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

(57) Abstract: The invention is directed to methods for treating disorders associated with hyperlipidemia in a mammal. The methods involve combination therapies using a microsomal triglyceride transfer protein (MTP) inhibitor (for example, BMS-201038 and

METHODS 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] This invention relates generally to methods of reducing the concentration of cholesterol and/or triglycerides in the blood of a mammal. More particularly, the invention relates to combination therapies using a microsomal triglyceride transfer protein (MTP) inhibitor and a fibrate for reducing the concentration of cholesterol and/or triglycerides in the blood but with a reduced adverse event profile relative to MTP inhibitor monotherapy.

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 perturbations, 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 but with fewer or reduced adverse effects that typically result when higher dosages of the MTP inhibitor are used alone in monotherapy.

SUMMARY OF THE INVENTION

[0009] The invention provides methods for lowering the concentration of cholesterol and/or triglycerides in the blood, and/or reducing the amount of one or more markers of atherosclerosis. The method includes administering an MTP inhibitor, such as, BMS-201038 or implitapide, in combination with a fibrate, such as fenofibrate. The MTP inhibitors can be administered at certain lower dosages that are still therapeutically effective when combined with a fibrate but yet create fewer or reduced adverse effects when compared to therapies using therapeutically effective dosages of the MTP inhibitors during monotherapy.

[0010] In one aspect, the invention provides a method of reducing the concentration of cholesterol and/or triglycerides in the blood of a mammal, and/or the amount of a marker of atherosclerosis in a mammal. The method comprises a combination therapy whereby a combination of a fibrate and BMS-201038 are administered each day to the mammal. In this protocol, BMS-201038 initially is administered at a first dosage in the range of 1 to 5 mg/day for at least 4 weeks, is then administered at a second dosage in the range of 3 to 7 mg/day for at least 4 weeks, and is then administered at a third dosage in the range of 6 to 9 mg/day for at least 4 weeks. Optionally, the method further comprises administering a fourth dosage of BMS-201038 in the range of 9 to 12 mg/day for at least 4 weeks. Optionally, the method further comprises administering a fifth dosage of BMS-201038 in the range of 12 to 17 mg/day for at least 4 weeks.

[0011] In one embodiment, the first dosage of BMS-201,038 is 2.5 mg/day. In another embodiment, the second dosage is 5 mg/day. In another embodiment, the third dosage is 7.5 mg/day. In another embodiment, the optional fourth dosage is 10 mg/day. In another

embodiment, the optional fifth dosage is 15 mg/day. Furthermore, the fibrate is administered at a dosage of 25 to 500 mg/day, optionally at a dosage of 25 to 250 mg/day, and optionally at a dosage of 100 to 200 mg/day. In certain embodiments, the fibrate is administered at a dosage of 160 mg/day.

[0012] The fibrate and BMS-201038 can be administered together in the same dosage form, or in different dosage forms. In the case of the separate dosage forms, the fibrate can be administered before, after, or simultaneously with BMS-201038.

[0013] The foregoing method may reduce the concentration of at least one of cholesterol and triglycerides in the blood but with a reduced incidence of an adverse event as compared to administration of a dosage of 25 mg/day of BMS-201038 in monotherapy. In addition, the method may reduce the number or amount of plaques on a wall of a blood vessel of the mammal but with a reduced incidence of an adverse event as compared to administration of a dosage of 25 mg/day of BMS-201038 in monotherapy. Contemplated adverse events include, for example, gastrointestinal disturbances, abnormalities in liver function, and hepatic steatosis.

[0014] In another aspect, the invention provides a method of reducing the concentration of cholesterol and/or triglycerides in the blood of a mammal, and/or the amount of a marker of atherosclerosis in a mammal. The method comprises administering each day to the mammal a combination of a fibrate and implitapide.

[0015] The implitapide can be administered at a dosage in the range of 0.01 to 60 mg/day. It is understood that the implitapide preferably is administered at a dosage in the range of 20-60 mg/day, for example, 20 mg/day, 25 mg/day, 30 mg/day, 35 mg/day, 40 mg/day, 45 mg/day, 50 mg/day, 55 mg/day or even 60 mg/day. The fibrate can be administered at a dosage of 25 to 250 mg/day, and optionally in the range of 100 to 200 mg/day. In one embodiment, the fibrate is administered at a dosage of 160 mg/day. The implitapide and fibrate can be administered together in the same dosage form or in different dosage forms. In the case of separate dosage forms, the fibrate can be administered before, after, or simultaneously with implitapide.

[0016] This method may reduce the concentration of at least one of cholesterol and triglycerides in the blood but with a reduced incidence of an adverse event as compared to administration of a dosage of 80 mg/day or greater of implitapide, for example, 80 mg/day and 160 mg/day, during monotherapy. Furthermore, this method may reduce the number and/or amount of plaques on a wall of a blood vessel of the mammal but with a reduced incidence of an adverse event as

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