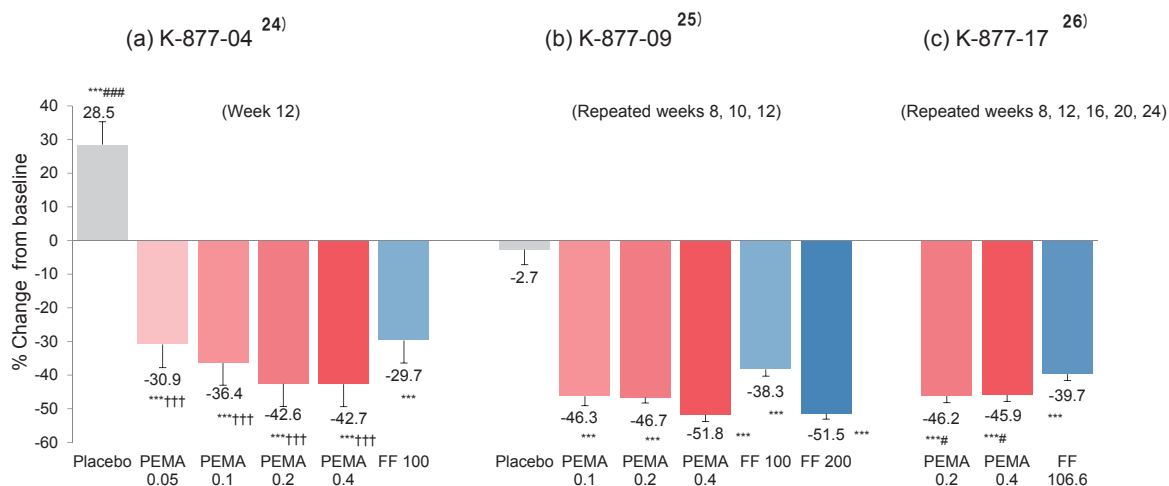


Fig. 3. Effects of Pemafibrate on Serum Triglycerides Levels

PEMA 0.05, pemafibrate 0.05 mg/day; PEMA 0.1, pemafibrate 0.1 mg/day; PEMA 0.2, pemafibrate 0.2 mg/day; PEMA 0.4, pemafibrate 0.4 mg/day; FF100, fenofibrate micronized capsule 100 mg/day; FF200, fenofibrate micronized capsule 200 mg/day; FF106.6, fenofibrate tablet 106.6 mg/day.

The data are presented as the least squares mean \pm standard error. (a) *** $p < 0.001$ vs. baseline. ††† $p < 0.001$ vs. placebo (Dunnett). ### $p < 0.001$ vs. fenofibrate 100 mg. (b) In repeated measures ANCOVA (baseline as the covariate and weeks 8, 10, and 12 as repetition points). *** $p < 0.001$ vs. baseline. (c) In repeated measures ANCOVA (baseline as the covariate and weeks 8, 12, 16, 20, and 24 as repetition points). *** $p < 0.001$ vs. baseline. # $p < 0.05$ vs. fenofibrate 106.6 mg.

Table 3. Incidence of Adverse Events by Pemafibrate and Fenofibrate

Study	Types	Placebo	Pemafibrate				Fenofibrate		
			0.05 mg	0.1 mg	0.2 mg	0.4 mg	100 mg	106.6 mg	200 mg
K-877-04 Ishibashi S, <i>et al.</i> ¹⁾	Total	17/36 (47.2%)	21/37 (56.8%)	12/37 (32.4%)	18/38 (47.4%)	16/39 (41.0%)	21/37 (56.8%)	-	-
	Liver-related	4/43 (9.3%)	-	2/45 (4.4%)	3/128 (2.3%)	7/85 (8.2%)	13/85 (15.3%)	-	34/140 (24.3%)
K-877-09 Arai H, <i>et al.</i> ²⁾	Total	18/43 (41.9%)	-	15/45 (33.3%)	49/128 (38.3%)	34/85 (40.0%)	36/85 (42.4%)	-	79/140 (56.4%)
	Rhabdomyolysis-/ myopathy-related	3/43 (7.0%)	-	1/45 (2.2%)	2/128 (1.6%)	2/85 (2.4%)	3/85 (3.5%)	-	7/140 (5.0%)
K-877-17 Ishibashi S, <i>et al.</i> ³⁾	Total	-	-	-	28/73 (38.4%)	37/74 (50.0%)	-	45/76 (59.2%)	-
	Liver-related	-	-	-	5/73 (6.8%)	0/74	-	30/76 (39.5%)	-
	Kidney-related	-	-	-	0/73	0/74	-	3/76 (3.9%)	-

¹⁾ Ishibashi S, Yamashita S, Arai H, Araki E, Yokote K, Suganami H, Fruchart JC and Kodama T: Effects of K-877, a novel selective PPAR α modulator (SPPARM α), in dyslipidaemic patients: A randomized, double blind, active- and placebo-controlled, phase 2 trial. *Atherosclerosis*, 2016; 249: 36-43

²⁾ Arai H, Yamashita S, Yokote K, Araki E, Suganami H and Ishibashi S: Efficacy and safety of pemafibrate versus fenofibrate in patients with high triglyceride and low HDL cholesterol levels: A multicenter, placebo-controlled, double-blind, randomized trial. *J Atheroscler Thromb*, 2018; 25: 521-538

³⁾ Ishibashi S, Arai H, Yokote K, Araki E, Suganami H and Yamashita S: Efficacy and safety of pemafibrate (K-877), a selective peroxisome proliferator-activated receptor alpha modulator, in patients with dyslipidemia: Results from a 24-week, randomized, double blind, active-controlled, phase 3 trial. *J Clin Lipidol*, 2018; 12: 173-184

2.2 Effect of Pemafibrate on Lipid Metabolism

High fasting TG levels are directly linked to increased TG-rich lipoproteins (TRL), such as chylomicrons (CM) derived from small intestines, very low-density lipoprotein (VLDL) derived from the liver, and their TG-hydrolyzed remnant lipoproteins (CM remnants, VLDL remnants (intermediate-density lipoprotein [IDL])). These remnant lipoproteins have proatherogenic properties^{31, 32}. Increased TRL often increases small dense low-density lipoprotein (LDL), which strongly correlates with atherosclerosis, and reduces HDL-C. Administration of pemafibrate significantly reduces remnant lipoprotein cholesterol (RemL-C), non-HDL-C, Apolipoprotein B (ApoB), ApoB48, and ApoC3 levels. Furthermore, the results of the subfractions of LDL and HDL, evaluated by high performance liquid chromatography (HPLC) (Liposearch, Skylight Biotech, Tokyo, Japan), showed that dose-related reductions by pemafibrate were observed in small LDL particles while dose-dependent increases were demonstrated in small HDL particles²⁴.

A recent study reported that non-fasting TG levels are a better indicator of CV events than fasting TG³³. In Japan, it was also reported that non-fasting TG is one of the risk factors for coronary artery disease (CAD) similar to fasting TG³⁴. Postprandial hyperlipidemia, a metabolic condition with a delayed metabolism of CM remnants after eating, increases susceptibility to CV events, including CAD. Postprandial hyperlipidemia is characterized by 1) higher serum TG levels after meal, 2) the peak of serum TG concentration is delayed, and 3) failing to decline to the pre-meal levels even after 8 h³⁵. Pemafibrate (0.4 mg/day) was administered for four weeks in dyslipidemic patients. The effect of pemafibrate on postprandial hyperlipidemia was demonstrated by a reduction in TG, RemL-C, and ApoB-48 in both fasting and non-fasting states³⁶. Sairyo *et al.* reported that pemafibrate tended to inhibit the expression of *Npc1l1* and *Mttp* mRNA in the small intestine mucosa more strongly than fenofibrate in mice fed a high-fat diet (HFD)³⁷. Similarly, Takei *et al.* reported that pemafibrate inhibited the expression of cholesterol transporter *Npc1l1* and promoted expression of *Abca1* in the small intestine of *Ldlr*^{-/-} mice. These two actions were mediated by the activation of PPAR α ³⁸. These reports suggest that pemafibrate may attenuate postprandial hyperlipidemia, by repressive effects on CM synthesis and secretion processes, via suppression of cholesterol absorption by *Npc1l1*, in addition to PPAR α activation in the small intestines.

Pemafibrate is also believed to inhibit VLDL secretion from the liver by upregulating genes related to fatty acid β -oxidation^{19, 38}, in addition to fibroblast

growth factor 21 (FGF21). FGF21 is also known to be involved in fatty acid β -oxidation and is downstream of PPAR α ^{39, 40}. Furthermore, FGF21 is known to reduce VLDL secretion from the liver by regulating fatty acid uptake by adipose tissue⁴¹. Pemafibrate increases FGF21 expression even at smaller doses^{19, 38, 42}, which may be one of the mechanisms that inhibits VLDL secretion.

Lipoprotein lipase (LPL) promotes the catabolism of CM secreted from the intestine and VLDL secreted from the liver. An increase in LPL activity that affects CM and VLDL catabolism has been demonstrated in animal studies upon pemafibrate administration^{37, 38}. Increased LPL activity upon pemafibrate administration is linked to increased LPL synthesis due to the PPAR α activation. Furthermore, pemafibrate reduced ApoC3 levels, which inhibits LPL, and also downregulated angiotensin-like 3 (Angptl3), which in turn suppresses LPL activity¹⁹. Fibrates can also possibly affect ApoA5 levels due to PPAR α activation⁴³.

We have developed an algorithm for calculating the number of particles in 19 of the 20 lipoprotein fractions obtained from HPLC analysis data⁴⁴. The results of a sub-analysis from pemafibrate Phase 2 study²⁴ confirmed fewer small LDL particles which are involved in atherosclerosis and more small HDL particles which have a strong anti-atherosclerotic function⁴⁵. Reduced cholesterol efflux capacity (CEC) of HDL correlated with the presence of CAD, and CEC showed an inverse correlation to the risk of CV events⁴⁶. Thus, CEC is gaining attention as a new CAD risk factor. Smaller-sized HDLs are thought to have stronger CEC⁴⁷. We showed that administering pemafibrate 0.4 mg/day for 4 weeks to patients with dyslipidemia significantly increased the CEC from macrophages to HDL in the pemafibrate group as compared to the placebo group³⁶. In this study, the HDL-C, HDL3-C, pre β 1HDL, and ApoA-1 levels increased in the pemafibrate group. Pemafibrate also increased FGF21 levels, which are known to increase the expression of ATP binding cassette transporter A1 (ABCA1) and ATP binding cassette transporter G1 (ABCG1), ABC proteins involved in the releasing cholesterol from macrophages⁴⁸ (Fig. 4)^{19, 21, 36-38, 49}.

2.3 Effect of Co-administration of Pemafibrate and Statins

Two clinical studies of combined treatment with pemafibrate and statins have been reported⁵⁰. A 12-week administration of pemafibrate to patients with dyslipidemia taking pitavastatin, with a fasting TG of ≥ 200 mg/dL and a non-HDL-C of ≥ 150 mg/dL, reduced the fasting TG values by 6.9% in the pla-

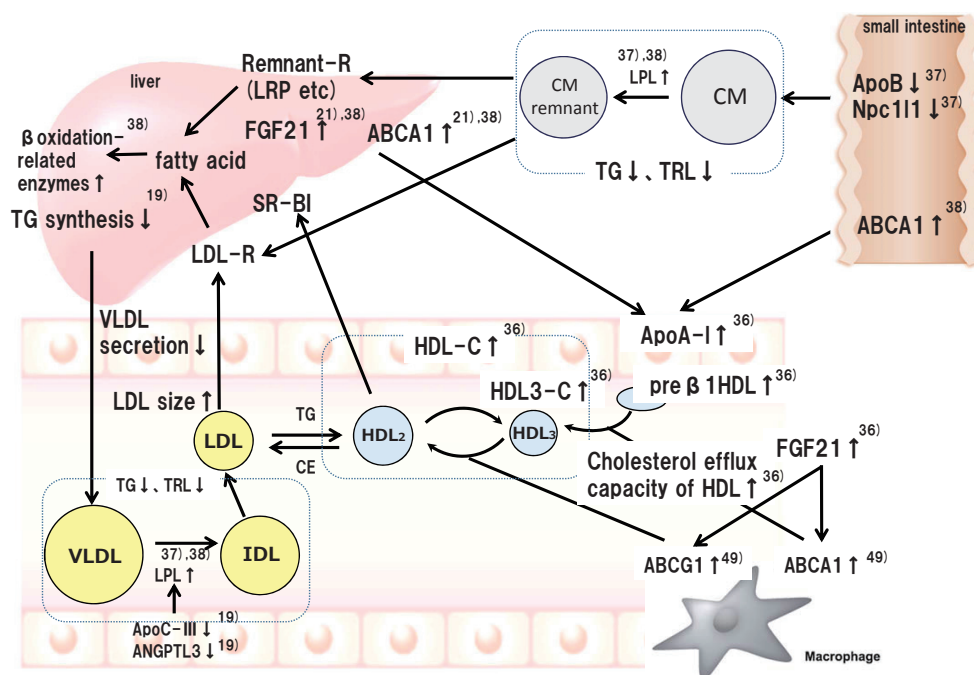


Fig. 4. Mechanism of Action of Pemafibrate on Lipoprotein Metabolism in the Liver, Small Intestine, and Macrophages

ABCA1, ATP-binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; ANGPTL3, angiopoietin-like 3; Apo, apolipoprotein; CE, cholesteryl ester; CM, chylomicron; FGF21, fibroblast growth factor 21; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-R, low-density lipoprotein receptor; LPL, lipoprotein lipase; LRP, low-density lipoprotein receptor-related protein; Npc111, niemann-pick c1-like 1; Remnant-R, remnant receptor; SR-BI, scavenger receptor class B type I; TG, triglyceride; TRL, triglyceride-rich lipoprotein; VLDL, very low-density lipoprotein.

cebo group, 46.1% in the 0.1 mg/day pemafibrate group, 53.4% in the 0.2 mg/day group, and 52.0% in the 0.4 mg/day group, respectively, demonstrating a superior fasting TG reducing activity of pemafibrate. In the long-term study, where 0.2–0.4 mg/day pemafibrate was administered for 24 weeks to patients with dyslipidemia (TG \geq 200 mg/dL) treated with any of these statins; pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin, or pitavastatin, pemafibrate demonstrated stable TG reduction over the mentioned period. Furthermore, there was no significant increase in adverse effects or clinical concerns associated with pemafibrate compared to placebo in any of the studies. As seen in the studies not combined with statins, pemafibrate decreased liver function test values and had little effects on kidney function test values.

Combined treatment with fibrates and statins increases the risk of rhabdomyolysis, particularly in patients with compromised kidney function. There is a particularly high incidence of rhabdomyolysis in patients using a combination of gemfibrozil and cerivastatin, which was reported as a typical case of drug-drug interaction⁷⁾. As a result, the sale of cerivastatin

worldwide was halted. One possible mechanism of the onset of rhabdomyolysis on co-administration of these two drugs is thought to be the inhibition of cerivastatin metabolism by gemfibrozil, thereby increasing cerivastatin exposure in patients. Drug interaction studies have been performed in healthy male volunteers with pemafibrate and high doses of various statins (pravastatin, simvastatin, fluvastatin, atorvastatin, pitavastatin, or rosuvastatin)⁵¹⁾. When pemafibrate was administered to healthy adults combined with various statins, there was no major change in C_{max} or areas under the curve in pemafibrate or in any of the statins. There was a decrease in the blood concentration of a single statin, simvastatin, and the simvastatin open acid form, but the HMG-CoA reductase inhibitory activity was still maintained. Hence, it has been confirmed that pemafibrate does not trigger drug interactions with statins.

2.4 Pemafibrate Administration to Patients with Impaired Kidney Function

Pemafibrate has a characteristic excretion route, mainly from the liver, with only 14.5% excretion in

Table 4. Major Excretion Route of SPPARM α and Fibrates, and Pharmacokinetics in Patients with Kidney Dysfunction

Category	Major drug name	Major excretion route	Excretion into the urine
Fibrates	Clofibrate	Kidney	95 ~ 99% ¹⁾
	Clinofibrate	Liver	≤ 1% ²⁾
	Bezafibrate	Kidney	69.1% ³⁾
	Fenofibrate	Kidney	64% ⁴⁾
	Gemfibrozil	Kidney	70% ⁵⁾
SPPARM α	Pemafibrate	Liver	14.5% ^{※ 6)} ※ Active form: < 0.5%

¹⁾ <https://pubchem.ncbi.nlm.nih.gov/compound/2796>. Accessed on 4 September 2018

²⁾ Sumitomo Dainippon Pharma Co., Ltd., Interview Form of Lipoclin Tab. 200, October 2018 [Japanese]

³⁾ Kissei Pharmaceutical Co., Ltd., Interview Form of Bezator SR Tab. 100 mg 200 mg, October 2018 [Japanese]

⁴⁾ ASKA Pharmaceutical Co., Ltd., Interview Form of Lipidyl Tablets, October 2018 [Japanese]

⁵⁾ FDA Approved Drug Products, Parke-Davis, Division of Pfizer Inc., LOPID (Gemfibrozil Tablets, USP) [package insert]. NY, NY; April 2018. <https://www.accessdata.fda.gov/scripts/cder/daff/index.cfm?event=overview.process&applno=018422>

⁶⁾ Hounslow N, Mair S, Suganami H and Nakamura M: Pemafibrate has high bioavailability and is principally excreted via the liver. *Atherosclerosis Supplements*, 2018; 32: 157 [ISA2018 Abstract]

the urine⁵²⁾. Pemafibrate is predominately metabolized in, and is almost exclusively excreted from, the liver. The main plasma metabolites are benzyl oxidized oxidant and a mixture of glucuronic acid conjugate and N-dealkylated dicarboxylic acid⁵³⁾. The urinary excretion rate of unaltered pemafibrate is < 0.5%, and almost all the metabolized compounds excreted in the urine show no activity as PPAR α agonists.

Pemafibrate exposure was not dependent on renal dysfunction severity⁵⁴⁾. Long-term administration of pemafibrate was found to be effective and safe in patients with dyslipidemia, including patients with impaired kidney function, since there was no increase in blood concentrations of pemafibrate, even with repeated dosage⁵⁵⁾. The main fibrates currently in use are bezafibrate and fenofibrate. These are renal excretory drugs, and increased blood concentration has been confirmed in patients with impaired renal function. Patients with high TG and low HDL-C, presenting a decreased kidney function, have been extremely difficult to treat because available drugs are limited. However, theoretically, pemafibrate may be safely administered to patients with decreased kidney function, as this drug is a SPPARM α and not excreted through the kidneys (Table 4). As stated above, pemafibrate may present an improved benefit-risk balance and can be considered to be a beneficial drug for patients with a limited ability to use conventional fibrates.

2.5 Non-lipid Effects of Pemafibrate

Long-term administration of pemafibrate in patients with hypertriglyceridemia and type 2 diabetes

has revealed lower fasting blood glucose and insulin levels compared to placebo group⁵⁶⁾. A clinical study investigating the effect of pemafibrate on liver or peripheral insulin resistance using a hyperinsulinemic-euglycemic clamp⁵⁷⁾ showed that pemafibrate significantly increased the rate of glucose uptake by the liver and improved insulin resistance. In mice with diet-induced obesity, pemafibrate not only reduced plasma TG, but was also expected to show metabolic effects such as inhibition of a HFD-induced weight gain, reduced plasma glucose and insulin, increased plasma FGF21, upregulation of genes related to thermogenesis and fatty acid oxidation, and improvement in obesity-induced metabolic abnormalities⁴²⁾.

PPAR α knockout mice have been reported to exhibit phenotypes, such as severe fatty liver and steatohepatitis⁵⁸⁾. Non-alcoholic steatohepatitis (NASH) patients had lower PPAR α expression in the liver⁵⁹⁾, so PPAR α agonists have attracted attention as therapeutic agents for non-alcoholic fatty liver disease (NAFLD). However, while a number of reports suggest fibrates' efficacy on NAFLD in animal studies⁶⁰⁻⁶²⁾, its efficacy in clinical practice has been relatively unclear. One possible reason for poor clinical performance of fibrates may be associated with the adverse reactions, leading to liver and kidney dysfunction which may eventually lower the drugs' efficacy. Therefore, we believe that SPPARM α , pemafibrate, can be a proof-of-concept drug to improve metabolic abnormalities better than existing fibrates, and can be expected to have an enhanced therapeutic effect on NASH/NAFLD. Pemafibrate improves liver function and histological findings in a number of rodent

Table 5. Study Design of PROMINENT⁷³⁾

Patients	Type 2 diabetes with fasting TG \geq 200 mg/dL and $<$ 500 mg/dL and HDL-C \leq 40 mg/dL
Primary Endpoint	4-component composite endpoint of 1) nonfatal myocardial infarction, 2) nonfatal ischemic stroke, 3) hospitalization for unstable angina requiring unplanned coronary revascularization, or 4) cardiovascular death
Treatment	Pemafibrate 0.4 mg/day (BID) vs Placebo
Design	Multi-regional, randomized, double-blind, placebo-controlled
Estimated Enrollment	10,000 patients
Estimated Period	March 2017—May 2022
Directors	Paul Ridker, Aruna Pradhan (CCVDP & The Brigham and Women's Hospital)

NASH/NAFLD models, including the suppression of fatty liver, inflammation, ballooning and fibrosis^{63, 64}. Pemafibrate is believed to help improve NAFLD pathology by regulating genes that govern lipid transport in and out of the liver, β -oxidation, and by improving energy metabolism by upregulation of uncoupling protein 3 (UCP3) genes. In clinical practice, administration of pemafibrate reduces serum ALT, γ -GT, alkaline phosphatase (ALP), and total bilirubin, especially in patients whose liver function values exceeded the baseline reference values⁶⁵. These results suggest that pemafibrate may be effective for treating fatty liver, NASH/NAFLD, or even primary biliary cholangitis (PBC).

A Phase 2 study evaluating the therapeutic effect of pemafibrate on NAFLD is currently underway in Japan (ClinicalTrials.gov Identifier: NCT03350165). A pharmacokinetic study is also being implemented for pemafibrate in patients with PBC (JapicCTI-173728).

3. Effect of Pemafibrate on Atherosclerosis

The main aim of treating dyslipidemia with pemafibrate is to prevent CV events. There are a number of reports that suggest an anti-atherosclerotic effect of pemafibrate. In human apoE2 knock-in mice which are fed a high-fat, high-cholesterol diet (Western Diet), pemafibrate administration reduced plasma total cholesterol, non-HDL-C and TG, and increased HDL-C. These mice also showed a downregulation in the transcription levels of small intestine ApoB mRNA, and liver ApoC-III mRNA, which demonstrated that pemafibrate (0.1 mg/kg body weight) exerted a superior effect equivalent to or better than fenofibrate treatment (250 mg/kg body weight). The area of atherosclerotic lesions was reduced further with 1 mg/kg pemafibrate treatment than with 250 mg/kg

fenofibrate. The mRNA expression of vascular cell adhesion molecule-1 (VCAM-1), F4/80 and interleukin-6 (IL-6) at the lesion site was also inhibited significantly, indicating pemafibrate's anti-inflammatory effect⁴⁹. Administration of pemafibrate in LDL receptor knockout mice resulted in reduced liver ApoC3 levels, and, in the event of vascular disorders, there was reduced neointimal formation and suppressed macrophage accumulation. This, in turn, is believed to inhibit CD64-positive cells in monocytes, inhibit M1 polarization in IFN γ -stimulated macrophages, and increase NcoR1 2 levels (co-repressor of pro-inflammatory cytokines), which decrease with IFN γ stimulation^{66, 67}. Administration of pemafibrate to LDL knockout mice fed a high-fat, high-cholesterol diet markedly reduced the lipid deposition area within the aortic sinus. Furthermore, the MOMA-2 positive area was reduced by 33% compared to the control, suggesting inhibited macrophage infiltration into the plaques⁶⁸. Pemafibrate (30 mg/day) was administered for 35 days in hyperlipidemia cardiovascular stent model pigs, with the stent indwelled on day 7, and the animals were observed for the following 28 days. The results showed the neointimal formation volume was reduced by 26.3% in the pemafibrate group compared to the control group, and pemafibrate also inhibited the accumulation of inflammatory cells caused by the placement of the stent⁶⁹. Furthermore, balloon failure was induced in an LDL receptor knockout pig model two weeks after starting administration of pemafibrate. Eight weeks later, there was a significant reduction in macrophage ratio in the plaques in the pemafibrate group compared to the control group. The mRNA levels of c-Jun, nuclear factor kappa-B (NF- κ B) and matrix metalloproteinase-9 (MMP-9) also showed a significant reduction in the pemafibrate

group as compared to the control group⁷⁰). These results suggest that pemafibrate has a more potent anti-atherosclerotic effect than fenofibrate.

Fibrates inhibit the expression of fibrinogen by activating PPAR α , and reduced fibrinogen level is a downstream effect common to all fibrates⁷¹). The results of the BIP study, a large-scale clinical study on bezafibrate, reported fibrinogen is a predictor of mortality⁷²), which suggests that reduction of fibrinogen levels is one of the mechanisms whereby fibrates inhibit CV events. Pemafibrate has also been confirmed to have a superior fibrinogen reducing effect than fenofibrate²⁴).

4. Future Expectations

The large-scale clinical study PROMINENT (Pemafibrate to Reduce cardiovascular Outcomes by reducing triglycerides IN diabetic patients), implemented to verify the effect of pemafibrate on inhibiting CV events in humans, is currently underway in 24 countries worldwide, including Japan, the U.S., the U.K., and Russia. The PROMINENT study aims to recruit 10,000 patients with type 2 diabetes who also have high TG/low HDL-C, with LDL cholesterol (LDL-C) controlled by drugs, including statins (ClinicalTrials.gov Identifier: NCT03071692 [Table 5](#))⁷³).

Fibrates are effective against diabetic microvascular disorders, as shown in a number of large-scale clinical studies⁷⁴). In the FIELD study, where fenofibrate was administered to patients with type 2 diabetes, the results demonstrated efficacy in the treatment of diabetic retinopathy and diabetic nephropathy, including a reduced number of photocoagulation procedures required for diabetic retinopathy and amelioration of microalbuminuria^{9, 75}). Administration of pemafibrate in db/db mice was reported to reduce NAD(P)H oxidase-4 (NOX4) expression associated with inhibiting protein kinase C (PKC) activity, reduce the diacylglycerol content in the kidneys, and reduce kidney damage by oxidative stress⁷⁶). Thus, pemafibrate should possess an anti-inflammatory and anti-oxidative function and, hence, have a favorable effect on diabetic microvascular disorders. In the PROMINENT study, the PROMINENT-Eye Ancillary Study (ClinicalTrials.gov Identifier: NCT03345901) is also in progress as a sub-study to evaluate pemafibrate's effect in inhibiting the progression of retinopathy. The study is expected to clarify whether pemafibrate has an effect on diabetic microvascular disorders. Since pemafibrate is a novel class of drug SPPARM α distinct from fibrates, it may have quite new efficacy on diabetic complications. Diabetic patients usually have reduced eGFR due to nephropathy; however, conventional

fibrates could not be used because they are renally metabolized. Pemafibrate can be used for diabetic patients with nephropathy. Thus, it could become an essential drug for diabetic patients.

Serum TG levels >1000 mg/dL increase the risk of acute pancreatitis. Pemafibrate was almost never administered to patients with TG levels >1000 mg/dL during developmental clinical studies. There are two studies currently underway in Europe and the U.S. in patients with severe hypertriglyceridemia (ClinicalTrials.gov Identifier: NCT03011450, NCT03001817). It may be necessary to verify pemafibrate's efficacy in such patients with severe hypertriglyceridemia in Japan, which has lower rates of fat consumption than western countries.

Conclusions

Pemafibrate is the world's first SPPARM α , developed based upon a completely new concept, which shows distinct differences from the conventional fibrates and exhibits high selectivity for PPAR α . Pemafibrate is not excreted by the kidneys and is mainly metabolized by the liver. Pemafibrate has no drug-drug interactions with statins. It has a better benefit-risk balance than the existing fibrates and is considered to be a safer drug for patients with limited response to existing fibrates, including patients taking statins, and patients with compromised kidney functions. The SPPARM α pemafibrate was developed in Japan ahead of the rest of the world, and is expected to have a significant efficacy as a new therapeutic option for dyslipidemia as well as diabetic complications and liver diseases.

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Conflict of Interest

SY received honoraria from Kowa Company Ltd., Kowa Pharmaceutical Co. Ltd., MSD K.K., Bayer Yakuhin, Ltd., Amgen-Astellas BioPharma K.K., Sonofi K.K., Skylight Biotech Inc., East Japan Institute of Technology Co., Ltd., clinical research funding from MSD K.K., Bayer Yakuhin, Ltd., Boehringer Ingelheim Japan, Inc., AstraZeneca Co., Takeda Phar-

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