Journal of Clinical Lipidology (2017) ■, ■–■

Journal of Clinical Lipidology

Original Article

Omega-3 carboxylic acids in patients with severe hypertriglyceridemia: EVOLVE II, a randomized, placebo-controlled trial

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KEYWORDS:
Triglyceride;
Omega-3 carboxylic acids;
Hypertriglyceridemia;
Non-high-density lipoprotein cholesterol

BACKGROUND: Adult patients with severe hypertriglyceridemia (SHTG) are at increased risk of developing acute pancreatitis and cardiovascular disease. Omega-3 carboxylic acids (OM3-CA) are approved for treatment as an adjunct to diet to reduce triglyceride (TG) concentrations in patients with SHTG.

OBJECTIVE: The aim of the study was to assess efficacy and safety of the intermediate dose of OM3-CA (2 g daily), compared with olive oil 2 g daily, in reducing serum TG and lipid concentrations in patients with SHTG.

METHODS: A randomized, double-blind, olive oil–controlled, parallel-group trial involving 162 adults with qualifying serum TG concentrations of at least 500 mg/dL (5.65 mmol/L) and <2500 mg/dL (28.25 mmol/L; <2000 mg/dL [22.60 mmol/L] in Canada). The treatment period after randomization was 12 weeks. Blood samples for measurement of fasting serum lipid concentrations were taken at baseline, 6, 10, and 12 weeks.

RESULTS: Treatment with OM3-CA 2 g daily led to a significant reduction in TG concentrations (median of differences, −14.2% [95% confidence interval: −26.2%, −2.8%; $P = .017$]) and non-high-density lipoprotein cholesterol concentrations (median of differences, −9.0% [95% confidence interval: −14.8%, −2.8%; adjusted $P = .018$]) from baseline to the Week 12 endpoint, when compared with olive oil 2 g daily. These treatment effects were more pronounced in patients with qualifying TG concentrations >885 mg/dL (10 mmol/L).

CONCLUSION: An intermediate dose of OM3-CA (2 g daily) significantly lowers TG and non-high-density lipoprotein cholesterol concentrations in patients with SHTG and may benefit individuals at risk of acute pancreatitis and cardiovascular disease.

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Submitted June 21, 2017. Accepted for publication October 4, 2017.

https://doi.org/10.1016/j.jacl.2017.10.012

Introduction

Adult patients with severe hypertriglyceridemia (SHTG) are at increased risk of developing acute pancreatitis and cardiovascular disease.[1–4] SHTG is characterized by a high serum triglyceride (TG) concentration (≥500 mg/dL [5.65 mmol/L]) and international lipid guidelines state that the treatment goal in SHTG is to minimize serum TG concentration to reduce the risk of developing acute pancreatitis, for example by administering, often in combination, omega-3 fatty acid formulations, fibrates, or nicotinic acid.[4–7] The omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) lower serum TG concentrations by reducing the number of TG-transporting lipoproteins, secondary to reduced hepatic very-low-density lipoprotein cholesterol (VLDL-C) production.[1,8] Omega-3 carboxylic acids (OM3-CA) comprise a complex mixture of polyunsaturated free fatty acids derived from fish oils, of which approximately 550 mg/g is EPA and approximately 200 mg/g is DHA. This novel formulation of OM3-CA provides improved bioavailability compared with ethyl ester formulations[9–11] and is approved for treatment of SHTG with a daily dose of 2 or 4 g as an adjunct to diet. A previous randomized, olive oil–controlled trial demonstrated that OM3-CA, in a dosage range of 2 to 4 g daily, significantly reduced TG concentrations in patients with SHTG.[12] This report presents results from the EpanoVa fOr Lowering Very high triglyceridEs II (EVOLVE II; NCT02009865) randomized, olive oil–controlled trial. EVOLVE II provides further evidence of the lipid-lowering efficacy and safety of an intermediate dose of OM3-CA (2 g daily) in patients with SHTG, including patients with qualifying TG concentrations >885 mg/dL (10 mmol/L)—the threshold at which the risk of pancreatitis is clinically significant and treatment of SHTG is mandatory according to European guidelines—and patients with Fredrickson type V hyperlipidemia, a rare condition with symptoms including SHTG.[2]

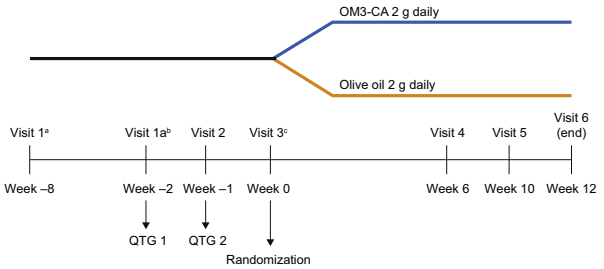

Figure 1 Study design of EVOLVE II. [a]Screening visit for patients who required washout or stabilization of lipid-lowering therapy. This included patients who were previously receiving drugs or supplements containing OM3-CA, required adjustment to or addition of permitted statin, CAI, or statin–CAI combination, and had not been receiving a permitted stable dose of statin, CAI, or statin–CAI combination for at least 4 weeks before visit 1, and/or needed washout of bile acid sequestrants, fibrates, niacin, and/or other supplements known to alter lipid metabolism. [b]Screening visit for patients not requiring washout or stabilization of lipid-lowering therapy. [c]To be eligible for randomization, patients needed to have a mean QTG of at least 500 mg/dL and <2500 mg/dL (or <2000 mg/dL in Canada). CAI, cholesterol-absorption inhibitor; EVOLVE II, EpanoVa fOr Lowering Very high triglyceridEs II; OM3-CA, omega-3 carboxylic acids; QTG, qualifying triglyceride measurement.

Methods

Study objectives

EVOLVE II was a randomized, multicenter, double-blind, parallel-group, phase 3 trial evaluating 162 patients with SHTG who were allocated to OM3-CA 2 g daily or olive oil 2 g daily (given as single doses; Fig. 1). The primary objectives were to determine the efficacy of OM3-CA 2 g once daily, compared with olive oil 2 g once daily, in lowering serum TG concentrations over a 12-week treatment period and to assess the safety of both treatments during that period. Primary objectives were evaluated in both the overall study population and in patients with a qualifying TG concentration >885 mg/dL. Secondary objectives of the study were to determine, over a 12-week treatment period, the effects of OM3-CA 2 g daily, compared with olive oil 2 g daily, on non-high-density lipoprotein cholesterol (non-HDL-C) concentrations and high-density lipoprotein cholesterol (HDL-C) concentrations in both the overall study population and in patients with a qualifying TG concentration >885 mg/dL and TG concentrations in patients with Fredrickson type V hyperlipidemia (biochemically defined as TG:VLDL-C ratio ≥ 6). Exploratory objectives discussed in this report were the effects of OM3-CA 2 g daily, compared with olive oil 2 g daily, on low-density lipoprotein cholesterol (LDL-C) and VLDL-C concentrations over the 12-week study period. The secondary and exploratory objectives in patients with a qualifying TG concentration >885 mg/dL were considered to be hypothesis generating and to facilitate comparison with the overall study population.

Study design

Qualifying TG concentrations were measured at Weeks −2 and −1, where baseline (Week 0) was when the first dose of the study drug was administered. Baseline TG concentrations were defined as the mean of the qualifying measurements and an additional measurement at Week 0. Patients were randomized at Week 0 in a 1:1 ratio to receive two 1 g soft gelatin capsules of OM3-CA or olive oil once daily for 12 weeks (capsules provided by Herd Mundy Richardson Ltd, Stockport, UK). Study drug was administered without regard to food intake and with the recommendation to be administered in the morning. Randomization was stratified according to qualifying TG measurements (≥500 to ≤885 mg/dL or >885 to <2500 mg/dL