Postgraduate Medicine

ISSN: 0032-5481 (Print) 1941-9260 (Online) Journal homepage: http://www.tandfonline.com/loi/ipgm20

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To cite this article: Anurag W. Kedia & Erin Lynch (2015): Effects of switching from omega-3-acid ethyl esters to icosapent ethyl in a statin-treated patient with elevated triglycerides, Postgraduate Medicine, DOI: 10.1080/00325481.2015.1100086

To link to this article: http://dx.doi.org/10.1080/00325481.2015.1100086

Published online: 09 Oct 2015.

Postgraduate Medicine

www.tandfonline.com/pgm
ISSN: 0032-5481 (print), 1941-9260 (electronic)

Postgrad Med, 2015; Early Online: 1–5
DOI: 10.1080/00325481.2015.1100086

Taylor & Francis
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CLINICAL FOCUS: CARDIOMETABOLIC CONDITIONS
CASE REPORT

Effects of switching from omega-3-acid ethyl esters to icosapent ethyl in a statin-treated patient with elevated triglycerides

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Abstract

In patients with dyslipidemia, elevated triglyceride (TG) levels, or TG-rich lipoproteins, and cardiovascular risk may remain despite statin therapy. Prescription omega-3 fatty acid formulations containing the ethyl esters of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) (omega-3-acid ethyl esters; Lovaza®) or high-purity EPA ethyl ester (icosapent ethyl; Vascepa®) are TG-lowering treatments that may be administered in addition to statins. Here we describe the effects of switching from omega-3-acid ethyl esters to icosapent ethyl in a 44-year-old obese man with dyslipidemia, hypertension, and hypothyroidism. The patient was receiving stable treatment with medications, including atorvastatin 40 mg/day and extended-release niacin 1000 mg/day. Owing to persistently elevated TG levels and other cardiovascular risk factors, the patient was initiated on omega-3-acid ethyl esters 4 g/day. After approximately 2 years on omega-3-acid ethyl esters, his total cholesterol (TC) level was 184 mg/dL, low-density lipoprotein cholesterol (LDL-C) level was 81 mg/dL, TG level was elevated at 307 mg/dL despite statin therapy, and non-high-density lipoprotein cholesterol (non-HDL-C) level was 144 mg/dL. After the switch to icosapent ethyl, TC level decreased by 34% to 121 mg/dL, LDL-C level decreased by 28% to 58 mg/dL, TG level decreased by 41% to 180 mg/dL, and non-HDL-C level decreased by 44% to 81 mg/dL. Switching from omega-3-acid ethyl esters containing both EPA and DHA to icosapent ethyl containing high-purity EPA resulted in beneficial and substantial changes in the lipid profile with a notable reduction of TG levels along with additional reductions in LDL-C levels in a statin-treated obese patient with persistently high TG levels. Treatment with icosapent ethyl was well tolerated.

Keywords

Docosahexaenoic acid, Dyslipidemia, Eicosapentaenoic acid, Hypertriglyceridemia, Icosapent ethyl, Lovaza, Obesity, Omega-3 fatty acid, Statin, Vascepa

History

Received 24 August 2015
Accepted 22 September 2015
Published online 13 October 2015

Introduction

Cardiovascular disease affects more than one in three adults in the United States, making it a leading cause of morbidity and mortality and major health concern.[1] Despite optimal treatment of elevated low-density lipoprotein cholesterol (LDL-C) levels with statin therapy, patients with dyslipidemia may have elevated triglyceride (TG) levels and other atherogenic parameters that may confer residual cardiovascular risk.[2–4] TG levels are notably affected by body mass, with higher TG levels found in groups considered to be overweight and obese.[2] Treatment with additional medications may be needed to help reduce residual cardiovascular risk in such individuals. Notably, the Residual Risk Reduction Initiative and the Clinical Practice Guideline on Hypertriglyceridemia of the Endocrine Society recommend treatment with adjunctive medications to reduce cardiovascular risk.[3,5]

High-dose omega-3 fatty acids are among the TG-lowering treatment options that may be administered on top of statin therapy. In addition to lowering TG levels, omega-3 fatty acids have other beneficial effects on atherogenic parameters, such as non-high-density lipoprotein cholesterol (non-HDL-C) and total cholesterol (TC). Omega-3 fatty acids may also confer cardiovascular benefit through effects on heart rate, arrhythmia, blood pressure, systemic vascular resistance, myocardial efficiency, arterial wall compliance, vasodilatory responses and thrombosis.[6] The omega-3 fatty acid eicosapentaenoic acid (EPA) also has antioxidant properties [7,8] and is incorporated into membrane phospholipids, including the atherosclerotic plaque itself, exerting beneficial and pleiotropic effects on endothelial function [9,10]; macrophage, monocyte and foam cell function [11–13]; inflammation [14,15]; plaque progression, formation and vulnerability [12,13,16–19]; and thrombus formation, all of which are involved in the atherothrombotic process.[20,21]

Prescription omega-3 fatty acid products are currently indicated as an adjunct to diet to reduce TG levels in adult patients with severe hypertriglyceridemia (≥500 mg/dL) and may contain a mixture of docosahexaenoic acid (DHA) and EPA or may be formulated to contain only high-purity EPA.[22–24] Notably,

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products that contain DHA have the potential to increase LDL-C levels.[23,25,26] In a systematic review and meta-analysis of 21 randomized controlled trials, both EPA and DHA were found to decrease serum TG levels, but only DHA significantly increased LDL-C levels [27]; a separate meta-analysis of 22 randomized controlled trials also found that LDL-C levels increased after treatment with DHA but not EPA.[28] The prescription product, omega-3-acid ethyl esters (Lovaza®, GlaxoSmithKline, Research Triangle Park, NC, USA), was approved in 2004 and contains the ethyl esters of both EPA and DHA.[23] As described in the product prescribing information, omega-3-acid ethyl esters raised LDL-C levels by approximately 49% compared with placebo in patients with TG levels ≥500 mg/dL; therefore, according to the Warnings and Precautions in the product label, LDL-C levels should be monitored periodically during therapy.[23] The same is also true for Lovaza generics and other EPA and DHA combination prescription products that are approved but not yet available on the market at the time of this writing.[23,25,26] In contrast, data from phase 3 clinical trials have demonstrated that the EPA-only product, icosapent ethyl (Vascepa®; Amarin Pharma Inc., Bedminster, NJ, USA) which contains only the ethyl ester of EPA, does not significantly increase LDL-C levels in statin-treated patients with TG levels ≥200 mg/dL to <500 mg/dL or in patients with TG levels ≥500 mg/dL as compared with placebo.[29,30] There are no warnings or precautions with regard to LDL-C in the icosapent ethyl product label.[24] Thus, icosapent ethyl may be a more appropriate treatment option for the management of patients with dyslipidemia given the lack of issues with LDL-C levels. Here we report a case of a patient who was switched from omega-3-acid ethyl esters (EPA + DHA) to icosapent ethyl (high-purity EPA) and the effects of this switch on serum lipid levels as well as other atherogenic parameters.

Case

An obese, adult white man (stable body mass index [BMI], 32 kg/m^2) with a history of dyslipidemia, hypertension and hypothyroidism was followed in our family care practice in Tallmadge, OH, USA. His medications included atorvastatin 40 mg/day, extended-release niacin 1000 mg/day, losartan 50 mg/day and levothyroxine 175 µg/day. The patient was receiving stable doses of these medications, in addition to maintaining stable diet and exercise, throughout the period of data collection for this report (December 2011 through March 2014). At age 42, the patient was initiated on omega-3-acid ethyl esters 4 g/day because of persistently elevated TG levels (206 mg/dL despite statin therapy) along with other cardiovascular risk factors including obesity and hypertension. The patient's overnight fasting plasma concentrations of lipids, apolipoprotein B (Apo B) and high-sensitivity C-reactive protein (hsCRP) were assessed at follow-up visits during treatment with omega-3-acid ethyl esters and after switching to icosapent ethyl. Lipoprotein particle measurements were made by nuclear magnetic resonance spectroscopy. Measurements reported herein were made by the same laboratory. For consistency and to provide the greatest information regarding the patient's atherosclerotic markers, the patient's two available advanced lipid tests taken during the study time frame were included in this analysis.

Table 1. Laboratory parameters in a statin-treated patient before and after switching from omega-3-acid ethyl esters to icosapent ethyl.

Parameter	On omega-3-acid ethyl esters (4 g/day)	On icosapent ethyl (4 g/day)	Change (%)
LDL-C (mg/dL)	81	58	–28
TG (mg/dL)	307	180	–41
Non-HDL-C (mg/dL)	144	81	–44
TC (mg/dL)	184	121	–34
HDL-C (mg/dL)	40	39	–2.5
Apo B (mg/dL)	88	54	–39
LDL-P (nmol/L)	1479	938	–37
sdLDL-C (mg/dL)	34	23	–32
HDL-P (µmol/L)	31.9	32.7	2.51
hsCRP (mg/L)	0.7	0.4	–43

Apo B: apolipoprotein B; HDL-C: high-density lipoprotein cholesterol; HDL-P: high-density lipoprotein particles; hsCRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; LDL-P: low-density lipoprotein particles; non-HDL-C: non-high-density lipoprotein cholesterol; sdLDL-C: small dense low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides.

After approximately 2 years of treatment with omega-3-acid ethyl esters, the patient's TC level was 184 mg/dL, LDL-C level was 81 mg/dL, and HDL-C level was 40 mg/dL. However, despite statin therapy, the patient's TG level was 307 mg/dL and non-HDL-C level was 144 mg/dL (Table 1). In addition, his Apo B, low-density lipoprotein particle (LDL-P) and small dense low-density lipoprotein cholesterol (sdLDL-C) levels were 88 mg/dL, 1479 nmol/L, and 34 mg/dL, respectively (Table 1).

The patient was later switched to icosapent ethyl on the basis of clinical data demonstrating the efficacy of icosapent ethyl in lowering TG levels without raising LDL-C levels and an excellent safety and tolerability profile.[24,29,30] The patient began a daily regimen of 4 g icosapent ethyl (two 1-g capsules twice daily). His plasma concentrations of lipids, LDL-P, Apo B and hsCRP were assessed after approximately 1 year on icosapent ethyl, when he was 47 years of age.

The patient's lipid parameters before and after switching from omega-3-acid ethyl esters to icosapent ethyl are shown in Table 1. After the switch from omega-3-acid ethyl esters to icosapent ethyl, the patient's LDL-C level decreased by 28% to 58 mg/dL, TG level decreased by 41% to 180 mg/dL, TC level decreased by 34% to 121 mg/dL, non-HDL-C level decreased by 44% to 81 mg/dL and his HDL-C level decreased nominally by 2.5% to 39 mg/dL (Table 1 and Figure 1). The patient's Apo B level decreased by 39% to 54 mg/dL, his LDL-P level decreased by 37% to 938 nmol/L, his sdLDL-C level decreased by 32% to 23 mg/dL, HDL-P level increased nominally by 2.51% to 32.7 µmol/L and his hsCRP level decreased by 43% to 0.4 mg/L (Table 1 and Figure 1). After switching from omega-3-acid ethyl esters to icosapent ethyl, the patient had an omega-3 index of 10% (omega-3 index data were not available while on omega-3-acid ethyl esters).

Both omega-3-acid ethyl esters and icosapent ethyl were well tolerated by the patient; no adverse events were reported, and the patient reported himself to be compliant with these therapies.

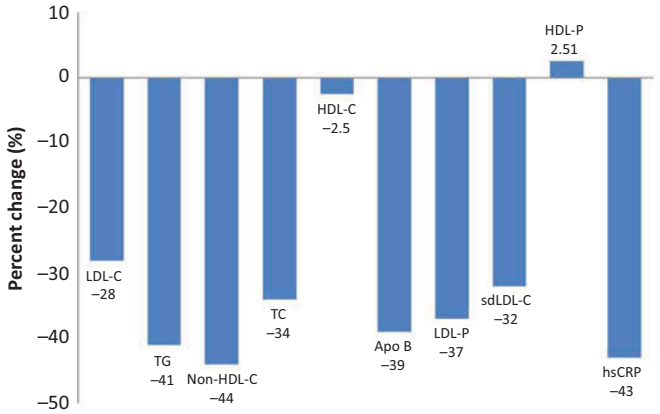

Figure 1. Percent change in laboratory parameters in a statin-treated patient after switching from omega-3-acid ethyl esters to icosapent ethyl (each at 4 g/day). Apo B: apolipoprotein B; HDL-C: high-density lipoprotein cholesterol; HDL-P: high-density lipoprotein particles; hsCRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; LDL-P: low-density lipoprotein particles; non-HDL-C: non-high-density lipoprotein cholesterol; sdLDL-C: small dense low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides.

Discussion

This case report outlines the changes in serum lipids and other atherogenic parameters in a statin-treated patient with multiple risk factors for cardiovascular disease after switching from omega-3-acid ethyl esters, which contains both EPA and DHA, to icosapent ethyl, which contains high-purity EPA. The switch resulted in beneficial and substantial changes in the lipid profile and other laboratory measures used in evaluating treatments for reducing cardiovascular risk. We observed a notable reduction in TG along with a notable reduction in LDL-C level to <60 mg/dL.

The lipid changes obtained with icosapent ethyl in this patient have been supported in other studies of patients with dyslipidemia whose omega-3 fatty acid therapy was switched from products containing both EPA and DHA to icosapent ethyl.[31–33] Two dyslipidemic patients with type 2 diabetes, one was receiving statin therapy and an omega-3 fatty acid nutritional supplement and the other was statin intolerant and receiving omega-3-acid ethyl esters, were switched to icosapent ethyl in an effort to achieve improved lipid control. In both cases, improvements occurred in the levels of TG, LDL-C, non-HDL-C and TC after the initiation of icosapent ethyl, and HDL-C levels did not change.[31] A retrospective review of the medical records of 14 dyslipidemic patients receiving statins or ezetimibe who had been switched from omega-3-acid ethyl esters to icosapent ethyl showed that, in the majority of patients, levels of TG, LDL-C, non-HDL-C and TC decreased after the switch, whereas changes in HDL-C levels varied among patients.[32] In a retrospective review of 10 dyslipidemic patients with diabetes or prediabetes (nine receiving statins) who had been switched from omega-3-acid ethyl esters to icosapent ethyl, levels of TG, LDL-C, non-HDL-C and TC improved in most patients, whereas HDL-C levels increased or did not change in most patients.[33] Thus, although no prospective studies have investigated switching patients from products containing both EPA and DHA to icosapent ethyl, case evidence from multiple clinical practices suggests a potential benefit in serum atherogenic parameters after switching.

With regard to prospective clinical investigation, the safety and efficacy of icosapent ethyl were evaluated in two randomized, placebo-controlled, phase 3 trials: the Multicenter Placebo-Controlled, Randomized, Double-Blind 12-Week Study with an Open-Label Extension (MARINE)[30] and the 12-week ANCHOR trial.[29] The MARINE trial enrolled patients with severe hypertriglyceridemia (≥500 mg/dL and ≤2000 mg/dL), 25% of whom were on statin therapy, and the ANCHOR trial enrolled patients with TG levels ≥200 and <500 mg/dL despite stable statin therapy. In the MARINE trial, administration of icosapent ethyl 4 g/day significantly reduced median TG levels by 33% ($p < 0.0001$) and non-HDL-C levels by 18% ($p < 0.0001$) while not significantly increasing LDL-C levels compared with placebo; the incidence of adverse events with icosapent ethyl was similar to that with placebo, and icosapent ethyl was well tolerated.[30] In the ANCHOR trial, administration of icosapent ethyl 4 g/day also produced significant reductions in median TG (22%; $p < 0.0001$) and non-HDL-C levels (14%; $p < 0.0001$), as well as reductions in LDL-C (6%; $p < 0.01$) and TC levels (12%; $p < 0.0001$), compared with placebo and was safe and generally well tolerated.[29] Thus, the lipid changes observed in our patient who was switched from omega-3-acid ethyl esters to icosapent ethyl are consistent with the established efficacy of icosapent ethyl.

With regard to other parameters assessed, Apo B is present as a single molecule in each atherogenic lipoprotein particle, and the Apo B level has been identified as a predictor of cardiovascular risk, as has LDL-P concentration.[4] Both Apo B and LDL-P elevations may contribute to residual risk in patients receiving statins.[4] In our patient, after the switch to icosapent ethyl, Apo B, LDL-P and sdLDL-C levels decreased. In the MARINE and ANCHOR trials, Apo B levels also decreased significantly with icosapent ethyl 4 g/day (by 9% in both trials; $p < 0.0001$).[29,30] In addition, results of an exploratory analysis of data from the MARINE trial largely support the lipid particle findings in this patient, as icosapent ethyl 4 g/day significantly reduced the particle concentrations of large very-low-density lipoproteins (VLDL-P), total LDL-P, small LDL-P and total HDL-P compared with placebo in the trial.[34] This effect was also studied in a similar analysis of the ANCHOR trial, which found significant decreases in total, large and medium VLDL-P, total LDL-P, small LDL-P, and total and large HDL-P levels with icosapent ethyl 4 g/day compared with placebo.[35] The omega-3 index represents the content of EPA and DHA in red blood cell membranes as a percentage of total fatty acids and reflects the content of these fatty acids in cardiac membranes.[36] It has been used as a tool for cardiovascular disease risk stratification with an optimal range of ≥8.0%.[36] A measurement for the omega-3 index was available for our patient after treatment with icosapent ethyl with a reading of 10%. As we did not have an omega-3 index measurement during the omega-3 ethyl esters treatment period, we could not compare the measurements before and after the switch to icosapent ethyl.

The patient was obese (BMI, 32 kg/m^2) and had hypertension and hyperlipidemia. During the treatment period in this report, our patient met several of the criteria for metabolic syndrome.[4] The results achieved with icosapent ethyl in this patient are supported by those obtained in a recent *post hoc* analysis of patients with metabolic syndrome who participated in the MARINE or ANCHOR trials.[37] The *post hoc* analysis found significant reductions in TG, non-HDL-C, Apo B and hsCRP levels, along with no significant increases in LDL-C levels, with icosapent ethyl 4 g/day compared with placebo in patients with metabolic syndrome.[37]

Effects of icosapent ethyl beyond lipids were examined in a separate analysis of patients from the MARINE and ANCHOR studies. The results showed that icosapent ethyl 4 g/day significantly decreased markers of inflammation, including hsCRP, compared with placebo.[15] In our patient, hsCRP levels were optimal with omega-3-acid ethyl esters and decreased further, by 43%, after the switch to icosapent ethyl. This may be a noteworthy benefit of icosapent ethyl owing to the important role of inflammation in atherosclerotic plaque formation.[38,39]

The finding that our patient tolerated omega-3-acid ethyl esters and icosapent ethyl well while on atorvastatin therapy is consistent with the safety and tolerability profiles of these drugs [23,24] and with previous findings of no drug-drug interactions for omega-3-acid ethyl esters or icosapent ethyl with atorvastatin.[40,41]

Although the current observations are limited to one patient at only a few selected time points, they may help provide insight for further study of the effects of switching from omega-3 fatty acid products containing both EPA and DHA to icosapent ethyl in high-risk patients with persistently elevated TG levels while on statin therapy. The ongoing phase 3, randomized, parallel-assignment, double-blind Reduction of Cardiovascular Events with EPA—Intervention Trial (REDUCE-IT) (NCT01492361) is investigating the effects of icosapent ethyl on cardiovascular outcomes in high-risk patients with persistent hypertriglyceridemia despite statin therapy. Recent results with ezetimibe in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) provide proof of principle that statin add-on therapy can reduce residual cardiovascular risk and that lower LDL-C levels are beneficial.[42] Agents that contain DHA may confound the treatment of patients with dyslipidemia because DHA may raise LDL-C levels. Per FDA equivalence codes,[43] products containing DHA are not therapeutically equivalent to icosapent ethyl and should not be substituted for it.

Limitations

This report is limited in that it provides results for one patient and thus may not be generalizable to other patients. However, together with the results of other case series, the data suggest that further prospective, larger studies may be warranted. As this case assessed atherogenic parameters, the benefits of switching from omega-3-acid ethyl esters to icosapent ethyl on cardiovascular outcomes remain to be proven.

Conclusions

Switching from omega-3-acid ethyl esters containing both EPA and DHA to icosapent ethyl containing high-purity EPA was safe and well tolerated and resulted in beneficial and substantial changes in the patient's potential residual risk factors as noted in the lipid profile of a statin-treated obese patient with dyslipidemia and other cardiovascular risk factors.

Acknowledgments

Medical scientific reference checks and associated assistance were provided by Sephy Philip, RPh, PharmD, and Joy Bronson of Amarin Pharma Inc. and Sumita Chowdhury, MD, MPH, FACC, MBA, a consultant for Amarin Pharma Inc.

Declaration of Interest

Amarin Pharma, Inc., Bedminster, NJ, sponsored this report. Medical writing assistance was provided by Peloton Advantage, Parsippany, NJ, and funded by Amarin Pharma Inc. AW Kedia received reimbursement for the costs associated with data extraction from Amarin Pharma Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed

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