CARDIOPROTECTION WITH SIMVASTATIN: AN APPRAISAL

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ABSTRACT
Statins, commonly known as 3-hydroxymethyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors are recognized as the foremost drug therapy to show cardioprotection in pathological conditions like dyslipidemia and hyperlipidemia by significantly reducing blood cholesterol levels. Additionally, a number of beneficial effects have been shown by statins apart from lipid lowering that are referred to as their pleiotropic effects. Simvastatin, a potent member of statins class, has been widely used for lowering blood cholesterol levels by inhibiting HMG-CoA reductase both experimentally and clinically. Simvastatin has been well documented to be an effective drug therapy for the treatment of dyslipidemias. In addition, simvastatin has been shown to possess a variety of other pleiotropic effects in way of its potentiality as a cardioprotective agent. The present review critically discusses about the various pleiotropic effects possessed by simvastatin in affording cardioprotection.

KEY WORDS: Statins, Simvastatin, Dyslipidemias, Cardioprotective

INTRODUCTION
Coronary heart disease (CHD) associated with dyslipidemia has been considered as the primary basis of cardiovascular morbidity and mortality1,2. Statins, the HMG-CoA reductase inhibitors, have been known to afford cardioprotection apart from their lipid lowering effects3. Simvastatin reduce cardiovascular disease events and total mortality irrespective of the initial cholesterol concentration4. Simvastatin, a member of the statin class of drugs, is a synthetic derivative of a fermentation product of Aspergillus terreus, initially marketed by Merck and Company under the trade name Zocor, which is now a days marketed under the trade names Zocor, Simlup, Simcard, Simvacor, Zimstat, Simvahexal, Lipex, Simvaxon, Simovil. In 1979, Merck scientists synthetically derived a potent HMG-CoA reductase inhibitor from a fermentation product of Aspergillus terreus, which was designated as MK-733 that later was named simvastatin5. Simvastatin is a potent hypolipidemic drug that is used to control elevated lipids in blood6. Moreover, a number of randomized controlled clinical trials have reported simvastatin as the most effective therapy in patients suffering from CHD with dyslipidemias7,8. Simvastatin has been a potent lipid-lowering drug that decreases low density lipoprotein (LDL), triglyceride (TG) and apolipoprotein B (apo B) levels and concurrently increases high density lipoprotein (HDL) levels9. Moreover, simvastatin has been reported to inhibit the progression of atherosclerosis and show inhibitory effects on macrophages in the atherosclerotic plaque lesions. Additionally, simvastatin has been noted to inhibit the risk of developing dementia or parkinson's disease due to its pleiotropic effects10. The present review article demonstrates about different pleiotropic effects exhibited by simvastatin in the course of affording cardioprotection.

Pharmacology of Simvastatin
Simvastatin is chemically (1S,3R,7S,8S,8aR)-8-(2-((2R,4R)-4-hydroxy-6-oxytetrahydro-2H-pyran-2-yl)ethyl)-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl2,2-dimethylbutoxynoate. Simvastatin is a white, non-hygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol. Simstatin acts by inhibiting HMG-CoA reductase, the rate-limiting enzyme of the HMG-CoA reductase pathway, the metabolic pathway that is responsible for the endogenous production of cholesterol. The drug is in the form of an inactive lactone which gets hydrolyzed after ingestion to produce the active agent to produce the effects. Initially, the dose of simvastatin for dyslipidemic patients is 20 mg, but the dispersion index is from 5 mg to 80 mg a.
day as the highest approved dose of simvastatin is 80 mg\textsuperscript{11}. Many studies have reported that drug combination especially with higher doses of simvastatin should be avoided as it may lead to the development and progression of various diseased states in the body. Warning has been issued by U.S. Food and Drug Administration (FDA) about simvastatin when used in combination with amiodarone as this combination shows the risk of developing rhabdomyolysis that futher may lead to kidney failure or death when simvastatin is used at doses exceeding 20 mg\textsuperscript{12}. Another report of FDA showed simvastatin to increase the risk of myopathy when taken at doses higher than 80 mg\textsuperscript{11}. Moreover, FDA review of Simvastatin drug-drug interactions documented that simvastatin in combination with the drugs that inhibit cytochrome P450 3A4 enzyme such as iraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, gemfibrozil, cyclosporine, danazol, amiodarone and verapamil should be avoided as these drugs decrease the metabolism of simvastatin thereby increasing the plasma activity of simvastatin leading to higher risk of developing rhabdomyolysis and myopathy\textsuperscript{9,11,13}. In addition, simvastatin therapy is strictly contraindicated during pregnancy as it is likely to cause harm to fetal growth development\textsuperscript{13,14}.

**Simvastatin and Cardioprotection: Potent Antioxidant Effect**

Simvastatin has been regarded as a potent cardioprotective agent due to its antioxidant properties\textsuperscript{15}. A wide array of experimental and clinical studies confirmed the cardioprotective potential of simvastatin attributed to its antioxidant property. Simvastatin has been noted to prevent the leukocytic and aortic productions of reactive oxygen species (ROS) alongwith inhibition of protein and lipid oxidation products such as thiobarbituric acid reactive oxygen species (TBARS) confirming its antioxidant potential\textsuperscript{16}. In addition, experimental studies have shown that treatment with simvastatin attenuated the oxidative stress and produced cardioprotection by decreasing malondialdehyde levels and increasing the superoxide dismutase and nitric oxide (NO) levels\textsuperscript{7,18}. Further, treatment with simvastatin reduced oxidative stress and infarction volume thereby ameliorating ischemic damage in rats that confirmed the cardioprotective potential of the drug. Simvastatin reduced the activity of NADPH-CoQ reductase, an enzyme required in generation of free radicals that further evidenced its potent role as an antioxidant\textsuperscript{19}. Additionally, clinical studies have also suggested the cardioprotective role of simvastatin in patients undergoing cardiopulmonary bypass surgery by decreasing lipid peroxidation levels\textsuperscript{20}. Moreover, experimental studies in rats have shown that the treatment with simvastatin decreased oxidative stress in diabetic-hypercholesterolemic rats further confirming its antioxidant potential\textsuperscript{11}. Furthermore, treatment with simvastatin significantly improved endothelial function and reduced oxidative stress to afford cardioprotection\textsuperscript{22}. In addition, simvastatin has been recently reported to significantly reduce total cholesterol, triglycerides, low density lipoproteins, conjugated diene, total peroxide and malondialdehyde levels that further evidenced its role as antioxidant and potent cardioprotective agent\textsuperscript{23}.

**Simvastatin: The Hypolipidemic Potential**

Statins have been widely used for the control of hyperlipidemia by a mechanism involving inhibition of cholesterol synthesis in the liver by blocking HMG-CoA reductase. Simvastatin, in a number of studies have shown to be inhibit hyperlipidemia. The efficacy of simvastatin in hyperlipidemic patients with CHD was confirmed by the fact that simvastatin significantly reduced total cholesterol (TC) and LDL; and increased HDL cholesterol that concluded its effectiveness as a lipid lowering therapy in patients with CHD\textsuperscript{24}. Moreover, results of an open multicenter study with simvastatin in a large cohort of patients with primary hyperlipidemia showed that simvastatin significantly lowered LDL and TG alongwith a slight increase in HDL levels\textsuperscript{25}. Another study confirming its antihyperlipidemic potential demonstrated reductions of 20 to 40% for serum levels of total cholesterol, 35 to 45% for LDL and 10 to 20% for TGs in patients with primary hyperlipidemia receiving 10 to 40 mg/day of simvastatin\textsuperscript{26,27}. Moreover, a 32-week study with simvastatin significant showed reductions in LDL, TG, apo B and very low density lipoprotein (VLDL) levels that further confirmed its hypolipidemic potential\textsuperscript{28}. Further, a long study of 10-years reported simvastatin as an effective and safe drug therapy with excellent tolerability as it shows persistent lipid-lowering effect during long-term treatment of hyperlipidemic patients\textsuperscript{29}. Surprisingly, comparing 40 mg dose with simvastatin 80 mg produced greater reductions in TC, LDL and TG levels\textsuperscript{30}. Moreover, simvastatin has been significantly noted to lower LDL and TG levels alongwith slight increase in HDL levels in diabetic patients\textsuperscript{31}. Additionally, comparison of simvastatin to atorvastatin across different hyperlipidemic patient subgroups have noted simvastatin to increases HDL-C and apo A-I more than atorvastatin at higher doses\textsuperscript{32}. An interesting study has noted that simvastatin should be taken in the evening rather than in the morning. However, the serum lipid parameters were not statistically different in morning and night time.
simvastatin but the inflammatory marker such as C-reactive proteins (CRP) levels were significantly reduced as a result of evening simvastatin administration. Furthermore, the hypolipidemic potential of simvastatin was confirmed by two large outcome trials namely Scandinavian Simvastatin Survival Study (4S) and the Heart Protection Study (HPS), both of which demonstrated beneficial effects of simvastatin on a variety of cardiovascular outcomes, with insignificant adverse effects.

**Pleiotropism with Simvastatin**

Numbers of studies have reported that apart from lipid lowering effects, simvastatin shows numerous pleiotropic effects. The study of simvastatin on MG63 cell line function showed an inhibitory effect on MG63 cell migration, finding a role in promoting bone defect regeneration by enhancing the bone-related genes expression\(^3\). The effect of simvastatin on a range of hemostatic variables in subjects with impaired fasting glucose (IFG) and isolated hypercholesterolemia was tested. The early glucose metabolism abnormalities are associated with disturbed coagulation and fibrinolysis contributing to the development and progression of atherosclerosis, which were found to be significantly inhibited by simvastatin\(^4\). Moreover, the basic parameters of experimental carcinogenesis after long-term simvastatin treatment in animals were assessed which showed that simvastatin treatment significantly suppressed tumour frequency, tumour incidence, mean tumor volume as well as lengthened the latency period confirming its potential against carcinogenesis\(^5\). In addition, the effects of simvastatin on selected biochemical parameters and reproductive outcome among patients with polycystic ovary syndrome (PCOS) undergoing in vitro fertilization (IVF) have been assessed. Administration of simvastatin showed companionable effects with gonadotropin therapy for IVF and produced beneficial endocrine and cardiovascular effects for patients with PCOS undergoing embryo transfer\(^6\). Furthermore, pre-treatment with simvastatin reversed dexamethasone induced plasminogen activator inhibitor-1 (PAI-1) secretion which showed that simvastatin exhibits preventive effects against steroid-induced osteonecrosis of the femoral head by suppressing PAI-1 secretion\(^7\). Simvastatin has been noted to regulate aquaporin 2 (AQP2) trafficking and urinary concentration via events involving down regulation of Rho GTPase activity and inhibiting endocytosis, which provides an alternative mechanism to regulate AQP2 trafficking and bypassing the vasopressin receptor signaling pathway\(^8\). Sickle cell disease (SCD) is characterized by progressive vascular injury and its pathophysiology is strikingly similar to that of atherosclerosis. Statins decrease inflammation and improve endothelial function in cardiovascular disease, but their effect in SCD is not known. Plasma NO metabolites, CRPs, interleukin-6 (IL-6), vascular cell adhesion molecule-1 (VCAM-1), tissue factor (TF) and vascular endothelial growth factor (VEGF) were analyzed for the potential of simvastatin in sickle cell disease (SCD). The findings of the study showed a dose-related effect of simvastatin on levels of NO, CRP and IL-6 suggesting a potential therapeutic role for simvastatin in SCD\(^9\). It has been noted that nuclear factor kappa B (NF-κB) plays an important role in the occurrence of pulmonary artery hypertension (PAH) and simvastatin showed beneficial effect on PAH by inhibiting the expression of NF-κB\(^10\). Mixed dyslipidemias has been found to be associated with enhanced secretory function of human lymphocytes and treatment with simvastatin significantly suppressed lymphocyte levels evidencing its potential in mixed dyslycemic patients\(^11\). Moreover, simvastatin has been shown to prevent diastolic dysfunction in experimental hyperlipidemic patients independent of its lipid lowering effect involving a mechanism of decrease in myocardial fibrosis and angiogenesis\(^12\). Treatment with simvastatin has been found to be protective against Staphylococcus aureus infection as shown by its enhanced bacterial clearance, anti-inflammatory and anti-coagulant activities. Such a study provides an approach into the mechanism by which statins confer protection in acute infections like asthma and sepsis\(^13,14\). In support to the above study, it has been noted that pretreatment with simvastatin decreased the severity of acute lung injury by decreasing inflammation and oxidative stress\(^15\). Simvastatin has demonstrated a potential role in wound healing also as during cell spreading, simvastatin has been noted to diminish Rac activation and altered cell migration, a mechanism that affects the response of gingival mesenchymal cells during wound healing\(^16\). Simvastatin is a cholesterol-lowering drug that is widely used to prevent and treat atherosclerotic cardiovascular disease. Simvastatin exhibits numerous pleiotropic effects including anti-cancer activity. However, the effect of simvastatin on cholangiocarcinoma has not been evaluated. An important study has evaluated the anticancer role of simvastatin as evidenced by induction of cholangiocarcinoma cancer cells death by disrupting Rac1/lipid raft colocalisation and depression of Rac1 activity\(^17\). Simvastatin has been noted to reduce heart expression and serum levels of interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) that helped in reducing inflammation and fibrosis in the left ventricle and right.
atrium showing its potential as a cardioprotective agent. Additionally, the electrophysiological effects of simvastatin in canine pulmonary vein (PV) sleeve preparations suggested that in addition to diminish atrial structural remodeling, simvastatin possessed a direct antiarrhythmic effect by suppressing the triggers responsible for the genesis of atrial fibrillation that further confirmed its cardioprotective potential due to pleiotropism

CONCLUSION
Simvastatin, a HMG-CoA reductase inhibitor, has long been preferred over other drug therapies for the treatment of hyperlipidemic and dyslipidemic patients. In addition, simvastatin has shown a number of pleiotropic effects such as cardiac remodeling, antiarrhythmic and atrial fibrillation in order to afford cardioprotection. Moreover, simvastatin shows anti-inflammatory, antioxidant, antidiabetic and anticancer properties that make the drug as a potent pharmacological and therapeutic agent. In addition, various clinical trials have assessed the effects of simvastatin on the morbidity and mortality in CHD patients that further confirmed the cardioprotective potential of the drug. However, more randomized trials are needed to definitively evaluate the safety and efficacy of simvastatin pretreatment to make it better than the other members of its class.

REFERENCES


