Editorial

Effects of a Novel Selective Peroxisome Proliferator-Activated Receptor *a* Modulator K-877 (Pemafibrate) on Postprandial hyperlipidemia

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Clinical trials with statin demonstrated that lowering of low-density lipoprotein (LDL) -cholesterol concentrations reduces atherosclerotic disease death and events[1]. Proprotein convertase subtilisin-kexin type 9 inhibitors also have additional significant effects[2,3]. However, residual risk remains because atherosclerotic diseases are multi-pathogenetic. As one of the candidates for the other risks, an increase in remnant lipoproteins in fasting and/or postprandial states (postprandial hyperlipidemia) is considered to be atherogenic[4,5]. Recent clinical examinations with the lipoprotein analysis also suggest that chylomicron remnants may serve as a marker for estimating coronary heart disease risk[6].

Fibrates, which activate peroxisome proliferator-activated receptor *α* (PPARα), have been used to reduce triglycerides (TG) and increase high-density lipoprotein (HDL)-cholesterol for many years, and a recent meta-analysis revealed that fibrates are effective for the primary and secondary prevention of cardiovascular disease[7,8]. Although total risk management is necessary for coronary plaque regression in diabetic patients with acute coronary syndrome[9], fibrate therapy reduces cardiovascular diseases in diabetic patients with hypertriglyceridemia and low HDL-cholesterol[10-12]. However, there are some limitations in the use of current fibrates due to the dose-related adverse effects, such as the elevation of serum creatinine and alanine aminotransferase levels.

K-877 (Pemafibrate), a novel selective PPARα modulator (SPPARMα), has a higher PPARα activity and selectivity, and a lower risk of adverse effects than the other existing PPARα agonists. Clinical trials have already demonstrated that pemafibrate monotherapy or combined therapy with statin result in a robust reduction of TG[13,14]. Pemafibrate administration in LDL receptor knock-out mice effectively increased the gene expression of PPARα and its target genes related to fatty acid oxidation in the liver and small intestine[15]. Interestingly, the same treatment significantly increased the expression of ATP-binding cassette A1 gene in the liver and small intestine and reduced the expression of Niemann Pick C1-like 1 (NPC1L1) gene expression in the small intestine[15].

Furthermore, a new finding has been reported by Sairyo *et al.* in J Atheroscler Thromb[16]. They examined the effects of pemafibrate on plasma lipid concentrations and associated several factors with pemafibrate in the male C57BL/6J mice fed a high-fat diet (HFD) compared with those of fenofibrate. After 4 weeks of feeding, they measured plasma lipid and apolipoproteins (apo) concentrations during fasting and after oral fat loading.

As expected, both pemafibrate and fenofibrate suppressed body weight gain and fasting and postprandial TG concentrations and enhanced LPL activity in mice fed an HFD. They suggested that pemafibrate is more effective in decreasing TG and chylomicron remnants during the postprandial state than fenofibrate. Furthermore, both pemafibrate and fenofibrate decreased the intestinal mRNA expression of apoB and NPC1L1. However, the hepatic mRNA expression of sterol regulatory element-binding transcription factor 1c (SREBP1c) and microsomal triglyceride transfer protein (MTTP) was increased by fenofibrate but not by pemafibrate. The hepatic mRNA expression of apoC-3 was decreased by pemafibrate but not by fenofibrate. They concluded that pemafibrate may attenuate postprandial hypertri-

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glyceridemia more effectively than fenofibrate by suppressing the postprandial increase of chylomicrons and the accumulation of chylomicron remnants. Thus, pemafibrate therapy may prevent cardiovascular events by not only reducing TG and remnant concentrations but also modulating the expressions of apoB, apoC-3, NPC1L1, SREBP1c, and MTTP.

Further investigations should be performed to reveal the favorable effect of pemafibrate on postprandial hyperlipidemia and atherosclerotic disease.

Conflict of Interest

None.

References

1) Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R: Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet, 2010; 376: 1670-1681

2) Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR; FOURIER Steering Committee and Investigators: Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med, 2017; 376: 1713-1722

3) Shapiro MD, Fazio S: PCSK9 and Atherosclerosis-Lipids and Beyond. J Atheroscler Thromb, 2017; 24: 462-472

4) Fujioka Y, Ishikawa Y: Remnant lipoproteins as strong key particles to atherosclerosis. J Atheroscler Thromb, 2009; 16: 145-154

5) Masuda D, Yamashita S: Postprandial hyperlipidemia and remnant lipoproteins. J Atheroscler Thromb, 2017; 24: 95-109

6) Manita D, Yoshida H, Hirowatari Y: Cholesterol levels of six fractionated serum lipoproteins and its relevance to coronary heart disease risk scores. J Atheroscler Thromb, 2017; 24: 928-939

7) Jakob T, Nordmann AJ, Schandelmaier S, Ferreira-González I, Briel M: Fibrate for primary prevention of cardiovascular disease events. Cochrane Database Syst Rev, 2016; 11: CD009753

8) Wang D, Liu B, Tao W, Hao Z, Liu M: Fibrate for secondary prevention of cardiovascular disease and stroke. Cochrane Database Syst Rev, 2015; 10: CD009580

9) Naito R, Miyauchi K, Daija H, Morimoto T, Hiro T, Kimura T, Nakagawa Y, Yamagishi M, Ozaki Y, Matsuzaki M; for the JAPAN-ACS Investigators: Impact of total risk management on coronary plaque regression in diabetic patients with acute coronary syndrome –sub analysis of JAPAN-ACS Study-. J Atheroscler Thromb, 2016; 23: 922-931

10) Sacks FM, Carey VJ, Fruchart JC: Combination lipid therapy in type 2 diabetes. N Engl J Med, 2010; 363: 692-694

11) Scott R, O'Brien R, Fulcher G, Pardy C, D'Emden M, Tse D, Taskinen MR, Ehnholm C, Keech A; Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study Investigators: Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetes Care, 2009; 32: 493-498

12) Elam MB, Ginsberg HN, Lovato LC, Corson M, Largay J, Leiter LA, Lopez C, O'Connor PJ, Sweeney ME, Weiss D, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm R, Ismail-Beigi F, Goff DC Jr, Fleg JL, Rosenberg Y, Byington RP; ACCORDION Study Investigators: Association of fenofibrate therapy with long-term cardiovascular risk in statin-treated patients with type 2 diabetes. JAMA Cardiol, 2017; 2: 370-380

13) Ishibashi S, Yamashita S, Arai H, Araki E, Yokote K, Suganami H, Fruchart JC, Kodama T; 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

14) Arai H, Yamashita S, Yokote K, Araki E, Suganami H, Ishibashi S; K-877 study group: Efficacy and safety of K-877, a novel selective peroxisome proliferator-activated receptor a modulator (SPPARMα), in combination with statin treatment: two randomized, double-blind, placebo-controlled clinical trials in patients with dyslipidemia. Atherosclerosis, 2017; 261: 144-152

15) Takei K, Nakagawa Y, Wang Y, Han SI, Satoh A, Sekiya M, Matsuzaka T, Shimano H: Effects of K-877, a novel selective PPARα modulator, on small intestine contribute to the amelioration of hyperlipidemia in low-density lipoprotein receptor knockout mice. J Pharmacol Sci, 2017; 133: 214-222

16) Sairyo M, Kobayashi T, Masuda D, Kanno K, Zhu Y, Okada T, Koseki M, Ohama T, Nishida M, Sakata Y, Yamashita S: a novel selective PPARα modulator (SPPARMα), K-877 (Pemafibrate), attenuates postprandial hypertriglyceridemia in mice. J Atheroscler Thromb, 2018; 25: 142-152