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(54) **METHODS FOR TREATING DISORDERS OR DISEASES ASSOCIATED WITH HYPERLIPIDEMIA AND HYPERCHOLESTEROLEMIA WHILE MINIMIZING SIDE EFFECTS**

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(57) **ABSTRACT**

The present invention provides methods and compositions for treating hyperlipidemia and/or hypercholesterolemia comprising administering to the subject an effective amount of an MTP inhibitor to inhibit hyperlipidemia and/or hypercholesterolemia in said subject, wherein said administration comprises an escalating series of doses of the MTP inhibitor. In some embodiments the method comprises administering at least three step-wise, increasing dosages of the MTP inhibitor to the subject. In some embodiments, the method further comprises the administration of one or more other lipid modifying compounds.

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METHODS FOR TREATING DISORDERS OR DISEASES ASSOCIATED WITH HYPERLIPIDEMIA AND HYPERCHOLESTEROLEMIA WHILE MINIMIZING SIDE EFFECTS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 10/591,923, which is a national phase application under 35 U.S.C. §371 of PCT/US05/007435 filed Mar. 7, 2005 which in turn claims priority benefit of U.S. Ser. No. 60/550,915, filed Mar. 5, 2004, all of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

The present invention generally relates to therapy for hypercholesterolemia and hyperlipidemia.

BACKGROUND OF THE INVENTION

Hypercholesterolemia is a well-known risk factor for ASCVD, the major cause of mortality in the Western world. Numerous epidemiological studies have clearly demonstrated that pharmacological lowering of total cholesterol (TC) and Low-density Lipoprotein (LDL) Cholesterol (LDL-C) is associated with a significant reduction in clinical cardiovascular events. Hypercholesterolemia is often caused by a polygenic disorder in the majority of cases and modifications in lifestyle and conventional drug treatment are usually successful in reducing cholesterol levels. However, in few cases, as in familial hypercholesterolemia (FH), the cause is a monogenic defect and the available treatment in homozygous patients can be much more challenging and far from optimal because LDL-C levels remain extremely elevated despite aggressive use of combination therapy. Therefore, for this group of high-risk patients, effective medical therapy is urgently needed.

Triglycerides are common types of fats (lipids) that are essential for good health when present in normal amounts. They account for about 95 percent of the body's fatty tissue. Abnormally high triglyceride levels may be an indication of such conditions as cirrhosis of the liver, underactive thyroid (hypothyroidism), poorly controlled diabetes, or pancreatitis (inflammation of the pancreas). Researchers have identified triglycerides as an independent risk factor for heart disease.

Higher-than-normal triglyceride levels are often associated with known risk factors for heart disease, such as low levels of HDL ("good") cholesterol, high levels of LDL ("bad") cholesterol and obesity. Triglycerides may also contribute to thickening of artery walls—a physical change believed to be a predictor of atherosclerosis.

Therefore, high triglyceride levels are at least a warning sign that a patient's heart health may be at risk. In response, physicians may be more likely to stress the importance of losing weight, getting enough exercise, quitting smoking, controlling diabetes and other strategies that patients can use to protect their own cardiovascular health.

A large number of genetic and acquired diseases can result in hyperlipidemia. They can be classified into primary and secondary hyperlipidemic states. The most common causes of the secondary hyperlipidemias are diabetes mellitus, alcohol abuse, drugs, hypothyroidism, chronic renal failure, nephrotic syndrome, cholestasis and bulimia. Primary hyperlipidemias include familial hypercholesterolemia, familial combined hyperlipidemia, familial hypercholesterolemia, remnant hyperlipidemia, chylomicronemia syndrome and familial hypertriglyceridemia.

A number of treatments are currently available for lowering serum cholesterol and triglycerides. However, each has its own drawbacks and limitations in terms of efficacy, side-effects and qualifying patient population.

Bile-acid-binding resins are a class of drugs that interrupt the recycling of bile acids from the intestine to the liver; e.g., cholestyramine (Questran Light®, Bristol-Myers Squibb), and colestipol hydrochloride (Colestid®, The Upjohn Company). When taken orally, these positively-charged resins bind to the negatively charged bile acids in the intestine. Because the resins cannot be absorbed from the intestine, they are excreted carrying the bile acids with them. The use of such resins, however, at best only lowers serum cholesterol levels by about 20%, and is associated with gastrointestinal side-effects, including constipation and certain vitamin deficiencies. Moreover, since the resins bind other drugs, other oral medications must be taken at least one hour before or four to six hours subsequent to ingestion of the resin; thus, complicating heart patient's drug regimens.

The statins are cholesterol-lowering agents that block cholesterol synthesis by inhibiting HMGCoA reductase—the key enzyme involved in the cholesterol biosynthetic pathway. The statins, e.g., lovastatin (Mevacor®, Merck & Co., Inc.), simvastatin (Zocor®, Merck & Co., Inc.), atorvastatin (Lipitor®, Pfizer), rosuva (Crestor®, Astra Zeneca) and pravastatin (Pravachol®, Bristol-Myers Squibb Co.), and combinations thereof are sometimes used in combination with bile-acid-binding resins. Statins significantly reduce serum cholesterol and LDL-serum levels, and slow progression of coronary atherosclerosis. However, serum HDL cholesterol levels are only moderately increased. The mechanism of the LDL lowering effect may involve both reduction of VLDL concentration and induction of cellular expression of LDL-receptor, leading to reduced production and/or increased catabolism of LDLs. Side effects, including liver and kidney dysfunction are associated with the use of these drugs (Physicians Desk Reference, Medical Economics Co., Inc., Montvale, N.J., 2004; hereinafter "PDR"). The FDA has approved atorvastatin to treat rare but urgent cases of familial hypercholesterolemia.

Ezetimibe is a cholesterol absorption inhibitor which reduces the amount of cholesterol absorbed by the body. Ezetimibe is used to reduce the amount of total cholesterol, LDL cholesterol (by about 18%), and apolipoprotein B. Ezetimibe is often used with a low cholesterol diet and, in some cases, other cholesterol lowering medications.

Niacin, or nicotinic acid, is a water soluble vitamin B-complex used as a dietary supplement and antihyperlipidemic agent. Niacin diminishes production of VLDL and is effective at lowering LDL. In some cases, it is used in combination with bile-acid binding resins. NIASPAN® has been approved to prevent recurrent heart attacks in patients with high cholesterol. Niacin can increase HDL when used at adequate doses, however, its usefulness is limited by serious side effects when used at such high doses.

Fibric acid derivatives ("fibrates") are a class of lipid-lowering drugs used to treat various forms of hyperlipidemia (i.e., elevated serum triglycerides) which may also be associated with hypercholesterolemia. Fibrates appear to reduce the VLDL fraction and modestly increase HDL. However, the effects of these drugs on serum cholesterol is variable. Fibrates are mainly used to lower high triglyceride levels. Although, fibrates typically do not appear as effective as

els, they are sometimes used in combination with statins or other medications to lower very high cholesterol levels. For example, fibrates are also sometimes added to statins to raise HDL cholesterol levels. In the United States, fibrates have been approved for use as antilipidemic drugs, but have not received approval as hypercholesterolemia agents. For example, clofibrate (Atromid-S®, Wyeth-Ayerst Laboratories) is an antilipidemic agent which acts to lower serum triglycerides by reducing the VLDL fraction. Although serum cholesterol may be reduced in certain patient subpopulations, the biochemical response to the drug is variable, and is not always possible to predict which patients will obtain favorable results. Atromid-S® has not been shown to be effective for prevention of coronary heart disease. The chemically and pharmacologically related drug, gemfibrozil (Lopid®, Parke-Davis) is a lipid regulating agent which moderately decreases serum triglycerides and VLDL cholesterol, and moderately increases HDL cholesterol—the HDL_2 and HDL_3 subfractions as well as both ApoA-I and A-II (i.e., the AI/AII-HDL fraction). However, the lipid response is heterogeneous, especially among different patient populations. Moreover, while prevention of coronary heart disease was observed in male patients between 40-55 without history or symptoms of existing coronary heart disease, it is not clear to what extent these findings can be extrapolated to other patient populations (e.g., women, older and younger males). Indeed, no efficacy was observed in patients with established coronary heart disease. Fenofibrate (Tricor, Secalip) is also used to reduce levels of cholesterol and triglycerides. Serious side-effects have been associated with the use of several fibrates including toxicity such as malignancy, (especially gastrointestinal cancer), gallbladder disease and an increased incidence in non-coronary mortality. Fibrates are often not indicated for the treatment of patients with high LDL or low HDL as their only lipid abnormality (Physician's Desk Reference, 2004, Medical Economics Co., Inc. Montvale, N.J.).

Oral estrogen replacement therapy may be considered for moderate hypercholesterolemia in post-menopausal women. However, increases in HDL may be accompanied with an increase in triglycerides. Estrogen treatment is, of course, limited to a specific patient population (postmenopausal women) and is associated with serious side effects including induction of malignant neoplasms, gall bladder disease, thromboembolic disease, hepatic adenoma, elevated blood pressure, glucose intolerance, and hypercalcemia.

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. Total plasma cholesterol levels are generally over 500 mg/dl and markedly premature atherosclerotic vascular disease is the major consequence. Untreated, most patients develop atherosclerosis before age 20 and generally do not survive past age 30. The primary goal of therapy consists of controlling the hypercholesterolemia to delay the development of atherosclerotic cardiovascular disease (ASCVD). However, patients diagnosed with hoFH are largely unresponsive to conventional drug therapy and have limited treatment options. A mean LDL-C reduction of only about 5.5% has been recently reported in patients with genotype-confirmed hoFH treated with the maximal dose of statins (atorvastatin or simvastatin 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. Several non-pharmacological options have also been tested. Surgical interventions, such as portacaval shunt and ileal bypass have resulted only in partial and transient LDL-C reduction. Liver transplantation has been demonstrated to substantially reduce LDL-C levels in hoFH patients, but obvious disadvantages and risks are associated with this approach. Although hoFH could be an excellent model for gene therapy, this modality of treatment is not foreseeable in the near future due to the limitations on the availability of safe vectors that provide long-term expression of LDL receptor gene. Thus, the current standard of care in hoFH is LDL apheresis, a physical method of filtering the plasma of LDL-C which as monotherapy can transiently reduce LDL-C by about 50%. Apheresis uses affinity columns to selectively remove apoB-containing lipoproteins. However, because of rapid re-accumulation of LDL-C in plasma, apheresis has to be repeated frequently (every 1-2 weeks) and requires 2 separate sites for IV access. Although anecdotally this procedure may delay the onset of atherosclerosis, it is laborious, expensive, and not readily available. Furthermore, although it is a procedure that is generally well tolerated, the fact that it needs frequent repetition and IV access can be challenging for many of these young patients. Therefore, there is a tremendous unmet medical need for new medical therapies for hoFH.

Patients with heterozygous FH can usually be successfully treated with combination drug therapy to lower the LDL-C to acceptable levels. In contrast, hoFH is unresponsive to conventional drug therapy and thus there are 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.

In July 2004, the NCEP published a paper entitled "Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines", updating certain elements of the "Adult Treatment Panel III (ATP III)" cholesterol guidelines released in 2001. For high-risk patients, individuals who have coronary heart disease (CHD) or disease of the blood vessels to the brain or extremities, or diabetes, or multiple (2 or more) risk factors that give them a greater than 20 percent chance of having a heart attack within 10 years, the ATP III update recommends that the overall goal for high-risk patients is still an LDL less than 100 mg/dL with a therapeutic option to set the goal at an LDL less than 70 mg/dL for very high-risk patients, those who have had a recent heart attack, or those who have cardiovascular disease combined with either diabetes, or severe or poorly controlled risk factors (such as continued smoking), or metabolic syndrome (a cluster of risk factors associated with obesity that includes high triglycerides and low HDL cholesterol). The ATP III update also recommends consideration of drug treatment in addition to lifestyle therapy for LDL levels 100 mg/dL or higher in high-risk patients, and characterizes drug treatment as optional for LDL less than 100 mg/dL. For moderately high-risk patients, individuals who have multiple (2 or more) CHD risk factors together with a 10-20 percent risk for a heart attack within 10 years, the ATP III update recommends the overall goal for moderately high-risk patients to be an LDL less than 130 mg/dL. There is a therapeutic option to set the treatment goal at an LDL less than 100 mg/dL, and to use drug treatment if LDL is 100-129 mg/dL. For high-risk and moderately high-risk patients, the ATP III update advises that the intensity of LDL-lowering drug treatment in high-risk and moderately high-risk patients be sufficient to achieve at least a 30 percent reduction in LDL levels.

Patients suffering from severe hypercholesterolemia may also be unable to reach the new goals for LDL and HDL described above. For example, a large number of patients may be unable to attain LDL levels less than 70 using maximally

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