Efficacy and Tolerability of Adding Prescription Omega-3 Fatty Acids 4 g/d to Simvastatin 40 mg/d in Hypertriglyceridemic Patients: An 8-Week, Randomized, Double-Blind, Placebo-Controlled Study

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ABSTRACT

Background: Patients with elevated serum triglyceride (TG) levels often have elevations in non–high-density lipoprotein cholesterol (non–HDL-C) levels as well. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) has identified non–HDL-C as a secondary therapeutic target in these patients, but treatment goals may not be reached with statin monotherapy alone.

Objective: This study evaluated the effects on non–HDL-C and other variables of adding prescription omega-3-acid ethyl esters (P-OM3; Lovaza™, formerly Omacor® [Reliant Pharmaceuticals, Inc., Liberty Corner, New Jersey]) to stable statin therapy in patients with persistent hypertriglyceridemia.

Methods: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adults who had received ≥8 weeks of stable statin therapy and had mean fasting TG levels ≥200 and <500 mg/dL and mean low-density lipoprotein cholesterol levels ≤10% above their NCEP ATP III goal. The study regimen consisted of an initial 8 weeks of open-label simvastatin 40 mg/d and dietary counseling, followed by 8 weeks of randomized treatment with double-blind P-OM3 4 g/d plus simvastatin 40 mg/d or placebo plus simvastatin 40 mg/d. The main outcome measure was the percent change in non–HDL-C from baseline to the end of treatment.

Results: The evaluable population included 254 patients, of whom 57.5% (146) were male and 95.7% (243) were white. The mean (SD) age of the population was 59.8 (10.4) years, and the mean weight was 92.0 (19.6) kg. At the end of treatment, the median percent change in non–HDL-C was significantly greater with P-OM3 plus simvastatin compared with placebo plus simvastatin (–9.0% vs –2.2%, respectively; $P < 0.001$). P-OM3 plus simvastatin was associated with significant reductions in TG (29.5% vs 6.3%) and very-low-density lipoprotein cholesterol (27.5% vs 7.2%), a significant increase in high-density lipoprotein cholesterol (HDL-C) (3.4% vs –1.2%), and a significant reduction in the total cholesterol:HDL-C ratio (9.6% vs 0.7%) (all, $P < 0.001$ vs placebo). Adverse events (AEs) reported by ≥1% of patients in the P-OM3 group that occurred with a higher frequency than in the group that received simvastatin alone were nasopharyngitis (4 [3.3%]), upper respiratory tract infection (4 [3.3%]),

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diarrhea (3 [2.5%]), and dyspepsia (3 [2.5%]). There was no significant difference in the frequency of AEs between groups. No serious AEs were considered treatment related.

Conclusion: In these adult, mainly white patients with persistent hypertriglyceridemia, P-OM3 plus simvastatin and dietary counseling improved non–HDL-C and other lipid and lipoprotein parameters to a greater extent than simvastatin alone. (*Clin Ther*. 2007;29: 1354–1367)

Key words: omega-3 fatty acids, hypertriglyceridemia, dyslipidemia, statins, lipoproteins, combination therapy, non–HDL-C.

INTRODUCTION

In persons with high triglyceride (TG) levels, levels of low-density lipoprotein cholesterol (LDL-C) alone do not adequately represent the risk associated with atherogenic lipoproteins.[1] Thus, in addition to the primary goal of LDL-C reduction, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines have identified non–high-density lipoprotein cholesterol (non–HDL-C) as a secondary target of therapy in persons with serum TG levels ≥200 mg/dL.[1] In the NEPTUNE (NCEP Evaluation Project Utilizing Novel E-Technology) II survey,[2] hypertriglyceridemia was present in 25% of patients undergoing treatment for dyslipidemia. Only 27% of patients with hypertriglyceridemia plus coronary heart disease (CHD) or NCEP ATP III–defined CHD risk equivalents had achieved their non–HDL-C treatment goal. This suggests a clinical need for effective treatment options to lower elevated levels of TG and non–HDL-C.

Non–HDL-C is calculated as the difference between total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C).[1] As a predictor of cardiovascular risk, it is as good as or better than LDL-C.[3,4] For example, in the Bypass Angioplasty Revascularization Investigation,[4] every 10-mg/dL increment in mean non–HDL-C increased the risk of nonfatal myocardial infarction by 5% and the odds of angina pectoris by 10%; however, LDL-C was not correlated with either outcome. Non–HDL-C includes the cholesterol contained in all the potentially atherogenic apolipoprotein (apo) B–containing lipoproteins, including TG-rich lipoproteins such as very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein, and chylomicron remnants, as well as LDL and lipoprotein (a).[1,3] Elevated fasting TG levels are associated with an increase in plasma concentrations of VLDL particles.[1] Under such hypertriglyceridemic conditions, VLDL-C becomes an important component of non–HDL-C.[1]

A statin is recommended as initial pharmacotherapy for lowering LDL-C and non–HDL-C in patients with hypertriglyceridemia,[1] but statin treatment alone may be insufficient to achieve non–HDL-C targets. As defined by the NCEP ATP III, the non–HDL-C target is 30 mg/dL higher than the corresponding LDL-C targets of <100 mg/dL for those with CHD or CHD risk equivalents, <130 mg/dL for those with ≥2 risk factors, and <160 mg/dL for those with ≤1 risk factor.[2,5] Statin-treated patients may remain at risk because of persistent hypertriglyceridemia and elevated non–HDL-C, despite achieving their NCEP ATP III goal for LDL-C.

In patients with persistent hypertriglyceridemia while receiving statin therapy, the addition of a TG-lowering agent is recommended as a therapeutic option to reduce levels of non–HDL-C.[1] In such patients, one approach is to combine prescription omega-3-acid ethyl esters* (P-OM3) with the statin. P-OM3 is approved by the US Food and Drug Administration for use as an adjunct to diet in adults with very high TG levels (≥500 mg/dL).[6] Each 1-g capsule of P-OM3 contains highly concentrated ethyl esters of omega-3 fatty acids, primarily eicosapentaenoic acid (EPA) 465 mg and docosahexaenoic acid (DHA) 375 mg.[6] The findings of 3 previous trials in patients with hypertriglyceridemia suggested that coadministration of P-OM3 with a statin was associated with greater improvements in the lipid profile than treatment with a statin alone: Nordoy et al[7] reported significant changes in TG ($P < 0.007$) and apo E ($P < 0.035$); Durrington et al[8] reported significant changes in TG ($P < 0.001$), VLDL-C ($P < 0.005$), TC ($P < 0.025$), and LDL-C ($P < 0.025$); and Chan et al[9] reported significant changes in TG ($P = 0.002$) and HDL-C ($P = 0.041$).

*Trademark: Lovaza™, formerly Omacor® (Reliant Pharmaceuticals, Inc., Liberty Corner, New Jersey). The name has been changed as of August 2007 at the request of the US Food and Drug Administration in response to a limited number of reports of prescribing and dispensing errors (data on file, Reliant Pharmaceuticals) resulting from the similarity in the names of Omacor and Amicar® (aminocaproic acid; Xanodyne Pharmaceuticals, Inc., Newport, Kentucky).

However, these studies were small (<60 patients each) and were not powered to provide a full evaluation of the addition of P-OM3 to a statin.

The present study (clinicaltrials.gov identifier: NCT 00246701) assessed the efficacy and tolerability of P-OM3 in combination with simvastatin and dietary counseling for lowering non–HDL-C levels in patients with persistent hypertriglyceridemia despite statin therapy. It was designed to determine whether the addition of P-OM3 to simvastatin would achieve a robust decrease in non–HDL-C in these patients, primarily through reduction of TG, without attenuating the LDL-C–lowering effect of the statin. This was the first study powered to evaluate both the non–HDL-C and LDL-C end points.

PATIENTS AND METHODS

Patients

Eligible patients were men or women between the ages of 18 and 79 years who had been receiving a stable dose of a statin for the control of LDL-C levels for ≥8 weeks before screening and were judged to be in good health on the basis of a medical history, physical examination, electrocardiogram, and laboratory tests, including serum chemistry, hematology, and urinalysis. Major inclusion criteria included a mean fasting TG level ≥200 and <500 mg/dL, and a mean LDL-C level below or within 10% of the patient's NCEP ATP III goal.

Major exclusion criteria included poorly controlled diabetes mellitus (glycosylated hemoglobin [HbA_{1c}] >8.0% at screening); history of a cardiovascular event, a revascularization procedure, or an aortic aneurysm or resection within 6 months of screening; history of pancreatitis; sensitivity to statins or omega-3 fatty acids; poorly controlled hypertension (resting blood pressure ≥160 mm Hg systolic and/or ≥100 mm Hg diastolic at 2 consecutive visits); serum creatinine level ≥2.0 mg/dL; serum transaminase (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) >1.5 times the upper limit of normal (ULN) (45 U/L for ALT, 31 U/L for AST); or creatine kinase (CK) level >2 times the ULN.

Study Design and Procedures

This randomized, double-blind, placebo-controlled, parallel-group study was conducted at 41 clinical sites throughout the United States. The study consisted of 7 clinic visits: 1 screening visit, 3 visits during the lead-in/baseline period, and 3 visits during double-blind treatment. Written informed consent was obtained from all patients. The protocol and consent form were reviewed and approved by the appropriate institutional review board for each site. The study was conducted in accordance with the Good Clinical Practice Guidelines,[10] the Declaration of Helsinki (2000),[11] and Title 21 of the US Code of Federal Regulations.[12]

At screening (week –8), patients meeting the initial eligibility criteria received open-label treatment with simvastatin* 40 mg/d, which was continued for the remainder of the study. Simvastatin replaced any previous statin. Patients discontinued all lipid-altering drugs (other than simvastatin 40 mg/d), omega-3 fatty acid supplements, and supplements known to alter lipid metabolism. In addition, they received dietary counseling on the NCEP Therapeutic Lifestyle Changes diet.[1] Dietary instructions were reinforced at each subsequent clinic visit. During the 8-week lead-in phase, patients attended clinic visits at weeks –2, –1, and 0.

After the lead-in phase, patients whose compliance (measured by the number of capsules consumed relative to the number expected to be consumed) with simvastatin therapy was ≥80% and who had mean TG levels (mean of weeks –2 and –1) ≥200 and <500 mg/dL and LDL-C levels ≤10% above their NCEP ATP III goal were randomized to receive 8 weeks of double-blind P-OM3 4 g/d (four 1-g capsules, the approved dosage) or placebo (4 matching vegetable oil capsules). Patients were allocated to double-blind treatment according to a randomization schedule with a block size of 4; sequentially numbered drug-supply kits were provided to sites in balanced blocks of 4, and patients were assigned sequential kit numbers at enrollment. All participants continued to receive simvastatin 40 mg/d. During the 8-week, double-blind treatment phase, patients attended clinic visits at weeks 4, 6, and 8.

Outcome Variables

The prespecified primary outcome variable was the percent change in non–HDL-C from baseline (mean of weeks –2, –1, and 0) to the end of treatment (mean of weeks 6 and 8), as computed for each patient. Additional outcome variables included the percent changes from baseline to the end of treatment in levels of TG, VLDL-C, LDL-C, HDL-C, TC, and apo B.

*Trademark: Zocor® (Merck & Co., Inc., West Point, Pennsylvania).

Mayo Central Laboratory for Clinical Trials (Rochester, Minnesota) performed all clinical laboratory testing. Serum lipids (non–HDL-C, TG, LDL-C, HDL-C, and TC) were analyzed according to the Standardization Program of the Centers for Disease Control and Prevention and the National Heart, Lung, and Blood Institute. Laboratory assessments included hematology (Coulter LH 750 Hematology Analyzer, Beckman Coulter, Inc., Fullerton, California); chemistry; urinalysis (reagent strip chemistry with microscopic analysis); pregnancy testing for women of childbearing potential (chemiluminometric immunoassay); HbA_{1c} (turbidimetric inhibition immunoassay); lipid panel (selective precipitation/enzymatic colorimetry or Friedewald equation); apo A-I, B, and C-III (automated turbidimetric immunoassay); remnant lipoprotein cholesterol (immunoaffinity isolation of remnant lipoprotein, followed by enzymatic cholesterol determination); and LDL (direct measurement by ultracentrifugation/selective precipitation/enzymatic colorimetry). For each test, accuracy and performance were verified when control pools in a matrix behaved in the same way as patient samples. Precision data and acceptable limits were established for each analyte and each level of control, and performance was evaluated before disclosure of the results.

Safety Assessments

The safety profile was assessed by monitoring of adverse events (AEs) and measurement of vital signs at each clinic visit, as well as by serum chemistry, hematology, and urinalysis at visits 1, 4, and 7. AEs were categorized as not related, unlikely, possibly, probably, or definitely related to study drug.

A post hoc analysis of fructosamine concentrations was performed for further evaluation of increases in blood glucose levels. EDTA-treated plasma samples were assayed for fructosamine concentrations using a validated colorimetric rate reaction method. The fructosamine assay is a colorimetric test based on the ability of ketoamines to reduce nitroblue tetrazolium to formazan in an alkaline medium. The rate of formation of formazan is directly proportional to the concentration of fructosamine and is measured photometrically at 546 nm.[13]

Statistical Methods

An evaluable sample of ≥200 patients (100 per treatment group) was expected to provide >99% power (2-sided $\alpha = 0.05$) to detect an 8% difference in the mean percent change in non–HDL-C levels between the 2 treatment groups (assumed pooled SD, 13%). This sample size was also expected to provide 80% power (2-sided $\alpha = 0.05$) to detect a 6% between-group difference in the mean percent change in LDL-C (assumed pooled SD, 15%) to rule out a possible marked attenuation of the LDL-C–lowering effect of the statin.

The intent-to-treat (ITT) population included all randomized patients. Efficacy analyses involved all patients in the ITT population who received at least 1 dose of study medication and provided at least 1 post-randomization blood sample. The last-observation-carried-forward (LOCF) method was used to impute missing nonbaseline data for patients who did not complete the treatment period. Percent changes from baseline were evaluated by analysis of variance (ANOVA)[14] with treatment as a factor. In the case of variables for which baseline values differed between groups, the baseline value was included as a covariate in the model. The statistical analysis plan included use of the Shapiro-Wilk test[15] to evaluate assumptions for the use of parametric tests. In cases in which these assumptions were rejected, rank transformations were performed before running the ANOVA. Because the percent-change-from-baseline data were not normally distributed for the primary or secondary efficacy end points, medians rather than means are reported here as the most appropriate descriptor of central tendency. There were no planned statistical corrections for multiple comparisons of secondary outcomes.

All patients who received at least 1 dose of double-blind study drug and returned to the clinic for at least 1 safety assessment after randomization were included in the safety population. The Fisher exact test (2-tailed)[16] was used to compare the incidence of AEs between treatment groups.

RESULTS

Population

Of 690 patients screened, 256 qualified for entry and were randomized to treatment, 123 to P-OM3 plus simvastatin and 133 to placebo plus simvastatin. The unequal number of patients in the 2 treatment groups resulted from 41 of the participating sites enrolling patients who were not in multiples of 4 at all sites. The efficacy-evaluable and safety populations included 122 patients in the P-OM3 group and 132 in

the placebo group who returned for at least 1 evaluation after randomization. Patient disposition is summarized in **Figure 1**.

The number of patients completing the study was comparable in the P-OM3 (116/123 [94.3%]) and placebo (127/133 [95.5%]) groups. There were 7 non-completers in the P-OM3 group: 3 patients discontinued due to AEs, 1 was lost to follow-up, 1 was withdrawn for a laboratory abnormality (TG >500 mg/dL), 1 discontinued due to difficulty swallowing study medication, and 1 was discontinued after being found to be receiving an exclusionary medication (warfarin). There

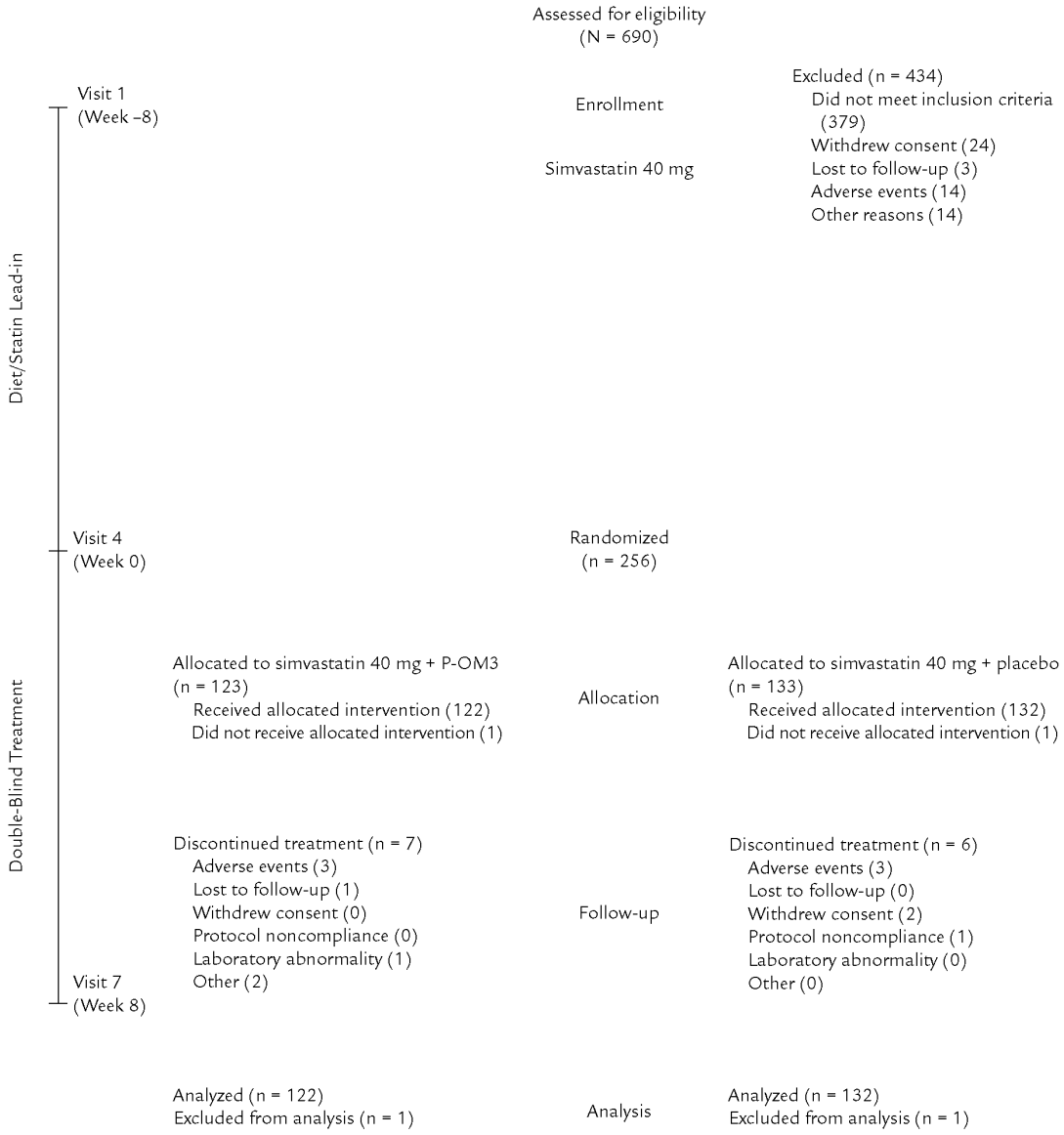

Figure 1. Patient disposition throughout the study. P-OM3 = prescription omega-3-acid ethyl esters.

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