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Efficacy and Safety of Adding Omega-3 Fatty Acids in Statin-Treated Patients with Residual Hypertriglyceridemia: ROMANTIC (Rosuvastatin-OMAcor iN residual hyperTrIglyCeridemia), a Randomized, Double-blind, and Placebo-controlled Trial

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ABSTRACT

Purpose: The purpose of this study was to examine the efficacy and safety of adding ω-3 fatty acids to rosuvastatin in patients with residual hypertriglyceridemia despite statin treatment.

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Methods: This study was a multicenter, randomized, double-blind, placebo-controlled study. After a 4-week run-in period of rosuvastatin treatment, the patients who had residual hypertriglyceridemia were randomized to receive rosuvastatin 20 mg/d plus ω-3 fatty acids 4 g/d (ROSUMEGA group) or rosuvastatin 20 mg/d (rosuvastatin group) with a 1:1 ratio and were prescribed each medication for 8 weeks.

Findings: A total of 201 patients were analyzed (mean [SD] age, 58.1 [10.7] years; 62.7% male). After 8 weeks of treatment, the percentage change from baseline in triglycerides (TGs) and non–HDL-C was significantly greater in the ROSUMEGA group than in the rosuvastatin group (TGs: −26.3% vs −11.4%, $P < 0.001$; non–HDL-C: −10.7% vs −2.2%, $P = 0.001$). In the linear regression analysis, the lipid-lowering effect of ω-3 fatty acids was greater when baseline TG or non–HDL-C levels were high and body mass index was low. The incidence of adverse events was not significantly different between the 2 groups.

Implications: In patients with residual hypertriglyceridemia despite statin treatment, a combination of ω-3 fatty acids and rosuvastatin produced a greater reduction of TGs and non–HDL-C than rosuvastatin alone. Further study is needed to determine whether the advantages of this lipid profile of ω-3 fatty acids actually leads to the prevention of cardiovascular event. ClinicalTrials.gov identifier: NCT03026933. (*Clin Ther*. 2017;▮:▮▮▮–▮▮▮) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

Key words: combination, hypertriglyceridemia, non–HDL-C, ω-3 fatty acids, rosuvastatin, triglycerides.

INTRODUCTION

Control of blood cholesterol levels apparently reduces atherosclerotic cardiovascular disease.[1] The first recommended therapy for dyslipidemia is statins, which effectively prevents cardiovascular disease by lowering LDL-C levels. However, hypertriglyceridemia is also well known as an independent risk factor associated with cardiovascular events.[2–4] Statins are not effective at lowering triglycerides (TGs), which partly explains the reason why cardiovascular events occur even with the use of statins. Therefore, in patients with mixed dyslipidemia, controlling TG levels in addition to lowering LDL-C levels should be considered.

Treatment options to lower TG levels are fibrates, niacin, and ω-3 fatty acids.[5] Among these, fibrates and niacin are associated with tolerability problems. Contrariwise, ω-3 fatty acids have proven its TG-lowering effect with good tolerability.[6] However, there are mild LDL-C–increasing effects in ω-3 fatty acids.[7] For appropriate combination therapy of statin and ω-3 fatty acids, further studies are needed.

Previous studies have found the efficacy of combining ω-3 fatty acids with several statins on controlling TG levels.[8–10] However, the efficacy and tolerability of the combination of ω-3 fatty acids and rosuvastatin, which is the most potent statin currently used, have not yet been proven. This Phase III study aimed to examine the efficacy and safety of the combination of ω-3 fatty acids and rosuvastatin compared with rosuvastatin alone in patients with residual hypertriglyceridemia despite statin treatment.

METHODS

Study Design

The study was an 8-week, prospective, randomized, double-blind, parallel group, Phase III multicenter trial conducted in 33 centers in South Korea. The study period was from June 18, 2014, through March 31, 2016.

Patients with hypercholesterolemia at high risk for cardiovascular disease according to the National Cholesterol Education Program (NCEP): Adult Treatment Panel III (ATP III) were screened.[11] To be eligible in first screening, participants were required to meet the following criteria: (1) age from 19 to 80 years, (2) fasting TG level ≥300 mg/dL and LDL-C level ≥100 mg/dL and <160 mg/dL for individuals who were not taking statins for 4 weeks, (3) TG level ≥200 mg/dL and <500 mg/dL, and LDL-C level <110 mg/dL for individuals who were taking statins for last 4 weeks, and (4) nonsmoking during the study period. Then eligible participants underwent a 4-week run-in period. During the run-in period, all participants received 20 mg/d of open-label rosuvastatin calcium and discontinued use of other lipid-lowering agents. After the run-in period, the levels of LDL-C and TGs were measured repeatedly. To be eligible in the second screening, participants were required to meet the