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Safety and lipid-altering efficacy of a new omega-3 fatty acid and antioxidant-containing medical food in men and women with elevated triacylglycerols ☆

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ABSTRACT

This randomized, double-blind, placebo-controlled multi-center trial investigated the lipid-altering effects of a medical food (PDL-0101) providing 1.8 g/d eicosapentaenoic acid; 12 mg/d astaxanthin, a marine algae-derived carotenoid; and 100 mg/d tocopherol-free gamma/delta tocotrienols enriched with geranylgeraniol, extracted from annatto, on triacylglycerols (TAG), other lipoprotein lipids, and oxidized low-density lipoprotein (LDL) in 102 subjects with TAG 150–499 mg/dL (1.69–5.63 mmol/L) and LDL cholesterol (LDL-C) ≥ 70 mg/dL (1.81 mmol/L). Compared to placebo, after eight weeks of treatment, PDL-0101 significantly reduced median TAG (−9.5% vs. 10.6%, $p < 0.001$), while not significantly altering mean LDL-C (−3.0% vs. −8.0% for PDL-0101 and placebo, respectively, $p = 0.071$), mean high-density lipoprotein cholesterol (~3% decrease in both groups, $p = 0.732$), or median oxidized LDL concentrations (5% vs. −5% for PDL-0101 and placebo, respectively, $p = 0.112$). These results demonstrate that PDL-0101 is an effective medical food for the management of elevated TAG.

1. Introduction

Hyperlipidemias, i.e., hypercholesterolemia, hypertriacylglycerolemia, and mixed dyslipidemia (the combination of elevated triacylglycerols [TAG] and low-density lipoprotein cholesterol [LDL-C]), are associated with a wide variety of disease states, particularly atherosclerotic cardiovascular disease [1,2]. Average serum TAG levels have increased steadily in the United States in the past 30+ years along with increasing incidence rates of obesity, type 2 diabetes mellitus, and insulin resistance [1]. Approximately one-third of the U.S. population has a TAG concentration above the level classified as normal (≥ 150 mg/dL; ≥ 1.69 mmol/L), whereas high (≥ 200 mg/dL; ≥ 2.26 mmol/L) and very high (≥ 500 mg/dL; ≥ 5.65 mmol/L) TAG levels are present in 16% and 1–2% of U.S. adults, respectively [1].

Diet and lifestyle changes (including dietary adjuncts) are the cornerstones of treating dyslipidemias, followed by pharmaceutical intervention when necessary [3,4]. Lipid-altering pharmaceutical products with effects on TAG have been shown to reduce TAG by approximately 7–30% for statins, 20–50% for fibrates, 20–50% for niacin, and 19–44% for omega-3 fatty acids [1,4]. There are currently five prescription omega-3 fatty acid drugs with Food and Drug Administration (FDA) approval for treating severe hypertriacylglycerolemia (TAG ≥ 500 mg/dL; ≥ 5.65 mmol/L) a condition that places individuals at high risk for developing pancreatitis [1,5–9].

PDL-0101 is an investigational medical food comprised of a combination of high purity (92%) eicosapentaenoic acid (EPA; in TAG form) plus astaxanthin (ATX), a marine algae-derived carotenoid, and tocopherol-free gamma/delta tocotrienols (TCT) enriched with geranylgeraniol (GG), extracted from annatto. Animal and human studies of ATX have demonstrated its ability to lower TAG and LDL-C and to reduce LDL oxidation [10–14]. TCT are potent antioxidants that has been reported to lower total cholesterol (Total-C) and LDL-C in a dose-dependent manner with few side effects [15–22]. The TCT ingredient naturally contains a small amount of GG, a diterpene used in the synthesis of isoprenoid

Abbreviations: Apo, apolipoprotein; ATX, astaxanthin; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GG, geranylgeraniol; HDL-C, high-density lipoprotein cholesterol; ITT, intent to treat; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; Total-C, total cholesterol; TCT, tocotrienols; TAG, triacylglycerols

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molecules such as coenzyme Q10, vitamin K, and other prenylated proteins, some of which participate in the mevalonate pathway. It has been used in conjunction with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors to reduce neurologic and myopathic effects [23,24].

The objectives of this study were to determine whether PDL-0101 would be effective for lowering serum TAG concentration while preserving LDL-C and HDL-C levels (i.e., not raising LDL-C and not lowering HDL-C), compared to placebo, among men and women with TAG 150–499 mg/dL (1.69–5.63 mmol/L) and LDL-C $\geq$ 70 mg/dL ($\geq$ 1.81 mmol/L).

2. Materials and methods

2.1. Study design

This was a randomized, double-blind, placebo-controlled trial conducted at three investigative sites (Biofortis Clinical Research, Addison, IL; Evanston Premier Healthcare Research, Evanston, IL; and Medicus Research LLC, Agoura Hills, CA). Study subjects were identified from the databases of the clinical research centers and through advertising. The study was conducted under institutional review board oversight (Quorum Review, Seattle, WA) according to Good Clinical Practice Guidelines, the Declaration of Helsinki (2000), and the United States 21 Code of Federal Regulations. A signed informed consent form and authorization for disclosure of protected health information were obtained from all subjects before protocol-specific procedures were carried out.

Subjects were randomly assigned in a 1:1 ratio to receive either placebo capsules (1 g olive oil) twice daily or PDL-0101 capsules (1 g 92% pure EPA TAG+6 mg ATX+50 mg TCT-GG) twice daily. Both products were formulated in identical-appearing, opaque gel caps. The EPA and ATX were provided by Designs for Health, Inc. (Suffield, CT) and the TCT-GG was obtained from American River Nutrition, Inc. (Hadley, MA). Subjects returned to the clinic for evaluation four and eight weeks after randomization at which times fasting blood samples were collected for laboratory analyses, vital signs and body weight were measured, and adverse events were recorded.

2.2. Subjects

Potential subjects were prescreened for TAG $\geq$ 150 mg/dL ($\geq$ 1.69 mmol/L) and $\leq$ 499 mg/dL ($\leq$ 5.63 mmol/L) and LDL-C $\geq$ 70 mg/dL ($\geq$ 1.81 mmol/L) using finger stick lipid measurements. Qualifying subjects advanced to a full screening/baseline visit at which serum lipids and other clinical laboratory tests (serum chemistry and hematology) were measured by a central reference laboratory (LabConnect, LLC, Seattle, WA), and a physical examination was conducted. In addition to the TAG entry criteria (80% of subjects had TAG levels between 200 and 499 mg/dL [2.26–5.63 mmol/L] and 20% had TAG levels of 150–199 mg/dL (1.69–2.25 mmol/L) and LDL-C entry criteria ($\geq$ 70 mg/dL; $\geq$ 1.81 mmol/L), other major inclusion criteria included men and nonpregnant, nonlactating women in general good health, between 25 and 85 years of age with consistent dietary habits and not using any serum lipid-altering drugs, medical foods, nutraceuticals, or dietary supplements with the potential to alter serum lipids. Randomization proceeded in groups of five, with four subjects having TAG between 200 and 499 mg/dL (2.26–5.63 mmol/L) before randomization of a subject with TAG between 150 and 199 mg/dL (1.69–2.25 mmol/L). The randomization code for each research site was generated using SAS in randomly permuted blocks, with a block size of four (version 9.3, SAS Institute, Cary, NC). Subjects and investigators/staff were blinded to treatment assignment.

Individuals were excluded from study participation for any of the following: use of any serum lipid-altering agent within eight weeks of the screening visit; history of pancreatitis, cholecystectomy, or any intestinal disease that might interfere with absorption; active malignancy or history of malignancy within the past three years, except basal cell carcinoma or cervical carcinoma in situ curatively treated; uncontrolled hypertension (defined as systolic blood pressure $\geq$ 160 mm Hg and/or diastolic blood pressure $\geq$ 100 mm Hg); unstable angina, congestive heart failure, or uncontrolled cardiac disease; uncontrolled diabetes mellitus (glycated hemoglobin $>$ 9%) or diabetes mellitus not on stable therapy for at least three months; abnormal laboratory results including aspartate transaminase, alanine transaminase or bilirubin concentrations $>$ 1.3 times the upper limit or normal, or serum creatinine $>$ 2.0 mg/dL (176.8 μmol/L); and known history of allergies to carotenoids, vitamin E, or fish products.

2.3. Laboratory measurements

Other than the finger stick lipid measurements conducted at prescreening using the Alere Cholestech LDX Lipid Profile System® (Alere, San Diego, CA), and a urine pregnancy test for women of childbearing potential at screening, all other laboratory measurements were conducted by a central research laboratory according to their standardized procedures (LabConnect, LLC, Seattle, WA). Fasting blood samples drawn at screening were analyzed for serum chemistry, hematology, and lipid profiles (Total-C, LDL-C, HDL-C, and TAG, and calculation of non-HDL-C [Total-C minus HDL-C]). The fasting serum lipid profile was repeated at baseline and weeks 4 and 8; serum apolipoprotein (Apo) B was measured at baseline and weeks 4 and 8; and serum oxidized LDL was measured at screening and week 8. Lipids were analyzed on the Beckman Coulter AU analyzer (Beckman Coulter, Inc., Brea, CA) using selective detergent, enzymatic and glycerol phosphate oxidase reagents [25–28]. Apo B was measured by nephelometry on a Behring Nephelometer II (Siemens Medical Solutions USA, Inc., Malvern PA) [29]. Oxidized LDL was analyzed using an enzyme linked immunosorbent assay from Mercodia AB (Uppsala, Sweden) [30]. Vital signs and body weight were measured at each clinic visit throughout the trial. Adverse events were assessed after four and eight weeks of treatment.

2.4. Statistical methods

Efficacy endpoints included percent change from baseline (average of values obtained at the screening and baseline visits) to week 4 and week 8 in TAG and other lipoprotein lipid concentrations. Exploratory endpoints included percent changes from baseline to week 4 and week 8 in Apo B and percent change from screening to week 8 in oxidized LDL concentrations. Subgroup analyses of lipid responses were also conducted according to screening TAG concentrations $<$ or $\geq$ 200 mg/dL (2.26 mmol/L). A sample size of 100 subjects (50 per group) was estimated to provide 80% power (two-sided α=0.05) to detect a difference of 15% between groups in the percent change from week 0 to week 8 in TAG level, assuming a 26.5% pooled standard deviation, based on prior work completed by one of the investigators (KCM).

Statistical analyses were generated using SAS version 9.3 (SAS Institute, Cary, NC). Analyses were completed on an intent-to-treat (ITT) population, which included all subjects who were randomized, took at least one dose of study product, and provided at least one post-randomization lipid value. The method of last observation carry forward was utilized for incomplete data by