

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

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a national phase application under 35 U.S.C. § 371 of PCT/US05/007435 filed March 7, 2005 which in turn claims priority benefit of U.S. Serial No. 60/550,915, filed March 5, 2004, all of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

[0002] The present invention generally relates to therapy for hypercholesterolemia and hyperlipidemia.

BACKGROUND OF THE INVENTION

[0003] 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.

[0004] 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.

[0005] 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.

[0006] 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.

[0007] 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 have also been classified into common hypercholesterolemia, familial combined hyperlipidemia, familial hypercholesterolemia, remnant hyperlipidemia, chylomicronemia syndrome and familial hypertriglyceridemia.

[0008] 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.

[0009] 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.

[0010] 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.

[0011] 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.

[0012] 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.

[0013] 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 statins in lowering total cholesterol and LDL cholesterol levels, 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 HDL₂ and HDL₃ 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.).

[0014] 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.

[0015] 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 lowering. Orthotopic 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.

[0016] 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.

[0017] 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

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