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(54) Title: METHODS AND COMPOSITIONS FOR TREATING DISORDERS ASSOCIATED WITH HYPERLIPIDEMIA IN A MAMMAL

(57) Abstract: The invention provides methods and compositions for treating hyperlipidemia and disorders associated with hyperlipidemia in a mammal. Compositions useful in the practice of the invention include a microsomal triglyceride transport protein inhibitor ("MTPI") and at least two other cholesterol lowering drugs selected from the group consisting of a cholesterol absorption inhibitor ("CAI"), a HMG-CoA reductase inhibitor, a bile acid sequestrant, a fibric acid derivative, niacin, and squalene sythetase inhibitor.

METHODS AND COMPOSITIONS FOR TREATING DISORDERS ASSOCIATED WITH HYPERLIPIDEMIA IN A MAMMAL

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/788,616, filed April 3, 2006, and U.S. Provisional Patent Application Serial No. 60/727,664, filed October 18, 2005, the entire disclosures of which are incorporated by reference herein.

FIELD OF THE INVENTION

[0002] The present invention relates generally to the field of pharmaceutical compositions and their use in the treatment of hyperlipidemia, and more particularly relates to therapeutic combinations comprising a microsomal triglyceride transfer protein inhibitor and at least two other cholesterol lowering agents, and their use in the treatment of hyperlipidemia.

BACKGROUND OF THE INVENTION

[0003] There are several known risk factors for atherosclerotic cardiovascular disease (ASCVD), the major cause of mortality in the Western world. One key risk factor is hyperlipidemia, which is the presence of elevated levels of lipids in blood plasma. Various epidemiological studies have demonstrated that drug mediated lowering of total cholesterol (TC) and low density lipoprotein (LDL) cholesterol (LDL-C) is associated with a significant reduction in cardiovascular events. The National Cholesterol Education Program's (NCEP's) updated guidelines recommends that the overall goal for high-risk patients is to achieve less than 100 mg/dL of LDL, with a therapeutic option to set the goal for such patients to achieve a LDL level less than 70 mg/dL.

[0004] One form of hyperlipidemia is known as hypertriglyceridemia and results in the presence of elevated amounts of triglycerides in the blood. Although triglycerides are necessary for good health, higher-than-normal triglyceride levels, often are associated with known risk factors for heart disease.

[0005] Another form of hyperlipidemia, known as hypercholesterolemia, which is the presence

of elevated amounts of cholesterol in the blood, is a polygenic disorder. Modifications in lifestyle and conventional drug treatment are usually successful in reducing cholesterol levels. However, in some cases, as in familial hypercholesterolemia (FH), the cause is a monogenic defect. Treatment of a patient with FH can be more challenging because the levels of LDL-C remain elevated despite aggressive use of conventional therapy.

[0006] For example, one type of FH, homozygous familial hypercholesterolemia (hoFH), is a serious life-threatening genetic disease caused by homozygosity or compound heterozygosity for mutations in the low density lipoprotein (LDL) receptor. Patients with hoFH typically have total plasma cholesterol levels over 400 mg/dL resulting in premature atherosclerotic vascular disease. When left untreated, most patients develop atherosclerosis before age 20 and generally do not survive past age 30. However, patients diagnosed with hoFH are largely unresponsive to conventional drug therapy and have limited treatment options. Specifically, treatment with statins, which reduce LDL-C by inhibiting cholesterol synthesis and upregulating the hepatic LDL receptor, have negligible effect in patients whose LDL receptors are non-existent or defective. A mean LDL-C reduction of only less than about 20% has been recently reported in patients with genotype-confirmed hoFH treated with the maximal dose of statins (atorvastatin or simvastatin administered at 80 mg/day). The addition of ezetimibe 10 mg/day to this regimen resulted in a total reduction of LDL-C levels of 27%, which is still far from optimal. Non-pharmacological options have also been tested, including surgical interventions, such as portacaval shunt and ileal bypass, and orthotopic liver transplantation, but with clear disadvantages and risks. Therefore, there is a tremendous unmet medical need for new medical therapies for hoFH.

[0007] Microsomal triglyceride transfer protein (MTP) inhibitors have been developed as potent inhibitors of MTP-mediated neutral lipid transfer activity. MTP catalyzes the transport of triglyceride, cholesteryl ester, and phosphatidylcholine between small unilamellar vesicles. One exemplary MTP inhibitor is BMS-201038, developed by Bristol-Myers Squibb. *See*, U.S. Patent Nos. 5,739,135; and 5,712,279. Studies using an animal model for homozygous FH indicated that BMS-201038 effectively reduced plasma cholesterol levels in a dose dependent manner, for example, at 25 mg/day, suggesting that this compound might be effective for treating patients with hoFH. It was noticed, however, that certain patients treated with 25 mg/day of BMS-201038 experienced certain adverse events, for example, gastrointestinal disturbances,

abnormalities in liver function, and hepatic steatosis. Although a promising therapeutic agent, large scale clinical trials of BMS-201038 have been discontinued. Another potent MTP inhibitor known as implitapide has been developed. *See*, U.S. Patent Nos. 6,265,431, 6,479,503, 5,952,498. During clinical studies, dosages of implitapide of 80 mg/day or greater, although therapeutically effective, were found to result in certain adverse events, for example, gastrointestinal disturbances, abnormalities in liver function, and hepatic steatosis. Large scale clinical studies using implitapide have also been discontinued.

[0008] Accordingly, there is still a need for methods for aggressively treating hyperlipidemias that effectively lower, for example, circulating cholesterol and triglycerides levels so as to improve the rates of achieving goals of therapy based on published guidelines, for example, NCEP guidelines, but with fewer or reduced adverse effects that typically result when higher dosages of the MTP inhibitor are used alone in monotherapy.

BRIEF SUMMARY OF THE INVENTION

[0009] The invention is based, in part, upon the development of compositions comprising an MTP inhibitor in combination with at least two other cholesterol lowering agents. It is contemplated that the combination of active ingredients will not only provide a greater degree of goal attainment, but it will also permit the goals to be achieved at lower dosages of the individual active ingredients thereby reducing the incidence and/or severity of dose-related adverse events associated with the individual active ingredients. It is contemplated that, for example, lowering blood LDL levels below those already achieved in earlier clinical trials by using, for example, an MTP inhibitor in combination with a HMG-CoA reductase inhibitor plus a cholesterol absorption inhibitor (CAI) will provide further improvements in cardiovascular event rate reduction and/or plaque regression.

[0010] For example, the compositions can be used to reduce the fasting levels of cholesterol and/or triglycerides in the blood of a mammal to meet a clinical endpoint but with fewer or reduced adverse events than (i) when the MTP inhibitor is administered alone in a monotherapy at a dosage sufficient to meet the clinical endpoint or (ii) when the MTP inhibitor is administered together with another cholesterol lowering agent, where the MTP inhibitor and the other cholesterol lowering agent are administered at dosages sufficient to meet the clinical end point.

[0011] Furthermore, the compositions can be used to reduce by at least 55%, 60%, or 65%, the blood LDL concentration in a population of patients who, prior to therapy have circulating LDL

concentrations of at least 130 mg/dL, so as to meet the goal of having an LDL concentration of 70 mg/dL or less, where (i) less than 2% of the patients in the population have Liver Function Test results three times greater than the upper limit of normal of a standard clinical laboratory range or (ii) the patients have statistically significant lower rates of skeletal muscle side effects (e.g., myalgia and/or myopathy) relative to patients receiving the maximum permitted dose of a HMG-CoA reductase inhibitor. In this context, the term "permitted" refers to a maximum dosage permitted by a regulatory agency, for example, the U.S. Food and Drug Agency.

[0012] Furthermore, it is contemplated that the compositions, when administered to the recipient, will not only permit the recipient to meet a cholesterol goal but will also slow down or stop the build up of plaques, for example, atherosclerotic plaques, on the walls of blood vessels. Under certain circumstances, it is contemplated that the compositions, when administered, will also induce regression of existing plaques.

[0013] In one aspect, the invention provides a pharmaceutical composition comprising (i) a MTP inhibitor, (ii) a CAI, and (iii) at least one cholesterol lowering drug selected from the group consisting of a HMG-CoA reductase inhibitor, a bile acid sequestrant, a fibric acid derivative, niacin, and a squalene sythetase inhibitor. In another aspect, the invention provides a pharmaceutical composition comprising (i) an MTPI, (ii) a HMG-CoA reductase inhibitor, and (iii) at least one cholesterol lowering drug selected from the group consisting of a bile acid sequestrant, a fibric acid derivative, niacin, and a squalene sythetase inhibitor.

[0014] It is possible that the pharmaceutical composition can comprise an MTPI, (ii) a CAI, (iii) a HMG-CoA reductase inhibitor, and (iv) a cholesterol lowering drug selected from the group consisting of a bile acid sequestrant, a fibric acid derivative, and niacin.

[0015] The MTPI can be selected from known compounds selected from the group consisting of BMS-201038, implitapide, JTT-130 and CP-346086, and SLx-4090. The HMG-CoA reductase inhibitor can be selected from the group consisting of mevastatin, lovastatin, pravastatin, simvastatin, fluvastatin, cerivastatin, atorvastatin, tenivastatin, rosuvastatin, pitavastatin. The CAI can be selected from the group consisting of ezetimibe or a derivative thereof, MD-0727, FM-VP4, LPD-179, LPD84, and LPD145. The bile acid sequestrant can be selected from the group consisting of cholestyramine, colesevelam and colestipol. The fibric acid derivative can be selected from the group consisting of fenofibrate, bezafibrate, ciprofibrate, clofibrate, and gemfibrozil.

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