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(54) Title: OMEGA-3 FATTY ACIDS AND DYSLIPIDEMIC AGENT FOR LIPID THERAPY

(57) Abstract: A method and composition for blood lipid therapy by administering to the subject an effective amount of a dyslipidemic agent and omega-3 fatty acids. The method utilizes a single administration or a unit dosage of a combination of dyslipidemic agent and omega-3 fatty acids for the treatment of patients with hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia, coronary heart disease (CHD), vascular disease, artherosclerotic disease and related conditions, and the prevention or reduction of cardiovascular and vascular events.

OMEGA-3 FATTY ACIDS AND DYSLIPIDEMIC AGENT FOR LIPID THERAPY

[0001] The present application claims priority from provisional patent application Serial No. 60/633,125, filed December 6, 2004, Serial No. 60/659,099, filed March 8, 2005, and Serial No. 60/699,866, filed July 18, 2005. The disclosure of the provisional applications is hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to a method utilizing a single administration or a unit dosage of a combination of a dyslipidemic agent and omega-3 fatty acids for the treatment of patients with hypertriglyceridemia, coronary heart disease (CHD), vascular disease, artherosclerotic disease and related conditions, and the prevention or reduction of cardiovascular and vascular events.

BACKGROUND OF THE INVENTION

[0003] In humans, cholesterol and triglycerides are part of lipoprotein complexes in the bloodstream, and can be separated via ultracentrifugation into high-density lipoprotein (HDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) fractions. Cholesterol and triglycerides are synthesized in the liver, incorporated into VLDL, and released into the plasma. High levels of total cholesterol (total-C), LDL-C, and apolipoprotein B (a membrane complex for LDL-C and VLDL-C) promote human atherosclerosis and decreased levels of HDL-C and its transport complex, apolipoprotein A, which are associated with the

development of atherosclerosis. Further, cardiovascular morbidity and mortality in humans can vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. In addition, researchers have found that non-HDL cholesterol is an important indicator of hypertriglyceridemia, vascular disease, artherosclerotic disease and related conditions. In fact, recently non-HDL cholesterol reduction has been specified as a treatment objective in NCEP ATP III.

[0004] Agents, such as dyslipidemic agents and omega-3 fatty acids, have been used to treat post-myocardial infarction (MI) and adult endogenous hyperlipidemias of hypercholesterolemias and of hypertriglyceridemias, which are generally categorized as "cardiovascular events".

[0005] Dyslipidemic agents commonly include HMG CoA inhibitors (statins), cholesterol absorption inhibitors, niacin and derivatives such as nicotinamide, fibrates, bile acid sequestrants, MTP inhibitors, LXR agonists and/or antagonists and PPAR agonists and/or antagonists.

[0006] Statins, which are 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors, have been used to treat hyperlipidemia and arthrosclerosis, for example. Typically, statin monotherapy has been used to treat cholesterol levels, particularly when a patient is not at an acceptable LDL-C level. Statins inhibit the enzyme HMG-CoA reductase, which controls the rate of cholesterol production in the body. Statins lower cholesterol by slowing down the production of cholesterol and by increasing the liver's ability to remove the LDL-cholesterol already in the blood. Accordingly, the major effect of the statins is to lower LDL-cholesterol levels. Statins have been

shown to decrease CHD risk by about one-third. However, statins only appear to have a modest effect on the TG-HDL axis.

[0007] Cholesterol absorption inhibitors, such as ezetimibe and MD-0727, are a class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol. Ezetimibe acts on brush border of the small intestine and decreases biliary and dietary cholesterol from the small intestine uptake into the enterocytes.

[0008] Cholesteryl ester transfer protein (CETP) inhibitors, such as torcetrapib, inhibit the CETP molecule which, among other things, moves cholesterol from the HDL form to the LDL form. Inhibiting this molecule is, therefore, a promising approach to increasing HDL cholesterol levels.

[0009] Niacin (nicotinic acid or 3-pyridinecarboxylic acid) has previously been used to treat hyperlipidemia and atherosclerosis. Niacin is known to reduce total cholesterol, LDL-C and triglycerides and increase HDL-C. Niacin therapy is also known to decrease serum levels of apolipoprotein B (Apo B), the major protein component of VLDL-C and LDL-C fractions. However, the magnitude of the individual lipid and lipoprotein response from niacin therapy may be influenced by the severity and type of underlying lipid abnormality.

[00010] Fibrates such as fenofibrate, bezafibrate, clofibrate and gemfibrozil, are PPAR-alpha agonists and are used in patients to decrease lipoproteins rich in triglycerides, to increase HDL and to decrease atherogenic-dense LDL. Fibrates are typically orally administered to such patients.

[00011] Fenofibrate or 2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester, which belongs to the fibrate family, has been known for many years as a medicinal active principle because of its efficacy in

lowering blood triglyceride and cholesterol levels. Fenofibrate is an active principle which is very poorly soluble in water and the absorption of fenofibrate in the digestive tract is limited. A treatment of 40 to 300 mg of fenofibrate per day enables a 20 to 25% reduction of cholesterolemia and a 40 to 50% reduction of triglyceridemia to be obtained.

[00012] Bile acid sequestrants, such as cholestyramine, colestipol and colesevelam, are a class of drugs that binds bile acids, prevents their reabsorption from the digestive system, and reduces cholesterol levels. The usual effect of bile acid sequestrants is to lower LDL-cholesterol by about 10 to 20 percent. Small doses of sequestrants can produce useful reductions in LDL-cholesterol.

[00013] MTP inhibitors, such as implitapide, are known to inhibit the secretion of cholesterol and triglyceride.

[00014] Liver X receptors (LXRs) are "cholesterol sensors" that regulate the expression of genes involved in lipid metabolism in response to specific oxysterol ligands (Repa et al., *Annu. Rev. Cell Dev. Biol.* **16**: 459-481(2000)). LXR agonists and antagonists are potential therapeutic agents for dyslipidemia and atherosclerosis.

[00015] PPAR-gamma agonists, such as the thiazolidinediones pioglitazone and rosiglitazone, have been shown to improve surrogate markers of cardiovascular risk and atherosclerosis. For example, thiazolidinediones decrease C-reactive protein and carotid intima-media thickness. Non-thiazolidinediones, such as tesaglitazar, naviglitizar and muraglitazar, are dual alpha/gamma PPAR agonists. These compounds are used for lowering glucose, insulin, triglycerides and free fatty acids.

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