Drug Design, Development and Therapy

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REVIEW

Update on the management of severe hypertriglyceridemia – focus on free fatty acid forms of omega-3

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This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
10 April 2015
Number of times this article has been viewed

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Abstract: High levels of plasma triglycerides (TG) are a risk factor for cardiovascular diseases, often associated with anomalies in other lipids or lipoproteins. Hypertriglyceridemia (HTG), particularly at very high levels, significantly increases also the risk of acute pancreatitis. Thus, interventions to lower TG levels are required to reduce the risk of pancreatitis and cardiovascular disease. Several strategies may be adopted for TG reduction, including lifestyle changes and pharmacological interventions. Among the available drugs, the most commonly used for HTG are fibrates, nicotinic acid, and omega-3 polyunsaturated fatty acids (usually a mixture of eicosapentaenoic acid, or EPA, and docosahexaenoic acid, or DHA). These last are available under different concentrated formulations containing high amounts of omega-3 fatty acids, including a mixture of EPA and DHA or pure EPA. The most recent formulation contains a free fatty acid (FFA) form of EPA and DHA, and exhibits a significantly higher bioavailability compared with the ethyl ester forms contained in the other formulations. This is due to the fact that the ethyl ester forms, to be absorbed, need to be hydrolyzed by the pancreatic enzymes that are secreted in response to fat intake, while the FFA do not. This higher bioavailability translates into a higher TG-lowering efficacy compared with the ethyl ester forms at equivalent doses. Omega-3 FFA are effective in reducing TG levels and other lipids in hypertriglyceridemic patients as well as in high cardiovascular risk patients treated with statins and residual HTG. Currently, omega-3 FFA formulation is under evaluation to establish whether, in high cardiovascular risk subjects, the addition of omega-3 to statin therapy may prevent or reduce major cardiovascular events.

Keywords: omega-3 fatty acids, eicosapentaenoic acid, docosahexaenoic acid, hypertriglyceridemia

Introduction

High levels of plasma triglycerides (TG) represent a risk factor for atherosclerosis and related cardiovascular diseases,[1–3] although several contrasting observations have been reported. In fact, increased TG levels usually associated with decreased high-density lipoproteins (HDL) cholesterol levels and increased small, dense low-density lipoprotein (LDL) particles;[4] thus, the relation between hypertriglyceridemia (HTG) and coronary heart disease risk may be indirect, reflecting other risk factors associated with elevated TG. Accordingly, the relevant correlation of TG levels with an increased risk of coronary artery disease (CAD) was abolished after adjustment for HDL and non-HDL-cholesterol (that represents the marker of cholesterol content in all proatherogenic lipoproteins).[5] Despite these controversies, it is well established that severe HTG, defined as TG levels ≥500 mg/dL (≥5.65 mmol/L) significantly increases the risk of acute pancreatitis.[6,7]

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Elevated TG per se are probably not directly atherogenic; their role is most probably related to their association with atherogenic lipoproteins and apolipoprotein CIII (apoC-III), as suggested by the lack of cardiovascular disease in people with extreme TG plasma levels on one side and the role of remnants on the other.[8,9] Under normal circumstances, TG are mainly transported by TG-rich lipoproteins such as the liver-derived very low-density lipoproteins (VLDL), while intestine-derived chylomicrons and their remnants predominate in some forms of HTG, such as familial hyperchylomicronemia and hyperlipoproteinemias types III and V. Both VLDL and chylomicrons provide fatty acids to tissues by the action of lipoprotein lipase (LPL) present on the luminal surface of capillary endothelial cells.[10] The activity of LPL requires several cofactors; among them, apolipoprotein CII (apoC-II) is an essential activator of LPL activity, while apoC-III is an LPL-inhibitor.[10] Following LPL-mediated hydrolysis of TG to free fatty acids (FFAs), VLDL and chylomicron remnants are formed, and are then cleared by the liver.[10] Remnant lipoproteins may be atherogenic, and their levels are increased in subjects with HTG.[11,12] In addition, high TG levels are associated with an increase of circulating small dense proatherogenic LDL.[11] This is due to the fact that, under hypertriglyceridemic conditions, TG-rich lipoprotein metabolism shifts from an apoE-dominated system, characterized by rapid clearance of VLDL from circulation, to an apoC-III-dominated system, characterized by reduced clearance of TG-rich lipoproteins and a preferential conversion into small dense LDL.[13]

HTG has a direct impact on lipoprotein composition and metabolism; in fact, increased VLDL TG activates cholesteryl ester transfer protein, thus resulting in the enrichment of HDL and LDL with TG, that in turn are hydrolyzed by the hepatic TG lipase, thus producing small dense HDL and LDL,[6] a typical finding in HTG. TG-enriched HDL become dysfunctional and lose several of their antiatherogenic properties while small dense LDL are more susceptible to oxidation, and thus represent forms of proatherogenic lipoproteins, whose increase may raise the risk of cardiovascular disease.[6] In addition, TG-rich lipoproteins are themselves proatherogenic and are involved in several proatherosclerotic processes, including the induction of endothelial dysfunction and activation, as well as inflammation and apoptosis[6] in the arterial wall.

HTG is a well established common cause of acute pancreatitis, accounting for up to 10% of all cases of pancreatitis,[14] Both genetic and secondary disorders of lipoproteins associate with hypertriglyceridemic pancreatitis; pancreatic lipase-induced hydrolysis of TG and subsequent formation of FFA trigger inflammation and seem to be involved in the development of HTG-induced pancreatitis. Very high levels of TG (>1,000 mg/dL, 11.3 mmol/L) significantly increased the risk of pancreatitis, but more moderate increases of TG (177–885 mg/dL, 2–10 mmol/L) may be usually present during the early phases of acute pancreatitis.[14] Several studies have also observed that the severity of pancreatitis is higher in subjects with HTG-induced pancreatitis compared with those with pancreatitis from other causes, with a higher frequency of complications, including renal failure, shock, and infections.[15–17]

Usually TG levels are classified as normal (<150 mg/dL; <1.7 mmol/L), borderline high (150–199 mg/dL; 1.7–2.25 mmol/L), high (200–499 mg/dL; 2.26–5.6 mmol/L), or very high (≥500 mg/dL; ≥5.65 mmol/L).[6] HTG may result either from an increased TG production or a reduced TG elimination, and may have different causes, including genetic disorders of TG metabolism (LPL deficiency, apoC-II deficiency, genetic variants of *APOC3* and *APOA5*, familial combined hyperlipidemia, familial HTG, and dysbetalipoproteinemia).[6,18,19] Acquired disorders of metabolism, drugs (estrogens, steroids, and bile acid resins), dietary habits (marked alcohol consumption and high fat ingestion), and medical conditions, including poorly controlled diabetes and nephritic syndrome,[6,18–20] can also contribute. The risk of acute pancreatitis is significantly higher in the presence of TG levels above ~880 mg/dL (10 mmol/L), although it may develop even with TG levels between 440 and 880 mg/dL (5–10 mmol/L); thus, lifestyle changes and pharmacological interventions may be required to reduce the risk of pancreatitis.[21] In the presence of TG levels 200–500 mg/dL (2.26–5.65 mmol/L), TG lowering is recommended to reduce the cardiovascular risk.[21] Several therapeutic strategies to lower TG levels are available, and they must be always associated with changes of dietary habits (restriction of calories, reduction of fat ingestion, and alcohol abstinence). The available pharmacological interventions to lower TG levels include statins, fibrates, nicotinic acid, and omega-3 polyunsaturated fatty acids.[21] Here we shall discuss the role of omega-3 fatty acids, focusing on the recent data on the FFA form.

Overview of omega-3 fatty acids and mechanisms of action

Omega-3 polyunsaturated fatty acids are essential fatty acids present in fish and other seafood, and include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

EPA and DHA may be also obtained from the conversion of essential fatty acid plant-derived α-linolenic acid, but this pathway does not seem to be efficient enough to produce adequate amounts of EPA and DHA in humans.[22] Thus, to ensure adequate amounts of omega-3 fatty acids, fish oils, containing both EPA and DHA representing about 30% of the total fatty acids, may be used. However, due to the need of high doses of EPA and DHA for the pharmacological effect, preparations enriched with these fatty acids are also available.

At pharmacological doses (at least 2 g/d), omega-3 fatty acids significantly reduce TG levels, but may also affect other classes of lipids, including LDL-C.[23] In fact, omega-3 fatty acids increase LDL-C levels, and this observation has been reported remarkably in subjects with very high TG levels[23] and following the use of DHA.[24] This raise in LDL-C levels seems to be attributable to an increase of LDL size rather than an increase of LDL particle number, thus resulting in a shift from the smaller TG-rich, dense proatherogenic LDL to the larger, less atherogenic LDL particles.[23] Other studies have shown that EPA increases LDL particle size without increasing LDL-C levels;[25,26] this may depend on the starting TG plasma levels and LDL subspecies distribution in the patients investigated. In fact, in subjects with mild-to-moderate HTG, the increase of LDL-C levels is less significant.[23] Omega-3 fatty acids have only a slight HDL-raising effect in HTG patients.[23] Besides the TG-lowering properties, EPA and DHA improve cardiovascular hemodynamics, and reduce the risk of cardiovascular events, such as fatal cardiac events or atrial fibrillation.[27]

Among head-to-head studies, both EPA and DHA significantly reduce TG levels, but DHA demonstrated a greater efficacy to reduce TG compared with EPA (DHA from −8.0% to −43.7%; EPA from +1.8% to −34.9%).[24,28] LDL-C increased by 2.6%±4.3% with DHA treatment and decreased by 0.7%±4.2% with EPA; the increase in LDL-C levels following DHA treatment was directly associated with baseline TG levels.[24]

Several mechanisms are involved in the TG-lowering properties of omega-3 fatty acids. Omega-3 fatty acids reduce hepatic lipogenesis by inhibiting diacylglycerol acetyl-transferase and phosphatidic acid phosphohydrolase, two key enzymes involved in the synthesis of TG, thus decreasing TG production in the liver, and as a consequence of the reduced substrate availability, VLDL assembly and secretion.[23] This effect may also be related to the reduced availability of substrate owing the hepatic β-oxidation of other fatty acids induced by omega-3 fatty acids.[23] These effects are mainly due to the omega-3 fatty acids interaction with hepatic nuclear receptors, including peroxisome proliferators-activated receptor (PPAR) α, hepatic nuclear factor (HNF)-4α and LXR-α, and to the regulation of the transcription factor sterol regulatory element-binding protein (SREBP) 1c, which play a key role in the lipogenesis process.[29] Thus, the binding of omega-3 fatty acids to PPARα rapidly induced changes in the expression of genes involved in hepatic fatty acid oxidation.[29,30] Omega-3 fatty acids inhibit hepatic fatty acid synthesis by suppressing *SREBP-1c* gene transcription and enhancing degradation of SREBP-1c mRNA, thus resulting in a reduced SREBP-1c nuclear abundance.[29,30] Omega-3 fatty acids increase LPL activity in extrahepatic tissues, including heart and skeletal muscle, and also increase β-oxidation of fatty acids in skeletal muscle, thus contributing to the reduction of plasma TG levels.[31] In vitro, VLDL particles enriched with omega-3 fatty acids are more quickly converted to LDL,[32] suggesting an increased percentage conversion of VLDL to LDL,[33,34] and explaining the observed increase of LDL in HTG subjects treated with omega-3 fatty acids.

Introduction to the management of HTG

Most fish oils contain high levels of EPA and DHA. The required doses for a significant lipid effect are at least 2 g/d or more; patients with severe HTG must be treated with 2–4 g/d of omega-3 fatty acids to reduce TG by 25%–30%, with a higher decrease in subjects with higher baseline TG levels.[35] For these reasons, omega-3 fatty acid intake with the diet, although strongly recommended, is not adequate for the management of high TG level subjects. Thus, concentrated preparations of omega-3 fatty acids have been formulated.

The first available pharmaceutical form of omega-3 was composed by 47% EPA and 38% DHA in their ethyl ester forms (OM3-EE), and was approved as an adjunct to diet for the treatment of severe HTG (TG ≥500 mg/dL, ≥5.65 mmol/L) (Table 1).[36] In patients with severe HTG, OM3-EE 4 g/d for 16 weeks significantly decreased TG levels (−45%), associated with a relevant reduction of VLDL-C (−32%);[35] LDL-C and HDL-C increased significantly (+31%, P=0.0014 and +13%, P=0.01, respectively) (Table 2).[35] Similar results were obtained in another study in patients with severe HTG: 4 g/d for 6 weeks reduced TG levels by 38.9% (P=0.001), VLDL-C by 29.2% (P=0.001), and total cholesterol (TC) by 9.9% (P=0.004), with concomitant raise in LDL-C and HDL-C (+16.7%, P=0.007 and +5.9%, P=0.57, respectively) (Table 2).[37] As patients with high TG levels

Table 1 Prescription omega-3 fatty acids formulations

Formulations	Description	EPA and DHA content
OM3-EE	Contains EPA and DHA ethyl esters	47% EPA, 38% DHA
EPA-EE	Contains EPA ethyl ester (icosapent ethyl)	≥96% EPA
OM3-FFA	Contains EPA and DHA FFAs	55% EPA, 20% DHA

Abbreviations: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; FFAs, free fatty acids.

often also exhibit higher non-HDL-C levels, they need to be treated with combination therapies that may include a statin to lower cholesterol and omega-3 fatty acids to lower TG.[38] When added to simvastatin therapy in patients with persistent HTG, OM3-EE significantly reduced TG, VLDL-C, and non-HDL-C, compared with simvastatin alone (−29.5%, −27.5%, and −9.0% vs −6.3%, −7.2% and −2.2% respectively) (Table 2).[39] Similar results were obtained when OM3-EE was used in association with atorvastatin (Table 2).[40]

A high-purity ethyl ester form of EPA (EPA-EE) was formulated containing ≥96% EPA and no DHA (Table 1) to avoid LDL-C increase observed with EPA/DHA or DHA alone, particularly in subjects with very high TG levels.[24,41] This formulation has been approved as an adjunct to diet for the treatment of adults with severe HTG (TG ≥500 mg/dL, ≥5.65 mmol/L).[42] In subjects with very high TG levels (≥500 mg/dL and ≤2,000 mg/dL; ≥5.65 mmol/L and ≤22.60 mmol/L), with or without background statin therapy (MARINE study), EPA-EE significantly decreased TG levels (−19.7% and −33.1% with 2 and 4 g/d, respectively), and improved other lipid parameters, including VLDL-C (−15.3% and −28.6% with 2 and 4 g/d, respectively), non-HDL-C (−8.1% and −17.7% with 2 and 4 g/d, respectively), and TC (−6.8% and −16.3% with 2 and 4 g/d, respectively) without increasing LDL-C levels (Table 2).[43] In subjects with baseline TG levels ≥750 mg/dL (≥8.47 mmol/L), the effect of EPA-EE on TG levels was even greater (−32.9% at 2 g/d, −45.4% at 4 g/d).[43] In the ANCHOR study, EPA-EE was tested in statin-treated patients with persistent high TG levels (≥500 mg/dL and ≤2,000 mg/dL; ≥5.65 mmol/L and ≤22.60 mmol/L) at 2 and 4 g/d for 12 weeks.[44] TG levels were lowered by 10.1% and 21.5%, respectively (Table 2), and the reduction was even higher in subjects taking higher-efficacy statin regimens or in subjects with higher baseline TG levels (at 4 g/d: −10.9% in the first tertile, −19.3% in the second, and −21.8% in the third tertile).[44] VLDL-C, non-HDL-C, and TC were also significantly reduced (Table 2).[44] LDL-C levels were reduced, but only at 4 g/d the decrease was significant (Table 2).[44] The ongoing trial REDUCE-IT will evaluate the ability of long-term use of EPA-EE to reduce cardiovascular events in high-risk statin-treated patients with HTG compared with statin therapy alone.[45]

Novel formulations of omega-3 fatty acids

To be absorbed in the intestine, the EE form of omega-3 fatty acids must be converted into FFA by pancreatic lipase enzymes, largely secreted in the intestine in response to dietary fat intake. Thus, while the EE forms of omega-3 fatty acids need this hydrolysis step, the FFA forms are not dependent on pancreatic enzyme activity and are more readily absorbed.[46–49] In addition, current guidelines recommend that patients with severe HTG follow a very low-fat diet;[21,50] this will lead to a reduced pancreatic lipase release and, as a consequence, to a reduced absorption of the EE formulations. Omega-3 carboxylic acids is the first FFA form of long-chain omega-3 fatty acids containing 55% EPA and 20% DHA (Table 1), and approved by US Food and Drug Administration (FDA) for the treatment of adults with severe HTG.[51]

Comparison of current pharmacological and pharmacokinetic studies on omega-3 fatty acid forms

After oral administration, omega-3 FFA are directly absorbed in the small intestine, and then enter the systemic circulation. Maximum EPA and DHA plasma concentrations are reached after 5–8 hours and 5–9 hours, respectively, after repeat daily dosing of 4 g OM3-FFA/d under low-fat diet conditions for 2 weeks; steady-state plasma concentrations of both EPA and DHA are reached within 2 weeks of repeat daily dosing.[52] Following a single dose, EPA and DHA are mainly incorporated in phospholipids, TG, and cholesteryl esters.[52] OM3-FFA are mainly oxidized in the liver similarly to dietary-derived fatty acids, and are not excreted by kidneys.[52]

Two studies have investigated the pharmacokinetics of omega-3 FFA formulation. The ECLIPSE (Epanova® compared to Lovaza® in a pharmacokinetic single-dose evaluation) study evaluated the bioavailability of EPA and DHA from single 4 g doses of omega-3 FFAs and omega-3 EEs in overweight adults during low-fat or high-fat consumption periods.[53] During the low-fat period, the free FFA form showed a higher bioavailability for EPA + DHA compared with the EE form, with a baseline-adjusted AUC_{0-t} for EPA + DHA 4-fold higher and C_{max} 3.7-fold

Table 2 Lipid-modulating effects of available omega-3 fatty acids formulations

TG levels	Clinical trial	Effects
OM3-EE		
HTG patients (500–2,000 mg/dL; 5.65–22.60 mmol/L)	OM3-EE[34]	TG: −45% VLDL-C: −32% TC: −15% LDL-C: +31% HDL-C: +13%
HTG patients (500–2,000 mg/dL; 5.65–22.60 mmol/L)	OM3-EE[36]	TG: −38.9% VLDL-C: −29.2% TC: −9.9% LDL-C: +16.7% HDL-C: +5.9%
Patients with persistent HTG (≥200, <500 mg/dL; ≥2.26, <5.65 mmol/L)	COMBOS study (OM3-EE + simvastatin)[39]	TG: −29.5% (simva: −6.3%) VLDL-C: −27.5% (simva: −7.2%) HDL-C: +3.4% (simva: −1.2%) LDL-C: +0.7% (simva: −2.8%) TC: −4.8% (simva: −1.7%) Non-HDL-C: −9.0% (simva: −2.2%)
HTG patients (≥250, <599 mg/dL; ≥2.82, <6.76 mmol/L)	OM3-EE + atorvastatin[40]	TG: −45.4% (atorva: −26.9%) VLDL-C: −54.3% (atorva: −37%) LDL-C: −29.3% (atorva: −31.5%) HDL-C: +12.4% (atorva: +10%) TC: −31.5% (atorva: −27.4%) Non-HDL-C: −40.2% (atorva: −33.7%)
EPA-EE		
HTG patients (≥500, ≤2,000 mg/dL; ≥5.65, ≤22.60 mmol/L)	MARINE study[43]	TG: −19.7% (2 g), −33.1% (4 g) VLDL-C: −15.3% (2 g), −28.6% (4 g) TC: −6.8% (2 g), −16.3% (4 g) Non-HDL-C: −8.1% (2 g), −17.7% (4 g) LDL-C: +5.2% (2 g), −2.3% (4 g) HDL-C: +1.5% (2 g), −3.6% (4 g)
Statin-treated patients with persistent HTG (≥500, ≤2,000 mg/dL; ≥5.65, ≤22.60 mmol/L)	ANCHOR study[44]	TG: −10.1% (2 g), −21.5% (4 g) VLDL-C: −10.5% (2 g), −24.4% (4 g) TC: −4.8% (2 g), −12% (4 g) Non-HDL-C: −5.5% (2 g), −13.6% (4 g) LDL-C: −3.6% (2 g), −6.2% (4 g) HDL-C: −2.2% (2 g), −4.5% (4 g)
OM3-FFA		
HTG patients (≥500, <2,000 mg/dL; ≥5.65, <22.60 mmol/L)	EVOLVE study[55]	TG: −25.9% (2 g), −30.9% (4 g) VLDL-C: −26.6% (2 g), −33.0% (4 g) TC: −5.4% (2 g), −7.5% (4 g) Non-HDL-C: −7.6% (2 g), −9.6% (4 g) LDL-C: +19.2% (2 g), +19.4% (4 g) HDL-C: +7.4% (2g), +5.8% (4 g)
Statin-treated patients with residual HTG (≥200, <500 mg/dL; ≥2.26, <5.65 mmol/L)	ESPRIT study[60]	TG: −14.6% (2 g), −20.6% (4 g) VLDL-C: −14.3% (2 g), −21.5% (4 g) TC: −1.7% (2 g), −3.8% (4 g) Non-HDL-C: −3.9% (2 g), −6.9% (4 g) LDL-C: +4.6% (2 g), +1.3% (4 g) HDL-C: +2.6% (2 g), +3.3% (4 g)

Abbreviations: TG, triglycerides; HTG, hypertriglyceridemia; OM3-EE, contains EPA and DHA ethyl esters; EPA-EE, contains EPA ethyl ester; OM3-FFA, contains EPA and DHA FFAs; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; VLDL-C, very low density lipoproteins-cholesterol; TC, total cholesterol; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoproteins-cholesterol.

higher with the FFA form compared with the EE form.[53] When analyzed separately, both EPA and DHA showed a higher bioavailability profile in subjects taking the FFA form (9.0-fold and 2.0-fold, respectively).[53] Particularly relevant is the greater bioavailability of DHA with the FFA formulation during both low-fat and high-fat periods, although the starting amount of DHA was significantly lower (−42%) with the FFA formulation compared with

the EE formulation.[53] Altogether, these findings suggest a therapeutic advantage of the FFA form omega-3 during the treatment of subjects with severe HTG under low-fat diet.

The ECLIPSE II study compared the bioavailability of the FFA form with the EE form following repeat dosing.[54] After 14 days of treatment under a low-fat diet condition, a higher plasma level of EPA + DHA was found in subjects taking the FFA form compared with subjects taking the EE form; when adjusted for baseline values, the difference was even greater, with 5.8-fold higher in AUC_{0-24h} and 6.5-fold higher in C_{max}.[54] TG levels were reduced to a greater extent with the FFA form compared with the EE form (geometric least-square means 21% and 8%, respectively; P=0.013), while no differences in percent change from baseline in LDL-C, non-HDL-C, and HDL-C were observed between the two treatment groups.[54] These results suggest that omega-3 FFAs provide more EPA and DHA under low-fat diet conditions so that the higher bioavailability translates into a greater effect on plasma TG levels, and that the TG-lowering efficacy with the FFA form may be greater than that with the EE form at equivalent daily doses.

The TG-lowering efficacy of the omega-3 FFA formulation has then been tested in subjects with severe HTG (≥500 mg/dL and <2,000 mg/dL; ≥5.65 mmol/L and <22.60 mmol/L) at three dosages (2, 3, and 4 g/d) in the double-blind, randomized EVOLVE (Epanova for lowering very high triglycerides) trial.[55] After 12 weeks, during which the subjects also followed the diet (low-fat diet) indications based on NCEP ATP III,[50] fasting serum TG levels decreased significantly with all omega-3 FFA doses compared with controls (olive oil 4 g/d) (−25.9%, −25.5%, and −30.9% with 2, 3, and 4 g/d, respectively, vs −4.3% of controls) (Table 2).[55] TC and non-HDL-cholesterol decreased in all treatment groups compared with control (TC: −5.4%, −4.9%, −7.5% vs +3.2%; non-HDL-C: −7.6%, −6.9%, −9.6% vs +2.5%);[55] a significant increase of LDL-C was observed (+19.2%, +14.3%, +19.4% vs +3.0%) (Table 2), but no increase in apoB levels was reported,[55] indicating no increase in the number of circulating atherogenic particles. VLDL-C and remnant lipoprotein cholesterol (RLP-C) were also significantly reduced in all treatment groups.[55] Thus, the net effect was a reduction of the amount of cholesterol carried by apoB-containing particles. The main finding of this study is that, due to its greater bioavailability, this omega-3 formulation may have a higher efficacy at lower doses. When subgroups of high-risk patients with diabetes, or baseline TG ≥750 mg/dL (≥8.47 mmol/L), or the highest tertile of apoC-III or remnant-like particle cholesterol were analyzed, the most significant decreases of TG and non-HDL-C levels were observed,[56] suggesting that particular subgroups may benefit from the treatment with the omega-3 FFA formulation. ApoC-III that plays a negative role on TG metabolism by inhibiting LPL activity was significantly reduced (−11%, −12%, and −14%, respectively, vs +1.6%),[55] which may represent a further clinical benefit. This finding was consistent with results obtained in studies with the omega-3 EE formulation.[57,58]

Omega-3 FFA treatment also reduced the levels of other key players in the inflammatory process, such as arachidonic acid (AA) and lipoprotein-associated phospholipase A_2 (Lp-PLA_2).[55] AA, as a substrate of different enzymes that can generate several mediators involved in inflammation,[59] was reduced by 15.1%, 16.0%, and 23.2% with 2, 3, and 4 g/d, respectively, compared with a 2.2% increase of controls.[55] Lp-PLA_2 that was shown to be reduced by the treatment with omega-3 EEs[57,58] significantly decreased also in subjects treated with omega-3 FFA (−14.9%, −11.1%, and −17.2%, respectively, compared with −1.9% reduction of controls).[55]

Finally, the FFA formulation (2 or 4 g/d) has been evaluated in high cardiovascular risk patients treated with statin and with persistent HTG (≥200 mg/dL and <500 mg/dL; ≥2.26 mmol/L and <5.65 mmol/L) in the Phase III ESPRIT trial (Epanova combined with a statin in patients with HTG to reduce non-HDL-cholesterol).[60] This study confirmed the efficacy of FFA formulation of omega-3 as an adjunct to statin therapy and low-diet in these patients: TG levels significantly decreased (−14.6% and −20.6% with 2 and 4 g/d, respectively) compared with controls (−5.9%, statin + olive oil 4 g/d) (Table 2); omega-3 FFA also reduced TC (−1.7% and −3.8% vs +0.5%), non-HDL-C (−3.9% and −6.9% vs −0.9%), and VLDL-C (−14.3% and −21.5% vs −5.9%) (Table 2).[60] When the results were analyzed based on statin potency, TG and non-HDL-C reductions were greater in patients taking high-potency statins.[60] EPA and DHA plasma levels were significantly increased (DHA: +49.5% and +71.4% with 2 and 4 g/d; EPA: +188% and +348%), with values greater than those reported following the treatment with the EE formulation.[60] This would be a further benefit, as elevated plasma omega-3 fatty acid levels are associated with a reduction of cardiovascular risk.[61] The increased levels of EPA and DHA were associated with significant reductions of AA levels (−11.1% and −19.8%, respectively).[60] LDL-C was observed to increase significantly (+4.6%, P<0.05) in the 2 g/d group, but not in the 4 g/d group.[60]

The ongoing STRENGTH trial (a long-term outcomes study to assess statin residual risk reduction with Epanova in high cardiovascular risk patients with HTG) will evaluate the efficacy of omega-3 FFA formulation adjunct to statin therapy in high-risk subjects in the prevention and reduction of major cardiovascular events.[62] This trial will assess the time to the first occurrence of any component of major adverse cardiovascular events (including cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina). Patients will be enrolled on the basis of their high cardiovascular risk, having optimal LDL-C levels (≤100 mg/dL) but with residual atherogenic dyslipidemia (TG: ≥200 mg/dL and ≤500 mg/dL; HDL-C <40 mg/dL for men and <45 mg/dL for women), and will be in the study for up to 5 years.

Safety and tolerability of FFA form of omega-3

In the ECLIPSE study, both FFA and EE formulations were well tolerated and no serious adverse effects or death have been reported.[53] Among all treated subjects, 53.7% subjects reported 51 adverse effects, but all were considered mild, the most common being headache, diarrhea, dizziness, and hyperglycemia.[53] Similarly, in the ECLIPSE II study, both treatments were well tolerated; only one subject in the FFA treatment group exhibited an increase in bilirubin level and a decrease of neutrophil count, and the authors concluded that these effects were likely not related to the treatment.[54] However, previous studies showed reduced neutrophil count in subjects whose diet was enriched with DHA, in the absence of EPA,[63,64] suggesting the need of further studies to clarify this aspect.

During the 12 weeks of treatment in the EVOLVE trial, omega-3 FFA were safe and generally well tolerated; the frequency of one or more treatment-related adverse reactions was higher in the omega-3 FFA treatment group compared with controls (40%, 43%, and 44% at 2, 3, and 4 g/d, respectively, vs 26%).[55] Discontinuation due to adverse events was 5%–7%, and was mainly due to gastrointestinal effects in the groups treated with omega-3 FFA, while no discontinuation was registered in the control group.[55] The most common adverse events reported in the groups treated with omega-3 FFA were mild-to-moderate gastrointestinal disorders.[55] Similarly, in the ESPRIT trial, the frequency of adverse events related to treatment was higher in the omega-3 FFA groups (33.0% with 2 g/d and 41.7% with 4 g/d) compared with controls (27.9%).[60] Gastrointestinal disorders were the most frequent adverse events, observed particularly in the group taking the higher dosage of omega-3 FFA.[60] Discontinuation due to treatments ranged from 0.9% in the control group to 3.2% in the 4 g/d group.[60]

Conclusion

Reducing very high TG is important for the control of risk of acute pancreatitis and may be helpful to reduce the risk of coronary heart disease, and long-chain omega-3 fatty acids represent an efficient tool for the management of subjects with high TG levels. The recent FFA formulation seems to be a promising therapeutic approach with the advantage of a higher TG-lowering efficiency at lower doses, which can be an important parameter to increase drug compliance. Ongoing trials are evaluating the efficacy of omega-3 FFA formulation in the prevention of cardiovascular events.

Disclosure

A Pirillo has no conflicts of interest. AL Catapano is on the advisory board or a member of the speaker bureau for AstraZeneca, Amgen, Aegerion, Eli-Lilly, Genzyme, Mediolanum, Merck-MSD, Pfizer, Recordati, Rottapharm, Sanofi, and Sigma-Tau.

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