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Icosapent ethyl: Eicosapentaenoic acid concentration and triglyceride-lowering effects across clinical studies

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ABSTRACT

Icosapent ethyl is a high-purity prescription form of eicosapentaenoic acid (EPA) 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 (≥500 mg/dL) hypertriglyceridemia. This post-hoc exploratory analysis examined the relationship of icosapent ethyl dose with EPA concentrations in plasma and red blood cells (RBCs) across 3 clinical studies—a phase 1 pharmacokinetic study in healthy adult volunteers and 2 pivotal phase 3 studies (MARINE and ANCHOR) in adult patients with hypertriglyceridemia—and examined the relationship between EPA levels and TG-lowering effects in MARINE and ANCHOR. In all 3 studies, icosapent ethyl produced dose-dependent increases in the concentrations of EPA in plasma and RBCs. In both MARINE and ANCHOR, these dose-dependent EPA increases correlated with the degree of TG level lowering (all $P<0.01$). In patients with high TG levels (≥200 mg/dL) and treated with icosapent ethyl 4 g/day, the end-of-treatment plasma and RBC EPA concentrations were >170 μg/mL and >70 μg/mL, respectively. These studies support icosapent ethyl as producing predictable dose-dependent pharmacokinetics/pharmacodynamics, with TG level lowering dependent upon icosapent ethyl dose and EPA concentrations in plasma and RBCs.

1. Introduction

Icosapent ethyl (Vascepa®; Amarin Pharma, Inc., Bedminster, NJ) is a high-purity prescription form of eicosapentaenoic acid (EPA) ethyl ester approved by the Food and Drug Administration as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia [1]. Epidemiological and clinical data suggest that high TG levels are a risk factor for atherosclerotic cardiovascular disease (ASCVD) [2]. Genetic data also support a role for elevated TG levels in the causal pathway of ASCVD [3–12]. Compared with placebo, in the Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-week Study with an Open-Label Extension (MARINE) and ANCHOR pivotal studies, icosapent ethyl significantly reduced TG levels in adult patients with very high TG levels (TG ≥ 500 and ≤2000 mg/dL) in MARINE and in statin-treated adult patients with high TG levels (TG≥200 and < 500 mg/dL) in ANCHOR [13,14]. In these studies, icosapent ethyl also significantly reduced the levels of other atherogenic lipid and lipoprotein parameters compared with placebo (e.g., non-high-density lipoprotein cholesterol, apolipoprotein B, apolipoprotein C-III, very-low-density lipoprotein cholesterol, remnant lipoprotein cholesterol, and low-density lipoprotein [LDL] particles) and decreased markers of inflammation (e.g., oxidized LDL particles, lipoprotein-associated phospholipase A_2, and C-reactive protein) [13–19].

While other omega-3 fatty acid products that contain both EPA and docosahexaenoic acid (DHA) may significantly raise LDL cholesterol (LDL-C) levels when administered to patients with elevated TG levels [20–23], icosapent ethyl did not raise LDL-C levels compared with placebo [13,14]. In addition to the effects on lipids, which may be expected to reduce ASCVD risk, other hypotheses behind the ongoing Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT; NCT01492361) are that EPA, when added to a statin, may favorably affect other steps in atherosclerosis, including endothelial dysfunction, oxidative stress, foam cell formation, inflammation, plaque formation and progression, platelet aggregation, thrombus formation, and plaque rupture

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[24,25]. It should be noted that icosapent ethyl is not approved by the US FDA to reduce the risk of coronary heart disease; the effect of icosapent ethyl on the risk of cardiovascular mortality and morbidity has not been determined.

In the MARINE and ANCHOR studies, 12 weeks of treatment with icosapent ethyl 4 g/day or 2 g/day significantly increased end-of-treatment plasma EPA levels and the EPA/arachidonic acid (AA) ratio [26,27]. In the Japan EPA Lipid Intervention Study (JELIS), ethyl icosapentate 1.8 g/day (another highly purified prescription EPA ethyl ester, approved in Japan but not in the US) significantly increased plasma EPA levels and the EPA/AA ratio at the 5-year follow-up, and decreased risk of major coronary events by 19% ($P = 0.011$) [28]. In a phase 1 pharmacokinetic study of healthy volunteers, plasma EPA concentration increased in a dose-dependent fashion [29]. This may be of clinical importance because ASCVD risk seems to increase with decreased EPA plasma [28] and red blood cell (RBC) membrane concentrations [30]. A low omega-3 index (the ratio of EPA plus DHA relative to other fatty acids in the RBC membrane) is a cardiovascular risk factor associated with poor ASCVD outcomes [31,32]. A lower plasma EPA/AA ratio is correlated with a higher risk of atherosclerosis progression and adverse cardiovascular outcomes [33–36]. Thus, both the dose of icosapent ethyl, as well as EPA plasma and RBC concentrations, may provide clinically meaningful insight into the potential ASCVD benefits of icosapent ethyl. This analysis included data from the MARINE and ANCHOR studies as well as the pharmacokinetic phase 1 study in healthy volunteers. The intent was to explore the effects of icosapent ethyl on EPA concentrations in plasma and RBCs in response to dose and the relationship to TG lowering across these 3 clinical studies.

2. Materials and methods

2.1. Study design

This post-hoc exploratory analysis examined pharmacokinetic and pharmacodynamic data from 3 clinical studies. The first study was an open-label, randomized, multidose, phase 1 pharmacokinetic study including a 14-day screening period followed by a 4-week treatment period [29]. The study enrolled healthy, non-smoking volunteers aged ≥ 18 and ≤55 years with a body mass index of > 18 and ≤30 kg/m^2. Use of lipid-altering medications or supplements was not allowed within 6 weeks prior to randomization until the end of the study. The study randomized eligible subjects (6 men and 6 women per group) to icosapent ethyl 2 g/day administered as one 1-g capsule twice daily, icosapent ethyl 4 g/day administered as two 1-g capsules twice daily, icosapent ethyl 2 g/day administered as two 1-g capsules once daily, or icosapent ethyl 2 g/day administered as two 0.5-g capsules twice daily. The present analysis includes data from the first 2 groups.

The other 2 studies, MARINE and ANCHOR, were pivotal, phase 3, placebo-controlled, randomized, double-blind, multicenter studies, with details previously described [13,14]. Briefly, both studies had a 4- to 6-week lead-in period of diet, lifestyle, and medication stabilization, with washout of prohibited lipid-altering medications, followed by a 12-week, double-blind treatment period. Patients aged ≥18 years with qualifying lipid levels (TGs ≥ 500 mg/dL to ≤2000 mg/dL in MARINE; TGs≥200 mg/dL to <500 mg/dL with statin-stabilized LDL-C ≥40 mg/dL and ≤115 mg/dL in ANCHOR) entered the treatment period and were randomized to receive icosapent ethyl 4 g/day (two 1-g capsules twice daily), icosapent ethyl 2 g/day (one 1-g capsule and one matched placebo capsule twice daily), or placebo (two matched capsules twice daily). In MARINE, stable statin therapy with or without ezetimibe was permitted but not required. ANCHOR required eligible patients to be at high risk for cardiovascular disease as defined by the National Cholesterol Education Program Adult Treatment Panel III guidelines [37] and to be receiving a stable dose of statin therapy (atorvastatin, rosuvastatin, or simvastatin with or without ezetimibe).

Investigators instructed subjects in each study to take study medication orally with or after their morning and evening meal, and subjects agreed to maintain a stable diet and physical activity level throughout the study. Eligible women had a negative urine pregnancy test at screening, agreed to use an effective method of contraception, could not be pregnant or breastfeeding, and could not be planning on becoming pregnant during the study. Each study was conducted in accordance with the principles originating in the Declaration of Helsinki and in accordance with Good Clinical Practice and all applicable laws and regulations. An institutional review board at each site approved the respective study protocol before any subjects were enrolled at that site. All subjects provided written informed consent.

2.2. Assessments

In the MARINE and ANCHOR studies, fasting baseline EPA measurements were taken before the first dose of study drug, and fasting trough (minimum concentration [C_{min}]) EPA concentrations were based on measurements taken before the morning icosapent ethyl dose at 12 weeks of treatment. For the time points relevant to this analysis, fasting EPA measurements were taken in the phase 1 pharmacokinetic study before the morning icosapent ethyl dose on the first day (pre-treatment baseline) and at 28 days (pre-dose trough EPA concentration).

These studies measured EPA concentrations in plasma and in RBCs using a liquid chromatography-tandem mass spectrometry (LC–MS/MS) method (Charles River Laboratories Ltd, Elphinstone Research Center, Tranent, Edinburgh, Scotland) as previously described [29]. Total plasma EPA comprised all EPA forms, including unesterified EPA as well as that incorporated into phospholipids, triacylglycerols, and cholesteryl esters, whereas EPA in RBCs was from cell membranes, where it is mainly incorporated into phospholipids. For these measurements, lipids were isolated from plasma and RBC suspensions by acid/methanol/chloroform extraction followed by centrifugation, and purified by isohexane extraction and filtration on a solid-phase extraction column after confirmed complete lipid hydrolysis and transmethylation following an overnight incubation at 50 °C with acid/methanol. Quantitation of EPA in each sample utilized linolenic acid as an internal standard and a standard EPA calibration curve. The lower limits of quantitation (LLOQ) were 10 μg/mL for total plasma EPA and 5 μg/mL for total RBC EPA.

The MARINE and ANCHOR studies evaluated serum TG levels as previously described [26], using enzymatic colorimetric tests (Olympus AU2700 or AU5400 Analyzer, Olympus Center Valley, PA) with calibration directly traceable to US Centers for Disease Control reference procedures.

2.3. Data analysis

The phase 1 pharmacokinetic study determined EPA concentrations in plasma and RBCs for subjects in the per-protocol population, which included all randomized subjects who completed the 28-day treatment period without any protocol violations and who provided baseline and day 28 samples. The MARINE and ANCHOR studies determined EPA concentrations for patients in the intent-to-treat population (all randomized patients who took ≥ 1 dose of study drug and had valid baseline laboratory efficacy measurements and at least 1 post-randomization laboratory efficacy measurement) who had EPA values at baseline and at the week-12