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Efficacy and safety of K-877, a novel selective peroxisome proliferator-activated receptor α modulator (SPPARMα), in combination with statin treatment: Two randomised, double-blind, placebo-controlled clinical trials in patients with dyslipidaemia

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ABSTRACT

Background and aims: Substantial residual cardiovascular risks remain despite intensive statin treatment. Residual risks with high triglyceride and low high-density lipoprotein cholesterol are not the primary targets of statins. K-877 (pemafibrate) demonstrated robust efficacy on triglycerides and high-density lipoprotein cholesterol and a good safety profile as a monotherapy. The aim of these studies was to evaluate the efficacy and safety of K-877 add-on therapy to treat residual hypertriglyceridaemia during statin treatment.

Methods: The objectives were investigated in two, multicentre, randomised, double-blind, placebo-controlled, parallel group comparison clinical trials: (A) K-877 0.1, 0.2, and 0.4 mg/day in combination with pitavastatin for 12 weeks in 188 patients, (B) K-877 0.2 (fixed dose) and 0.2 (0.4) (conditional up-titration) mg/day in combination with any statin for 24 weeks in 423 patients.

Results: In both studies, we found a robust reduction in fasting triglyceride levels by approximately 50% in all combination therapy groups, which was significant compared to the statin-monotherapy (placebo) groups ($p < 0.001$). High-performance liquid chromatography analysis for lipoprotein subfractions revealed that atherogenic lipoprotein profiles were ameliorated by K-877 add-on therapy, i.e. small low-density lipoproteins decreased whereas larger ones increased, and larger high-density lipoproteins decreased whereas smaller ones increased. The incidence rates of adverse events and adverse drug reactions in K-877 combination therapy groups were comparable to those in statin-monotherapy groups without any noteworthy event in both studies.

Conclusions: These results strongly support the favourable benefit-to-risk ratio of K-877 add-on therapy in combination with statin treatment.

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) risk remains despite improved treatments provided by lipid-lowering agents [1,2]. Low-density lipoprotein cholesterol (LDL-C) is a well-established ASCVD risk factor and statins are recommended as the first-line treatment for hypercholesterolaemia across the world

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[3–5]. Although intensive statin treatment provided significant ASCVD risk reductions by 20–30%, in other words, 70–80% remained as residual risk [6], which should be urgently addressed. The remaining residual risks of elevated triglyceride (TG) and decreased high-density lipoprotein cholesterol (HDL-C) are not primary targets of statins and are known as independent ASCVD risk factors [7–11]. Furthermore, TG-rich lipoproteins represented by chylomicron remnant and remnant lipoprotein cholesterol are well-known atherogenic lipids and independent ASCVD risk factors [10–12]. Fibrates, which particularly activate peroxisome proliferator-activated receptor α (PPARα), exert good efficacy for the treatment of elevated TG and low HDL-C levels [13]. Meta-analyses revealed that fibrates could reduce CV risk [14,15]. A pre-specified subgroup analysis showed statistically significant reduction in CV events in patients with type 2 diabetes, elevated TG, and low HDL-C levels [16,17]. According to a meta-analysis of five major fibrate trials, the use of fibrate resulted in favourable cardiovascular outcomes in patients with high TG and low HDL-C levels [18]. Thus, the combination therapy of fibrate and statin would be a useful option for ASCVD risk reduction. However, there are some limitations of the use of fibrates that are currently available on the market due to the concern of an elevation of creatine kinase (CK), alanine aminotransferase (ALT), serum creatinine, and homocysteine levels in monotherapy and increased risk for myopathy in combination with statins [5].

K-877 (pemafibrate) is a novel selective PPARα modulator (SPPARMα), which was designed to possess higher PPARα activity and selectivity than existing PPARα agonists. In a previous clinical trial, K-877 monotherapy showed robust TG-lowering effects without increasing adverse events (AEs) or adverse drug reactions (ADRs) compared to a placebo in dyslipidaemic subjects with elevated TG and low HDL-C [19]. To evaluate the safety and efficacy of K-877 for the treatment of residual hypertriglyceridaemia in patients treated with statins, we performed two clinical trials. In the first trial, the dose-response relationship of the efficacy and safety of K-877 in combination with pitavastatin for 12 weeks was investigated (Study A). In the second study, the long-term efficacy and safety for 24 weeks in combination with any statin was investigated (Study B).

2. Patients and methods

In Study A, dyslipidaemic patients under pitavastatin administration with fasting TG $\geq$ 200 mg/dL (2.3 mmol/L) and non-HDL-C $\geq$150 mg/dL (3.9 mmol/L) were randomly assigned to placebo and 0.1, 0.2, and 0.4 mg/day of K-877 and treated for 12 weeks. In Study B, dyslipidaemic patients treated with a statin, with fasting TG $\geq$ 200 mg/dL, were randomly assigned to placebo and 0.2 and 0.2 (0.4) mg/day of K-877 and treated for 24 weeks. K-877 treatment at 0.2 mg/day was initiated in the K-877 0.2 (0.4) mg/day group followed by up-titration to 0.4 mg/day after week 12 if fasting TG $\geq$ 150 mg/dL (1.7 mmol/L) at week 8. Lipoprotein cholesterol levels were measured by homogeneous assays, Determiner L LDL-C (Kyowa Medex Co., Ltd., Tokyo, Japan) for LDL-C and MetaboLead HDL-C (Kyowa Medex) for HDL-C. The primary efficacy endpoint was the percent change of fasting TG from baseline (to week 12 in Study A and at the end of the treatment in Study B), and it was analysed using an analysis of covariance (ANCOVA) model with the baseline value as a covariate. The primary safety endpoints were the incidence rates of AEs and ADRs self-reported by investigators, and the differences between the K-877 groups and the placebo group were assessed using Fisher's exact test. Detailed information is available in the Supplementary material, Supplementary Fig. 1 and Table 1.

3. Results

3.1. Study A: dose-finding study of K-877 in combination with pitavastatin

The patient disposition is summarised in Supplementary Fig. 2. A total of 751 patients provided written informed consent, and 188 patients were randomly assigned to either treatment group. Of those, 18 patients were excluded from per-protocol-set (PPS) for the primary efficacy analysis. The following results from PPS were similar to those from full-analysis-set (FAS). Baseline patient characteristics are summarised in Supplementary Table 2. Approximately 80% were male, and the mean age in each group ranged from 52 to 56 years, and BMI from 26 to 28 kg/m^2. They had residual dyslipidaemia with the mean fasting TG levels ranging from 347 to 382 mg/dL (3.9–4.3 mmol/L), despite pitavastatin treatment with the mean LDL-C from 116 to 125 mg/dL (3.0–3.2 mmol/L). No statistically significant differences were found across the treatment groups.

TG levels significantly reduced by approximately 50% from baseline to week 12 in all combination therapy groups, while no significant change was observed in the pitavastatin monotherapy group (Fig. 1A). The dose-response relationship in TG reductions was confirmed, and the TG reductions from baseline to week 12 in all K-877 combination treatment groups were significant ($p < 0.001$) compared with the pitavastatin monotherapy group.

The percent changes or changes from baseline to week 12 in key secondary efficacy parameters are shown in Table 1. The reductions from baseline in remnant lipoprotein cholesterol (RemL-C), TG/HDL-C, apolipoprotein (Apo) B48 (ApoB48), and ApoCIII in all combination therapy groups were statistically significant, and were also significant compared to the pitavastatin monotherapy group. Additionally, the increases in HDL-C, ApoAII, and fibroblast growth factor 21 (FGF21) were significant. The difference in the percent changes in LDL-C between the K-877 0.2 mg/day and placebo groups was statistically significant; however, the mean LDL-C was almost unchanged, and non-HDL-C was significantly reduced compared to the placebo group. Moreover, high-performance liquid chromatography (HPLC) analyses showed that the cholesterol content in LDL particles was significantly reduced in the small and very small LDL subclasses, but was increased in large and medium subclasses in all combination groups (Fig. 2A). HPLC analyses also showed that the cholesterol content in HDL particles was significantly increased in the medium, small, and very small HDL subclasses in all combination therapy groups.

Incidence rates of AEs and ADRs during the treatment period were similar across all treatment groups without any statistically significant difference or dose dependency (Table 2). Two serious AEs (cervix carcinoma and upper limb fracture) were observed in two subjects in the K-877 0.1 mg/day group; however, in both cases, a causal relationship to the treatment was ruled out by the investigators. Among four discontinuations due to AEs, one case in the K-877 0.2 mg/day group had an elevation in CK, which is also indicated in the Table as CK > 10x ULN (3725 U/L after administration for 2 weeks in a 38-year-old man with no complaint of muscle symptoms, and resolved without additional interventions 22 days after the incidence). A causal relationship to the treatment could not be ruled out by the investigators for both pitavastatin and K-877. The proportion of patients who experienced elevated ALT, CK, and serum creatinine was less than 5% (no more than two patients), and was comparable across all treatment groups. The changes in clinical laboratory tests of interest are summarised in Supplementary Table 3. ALT, γ-GT, and fibrinogen levels were decreased especially in the K-877 0.2 and 0.4 mg/day groups. Serum creatinine levels slightly increased and eGFR slightly decreased

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