Journal of Clinical Lipidology (2015) 9, 377–383

Journal of Clinical Lipidology

Effects of icosapent ethyl on lipoprotein particle concentration and size in statin-treated patients with persistent high triglycerides (the ANCHOR Study)

Christie M. Ballantyne, MD*, Rene A. Braeckman, PhD, Harold E. Bays, MD, John J. Kastelein, MD, PhD, James D. Otvos, PhD, William G. Stirtan, PhD, Ralph T. Doyle Jr., BA, Paresh N. Soni, MD, PhD, Rebecca A. Juliano, PhD

Baylor College of Medicine and the Houston Methodist DeBakey Heart and Vascular Center, Houston, TX, USA (Dr Ballantyne); Amarin Pharma Inc., Bedminster, NJ, USA (Drs Braeckman, Stirtan, Soni, Juliano, and Mr Doyle); Louisville Metabolic and Atherosclerosis Research Center, Louisville, KY, USA (Dr Bays); Academic Medical Center, Amsterdam, The Netherlands (Dr Kastelein); and LipoScience, Raleigh, NC, USA (Dr Otvos)

KEYWORDS:
Apolipoprotein B;
Eicosapentaenoic acid;
High-density lipoproteins;
Hypertriglyceridemia;
Icosapent ethyl;
Low-density lipoproteins;
Omega-3 fatty acid;
Statin;
Triglycerides

BACKGROUND: Icosapent ethyl (IPE) is a high-purity prescription form of eicosapentaenoic acid ethyl ester approved at a dose of 4 g/day as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe hypertriglyceridemia (TG ≥ 500 mg/dL).

OBJECTIVE: In this prespecified exploratory analysis from the ANCHOR study of patients at high cardiovascular risk with TG ≥ 200 and <500 mg/dL despite statin control of low-density lipoprotein cholesterol, we assessed the effects of IPE on lipoprotein particle concentration and size and examined correlations of atherogenic particles with apolipoprotein B (ApoB).

METHODS: Nuclear magnetic resonance spectroscopy was used to measure lipoprotein particle concentration and size.

RESULTS: Compared with placebo (n = 211), IPE 4 g/day (n = 216) significantly reduced concentrations of: total (12.2%, $P = .0002$), large (46.4%, $P < .0001$), and medium (12.1%, $P = .0068$) very-low-density lipoprotein (VLDL) particles; total (7.7%, $P = .0017$) and small (13.5%, $P < .0001$) LDL particles; and total (7.4%, $P < .0001$) and large (31.0%, $P < .0001$) high-density lipoprotein particles. Atherogenic lipoprotein particles (total VLDL and total LDL) correlated with ApoB at baseline ($R^2 = 0.57$) and week 12 ($R^2 = 0.65$) as did total LDL particle concentration at baseline ($R^2 = 0.53$) and week 12 ($R^2 = 0.59$). Compared with placebo, IPE 4 g/day significantly reduced VLDL (7.7%, $P < .0001$) and high-density lipoprotein (1.2%, $P = .0014$) particle sizes with a modest but significant increase in LDL particle size (0.5%, $P = .0031$).

This study was designed and sponsored by Amarin Pharma Inc., Bedminster, NJ, USA. The role of the funding source, Amarin Pharma Inc., is detailed under the author contributions section.

* Corresponding author. Baylor College of Medicine, 6565 Fannin St., MSA 601, Houston, TX 77030.

E-mail address: cmb@bcm.tmc.edu

Submitted August 28, 2014. Accepted for publication November 23, 2014.

http://dx.doi.org/10.1016/j.jacl.2014.11.009

CONCLUSIONS: Compared with placebo, treatment with IPE 4 g/day for 12 weeks reduced key atherogenic lipoprotein particle concentrations. At both baseline and end of study, atherogenic lipoprotein concentrations correlated with ApoB.

Introduction

Icosapent ethyl (IPE; Vascepa; Amarin Pharma Inc., Bedminster, NJ) is a high-purity prescription form of eicosapentaenoic acid (EPA) ethyl ester approved by the US Food and Drug Administration as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.[1] The Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-week study with an open-label Extension (MARINE) (N = 229) demonstrated that, compared with placebo, IPE 4 g/day significantly reduced levels of TG (33.1%, $P < .0001$), total cholesterol (TC; 16.3%, $P < .0001$), non–high-density lipoprotein cholesterol (non-HDL-C; 17.7%, $P < .0001$), and apolipoprotein B (ApoB; 8.5%, $P = .0019$) in patients with very high TG levels (≥500 and ≤2000 mg/dL) without significantly increasing low-density lipoprotein cholesterol (LDL-C).[2]

The ANCHOR study evaluated IPE in statin-treated patients at high risk for cardiovascular disease with persistently high TG (≥200 and <500 mg/dL) and well-controlled LDL-C (≥40 and ≤115 mg/dL).[3] Compared with placebo, IPE 4 g/day significantly (all $P < .0001$) reduced levels of TG (21.5%), TC (12.0%), non-HDL-C (13.6%), and ApoB (9.3%); LDL-C was also significantly reduced by 6.2% ($P = .0067$).[3]

Although the non-HDL-C–lowering effects of lipid-lowering agents are central in clinical practice for the management of cardiovascular disease and risk, lipoprotein particle parameters and ApoB may also be clinically relevant and useful.[4,5] Lipoprotein particle concentration, LDL particle size, and ApoB levels may influence atherogenicity and coronary heart disease risk.[6–9] Indeed, LDL particle concentrations and/or ApoB have been included in recent treatment recommendations and consensus statements regarding lipid management.[9–12]

The objective of this prespecified exploratory analysis from the ANCHOR study was to assess the effects of IPE on lipoprotein particle concentration and size and to assess the correlation of LDL and total atherogenic particle concentrations with ApoB in statin-treated patients.

Methods

ANCHOR was a phase 3, 12-week, multicenter, double-blind, randomized, placebo-controlled study of IPE in patients receiving atorvastatin, rosuvastatin, or simvastatin with or without ezetimibe and at high cardiovascular risk with TG levels ≥200 and <500 mg/dL and LDL-C levels ≥40 and ≤115 mg/dL.[3] Briefly, eligible patients aged >18 years entered a 4- to 6-week diet, lifestyle, and medication stabilization lead-in period with washout of prohibited non-statin lipid-altering medications (including fibrates, niacins, and omega-3 fatty acids). This was followed by a 2- to 3-week lipid-qualifying period after which patients entered the 12-week treatment period with IPE 4 g/day, IPE 2 g/day, or matched placebo.[3] This brief report focuses on the Food and Drug Administration–approved dose of 4 g/day.

Lipoprotein particle concentration and size were measured by nuclear magnetic resonance spectroscopy at LipoScience, Inc. (Raleigh, NC), as previously described.[13] Statistical analyses were performed using SAS 9.2 software. The data set included values from the intent-to-treat (ITT) population, defined as all randomized patients who had a baseline TG primary efficacy end point measurement, received ≥1 dose of study drug, and had ≥1 postrandomization efficacy measurement. Patients with missing baseline or week 12 measurements were excluded. Lipoprotein particle end points were prespecified and exploratory with statistical significance predefined as $P \leq .05$; no adjustments were made for multiplicity. Medians and interquartile ranges were calculated for each treatment group at baseline, week 12, and for percent change from baseline at week 12. Between-treatment differences in percent change from baseline for each lipoprotein particle variable were examined using the Wilcoxon rank-sum test with Hodges-Lehmann medians presented. Lipid values and ApoB were assessed as previously described.[3]

Results

Baseline characteristics were comparable across treatment groups in the ANCHOR study; most patients were white, overweight men younger than age 65 years with diabetes mellitus and were receiving medium- or high-efficacy statin regimens. In this prespecified exploratory analysis of the ANCHOR study, 216 patients in the IPE 4 g/day group and 211 in the placebo group had evaluable lipoprotein particle samples, which represented 96% and 93% of the 4 g/day and placebo groups, respectively. In this subset of patients with lipoprotein data, baseline TG, LDL-