The Effect of a 12-Week Course of Omega-3 Polyunsaturated Fatty Acids on Lipid Parameters in Hypertriglyceridemic Adult HIV-infected Patients Undergoing HAART: A Randomized, Placebo-Controlled Pilot Trial

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ABSTRACT

Background: Hypertriglyceridemia is common in patients with HIV treated with highly active antiretroviral therapy (HAART).

Objective: The goal of this study was to investigate the effect of the polyunsaturated fatty acids (PUFA) docosahexaenoic acid (DHA) 460 mg/eicosapentaenoic acid (EPA) 380 mg on hypertriglyceridemia in HIV-treated patients.

Methods: A double-blind, placebo-controlled, randomized, multicenter pilot study was undertaken in 48 evaluable HIV-infected patients undergoing HAART, with fasting triglyceride levels of 3.39 to 11.3 mmol/L. Patients were allowed fibrate or niacin but not statins and were randomized to PUFA 4 g daily versus placebo for 12 weeks. The primary end point was mean fasting triglyceride levels.

Results: The study included 48 patients; 23 in the PUFA group (mean age, 46.1 years) and 25 in the placebo group (mean age, 43.6 years). All except one were male. All patients in the PUFA group were white; in the placebo group, 20 were white, 4 Asian, and 1 black. The PUFA group had a mean body mass index of 24.7 kg/m^2; the placebo group, 24.1 kg/m^2. All patients were receiving concomitant fibrate therapy. Median baseline triglyceride levels were 5.58 (1.76–10.6) mmol/L for the PUFA group and 4.29 (1.81–6.14) mmol/L for the placebo group. PUFA reduced triglycerides by a median of 1.75 mmol/L versus a 0.41 mmol/L increase for the placebo group (baseline-corrected percentage change relative to placebo [95% CI, −69.48% to −6.53%; $P = 0.019$). No effect was seen on biochemical or virologic safety parameters. No severe treatment-emergent adverse events (TEAEs) occurred. Mild and moderate TEAEs occurred in 20 PUFA-treated patients versus 19 patients receiving placebo. Five were adjudged treatment related, and one was due to cholelithiasis, which led to early discontinuation. Most TEAEs affected the gastrointestinal tract (DHA/EPA, n = 7; placebo, n = 4) and comprised diarrhea, nausea, and flatulence (DHA/EPA vs placebo: 3, 2, and 2 vs 2, 0, and 0, respectively).

Conclusions: PUFA therapy with DHA/EPA reduced triglyceride levels significantly compared with placebo in HIV-infected patients with HAART-associated hypertriglyceridemia. ClinicalTrials.gov identifier: NCT00598910. (*Clin Ther.* 2012;34:67–76)

Key words: HAART, highly active antiretroviral therapy, HIV, omega-3 fatty acid, triglyceride, trial.

INTRODUCTION

Highly active antiretroviral therapy (HAART) has transformed the prognosis of HIV infection. However, chronic diseases of aging have assumed considerable importance. For example, the incidence of cardiovascular disease (CVD) has increased in people with HIV, and the relative risk of CVD is greater than in the

Accepted for publication December 7, 2011.
doi:10.1016/j.clinthera.2011.12.001
0149-2918/$ - see front matter

general population.[1–3] HAART is associated with an increased risk of CVD, partly due to lipid-perturbation effects, including both hypercholesterolemia and hypertriglyceridemia.[4] In addition to CVD, increased triglyceride levels form part of the definition of the metabolic syndrome[5,6] and are associated with an increased risk of developing type 2 diabetes and with the presence of lipodystrophy in HIV.[7]

Patients with moderate hypertriglyceridemia (<20 mmol/L [1800 mg/dL]) have an increased risk of CVD due to an atherogenic lipid profile.[6,8] There is no evidence-based target for triglyceride levels although many guidelines suggest that fasting triglycerides should be reduced to <2.3 mmol/L (200 mg/dL) on the basis of improving the atherogenic lipoprotein phenotype.[6] Statins are accepted first-line therapy for lipid disorders, with some evidence for triglyceride reduction in proportion to their capacity to reduce LDL-C up to 9.04 mmol/L (800 mg/dL),[9,10] and statins are therefore generally preferred for triglyceride levels <5.6 mmol/L. There is no consensus on the optimal therapy for hypertriglyceridemia exceeding 5.6 mmol/L (500 mg/dL), with fibrates, niacin, and omega-3 (n-3) polyunsaturated fatty acid (PUFA) therapy all having some benefit on lipid levels.[6,8,11] Trials of fenofibrate added to baseline statin therapy in type 2 diabetes (Action to Control Cardiovascular Risk in Diabetes [ACCORD]),[12] and niacin added to statin in patients with dyslipidemia and CVD (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health [AIM-HIGH]),[13] have reported no benefit on CVD events except possibly in high triglyceride: low HDL-C subgroups.

There is evidence that n-3 PUFA therapy reduces hypertriglyceridemia[14] and CVD events.[15,16] Two purified forms of ethyl esterized n-3 fatty acids, docosahexaenoic acid (*all-cis*-4,7,10,13,16,19-docosahexaenoic acid) and eicosapentaenoic acid (*all-cis*-5,8,11,14,17-eicosapentaenoic acid), are commonly used in combination (DHA/EPA). However, for the combination used in this study, we were unable to find (using a PubMed search for the years 1996 to August 2011 for the terms HIV, lipid lowering agents, triglycerides, DHA, EPA, EPA ratio, Omacor) any firm rationale or trial evidence for the ratio chosen. Trials of DHA/EPA in patients with CVD Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-Prevenzione, [Italian group for the study of the survival of Myocardial Infarction])[17] and EPA in patients receiving statin therapy with or without CVD in the Japan EPA Lipid Intervention Study[18] have reported significant reductions in CVD events in the absence of significant changes in lipid profiles. However, these therapies reduced CVD events at doses that were much lower than those that have significant effects on triglycerides.

Residual hypertriglyceridemia after statin or other lipid-lowering therapies is a common problem in patients with HIV.[19] This study was designed to investigate the short-term effects of a prescription-only preparation of n-3 PUFA ethyl esters comprising 460 mg of DHA and 380 mg of EPA per capsule on the lipid profiles of HIV-positive adults with fasting triglyceride levels 3.39 to 11.3 mmol/L (300–1000 mg/dL) receiving treatment with fibrate or niacin (but no statin therapy) within 3 months of trial entry. Using the PubMed search engine, only randomized, placebo-controlled studies were identified that evaluated DHA/EPA therapy in patients with HIV infection who were receiving HAART.[20–23] This study differs from previous randomized trials of n-3 PUFA in that we recruited patients with higher triglyceride levels (mean, 5.6 mmol/L) and stable, well-controlled HIV disease, and in that we mandated triglyceride-lowering therapy with a fibrate or niacin.

PATIENTS AND METHODS

Study Design

This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. The objective was to investigate the effect of DHA/EPA,* 2 g BID, on fasting lipid parameters in HIV-infected patients with HAART-associated hypertriglyceridemia who were already on dietary therapy and receiving a fibrate or niacin (but no statin therapy).

The study was approved by the ethics committees at the participating centers. It was performed at 2 centers in Germany and 3 in the United Kingdom during 2010 and 2011. DHA/EPA and matching placebo were supplied in anonymized packaging. Adequate compliance as measured by capsule count was defined as that within the range of ≥80% to ≤120%.

Volunteers were randomized 1:1 to receive DHA/EPA or matching placebo capsules BID for 12 weeks. Randomization was done by block size of 4, and a computer-

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