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Switching statin-treated patients from fenofibrate to the prescription omega-3 therapy icosapent ethyl: a retrospective case series

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Abstract

Introduction Patients receiving statin therapy for dyslipidaemia often require treatment with an additional agent to control triglyceride levels. Options for add-on therapy include fibrates and omega-3 fatty acids. This case series describes the effects of switching add-on therapy from fenofibrate to icosapent ethyl (the ethyl ester of the omega-3 fatty acid, eicosapentaenoic acid) on patient lipid profiles.
Methods This was a retrospective analysis of patient records from a private medical practice in western New York. Statin-treated patients with dyslipidaemia who had been treated with fenofibrate and later switched to icosapent ethyl were selected for analysis. Lipid profiles before and after the switch to icosapent ethyl were compared.
Results The records of five patients were analysed. All patients had hypertension and were overweight, male, and at high cardiovascular risk. After the switch to icosapent ethyl (treatment duration 3.9–5.8 months), triglyceride levels decreased in four patients, and low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and total cholesterol levels decreased in all patients. High-density lipoprotein levels increased in four patients. Icosapent ethyl was well tolerated.
Conclusions Switching from fenofibrate to icosapent ethyl as add-on to a statin therapy due to clinical need may provide an option for patients to maintain or improve lipid parameters.

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Introduction

Treatment of dyslipidaemia with statins is effective for lowering low-density lipoprotein cholesterol (LDL-C) levels and can improve levels of other lipids [1, 2]. However, triglyceride (TG) levels in statin-treated patients may remain uncontrolled, leaving patients at residual risk for cardiovascular events [3]. Fibrates, niacin, and prescription omega-3 fatty acids are indicated to reduce TG levels in patients with severe (≥500 mg/dL) hypertriglyceridaemia, and may be options as add-on therapy to statins in patients with persistently elevated TG levels [4]. Fibrates, available since the 1990s, effectively lower TG levels, but safety issues, such as the potential for myopathy and unwanted effects on LDL-C, may warrant reassessment of therapeutic use, particularly in some patients receiving statin therapy [5–8].

In 2012, icosapent ethyl (Vascepa®; Amarin Pharma Inc., Bedminster, NJ), a high-purity prescription formulation containing the ethyl ester of eicosapentaenoic acid (EPA), was approved by the US FDA. Icosapent ethyl is indicated as an adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridaemia [9]. EPA is the sole active ingredient in icosapent ethyl [9] and has been shown to reduce TG, non-high-density lipoprotein cholesterol (non-HDL-C), and total cholesterol (TC) levels without raising LDL-C levels in patients with very high TG levels (≥500 and ≤2000 mg/dL), as well as in statin-treated patients with residually high TG levels (≥200 and <500 mg/dL) [10, 11]. Icosapent ethyl has been found to be safe and generally well tolerated, with a safety profile similar to that of placebo [9–11]. In double-blind studies, arthralgia was the only adverse reaction reported to occur in >2 % of patients treated with icosapent ethyl and at an incidence rate greater than that for placebo [9].

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Because of the robust safety and efficacy profile of icosapent ethyl, patients receiving fibrate therapy were gradually switched to treatment with icosapent ethyl in a private medical practice in western New York, a geographical area known for its high risk of heart disease and stroke [12]. The objective of this analysis was to retrospectively assess the lipid profile effects of switching statin-treated patients from fibrate therapy to icosapent ethyl.

Methods

Study design

This retrospective chart review was carried out at a single private medical practice with offices located in Franklinville, Tonawanda, Lancaster, and Niagara Falls, NY. Patient records were eligible for review if the patients had TG levels ≥500 mg/dL at some point in their medical history and if they were receiving stable fibrate therapy in addition to stable statin therapy and were switched from fibrate therapy to icosapent ethyl while continuing with stable statin therapy. Patients were required to have been treated with icosapent ethyl plus a statin for >2 months, have available lipid measurements, and have been clinically stable for the period encompassing when the lipid measurements were made while on fibrate therapy and while on icosapent ethyl. Patients were excluded if they had any gaps in treatment, missing lipid measurements, known non-compliance, or any changes in clinical condition or medications that could affect lipid parameters. Written informed consent was received from all patients included in this case series.

Assessments

Lipid parameters were assessed a minimum of 2 months after the initiation of fenofibrate therapy and a minimum of 2 months after the switch to icosapent ethyl. Blood samples for lipid analysis were collected from patients after an overnight fast and analysed by local laboratories as specified by patient insurance. Parameters measured included TG, LDL-C, HDL-C, TC, and non-HDL-C levels.

Body mass index was calculated as weight in kilograms divided by height in metres squared. LDL-C levels were calculated using the Friedewald formula [i.e. LDL-C = TC minus HDL-C minus (TG/5)] in some instances (note, the Friedewald formula should not be used when TG levels are >400 mg/dL) [13]. Non-HDL-C levels were calculated as TC minus HDL-C [14]. Percentage changes in individual patient lipid parameters from before and after the switch from add-on fibrate therapy to treatment with icosapent ethyl were calculated.

Results

Patients and treatments

The medical records of five patients (aged 58–66 years) met the inclusion criteria and were analysed (Table 1). All patients were overweight men with hypertension and high cardiovascular risk. One patient had coronary heart disease and chronic kidney disease.

All patients were on stable doses of moderate-intensity statins, including lovastatin, extended-release fluvastatin, or atorvastatin therapy and subsequently initiated fibrate therapy between August 2007 and June 2010 (before the approval of icosapent ethyl). Fibrate therapy consisted of fenofibrate tablets 145 mg once daily (Tricor®; AbbVie Inc., North Chicago, IL) in two patients, and fenofibrate capsules 150 mg once daily (Lipofen®; Kowa Pharmaceuticals America, Inc., Montgomery, AL) in the remaining three patients.

Add-on therapy was switched from fibrate therapy to icosapent ethyl between March and September 2014. After the switch, all patients received two capsules of icosapent ethyl twice daily, for a total dosage of 4 g/day in addition to their stable statin regimen. All patients had been treated with icosapent ethyl + statin therapy for ≥3.9 months (range 3.9–5.8 months) before lipid measurements. Because of comorbidities, patients were also receiving other medications (antihypertensive agents: amlodipine/olmesartan, atenolol, nebivolol, olmesartan, quinapril, verapamil; others: albuterol, aspirin, azelastine, cetirizine, levothyroxine, mometasone furoate, montelukast sodium, omeprazole).

Lipid parameters

TG levels ranged from 91 to 278 mg/dL during the period when patients were receiving fenofibrate + statin and from 81 to 190 mg/dL when they were receiving icosapent ethyl + statin (Table 1). Four patients experienced a decrease in TG level after switching from fenofibrate to icosapent ethyl, with decreases ranging from 8 to 53 % (Table 1). The remaining patient had an increase of 4 % in TG level, from 182 mg/dL while on fenofibrate + statin to 190 mg/dL while on icosapent ethyl + statin (Table 1).

While patients were receiving fenofibrate + statin, their LDL-C levels ranged from 55 to 170 mg/dL (Table 1). After the switch to icosapent ethyl, LDL-C levels decreased in all patients, with a maximum decrease of 44 % in one patient (Table 1).

Reductions in non-HDL-C levels, ranging from 3 to 39 %, were observed in all patients following the switch from fenofibrate + statin to icosapent ethyl + statin

Table 1 Characteristics and lipid levels of statin-treated patients switched from fibrate therapy to icosapent ethyl

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Patient characteristics					
Age (years)[a]	58	63	61	64	66
Body mass index (kg/m^2)	26	28	30	33	28
Gender	Male	Male	Male	Male	Male
Relevant conditions	Hypertension; hypothyroidism; BPH	Hypertension; CHD; CKD	Hypertension; GORD; chronic sinusitis	Hypertension; allergic sinusitis; asthma	Hypertension; arthralgia; arthritis
Treatment dosage and duration					
Statin daily dosage (mg)	Lovastatin 40	Lovastatin 40	Fluvastatin ER 80	Atorvastatin 10	Atorvastatin 10
Fenofibrate daily dosage (mg)	145	145	150	150	150
Time on fibrate + statin (months)[b]	17.7	17.9	29.4	29.0	4.7
Time on icosapent ethyl + statin (months)[c]	5.0	5.8	4.8	3.9	3.9
Triglyceride levels (mg/dL)					
Before statin	545	564	509	522	592
Statin alone	245	279	271	300	217
Fibrate + statin	278	167	182	123	91
Icosapent ethyl + statin	130	81	190	107	84
% change[d]	−53.2	−51.5	+4.4	−13.0	−7.7
Low-density lipoprotein cholesterol levels (mg/dL)[e]					
Before statin	104	188	NR	NR	189
Statin alone	96	126	84	180	88[f]
Fibrate + statin	55	170	121	151	115
Icosapent ethyl + statin	54	96[f]	105[f]	135[f]	96
% change[d]	−1.8	−43.5	−13.2	−10.6	−16.5
Non-HDL-C levels (mg/dL)[f]					
Before statin	202	189	212	228	NR
Statin alone	153	137	138	200	131
Fibrate + statin	105	184	148	175	131
Icosapent ethyl + statin	77	112	143	155	127
% change[d]	−26.7	−39.1	−3.4	−11.4	−3.1
Total cholesterol levels (mg/dL)					
Before statin	232	235	235	NR	272
Statin alone	188	185	168	243	184
Fibrate + statin	136	231	177	211	178
Icosapent ethyl + statin	112	160	172	201	175
% change[d]	−17.7	−30.7	−2.8	−4.7	−1.7
HDL-C levels (mg/dL)					
Before statin	30	46	23	41	52
Statin alone	35	48	30	43	53
Fibrate + statin	31	47	29	36	47

Table 1 continued

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Icosapent ethyl + statin	35	48	29	46	48
% change[d]	+12.9	+2.1	0.0	+27.8	+2.1

BPH benign prostatic hypertrophy, *CHD* coronary heart disease, *CKD* chronic kidney disease, *ER* extended release, *GORD* gastro-oesophageal reflux disease, *HDL-C* high-density lipoprotein cholesterol, *NR* not reported

[a] Age at time of measurement while on icosapent ethyl

[b] Time from addition of fenofibrate to statin to when laboratory measurements were taken after initiation of fenofibrate

[c] Time from switch from fenofibrate + statin to icosapent ethyl + statin to when laboratory measurements were taken after icosapent ethyl was initiated

[d] Percentage changes in lipid levels from when patient was on fibrate therapy to when on icosapent ethyl

[e] Values were measured directly unless otherwise noted

[f] Value is calculated based on other information available (see "Methods" section)

(Table 1). TC levels decreased in all patients (range 2–31 %) following the switch from fenofibrate + statin to icosapent ethyl + statin (Table 1). An increase or no change in HDL-C level was observed in all patients (range 0–28 %).

Safety

The switch from fenofibrate + statin to icosapent ethyl + statin was well tolerated by all patients, with no adverse effects reported. All patients are currently continuing on this regimen. No changes in arthritis or arthralgia were observed in one patient who had these conditions, which were pre-existing to omega-3 fatty acid therapy.

Discussion

In this real-world retrospective analysis of high-risk patients receiving statin therapy, patient medical records were examined to evaluate the potential lipid effects of switching from add-on fibrate therapy to the prescription omega-3 fatty acid therapy icosapent ethyl while continuing stable statin therapy. After switching from fenofibrate to icosapent ethyl, lipid control was maintained or improved, with all patients experiencing improvements in atherogenic lipid parameters, including reductions in TC, LDL-C, and non-HDL-C levels, and all but one patient experienced a reduction in TG levels. The slight 4 % increase in TG levels in one patient (from 182 to 190 mg/dL) was not considered to be clinically significant; it is not known what factors could have resulted in this increase, but this may have been due to variability in laboratory measurements or changes in patient diet, exercise, or medication adherence that were not reported during the office visit.

Historically, fibrate and niacin products have been used as adjunctive therapy to statins, with fibrates being more commonly prescribed for high TG levels. This is reflected in this case series, wherein TG levels improved in four of the five patients when fenofibrate was added to statin treatment. Nonetheless, potential safety concerns have been recognized with the use of fibrates or niacin in combination with statins. Several statin labels mention that use in combination with fibrates or lipid-lowering doses of niacin may increase the risk of adverse skeletal muscle effects; however, in large outcomes trials, these events were not very common with fibrates [15–19]. Some statin labels specifically recommend avoiding concomitant therapy with gemfibrozil and/or note an increased risk of adverse skeletal muscle effects with gemfibrozil [16, 17, 20]. Fibrates also may increase levels of serum transaminases and serum creatinine, the former in combination with statins [5, 6]. Importantly, fibrates may be associated with increases in LDL-C levels, especially in patients with very high TG levels, or attenuation of statin-induced reductions in LDL-C levels [1, 7, 8, 21–27]. While the exact mechanism of this increase in LDL-C levels is unknown, it may in part be due to an increase in plasma PCSK9 levels resulting from fibrate therapy [28–30]. With niacins, flushing is a common tolerability concern, and other potential adverse effects may include increased serum glucose and hepatotoxicity or myopathy, especially when co-administered with a statin [31].

A meta-analysis of 19 randomized studies found that fibrate use was not associated with a reduced risk of all-cause or coronary heart disease mortality or stroke; these findings held true for the subset of studies in which fibrates were used in combination with statins, and, in this subset, fibrate therapy also did not reduce the risk of non-fatal myocardial infarction [32]. Supporting this, a retrospective analysis of patients with type 2 diabetes who were

receiving statins alone or in combination with fibrate therapy showed that the use of combination therapy did not reduce the incidence of cardiovascular disease compared with the use of statins alone [33]. Notably, in April 2015, the US FDA removed the indication for use of fenofibric acid delayed-release capsules (Trilipix®; AbbVie Inc.) and niacin extended-release tablets (Niaspan®; AbbVie Inc.) in combination with statins from the product labels [6, 31, 34]. Thus, other options are needed for add-on therapy with statins. The product label's 'limitations of use' notes that fenofibrate was not shown to reduce coronary heart disease morbidity and mortality in patients with type 2 diabetes. However, hypothesis-generating data from large cardio-vascular outcomes trials suggest that patients with diabetes and atherogenic dyslipidaemia characterized by high TG and low HDL-C levels may benefit from treatment with fenofibrate [18, 19]. This is yet to be proven in a large, prospective, randomized, placebo-controlled trial.

Prescription omega-3 fatty acid products first became commercially available in the USA in 2005 (Lovaza®; GlaxoSmithKline, Research Triangle Park, NC [35]) and contained a combination of both EPA and docosahexaenoic acid (DHA); additional EPA + DHA products were recently approved in 2014 (Omtryg®; Trygg Pharma Inc., Arlington, VA [36], and Epanova®; AstraZeneca Pharmaceuticals, Wilmington, DE [37]). Although these agents are also effective in lowering TG levels, their prescribing information warns that they may raise LDL-C levels [35–37]. In pivotal clinical studies of patients with TG levels ≥500 mg/dL, products that contain both EPA and DHA were found to increase LDL-C levels by ≈15 to 49 % versus placebo [35–37]. Meta-analyses and systematic reviews have found that EPA and DHA have differential effects on LDL-C, wherein DHA may significantly increase LDL-C levels while EPA may significantly decrease or have a neutral effect on LDL-C levels [38, 39]. Thus, omega-3 fatty acid products containing DHA may not be an optimal choice for patients with dyslipidaemia, as they may have unwanted effects on LDL-C. As noted earlier, icosapent ethyl, a high-purity form of EPA, does not raise LDL-C levels in patients with very high TG levels [9, 10]. Furthermore, in statin-treated patients with high TG (≥200 and <500 mg/dL) and well-controlled LDL-C (<100 mg/dL) levels, icosapent ethyl 4 g/day was found to significantly reduce LDL-C levels by 6 % versus placebo ($p = 0.007$) [11]. In the current analysis of statin-treated patients, LDL-C level decreases of 2–44 % were observed in all patients following the switch from fenofibrate to icosapent ethyl. In other retrospective chart analyses and case reports, switching from prescription omega-3 fatty acid products containing EPA + DHA to icosapent ethyl also resulted in decreases in TG and LDL-C levels, as was observed in this analysis of patients switched from fenofibrate therapy to treatment with icosapent ethyl [40–45].

In addition to TG-lowering effects, omega-3 fatty acids have other reported beneficial cardiovascular effects on inflammation, blood pressure, thrombosis, and arrhythmia [46]. Furthermore, EPA alone or in combination with a statin may exert pleiotropic beneficial effects in multiple steps of atherosclerosis, including antioxidant effects [47, 48]; endothelial function [49, 50]; effects on macrophages, monocytes, and foam cells [51–53]; inflammation [54, 55]; plaque progression, formation, and vulnerability [52, 53, 56–59]; and thrombus formation [60, 61]. Given that omega-3 fatty acid products containing DHA may raise LDL-C levels and are not considered to be therapeutically equivalent to icosapent ethyl, per FDA therapeutic equivalence codes, they should not be substituted for prescription icosapent ethyl [62]. It is worth noting that while many non-prescription omega-3 fatty acid products are available in the USA, these are dietary supplements, not over-the-counter medications. Dietary supplements are not required to prove or demonstrate safety or efficacy before marketing [63–65], and have been found to have highly variable product quality, purity, and EPA and DHA content within and between brands [66–69]. Dietary supplements may require a high pill burden to achieve prescription-strength therapeutic doses [70, 71], and they also may contain cholesterol, saturated fats [72, 73], contaminants such as polychlorinated biphenyl [69], and oxidation products [67, 74]. Given these considerations, it may be important to advise patients not to substitute omega-3 fatty acid dietary supplements for prescription icosapent ethyl.

While no adverse effects occurred in the patients in this assessment, safety and tolerability concerns regarding fibrate and niacin products, as noted earlier, have informed the switching of patients to safer, more tolerable options in my practice. In three patients, LDL-C levels were higher with fenofibrate + statin (170, 121, and 115 mg/dL, respectively) than on a statin alone (126, 84, and 88 mg/dL); an attenuation of LDL-C control after addition of fenofibrate to moderate- or high-intensity statins in patients with dyslipidaemia has been described in the literature [8, 21, 27]. After the switch from fenofibrate + statin to icosapent ethyl + statin, LDL-C levels decreased to 96, 105, and 96 mg/dL, respectively. As noted, omega-3 fatty acid products containing DHA may potentially raise LDL-C levels and have been associated with gastrointestinal concerns, such as eructation, dyspepsia, taste perversion, diarrhoea, nausea, abdominal pain or discomfort, and constipation, which may cause tolerability issues [35–37]. Thus, icosapent ethyl represents a TG-lowering option with fewer safety, tolerability, and efficacy concerns than other available choices. When combining an additional lipid-lowering agent with a statin, icosapent ethyl may offer

greater flexibility in adjusting or increasing statin doses than fenofibrate, given the potential safety issues and effects on LDL-C of fibrate agents.

As to whether addition of icosapent ethyl to statin therapy reduces cardiovascular risk, in the Japan EPA Lipid Intervention Study (JELIS) of 18,645 patients with hypercholesterolaemia, the ethyl ester of EPA, when added to statin therapy, significantly reduced the risk of a major coronary event by 19 % compared with statin alone (hazard ratio 0.81; 95 % confidence interval 0.69–0.95; $p = 0.011$) [75]. While the dosage of EPA in the JELIS study was 1.8 g/day, the plasma levels achieved in JELIS (169 μg/mL) were similar to those achieved with icosapent ethyl 4 g/day (183 μg/mL) in statin-treated patients with TG levels ≥200 and <500 mg/dL [75, 76]. The ongoing, phase III, placebo-controlled Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT; ClinicalTrials.gov identifier NCT01492361) is investigating whether icosapent ethyl 4 g/day in combination with statin therapy is more effective than statin alone in improving long-term cardiovascular outcomes in high-risk patients with hypertriglyceridaemia [77].

Based on clinical decisions or due to the recent removal of the indication for fenofibric acid use in combination with statin therapy from the product label (and the expectation of potentially similar revisions to the labels of generic products), clinicians may wish to consider a different statin add-on therapy for control of TGs and other lipids. The present exploratory analysis may be of interest for those wishing to identify other options for such patients.

The limitations of this case series include its small sample size, retrospective design, and patient heterogeneity regarding concomitant medications and underlying medical conditions. In real-world settings such as this, other limitations include lack of verification of patient compliance with fasting before lipid assessments, adherence to concomitant medications, and possible effects of changes in diet and exercise that were not reported to the physician. Larger, prospective studies are needed to confirm these hypothesis-generating findings.

Conclusion

Switching statin add-on therapy from fenofibrate to icosapent ethyl maintained or improved the lipid profile and was well tolerated with no adverse reactions in a series of patients with hypertension and high cardiovascular risk. Important differences between icosapent ethyl and other add-on therapy options include its good safety and tolerability profile and the fact that it does not increase LDL-C levels, as supported by clinical studies and the icosapent ethyl product label.

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