CASE SERIES

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Improving lipids with prescription icosapent ethyl after previous use of fish oil dietary supplements

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Managing dyslipidemia can be challenging in patients with statin intolerance. We describe the lipid effects of icosapent ethyl 4 g/day (high-purity prescription omega-3 eicosapentaenoic acid) in two coronary artery disease patients with statin intolerance who were self-treating with fish oil dietary supplements. After initiating icosapent ethyl, improvements were noted in the first and second patients, respectively, in total cholesterol (-12%; -21%), LDL cholesterol (-3%; -24%), triglycerides (-34%; -16%), non-HDL cholesterol (-12%; -22%), the omega-3 index (+42%; +8%) and eicosapentaenoic acid levels (+275%; +138%). Icosapent ethyl was well tolerated with no adverse events reported. These cases demonstrated favorable lipid effects with prescription icosapent ethyl treatment that may help optimize the care of high-risk coronary artery disease patients with statin intolerance.

First draft submitted: 20 November 2015; Accepted for publication: 8 January 2016;
Published online: 12 April 2016

In the USA, one person dies of cardiovascular disease every 40 seconds [1]. The odds are much worse for patients who have a previous history of cardiovascular disease [2]. In the secondary prevention arena, statin therapy has been successful in mitigating the risk of recurrent cardiac events by optimizing LDL cholesterol (LDL-C) levels. The 2013 American College of Cardiology/American Heart Association blood cholesterol guideline recommends statins for patients with atherosclerotic cardiovascular disease [3]. However, the management of patients with statin intolerance is challenging. Practitioners may consider providing other agents (such as prescription omega-3 fatty acids) that have the potential to offer beneficial cardiovascular effects, although robust reductions in LDL-C would not be expected.

While not all major outcome studies have demonstrated the benefit of lipid-lowering agents on top of statins, the incremental value of statin add-on therapies in reducing residual cardiovascular risk in patients with coronary artery disease (CAD) has been documented in the JELIS study, the IMPROVE-IT trial and by more recent preliminary data in trials evaluating PCSK9 inhibitors [4–7]. A secondary prevention analysis of JELIS demonstrated that adding the omega-3 fatty acid eicosapentaenoic acid (EPA) to a statin resulted in a 41% relative risk reduction in recurrent cardiac events in patients with previous myocardial infarction and a history of coronary intervention (percutaneous transluminal coronary angioplasty or coronary artery bypass graft) [8].

Atherosclerosis is an inflammatory disorder of the arterial wall initiated by atherogenic LDL and triglyceride (TG)-rich lipoproteins crossing the endothelial barrier [9,10]. Non-HDL cholesterol (non-HDL-C) comprises all atherogenic cholesterol-carrying particles including LDL, intermediate-density lipoprotein, very low-density lipoprotein and very low-density lipoprotein remnants, and

KEYWORDS

• atherosclerosis • dietary supplements • dyslipidemia • eicosapentaenoic acid • fish oil • icosapent ethyl • statin • Vascepa®

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has, therefore, been identified as a better primary target for modification than LDL-C by the National Lipid Association Expert Panel's consensus view [9].

Among the TG-lowering treatment options, prescription omega-3 fatty acids, including those that contain EPA alone or in combination with docosahexaenoic acid (DHA), may be added to statin therapy because of their reported beneficial effects on non-HDL-C and total cholesterol (TC) [11]. Cardiovascular benefits of EPA and DHA may also be mediated via their effects on arterial wall compliance, vasodilatory response, systemic vascular resistance, blood pressure, arrhythmia and thrombosis [12]. EPA has pleiotropic effects on endothelial function and affects the steps involved in the atherothrombotic process by its incorporation into membrane phospholipid bilayers and the atherosclerotic plaque, causing beneficial effects on foam cell function, inflammation and plaque formation, progression and rupture, as well as thrombus formation [13]. The prescription EPA-only product, icosapent ethyl (Vascepa®; Amarin Pharma Inc., Bedminster, NJ, USA) is a high-purity prescription form of EPA ethyl ester approved by the US FDA as an adjunct to diet to reduce TG levels in adult patients with severe (≥ 500 mg/dl) hypertriglyceridemia [14]. In Phase III clinical trials, icosapent ethyl significantly reduced TG and non-HDL-C levels without raising LDL-C levels compared with placebo in statin-treated patients with high TG levels (≥ 200 to < 500 mg/dl) and patients with very high TG levels (≥ 500 to ≤ 2000 mg/dl) [15,16]. Unlike the product labels for prescription omega-3 fatty acids containing a combination of EPA and DHA, the icosapent ethyl product label does not contain any warnings or precautions with regard to LDL-C. Because DHA may increase LDL-C levels [11], icosapent ethyl may be a more appropriate treatment option to consider for the management of certain patients with high or very high TG levels. Icosapent ethyl has also been documented to reduce harmful oxidized LDL by 13.3% compared with placebo when administered at a dose of 4 g/day as add-on therapy to statins for 12 weeks in patients with persistently high TG levels (200 to < 500 mg/dl) [17].

Despite the availability of several prescription omega-3 fatty acid products, patients may be more familiar with fish oil dietary supplements. In fact, fish oil dietary supplements have the distinction of being one of the most popular

supplements, and are used by more than a third of adults in the USA [18]. Because dietary supplements are under the regulatory category of foods instead of drugs, manufacturers are not required to demonstrate safety or efficacy prior to marketing and these products may have variable quality and inconsistent levels of EPA and DHA [19–27]. In addition, many commonly available fish oil dietary supplements are low-dose products and thus can necessitate a large pill burden if an individual attempts to attain levels of EPA and DHA comparable to those found in prescription products [20]. Given the lack of regulatory oversight, potentially high pill burden and presence of DHA, which may raise LDL-C, fish oil dietary supplements do not represent optimal choices for patients with dyslipidemia. Here, we describe two patients who were on a fish oil dietary supplement and subsequently initiated prescription high-dose icosapent ethyl.

Cases

In this report, we describe two patients with CAD and dyslipidemia who were seen in a private cardiology practice. Both patients refused statin therapy due to intolerance and instead were attempting to self-medicate their dyslipidemia with fish oil dietary supplements. In these cases, the fish oil product was Maxi Tears® Dry Eye Formula (MedOp Health, Inc, Oldsmar, FL, USA) wherein each serving of four 500-mg enteric-coated capsules is labeled to contain 600 mg EPA and 400 mg DHA in addition to other ingredients (e.g., cod liver oil, flaxseed oil, borage seed oil, mucin complex and turmeric root). Because fish oil dietary supplements are not recommended for treating disease, both patients were directed to switch from their fish oil dietary supplement (1 g/day EPA plus DHA) to prescription icosapent ethyl (4 g/day). Icosapent ethyl was selected based on clinical data documenting the efficacy of this high-purity EPA product in improving TG and other lipid and lipoprotein levels without raising LDL-C levels, as well as its safety and tolerability profile [15–16,28–29]. The burden of atherosclerotic laboratory parameters was assessed before and after initiation of treatment with icosapent ethyl; parameters included LDL-C, TGs, non-HDL-C, TC, HDL-C, Apo B, LDL particles (LDL-P), high-sensitivity C-reactive protein (hsCRP), Lp-PLA₂ and EPA plasma levels and the omega-3 index and ratio of TG/HDL-C.

Case no. 1

A 59-year-old man weighing 168 lbs with a history of CAD and dyslipidemia was followed in our private cardiology practice. He was taking a stable dose of clopidogrel (Plavix®; Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, Bridgewater, NJ, USA) 75 mg/day in addition to a heart-healthy diet and regular exercise during the entire period of this report (2013–2015). Regarding diet and exercise, the patient was provided guidelines based on the AHA recommendations and his diet and exercise patterns remained stable for the duration of the case study. After taking the fish oil dietary supplement (four capsules/day) for 27 months, the patient's lipid parameters (prior to switching) were: TC of 208 mg/dl, LDL-C of 115 mg/dl, HDL-C of 43 mg/dl, TGs of 230 mg/dl, non-HDL-C of 165 mg/dl, Apo B of 103 mg/dl, LDL-P of 2249 nmol/l, hsCRP of 0.9 mg/l, Lp-PLA₂ of 110 ng/ml, omega-3 index of 4.5% and EPA level of 0.4% (Table 1).

The patient was directed to discontinue use of the fish oil dietary supplement and to initiate prescription icosapent ethyl at a dose of 4 g/day. His follow-up laboratory assessment was conducted after 17 months of icosapent ethyl therapy. After treatment with icosapent ethyl, TC decreased by 12%, LDL-C decreased by 3%, TGs decreased by 34%, non-HDL-C decreased by 12%, Apo B decreased by 1%, LDL-P decreased by 8%, hsCRP remained

stable, Lp-PLA₂ decreased by 12%, omega-3 index increased by 42%, EPA levels increased by 275% and TG/HDL-C ratio decreased by 28% (Table 1).

The patient was compliant and tolerated both the fish oil dietary supplement and icosapent ethyl well with no adverse events reported. His care in our practice is ongoing.

Case no. 2

A 57-year-old man weighing 198 lbs with a history of CAD with a stent to the left anterior descending artery, hypertension and dyslipidemia was also followed in our private cardiology practice. He was taking stable doses of prasugrel (Effient®; Daiichi Sankyo, Inc., Parsippany, NJ, USA) 10 mg/day, aspirin 81 mg/day and vitamin D₃ 5000 IU/day in addition to a heart-healthy diet and regular exercise during the entire period of this report (2014–2015). Regarding diet and exercise, the patient was provided guidelines based on the AHA recommendations and his diet and exercise patterns remained stable for the duration of the case study. After taking the fish oil dietary supplement (four capsules/day) for over 3 months, the patient's lipid parameters were reported to be: TC of 229 mg/dl, LDL-C of 158 mg/dl, HDL-C of 68 mg/dl, TGs of 50 mg/dl, non-HDL-C of 161 mg/dl, Apo B of 120 mg/dl, LDL-P of 1876 nmol/l, hsCRP of 0.8 mg/l, Lp-PLA₂ of 217 ng/ml, omega-3 index of 9% and an EPA level of 2.4% (Table 2).

Table 1. Case no. 1: atherogenic parameters before and after switching from a fish oil dietary supplement to icosapent ethyl in a 59-year-old man with coronary artery disease, dyslipidemia and statin intolerance.

Parameter	On fish oil dietary supplement (1 g/day; 600 mg EPA and 400 mg DHA)	On icosapent ethyl [†] (4 g/day; EPA only)	Change (%)
LDL-C (mg/dl)	115	112	-3
TGs (mg/dl)	230	151	-34
Non-HDL-C (mg/dl)	165	145	-12
TC (mg/dl)	208	184	-12
HDL-C (mg/dl)	43	39	-9
TG/HDL-C ratio	5.35	3.87	-28
Apo B (mg/dl)	103	102	-1
LDL-P (nmol/l)	2249	2059	-8
hsCRP (mg/l)	0.9	1.0	+11
Lp-PLA ₂ (ng/ml)	110	97	-12
Omega-3 index (%)	4.5	6.4	+42
EPA (%)	0.4	1.5	+275

[†]Assessment after 17 months of treatment with icosapent ethyl.

DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; hsCRP: High-sensitivity C-reactive protein; P: Particle; TC: Total cholesterol; TG: Triglyceride.

Table 2. Case no. 2: atherogenic parameters before and after switching from a fish oil dietary supplement to icosapent ethyl in a 57-year-old man with coronary artery disease, dyslipidemia and statin intolerance.

Parameter	On fish oil dietary supplements (1 g/day; 600 mg EPA and 400 mg DHA)	On icosapent ethyl ^a (4 g/day; EPA only)	Change (%)
LDL-C (mg/dl)	158	120	-24
TGs (mg/dl)	50	42	-16
Non-HDL-C (mg/dl)	161	125	-22
TC (mg/dl)	229	180	-21
HDL-C (mg/dl)	68	55	-19
TG/HDL-C ratio	0.74	0.76	+3
Apo B (mg/dl)	120	95	-21
LDL-P (nmol/l)	1876	1509	-20
hsCRP (mg/l)	0.8	0.5	-38
Lp-PLA ₂ (ng/ml)	217	202	-7
Omega-3 index (%)	9.0	9.7	+8
EPA (%)	2.4	5.7	+138

^aAssessment after 3 months of treatment with icosapent ethyl.

DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; hsCRP: High-sensitivity C-reactive protein; P: Particle; TC: Total cholesterol; TG: Triglyceride.

As with the patient in case no. 1, the patient was directed to discontinue use of the fish oil dietary supplement and to initiate prescription icosapent ethyl 4 g/day. His follow-up laboratory assessment was conducted after 3 months of therapy with icosapent ethyl. After treatment with icosapent ethyl, TC decreased by 21%, LDL-C decreased by 24%, TGs decreased by 16%, non-HDL-C decreased by 22%, Apo B decreased by 21%, LDL-P decreased by 20%, hsCRP remained stable, Lp-PLA₂ decreased by 7%, omega-3 index increased by 8% and EPA levels increased by 138%. The TG/HDL-C ratio was low before and after the switch.

The patient was compliant and tolerated both the fish oil dietary supplement and icosapent ethyl well with no adverse events reported. His care in our practice is ongoing.

Discussion

This report describes the impact of prescription icosapent ethyl 4 g/day on lipid and lipoprotein levels, omega-3 index, EPA levels and inflammatory markers of two patients with CAD and dyslipidemia who had statin intolerance and self-treated their dyslipidemia with fish oil dietary supplements. Treatment with icosapent ethyl resulted in notable reductions in the burden of atherogenic cholesterol in both patients, including reductions in TG, TC and non-HDL-C levels, as well as a reduction in the TG/HDL-C

ratio in the patient in case no. 1; notably, LDL-C level did not increase in either patient.

The reductions in atherogenic cholesterol levels observed in these cases are consistent with those reported in two randomized, placebo-controlled, Phase III studies of icosapent ethyl: MARINE and ANCHOR [15,16]. In MARINE, patients with very high TG levels (≥ 500 mg/dl and ≤ 2000 mg/dl) who were administered icosapent ethyl 4 g/day with or without background statin treatment were noted to have significantly decreased median TG (33%) and non-HDL-C (18%) levels with a nonsignificant decrease of 2% in LDL-C levels compared with placebo [16]. Icosapent ethyl was generally well tolerated with a safety profile similar to that of placebo. Similarly, in ANCHOR, high-risk statin-treated patients with residually high TG levels (≥ 200 and < 500 mg/dl) despite LDL-C control with statins (≥ 40 and < 100 mg/dl) were administered icosapent ethyl 4 g/day for 12 weeks and were noted to have significant reductions in median TG (22%), non-HDL-C (14%), LDL-C (6%) and TC (12%) levels compared with placebo [15]. Icosapent ethyl was well tolerated. The lipid changes observed in these patients upon treatment with icosapent ethyl are consistent with those observed in other case reports of patients switched from DHA containing omega-3 fatty acid prescription or dietary supplement products to icosapent ethyl [30–34].

In the current report, treatment with icosapent ethyl also led to improvements in the TG/HDL-C ratio (case no. 1 patient) and in Apo B (case no. 2 patient) and LDL-P levels (both patients). Previous studies have documented that the TG/HDL-C ratio has been correlated with high remnant cholesterol and can independently predict cardiovascular events [35–37]. Combining TGs and HDL-C in a ratio has been shown to predict plasma atherogenicity [36,37]. In a recent study involving over 1.3 million individuals, a higher TG/HDL-C ratio was associated with an increasingly atherogenic lipid profile characterized by higher remnant lipoprotein cholesterol along with higher non-HDL-C and LDL density [37]. In this report, the first patient had a 28% improvement in the TG/HDL-C ratio after treatment with icosapent ethyl, whereas the second patient had a low ratio (<1) both before and after treatment with icosapent ethyl.

Apo B is directly correlated with the number of atherogenic lipid particles, as each such particle contains a single molecule of Apo B [9]. Both Apo B and LDL-P contribute to residual risk of cardiovascular disease, as levels may remain elevated in some patients who have achieved LDL-C and non-HDL-C goals, especially patients with elevated TG and low HDL-C levels [9]. The patient in case no. 1 experienced reductions in Apo B levels and both patients experienced reductions in LDL-P levels after treatment with icosapent ethyl. This is consistent with findings in the MARINE and ANCHOR studies, which documented significant reductions in Apo B and total LDL-P levels with icosapent ethyl 4 g/day compared with placebo [15–16,28–29].

In both of the patients described in this report, levels of inflammatory markers, including hsCRP, were in the normal range prior to and after treatment with icosapent ethyl. Similarly, Lp-PLA₂ levels were in the normal range prior to initiation of icosapent ethyl and declined further after treatment with icosapent ethyl. Both MARINE and ANCHOR demonstrated significantly decreased levels of markers of inflammation including hsCRP and Lp-PLA₂ after treatment with icosapent ethyl 4 g/day compared with placebo [17]. This effect of icosapent ethyl may help to explain the role of EPA in reducing inflammation in the atherosclerotic plaque [13].

Given the reliable content and higher dose of the prescription product, the switch from fish oil dietary supplements to icosapent ethyl also improved the omega-3 index and EPA levels in

both patients, as expected. The omega-3 index represents a novel indicator of cardiovascular risk and is obtained by measuring the concentration of EPA and DHA in red blood cell membranes expressed as a percentage of total fatty acids [38].

Differences in responses between the two patients may be attributable in part to differences in baseline levels. The patient in case no. 2 had higher LDL-C (158 mg/dl) and Apo B (120 mg/dl) levels while on fish oil dietary supplements and demonstrated greater reductions after switching to icosapent ethyl of 24 and 21%, respectively, compared with the patient in case no. 1, whose baseline levels were 115 mg/dl and 103 mg/dl and had reductions of 3 and 1%, respectively. While individual variability in responses is often observed in clinical studies, the patient in case no. 2 started with higher baseline levels and, therefore, greater decreases were expected. It may be worth noting that in the patient in case no. 2, the observed 24% reduction in LDL-C levels when adding IPE may have been due to the combined effects of discontinuing DHA and adding an EPA-only product. Such substantial reductions may not be expected for patients in whom EPA is initiated without prior use of a DHA-containing agent.

Fish oil dietary supplements may serve to complement an individual's diet when intake of dietary fish is inadequate and, thus, these supplements may have a role in general health promotion; however, these products are not indicated or appropriate for the treatment of any disease. Although patients do not need a physician's prescription in order to purchase fish oil dietary supplements, these supplements are not over-the-counter drugs and, therefore, are not subject to strict regulatory standards [39]. At present, there is no approved over-the-counter omega-3 fatty acid drug [39]. Recently, the safety of fish oil dietary supplements was questioned in a New Zealand study that documented that 83% of the assessed fish oil dietary supplements exceeded the recommended peroxide value, a marker of oxidation or oil spoilage [26]. The oils in fish oil dietary supplements are highly prone to oxidation; this may render them ineffective or potentially harmful due to altered biologic activity [40,41]. It is no surprise that both the American Diabetes Association and the International Atherosclerosis Society no longer recommend fish oil dietary supplements in the prevention or treatment of cardiovascular diseases [42–44]. Because fish oil products are dietary supplements, they should

not be considered appropriate substitutes for prescription omega-3 products in the treatment of diseases [39]. The current cases underscore the differences in efficacy between fish oil dietary supplements and prescription icosapent ethyl in patients with CAD and dyslipidemia. The potential impact on blood lipid parameters of the non-omega-3 ingredients contained in the fish oil dietary supplement used by these patients is not clear.

The current report is based on two high-risk patients with CAD and dyslipidemia who were intolerant to statins. Treatment with icosapent ethyl helped to optimize lipid parameters in both these patients; however, the results should be considered preliminary and hypothesis generating and should be further evaluated. The patients described in this report are being followed up at our practice. The ongoing, Phase III, randomized, parallel-assignment, double-blind REDUCE-IT (ClinicalTrials.gov: NCT01492361) is investigating the effects of high-dose prescription icosapent ethyl on cardiovascular outcomes in high-risk patients with persistent hypertriglyceridemia despite statin therapy [45]. The results of this trial will provide important information regarding the effect of add-on icosapent ethyl treatment on cardiovascular outcomes.

Conclusion & future perspective

In two high-risk patients with CAD and dyslipidemia who had statin intolerance and were

self-treating their dyslipidemia with fish oil dietary supplements, optimizing care by switching to icosapent ethyl (high-purity EPA) resulted in improvements in the omega-3 index and EPA levels, as well as reductions in the levels of atherogenic lipids and lipoproteins. Prospective, randomized clinical trials will be needed to gain a better understanding of the potential cardiovascular benefits of initiating a highly purified prescription EPA product in a statin-intolerant population.

Financial & competing interests disclosure

Amarin Pharma Inc. (NJ, USA) sponsored this report. Medical scientific reference checks and associated assistance were provided by S Philip, RPh, PharmD, and J Bronson of Amarin Pharma Inc. KJ Reddy has served as a speaker and consultant to Amarin Pharma Inc., and is a stock shareholder in that company. S Chowdhury is a consultant to 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.

Writing assistance was utilized in the production of this manuscript. Editorial assistance was provided by Peloton Advantage, (NJ, USA), and funded by Amarin Pharma Inc.

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EXECUTIVE SUMMARY

- These case reports examined unique clinical challenges of two patients with coronary artery disease and dyslipidemia who refused statin therapy due to intolerance and chose to take an omega-3 fatty acid dietary supplement containing both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).
- Dietary supplements are not over-the-counter drugs and are not recommended for treatment of diseases. Currently, there are no approved over-the-counter omega-3 fatty acid drugs.
- The efficacy, quality and safety of omega-3 fatty acid dietary supplements are questionable due to their lack of regulation and potential content variability and thus are not appropriate for the treatment of disease; they are not therapeutically equivalent to and should not be substituted for prescription omega-3 fatty acid products.
- As products containing DHA may raise LDL-C and potentially complicate the management of patients with dyslipidemia, the patients were switched from their omega-3 fatty acid dietary supplement to a high-purity EPA-only prescription formulation (icosapent ethyl, Vascepa®), which is known to provide beneficial lipid effects without raising LDL-C and may have pleiotropic cardiovascular effects.
- The cases presented here illustrate the improvement in the lipid profiles of statin-intolerant patients treated with the prescription high-purity EPA product, icosapent ethyl.

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