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Original Article

Effects of pemafibrate (K-877) on cholesterol efflux capacity and postprandial hyperlipidemia in patients with atherogenic dyslipidemia

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Selective peroxisome proliferator-activated receptor α modulator;
Triglycerides

BACKGROUND: Cardiovascular risk is negatively correlated with cholesterol efflux capacity (CEC) from macrophages to high-density lipoproteins (HDLs) and positively correlated with fasting and nonfasting triglyceride-rich lipoproteins (TRLs). Pemafibrate, a novel selective peroxisome proliferator-activated receptor α modulator, robustly decreases the fasting TRL level, increases the HDL cholesterol (HDL-C) level, and improves the atherogenic lipoprotein subclass profile, with an adverse event rate comparable to that of placebo treatment in previous clinical studies.

OBJECTIVE: This study aimed to investigate the effects of pemafibrate on CEC and postprandial hyperlipidemia.

METHODS: Using a single-center, double-blind, randomized, two-by-two crossover design, 33 patients were assigned to receive either 0.4 mg/d pemafibrate (twice daily) or placebo first. The assigned study drug was administered for 4 weeks. Subsequently, the alternate study drug was administered for another 4 weeks. CEC was measured using HDLs obtained from fasting blood samples. A meal tolerance test was performed to examine the postprandial lipid levels at weeks 0, 4, and 8.

RESULTS: CEC, HDL-C, and apolipoprotein A-I levels increased after pemafibrate treatment compared with placebo administration. Moreover, the percent change in CEC was correlated with that of HDL-C and apolipoprotein A-I levels. TRL levels markedly decreased after pemafibrate treatment in both fasting and nonfasting states.

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CONCLUSIONS: These findings suggest that pemafibrate enhances reverse cholesterol transport and may retard the progression and even promote the regression of atherosclerosis by comprehensively ameliorating the atherogenic lipid profile.

Introduction

High-density lipoproteins (HDLs) play a central role in the reverse cholesterol transport (RCT) system by collecting excessive cholesterol deposited in the peripheral tissues, especially lipid-laden macrophages in the arterial walls, and transporting cholesterol to the liver for biliary excretion. HDLs also perform various other anti-atherosclerotic functions via antioxidative, anti-inflammatory, and anticoagulant effects. Thus, both the quantity and function of HDLs are important targets for atherosclerotic cardiovascular disease (ASCVD) prevention.[1,2]

Recently, cholesterol efflux capacity (CEC) has been proposed to estimate the function of HDLs. CEC from macrophages to HDLs is largely mediated by ATP-binding cassette transporter A1 (ABCA1) expressed in macrophages and apolipoprotein (apo) A-I (apoA-I), which is the major component of HDLs. In particular, very small HDL species, that is, lipid-poor apoA-I secreted in the liver and small intestine, nascent HDL, or preβ1 HDL, show high ABCA1-mediated CEC.[3] HDLs can further collect cholesterol with the involvement of ATP-binding cassette G1 (ABCG1), which matures to larger HDL species such as HDL_3 and HDL_2.[4] Reduced CEC was associated with the presence of coronary artery disease,[5] and CEC was negatively correlated with cardiovascular event risk.[6] Therefore, enhancing CEC may reduce ASCVD risk.

On the other hand, serum triglyceride (TG) is a marker of triglyceride-rich lipoproteins (TRLs), that is, very low-density lipoproteins (LDLs), chylomicrons, and their remnants. Remnants play a pivotal role in the pathophysiology of ASCVD under the condition wherein they undergo degradation to be small enough to cross the endothelial barrier.[7] Patients with hypertriglyceridemia present with increased TRL production in the liver and small intestine, increased apoC-III levels, which inhibit lipoprotein lipase activity and TRL uptake, delayed TRL catabolism, and accumulation of small dense chylomicron-derived particles.[8,9] In addition, fasting levels of apoB-48, which is the major apo of chylomicrons and their remnants, were correlated with coronary artery disease prevalence and carotid artery intima-media thickness in patients with hypertriglyceridemia.[10,11] Furthermore, the ratio of apoB-48 to apoB-100 in human carotid and femoral endarterectomy samples was much higher than that anticipated based on the ratio of circulating apoB-48 to apoB-100 levels.[12] Recently, the amelioration of exposure to accumulated TRLs has been highlighted as an important therapeutic target for ASCVD risk reduction.[7,13,14]

Peroxisome proliferator–activated receptor α (PPARα) agonists are antidyslipidemic agents that decrease TG level and increase HDL cholesterol (HDL-C) level. They have been suggested to play a role in ASCVD risk reduction. The Helsinki Heart study[15] and the VA-HIT study[16] showed significant reductions in their primary endpoints with gemfibrozil treatment. However, no fibrate trial after these studies has shown significant reduction in the primary endpoint. In addition, the analyses of subgroup patients with elevated TG levels and decreased HDL-C levels all showed significant cardiovascular risk reductions, although they were not the primary analyses.[17] Moreover, a systematic review with meta-analysis, which is recognized as of the highest evidence level, showed that fibrate therapy was associated with a 10% relative risk reduction for major cardiovascular events ($P = .048$) and a 13% relative risk reduction for coronary events ($P < .0001$).[18] Another one showed a significant 12% reduction for the primary composite cardiovascular outcome.[19]

They increase apoA1 and ABCA1 mRNA expression but decrease apoC3 mRNA expression, resulting in increased HDL production and TRL clearance.[20,21] Pemafibrate, a novel selective PPARα modulator, has higher potency and subtype selectivity for PPARα than fenofibrate.[22] Phase 2 and 3 studies demonstrated that pemafibrate treatment, with or without statins, resulted in a significant decrease in fasting TG level and increase in HDL-C level and suggested that pemafibrate may have a superior risk/benefit profile to fenofibrate.[23–27] In vivo and in vitro studies found that pemafibrate enhanced CEC, RCT, and TRL catabolism, suppressed TRL production, and exerted anti-inflammatory and antiatherosclerotic effects.[28] Therefore, the present study aimed to investigate the effects of pemafibrate on CEC and postprandial hyperlipidemia in patients with atherogenic dyslipidemia.

Materials and methods

This study was conducted in a single center with a double-blind, randomized, two-by-two crossover design from June 7, 2014 to October 13, 2014, and registered at the Japan Pharmaceutical Information Center Clinical Trial Information registry (JapicCTI-142409). This study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and under the guidance of Good Clinical Practice and International Conference on Harmonization. The study protocol was approved by an independent institutional review board before the