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 Omnacor® [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 ≥28 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%]),...
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) Copyright © 2007 Excerpta Medica, Inc.

**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 atherosclerotic lipoproteins. 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. In the NEPTUNE (NCEP Evaluation Project Utilizing Novel E-Technology) II survey, 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). As a predictor of cardiovascular risk, it is as good as or better than LDL-C. For example, in the Bypass Angioplasty Revascularization Investigation, 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). Elevated fasting TG levels are associated with an increase in plasma concentrations of VLDL particles. Under such hypertriglyceridemic conditions, VLDL-C becomes an important component of non–HDL-C.

A statin is recommended as initial pharmacotherapy for lowering LDL-C and non–HDL-C in patients with hypertriglyceridemia, 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.

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. 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). 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. 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 reported significant changes in TG (P < 0.007) and apo E (P < 0.035); Durrington et al 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 reported significant changes in TG (P = 0.002) and HDL-C (P = 0.041).

*Trademark: LovazaTM, 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, the Declaration of Helsinki (2000), and Title 21 of the US Code of Federal Regulations.

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. 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); HbA1c (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.

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) 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 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) 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
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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

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### Figure 1. Patient disposition throughout the study. P-OM3 = prescription omega-3-acid ethyl esters.
were 6 noncompleters in the placebo group: 3 patients discontinued due to AEs, 2 withdrew consent, and 1 was withdrawn for noncompliance with the protocol. For the 13 patients who withdrew during the double-blind treatment period after providing at least 1 postrandomization blood sample for lipid analysis, the LOCF method was used to impute values for the missing data points. With the exception of 2 patients (1 lost to follow-up in the P-OM3 group, 1 who withdrew consent in the placebo group), neither of whom provided any postrandomization data, all noncompleters were included in the efficacy and safety populations.

The efficacy-evaluable and safety populations had a mean age of 59.8 years and were 57.5% (146/254) male and 95.7% white (243/254) (Table I). The 2 groups were comparable in age, sex, race, weight, height, body mass index, and waist circumference. With the exception of the TC:HDL-C ratio, which was significantly lower in the P-OM3 group compared with the placebo group (P = 0.012), there were no significant differences in any lipid/lipoprotein level between treatment groups at baseline in the efficacy-evaluable population.

**Efficacy Analyses**

Table II summarizes the results for the lipid and lipoprotein outcome variables. The percent change from baseline in non-HDL-C, the primary outcome variable, was significantly better with P-OM3 plus simvastatin compared with placebo plus simvastatin (~9.0% vs ~2.2%, respectively; P < 0.001) (Figure 2).

In the P-OM3 group, 91/122 (74.6%) patients were at their non-HDL-C treatment goal at baseline, and 102/122 (83.6%) were at their goal at the end of treatment. In the placebo group, the corresponding values at baseline and the end of treatment were 90/132 (68.2%) and 92/132 (69.7%). In the subset of patients who were not at their non-HDL-C goal at baseline, 16/31 (51.6%) patients in the P-OM3 group had attained their non-HDL-C goal by the end of treatment, compared with 10/42 (23.8%) in the placebo group (Figure 3).

The median percent change in TG levels was ~29.5% in the P-OM3 group, compared with ~6.3% in the placebo group (P < 0.001) (Table II). The median change in VLDL-C was ~27.5% in the P-OM3 group and ~7.2% in the placebo group (P < 0.001). LDL-C changed by a median of +0.7% in the P-OM3 group.

**Table I. Baseline characteristics of patients in the efficacy-evaluable population. Data are mean (SD), unless otherwise specified.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Simvastatin + P-OM3 (n = 122)</th>
<th>Simvastatin + Placebo (n = 132)</th>
<th>Total (N = 254)</th>
<th>P Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.3 (10.1)</td>
<td>59.3 (10.8)</td>
<td>59.8 (10.4)</td>
<td>0.44</td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>66 (54.1)</td>
<td>80 (60.6)</td>
<td>146 (57.5)</td>
<td>0.31</td>
</tr>
<tr>
<td>Female</td>
<td>56 (45.9)</td>
<td>52 (39.4)</td>
<td>108 (42.5)</td>
<td></td>
</tr>
<tr>
<td>Race, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>116 (95.1)</td>
<td>127 (96.2)</td>
<td>243 (95.7)</td>
<td>0.76</td>
</tr>
<tr>
<td>Black</td>
<td>2 (1.6)</td>
<td>3 (2.3)</td>
<td>5 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (0.8)</td>
<td>3 (2.3)</td>
<td>4 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>3 (2.5)</td>
<td>0</td>
<td>3 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>91.0 (19.3)</td>
<td>92.9 (20.0)</td>
<td>92.0 (19.6)</td>
<td>0.45</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170.9 (10.2)</td>
<td>171.4 (9.6)</td>
<td>171.2 (9.9)</td>
<td>0.71</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31.0 (5.4)</td>
<td>31.5 (5.5)</td>
<td>31.2 (5.4)</td>
<td>0.49</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>103.5 (13.5)</td>
<td>104.4 (14.5)</td>
<td>104.0 (14.0)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

P-OM3 = prescription omega-3-acid ethyl esters.

*One patient receiving simvastatin and placebo was self-described as both white and Hispanic.
Table II. Lipid and lipoprotein results.

| Lipid Parameter, mg/dL | Simvastatin + P-OM3 (n = 122) | Simvastatin + Placebo (n = 132) |  
|------------------------|-------------------------------|-------------------------------|---
|                        | Baseline*                     | End of Treatment              | Percent Change | Baseline*                     | End of Treatment              | Percent Change | P, Percent Change Between Groups |
|                        | Mean (SD) | Median | Mean (SD) | Median | Mean (SD) | Median | Mean (SD) | Median | Mean (SD) | Median | Mean (SD) | Median | Mean (SD) | Median |
| Non-HDL-C              | 135.8 (24.5) | 137.0 | 124.1 (14.4) | 122.8 (14.4) | -7.9 | -9.0 | 141.3 (29.3) | 141.3 | 138.8 (32.0) | 133.5 | -1.5 | -2.2 | <0.001 |
| TG                     | 282.0 (75.8) | 267.8 | 202.4 (18.7) | 182.3 (18.7) | -28.2 | -29.5 | 286.7 (77.5) | 270.7 | 275.9 (98.9) | 259.5 | -3.5 | -6.3 | <0.001 |
| VLDL-C                 | 52.1 (10.6) | 51.5 | 39.5 (10.1) | 36.5 (10.1) | -23.8 | -27.5 | 53.2 (11.8) | 52.0 | 50.0 (11.8) | 48.5 | -4.8 | -7.2 | <0.001 |
| LDL-C                  | 89.2 (21.6) | 90.7 | 90.4 (23.2) | 87.5 (23.2) | 3.4 | 0.7 | 92.3 (24.3) | 88.2 | 90.1 (24.3) | 85.0 | -1.9 | -2.8 | 0.052 |
| HDL-C                  | 47.3 (11.9) | 46.0 | 49.1 (12.7) | 48.0 (12.7) | 4.1 | 3.4 | 44.7 (9.3) | 43.3 | 44.0 (8.8) | 44.0 | -1.1 | -1.2 | <0.001 |
| TC                     | 183.1 (27.8) | 184.3 | 173.2 (9.3) | 172.0 (9.3) | -4.7 | -4.8 | 186.0 (9.3) | 183.5 | 182.8 (8.8) | 178.0 | -1.5 | -1.7 | 0.001 |
| TC:HDL-C ratio         | 4.0 (0.9) | 3.9 | 3.7 (1.0) | 3.5 (1.0) | -8.0 | -9.6 | 4.3 (0.8) | 4.2 | 4.3 (0.9) | 4.1 | 0.1 | -0.7 | <0.001 |
| apo B                  | 85.0 (14.7) | 85.5 | 81.2 (14.5) | 80.0 (14.5) | -3.8 | -4.2 | 86.8 (14.9) | 86.8 | 85.7 (17.1) | 84.5 | -1.2 | -1.9 | 0.023 |

P-OM3 = prescription omega-3 acid ethyl esters; non-HDL-C = non-high-density lipoprotein cholesterol; TG = triglycerides; VLDL-C = very-low-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TC = total cholesterol; apo B = apolipoprotein B. *P = NS, between-group comparisons of all baseline values except the TC:HDL-C ratio (P = 0.012).
Figure 2. Median percent change in non-high-density lipoprotein cholesterol (non-HDL-C), triglycerides (TG), calculated very-low-density lipoprotein cholesterol (VLDL-C), and low-density lipoprotein cholesterol (LDL-C) from baseline to the end of treatment. The analysis was completed after rank transformation due to non-normality in the distribution of responses. P-OM3 = prescription omega-3-acid ethyl esters. *P < 0.001.

The proportion of patients in the P-OM3 group at their LDL-C treatment goal remained constant from baseline to the end of treatment (92.6% [113/122]). P-OM3 plus simvastatin was associated with a median percent change in HDL-C of +3.4%, compared with −1.2% in the group receiving simvastatin plus placebo (P < 0.001). The change in the TC:HDL-C ratio was significantly greater in the P-OM3 group than in the placebo group (−9.6% vs −0.7%, respectively; P < 0.001). In addition, the change in apo B was significantly greater in the P-OM3 group compared with the placebo group (−4.2% vs −1.9%; P = 0.023).

Safety Analyses

There was no significant difference between groups in the proportion of patients experiencing AEs (Table III). Serious AEs (SAEs) occurred in 4/122 (3.3%) patients in the P-OM3 group and 1/132 (0.8%) patients in the placebo group. The 4 SAEs in the P-OM3 group were hospitalization for an exacerbation of congestive heart failure in a 68-year-old woman; hospitalization for supraventricular tachycardia in a 41-year-old man with a history of hypertension and supraventricular tachycardia; hospitalization for pneumonia in a 71-year-old woman with a history of chronic obstructive pulmonary disease; and elevated ALT and AST (98 and 68 U/L, respectively) in a 54-year-old woman. None of these SAEs were considered by the investigators to be related to study treatment.

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%]), diarrhea (3 [2.5%]), and dyspepsia (3 [2.5%]). There were no significant differences between groups in either the incidence of AEs in any system organ class or the incidence of any individual AE (Table III). No AEs involved myopathy (CK >10 × ULN) or rhabdomyolysis. The combination of P-OM3 and simvastatin had no significant effects on creati-
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Table III. Incidence of adverse events (no. [%] of patients).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Simvastatin + Simvastatin + P-OM3 (n = 122)</th>
<th>Placebo + Simvastatin (n = 132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>51 (41.8)</td>
<td>63 (47.7)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>4 (3.3)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Specific adverse events*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4 (3.3)</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4 (3.3)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (2.5)</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>3 (2.5)</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>2 (1.6)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Cystitis</td>
<td>2 (1.6)</td>
<td>1 (0.8)</td>
</tr>
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<td>Alanine aminotransferase elevation</td>
<td>2 (1.6)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>2 (1.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

P-OM3 = prescription omega-3-acid ethyl esters.

*Events reported by ≥1% of patients receiving simvastatin + P-OM3 that occurred with a higher frequency than in those receiving simvastatin + placebo.

Among persons aged ≥50 years, the proportion with serum TG levels ≥150 mg/dL was 42.8%. The Prospective Cardiovascular Munster Study reported the importance of lowering serum TG independent of other lipid variables. Given the aging of the US population, hypertriglyceridemia is likely to remain a common problem in clinical practice.

The most recent NCEP ATP III guidelines identify non-HDL-C as a secondary treatment target for CHD risk reduction in individuals with significant elevations in plasma TG levels (>200 mg/dL). However, in patients with hypertriglyceridemia, non-HDL-C levels may not be adequately controlled with statin monotherapy. The results of the NEPTUNE II survey indicated that inadequate treatment of hypertriglyceridemia is common; only 27% of patients with TG levels ≥200 mg/dL and CHD or CHD risk equivalents treated with diet and/or drug therapy (69.9% receiving statin monotherapy) achieved combined LDL-C and non−HDL-C goals. The present study was designed to investigate the efficacy and tolerability of

Figure 3. Proportions of patients who were not at their non−high-density lipoprotein cholesterol (non−HDL-C) goal at baseline but had achieved the goal by the end of treatment (P = NS). P-OM3 = prescription omega-3-acid ethyl esters.

DISCUSSION

The Third National Health and Nutrition Examination Survey reported that 30.0% of 8814 men and women evaluated had serum TG levels ≥150 mg/dL. Among persons aged ≥50 years, the proportion with serum TG levels ≥150 mg/dL was 42.8%. The Prospective Cardiovascular Munster Study reported the importance of lowering serum TG independent of other lipid variables. Given the aging of the US population, hypertriglyceridemia is likely to remain a common problem in clinical practice.

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coadministration of P-OM3 with simvastatin for lowering non–HDL-C in patients with persistent hypertriglyceridemia despite statin therapy.

In a previous placebo-controlled trial in patients with established CHD and hypertriglyceridemia (TG >200 mg/dL) who were receiving stable doses of simvastatin therapy (10–40 mg/d),8 the addition of P-OM3 (4 g/d) to simvastatin for 24 weeks resulted in further reductions compared with placebo in TG (28.9%; P < 0.005), VLDL-C (21.1%; P < 0.005), and apo B (3.4%; P = NS). Non–HDL-C was also reduced by 8.2% (not reported, but calculated from the data presented).

In the present study, coadministration of P-OM3 with simvastatin in patients with hypertriglyceridemia despite statin therapy was associated with a significantly greater reduction in non–HDL-C compared with simvastatin alone (P < 0.001). The addition of P-OM3 to simvastatin also increased the proportion of patients attaining their NCEP ATP III non–HDL-C treatment goal to an extent similar to that associated with doubling the statin dose.20,21 In one study of 4 statins given at 10, 20, 40, and 80 mg/d,20 the largest increases in the proportion of patients achieving non–HDL-C treatment goals upon doubling the dose were from 60% to 84% with atorvastatin 20 mg/d doubled to 40 mg/d and from 30% to 54% with simvastatin 10 mg/d doubled to 20 mg/d.

The effect of treatment on LDL-C levels, which were already at or near the NCEP ATP III goal at the start of treatment, did not differ significantly between groups. The proportion of patients at their LDL-C goal remained constant (92.6% [113/122]) from baseline to the end of treatment in the P-OM3 group. Therefore, the addition of P-OM3 did not affect maintenance of NCEP ATP III treatment goals for LDL-C with statin therapy. Although compared with the placebo group, the P-OM3 group had a numerically greater increase from baseline in LDL-C (0.7%; P = NS), the median LDL-C level in the P-OM3 group was 87.5 mg/dL at the end of treatment. This increase in the P-OM3 group may have reflected enhanced conversion of VLDL to LDL particles or some shift in cholesterol composition from TG-rich lipoproteins to LDL particles.22

The decrease in VLDL-C with P-OM3 was larger than the increase in LDL-C, resulting in a net decrease in atherogenic particles and reductions in non–HDL-C and total apo B levels. Although there was a trend toward greater reduction in apo B in the P-OM3 group (P = 0.023), this trial was not powered to show a significant difference in this variable after the number of comparisons completed was taken into account. P-OM3 also was associated with a significant increase in HDL-C and a significant reduction in the TC: HDL-C ratio (both, P < 0.001). Considering the combined effects of reducing TG and atherogenic lipoproteins, and modestly increasing HDL-C, the addition of P-OM3 to statin therapy may provide additional clinical benefits in patients with mixed dyslipidemia.23

Both treatments were well tolerated. The incidence and nature of AEs were similar in the 2 treatment groups. The safety profile of P-OM3 administered with simvastatin was consistent with the known safety profile of P-OM3 administered alone.6 In the simvastatin plus P-OM3 group, the most frequently occurring AEs were nasopharyngitis, upper respiratory tract infection, diarrhea, and dyspepsia, none of which differed significantly from the placebo group; these AEs were consistent with those reported in previous clinical studies of P-OM3.6 The slight elevations in ALT and AST were also consistent with previous experience with P-OM3.24,25

Fasting blood glucose was significantly increased with P-OM3 compared with placebo (P = 0.002). Two previous meta-analyses reported that elevations in glucose after omega-3 fatty acid supplementation were not accompanied by increases in HbA1c.26,27 The duration of the present study was too short to allow meaningful assessment of HbA1c, but a post hoc evaluation of fructosamine levels, which respond more rapidly to changes in blood glucose levels than HbA1c, found no significant difference in the change from baseline in fructosamine levels between the P-OM3 and placebo groups.

No drug–drug interaction between P-OM3 and simvastatin was expected. In a previous study in healthy volunteers,28 coadministration of P-OM3 and simvastatin did not affect the pharmacokinetics of simvastatin or its major metabolite, β-hydroxy-simvastatin. After 14 days of dosing to achieve steady state, neither the extent of exposure (AUC) nor Cmax of simvastatin or β-hydroxy-simvastatin was significantly different after coadministration of P-OM3 and simvastatin compared with simvastatin alone.

A limitation of this study was the short duration of double-blind treatment (8 weeks). Longer trials may better characterize the long-term efficacy and tolerability of coadministration of P-OM3 and simvastatin.
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and the impact of such coadministration on clinical outcomes. A long-term (24-month) open-label extension of this study is under way. Another potential study limitation is that 95.7% (243/254) of study participants were white, which limits the generalizability of the findings to minority populations. The trial’s inclusion and exclusion criteria similarly limit extrapolation to other patient populations.

Statins and omega-3 fatty acids may have complementary and additive effects. Preclinical and clinical studies have found that EPA and DHA affect TG metabolism through mechanisms including reduced synthesis of VLDL, increased rates of hepatic fatty acid oxidation, and enhanced TG clearance. Chan et al. studied the separate and combined effects of P-OM3 and atorvastatin in insulin-resistant men with dyslipidemia and concluded that the 2 drugs reduce serum TG levels through different mechanisms. They suggested that the combined effects of atorvastatin and P-OM3 therapy were additive, resulting from reduced hepatic secretion of VLDL-apo B (the effect of P-OM3) and enhanced clearance of all apo B-containing lipoproteins (the effect of the statin). The findings of the present study support these conclusions.

CONCLUSIONS

There is a clinical need for an effective and well-tolerated combination therapy to lower non-HDL-C. In the present study, the addition of P-OM3 4 g/d (465 mg EPA and 375 mg DHA per 1-g capsule) to ongoing simvastatin 40 mg/d in patients with persistent hypertriglyceridemia was effective in providing additional lowering of non-HDL-C, VLDL-C, and TG levels. The combination of P-OM3 and simvastatin improved the overall lipid profile without attenuating the efficacy of the statin.

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The statistician was Melissa Nelson of Radiant Research, Chicago, Illinois. Radiant Research received compensation for conducting the trial and for statistical services. An independent statistical analysis was conducted by Gary Cutter, PhD, Department of Biostatistics, University of Alabama at Birmingham School of Public Health. He received the trial database, including all raw data, not just the derived data sets, and independently computed the outcomes for the efficacy parameters.

In the past 3 years, Dr. Davidson has received grant/research support or honoraria from, has served as a consultant for, or has been on the speakers’ bureaus of the following companies: Abbott, AstraZeneca, Bristol-Myers Squibb, Kos, and Reliant. Dr. Stein has received grant/research support or honoraria from, has served as a consultant for, or has been on the speakers’ bureaus of the following companies: AstraZeneca, Daiichi Sankyo, Isis, Novartis, Reliant, Schering, Roche, and Takeda. Over almost 2 decades of clinical research, Dr. Bays has served as a clinical investigator for and has received research grants from pharmaceutical companies such as Abbott, Alteon, Arena, AstraZeneca, Aventis, Bayer, Boehringer Ingelheim, Boehringer Mannheim, Bristol-Myers Squibb, Ciba-Geigy, Eli Lilly, Esperion, Fujisawa, GelTex, Glaxo, Genentech, Hoechst Roussel, Kos, Kowa, Lederle, Marion Merrell Dow, Merck, Merck/Schering-Plough, Miles, Novartis, Parke-Davis, Pfizer, Pliva, Purdue, Regeneron, Reliant, Roche, Rorer, Sandoz, Sankyo, Sanofi, Searle, Shionogi, Schering-Plough, SmithKline Beecham, Takeda, TAP, Upjohn, Upsher-Smith, Warner-Lambert, and Wyeth-Ayerst. He has also served as a consultant, speaker, and/or advisor to pharmaceutical companies such as Arena, AstraZeneca, Aventis, Bayer, Bristol-Myers Squibb, Kos, Merck, Merck/Schering-Plough, Metabasis Therapeutics, Microbi-a, NicOx, Novartis, Ortho-McNeil, Parke-Davis, Pfizer, Roche, Sandoz, Sankyo, Sanofi-Aventis, Schering-Plough, SmithKline Beecham, Takeda, Upjohn, and Warner-Lambert. Dr. Maki has received research grant support and consulting fees from AstraZeneca, Merck, Reliant, Sanofi-Synthelabo, and Takeda. Mr. Doyle is an employee of Reliant Pharmaceuticals. Dr. Shalwitz was an employee of Reliant Pharmaceuticals at the time of the study and is currently a consultant to the
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