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Effects of K-877, a novel selective PPARα modulator (SPPARMα), in dyslipidaemic patients: A randomized, double blind, active- and placebo-controlled, phase 2 trial

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ABSTRACT

Background and aims: To assess the efficacy and safety of K-877 (Pemafibrate), a novel selective peroxisome proliferator-activated receptor α modulator (SPPARMα) that possesses unique PPARα activity and selectivity, compared with placebo and fenofibrate in dyslipidaemic patients with high triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) levels.

Methods and results: This study was a double blind, placebo-controlled, parallel-group 12-week clinical trial. The study randomized 224 patients to K-877 0.025, 0.05, 0.1, 0.2 mg BID, fenofibrate 100 mg QD, or placebo (1:1:1:1:1:1) groups. Least squares mean percent changes from the baseline TG levels were −30.9%, −36.4%, −42.6%, −42.7% for the K-877 0.025, 0.05, 0.1, 0.2 mg BID respectively ($p < 0.001$), which were greater than that of the fenofibrate 100 mg QD (−29.7%, $p < 0.001$) group. Statistically significant improvements from the baseline HDL-C, very-low-density lipoprotein cholesterol, chylomicron cholesterol, remnant lipoprotein cholesterol, apolipoprotein (apo) B (apoB), and apoC-III were also observed in the K-877 groups. The incidence of adverse events (AEs) in the K-877 groups (32.4–56.8%) was comparable to those in placebo (47.2%) and fenofibrate 100 mg QD (56.8%); adverse drug reactions (ADRs) in the K-877 groups (2.7–5.4%) were less than those in placebo (8.3%) and fenofibrate 100 mg QD (10.8%) groups.

Conclusion: In dyslipidaemic patients with high TG and low HDL-C, K-877 improved TG, HDL-C, and other lipid parameters without increasing AEs or ADRs, compared to placebo and fenofibrate. K-877 can be expected to improve atherogenicity and to be a new beneficial treatment for dyslipidaemic patients.

1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of mortality and morbidity, accounting for 31% of all deaths worldwide [1]. Of all deaths due to CVD, approximately 80% were due to coronary heart disease (CHD) or stroke. Dyslipidaemia is one of the major

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risk factors for CHD, along with hypertension, diabetes, smoking, and obesity [1].

Numerous studies show that blood cholesterol-lowering therapy reduces the occurrence of atherosclerotic cardiovascular disease (ASCVD) [2]. Meta-analysis of large clinical trials revealed that statins reduce the risk of ASCVD by approximately 20–30% [3]. This suggests that 70% of risk remains even after treatment of high low-density lipoprotein-cholesterol (LDL-C) by statins [4]. To further reduce this risk, other lipid risk factors such as high levels of triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C), and high non-HDL-C are potential viable targets for non-statin treatment. Many guidelines recommend treatment with bile acid sequestrants, nicotinic acids, fibrates, and n-3 (omega-3) fatty acids to manage these factors [5]. Fibrates or nicotinic acids are particularly recommended to manage elevated TG and low HDL-C levels. According to sub-analyses of recent trials, the use of fibrate resulted in favourable cardiovascular outcomes in patients with high TG and low HDL-C levels [6]. Moreover, a meta-analysis revealed that fibrates could reduce CV risks [7].

Peroxisome proliferator-activated receptors (PPARs) are a superfamily of nuclear hormone receptors that form complexes with the retinoid X receptor (RXR) and bind to PPAR response elements (PPRE) on DNA. There are three different types of PPAR (α, δ, and γ) [8]. In general, the activation of PPARα is associated with the attenuation of lipid and/or glucose metabolic dysfunction, inflammation, atherosclerosis, and vascular dysfunction. With regard to TG metabolism, PPARα targets genes that express proteins such as apolipoprotein (apo) CIII, apoAV and lipoprotein lipase (LPL), thereby reducing the amount of free fatty acids utilized for the synthesis and secretion of apoB-containing lipoproteins. With regard to HDL metabolism, PPARα targets apoAI, apoAII, scavenger receptor-BI (SR-BI), and ATP-binding cassette transporter A1 (ABCA1), thereby increasing HDL production and stimulating reverse cholesterol transport [9].

K-877 (Pemafibrate) is a novel member of the selective PPARα modulator (SPPARMα) family [10] that was designed to have a higher PPARα agonistic activity and selectivity than existing PPARα agonists (such as fibrates) [11]. In the present study, we report the results of a K-877 phase 2 study in dyslipidaemic patients with high TG and low HDL-C levels.

2. Methods

2.1. Patients/study design and participants

We undertook this randomized, double blind, active- and placebo-controlled phase 2 trial at 19 sites in Japan. The study took place between November 22, 2010, and July 7, 2011.

Men and postmenopausal women aged 20–74 years who had a history of documented dyslipidaemia and plasma TG of 200 mg/dL or higher as well as HDL-C less than 50 mg/dL in men or 55 mg/dL in women, during two consecutive evaluations were eligible. Major exclusion criteria were as follows: TG of 500 mg/dL or more during two consecutive evaluations; patients who needed additional drug treatment for dyslipidaemia during the study period; type 1 diabetes or poorly controlled type 2 diabetes (HbA1c of 8.4% or more); poorly controlled hypertension (systolic blood pressure of 160 mmHg or more or diastolic blood pressure of 100 mmHg or more); poorly controlled thyroid disorder; mild or more severe renal disorder (serum creatinine of 1.5 mg/dL or more); current or past history of hepatic impairment; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels more than 2-fold higher than the upper limit of the reference range; current gallbladder disease or a history of cholelithiasis; fibrinogen level less than the lower limit of the reference range; alcohol or drug addiction; habitual excessive alcohol consumption (γ-glutamyl transferase (γ-GT) levels 2.5-fold higher than the upper limit of reference range). The concomitant use of drug treatment for dyslipidaemia was prohibited. Patients were ineligible, if they received these drugs within four weeks prior to the first screening visit. Thiazolidinediones, insulin products and derivatives, adrenal corticosteroids, protease inhibitors, protein anabolic hormones, and luteum hormones were also prohibited during the study period owing to their potential effects on dyslipidaemia. Patients were instructed to maintain their diet, exercise, and pharmacological therapy during the study period.

The study protocol and amendment were approved by the independent ethic committee or institutional review board before the commencement of study. The study was conducted in accordance with the principle of the Declaration of Helsinki, and under the guidelines of Good Clinical Practice and the International Conference on Harmonization. All study participants provided written informed consent prior to involvement. This trial is registered with JAPIC Clinical Trials Information, number Japic CTI-101331.

2.2. Procedures

Fig. S1 shows the study design, depicting the duration of each period and timing of study visits. Fig. S2 shows the disposition of the patients. Patient demographics were assessed or recorded during the screening period. After randomization (week 0), patients were randomly assigned, in a 1:1:1:1:1:1 ratio, to treatment with either K-877 at a dose of 0.025, 0.05, 0.1, or 0.2 mg BID (twice daily; 0.05, 0.1, 0.2, and 0.4 mg/day, respectively), fenofibrate (LIPIDIL®) at a dose of 100 mg QD (once daily), or matching placebo. LIPIDIL® 100 mg micronized capsule had been marketed as equivalent to the LIPIDIL® 80 mg tablet. Randomization was done with a central computer-controlled system with stratification according to the HDL-C value at the first screening visit to avoid imbalance. This study comprised a screening period of a maximum of eight weeks before the commencement of the treatment, and then a 12-week, double-blind treatment period followed by a 4-week follow-up period. During the screening and treatment period, patients visited the site for at least two screening visits, and at baseline (randomization visit i.e. week 0), week 2, 4, 8, and 12, at which fasting (≥10 h) blood and urine samples were collected for the assessment of clinical laboratory findings, including lipids. Study eligibility was determined by the laboratory data sampled at two screening visits. Following the treatment period, patients stopped taking the study drug and a follow-up visit was performed after four weeks (at week 16) for safety assessment.

At each treatment visit, patients received press-through-packages of the study drug except at week 12, and were instructed to take one tablet and one capsule after breakfast and one tablet after dinner.

2.3. Clinical laboratory and lipoprotein analysis

Lipoprotein level was measured by the direct enzymatic method; apolipoprotein level was measured by the immunoassay method. Other laboratory parameters were analysed by a standardized laboratory method (all measurements were done by LSI Medience Corporation, Japan, or its affiliates). Fibroblast growth factor 21 (FGF21) level was measured by enzyme-linked immunosorbent assay (ELISA) (Bio Vendor HUMAN FGF-21 ELISA). The concentration of TG and cholesterol, phospholipid, and free cholesterol contained in lipoprotein fractions were measured by the high-performance liquid chromatography (HPLC) (LipoSEARCH©, Skylight Biothech, Japan) method. HPLC measured TG,