Effects of a Novel Selective Peroxisome Proliferator-Activated Receptor α 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. 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. Recent clinical examinations with the lipoprotein analysis also suggest that chylomicron remnants may serve as a marker for estimating coronary heart disease risk.

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.

Although total risk management is necessary for coronary plaque regression in diabetic patients with acute coronary syndrome, fibrate therapy reduces cardiovascular diseases in diabetic patients with hypertriglyceridemia and low HDL-cholesterol. 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.

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. 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.

Furthermore, a new finding has been reported by Sairyo et al. in J Atheroscler Thromb. 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 (MTP) 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-
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