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Review Article

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 mortality[1,2]. Statins, the HMG-CoA reductase inhibitors, have been known to afford cardioprotection apart form their lipid lowering effects[3]. Simvastatin reduce cardiovascular disease events and total mortality irrespective of the initial cholesterol concentration[4]. Simvastatin, a member of the statin class of drugs, is a synthetic derivate 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 simvastatin[5]. Simvastatin is a potent hypolipidemic drug that is used to control elevated lipids in blood[6]. Moreover, a number of randomized controlled clinical trials have reported simvastatin as the most effective therapy in patients suffering from CHD with dyslipidemias[7,8]. 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) levels[9]. 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 effects[10]. The present review article demostrates 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-oxotetrahydro-2H-pyran-2-yl)ethyl)-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl2,2-dimethylbu tanoate. 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[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[12]. Another report of FDA showed simvastatin to increase the risk of myopathy when taken at doses higher than 80 mg[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 itraconazole, 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[9,11,13]. In addition, simvastatin therapy is strictly contraindicated during pregnancy as it is likely to cause harm to fetal growth development[13,14].

Simvastatin and Cardioprotection: Potent Antioxidant Effect

Simvastatin has been regarded as a potent cardioprotective agent due to its antioxidant properties[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[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 dysmutase and nitric oxide (NO) levels[17,18]. 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[19]. Additionally, clinical studies have also suggested the cardioprotective role of simvastatin in patients undergoing cardiopulmonary bypass surgery by decreasing lipid peroxidation levels[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[21]. Furthermore, treatment with simvastatin significantly improved endothelial function and reduced oxidative stress to afford cardioproection[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[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[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[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[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[28]. Further, a long study of 10-years reported simvastatin as an effective and safe drug therapy with excellent tolerability that shows persistent lipid-lowering effect during long-term treatment of hyperlipidemic patients[29]. Surprisingly, comparing 40 mg dose with simvastatin 80 mg produced greater reductions in TC, LDL and TG levels[30]. Moreover, simvastatin has been significantly noted to lower LDL and TG levels alongwith slight increase in HDL levels in diabetic patients[31]. Additionally, comapriosn 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[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[9].

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[33]. 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[34]. 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[35]. 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[36]. 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[37]. 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[38]. 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[39]. 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[40]. 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 dyslipidemic patients[41]. Moreover, simvastatin has been shown to prevent diastolic dysfunction in experimental hyperlipidemic patients independent of its lipid lowering effect involving a mechnaism of decrease in myocardial fibrosis and angiogenesis[42]. 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[43,44]. 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[45]. 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[46]. 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 cell death by disrupting Rac1/lipid raft colocalisation and depression of Rac1 activity[47]. 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[48]. 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[49,50].

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

1. Tavridou A, Manolopoulos VG. Novel molecules targeting dyslipidemia and atherosclerosis. Curr Med Chem 2008; 15:792-802.
2. Tavridou A, Ragia G, Manolopoulos VG. Emerging targets for the treatment of dyslipidemia. Curr Med Chem 2011; 18:909-22.
3. Lander JS, Coplan NL. Statin therapy in the perioperative period. Rev Cardiovasc Med 2011; 12:30-7.
4. Wenger NK, Lewis SJ. Use of statin therapy to reduce cardiovascular risk in older patients. Curr Gerontol Geriatr Res 2010: 915296.
5. Liao JK, Laufs U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol 2005; 45:89-118.
6. Chen F, Maridakis V, O'Neill EA, Hubbard BK, Strack A, Beals C, Herman GA, Wong P. The effects of simvastatin treatment on plasma lipid-related biomarkers in men with dyslipidaemia. Biomarkers 2011, *in press*.
7. Lewin AJ, Kipnes MS, Meneghini LF, Plotkin DJ, Perevozskaya IT, Shah S, Maccubbin DL, Mitchel YB, Tobert JA. Effects of simvastatin on the lipid profile and attainment of low-density lipoprotein cholesterol goals when added to thiazolidinedione therapy in patients with type 2 diabetes mellitus: A multicenter, randomized, double-blind, placebo-controlled trial. Clin Ther 2004; 26:379-89.
8. Pearson T, Denke M, McBride P, Battisti WP, Brady WE, Palmisano J. Effectiveness of the addition of ezetimibe to ongoing statin therapy in modifying lipid profiles and attaining low-density lipoprotein cholesterol goals in older and elderly patients: subanalyses of data from a randomized, double-blind, placebo-controlled trial. Am J Geriatr Pharmacother 2005; 3:218-28.
9. Pedersen TR, Tobert JA. Simvastatin: a review. Expert Opin Pharmacother 2004; 5 : 2583-96.
10. Wolozin B, Wang SW, Li NC, Lee A, Lee TA, Kazis LE. Simvastatin is associated with a reduced incidence of dementia and Parkinson's disease. BMC Med 2007; 5:20.
11. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm204882.htm, assessed on April 2011.
12. Information on Simvastatin/Amiodarone".http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm118869.htm, assessed on March 2011.
13. http://www.rxlist.com/zocor-drug.html, assessed on April 2011.
14. Baselt R. Disposition of Toxic Drugs and Chemicals in Man, 8th edition, Biomedical Publications, Foster City, CA, 2008, pp. 1431-1433.
15. Di Napoli P, Antonio Taccardi A, Grilli A, Spina R, Felaco M, Barsotti A, De Caterina R. Simvastatin reduces reperfusion injury by modulating nitric oxide synthase expression: an ex vivo study in isolated working rat hearts. Cardiovasc Res 2001; 51: 283-93.
16. Delbosc S, Cristol JP, Descomps B, Mimran A, Jover B. Simvastatin prevents angiotensin II-induced cardiac alteration and oxidative stress. Hypertension 2002; 40:142-7.
17. Bayorh MA, Ganafa AA, Eatman D, Walton M, Feuerstein GZ. Simvastatin and losartan enhance nitric oxide and reduce oxidative stress in salt-induced hypertension. Am J Hypertens 2005; 18:1496-502.
18. Yin D, Liu M, Yang G, Huanga J, Gui M. Effects of simvasatin on early oxidative stress and endothelial function in apolipoprotein E-deficient mice. J Nanjing Med Uni 2007; 21: 359-62.
19. Kettawan A, Takahashi T, Kongkachuichai R, Charoenkiatkul S, Kishi T, Okamoto T. Protective effects of coenzyme q(10) on decreased oxidative stress resistance induced by simvastatin. J Clin Biochem Nutr 2007; 40:194-202.
20. Coccia R, Spadaccio C, Foppoli C, Perluigi M, Covino E, Lusini M, Chello M. The effect of simvastatin on erythrocyte membrane fluidity during oxidative stress induced by cardiopulmonary bypass: a randomized controlled study. Clin Ther 2007; 29:1706-17.
21. Kuzelová M, Adameová A, Sumbalová Z, Paulíková I, Harcárová A, Svec P, Kucharská J. The effect of simvastatin on coenzyme Q and antioxidant/oxidant balance in diabetic-hypercholesterolaemic rats. Gen Physiol Biophys 2008; 27:291-8.
22. Tong XK, Nicolakakis N, Fernandes P, Ongali B, Brouillette J, Quirion R, Hamel E. Simvastatin improves cerebrovascular function and counters soluble amyloid-beta, inflammation and oxidative stress in aged APP mice. Neurobiol Dis 2009; 35:406-14.
23. Kumar A. Effect of simvastatin on paraoxonase 1 (PON1) activity and oxidative stress. Asian Pacific J Trop Med 2010; 3:310-4.
24. French JK, White HD, Greaves SC. Simvastatin therapy for hypercholesterolaemia in patients with coronary heart disease. N Z Med J 1990; 103:41-3.
25. Simons LA. Simvastatin in severe primary hypercholesterolemia: efficacy, safety, and tolerability in 595 patients over 18 weeks. The Principal Investigators. Clin Cardiol 1993; 16:317-22.

26. Bilheimer DW. Long-term clinical tolerance of lovastatin and simvastatin. Cardiology 1990; 77:58-65.
27. Plosker GL, McTavish D. Simvastatin. A reappraisal of its pharmacology and therapeutic efficacy in hypercholesterolaemia. Drugs 1995; 50:334-63.
28. Leiter LA, Hanna K. Efficacy and safety of cerivastatin in primary hypercholesterolemia: a long term comparative titration study with simvastatin. Can J Cardiol 1999; 15:545-55.
29. Molgaard J, Wärjerstam-Elf S, Olsson AG. Efficacy and safety of simvastatin for high-risk hypercholesterolemia. Am J Cardiol 1999; 83:1043-8.
30. Ose L, Davidson MH, Stein EA, Kastelein JJ, Scott RS, Hunninghake DB, Campodonico S, Insull W, Escobar ID, Schrott HG, Stepanavage ME, Wu M, Tate AC, Melino MR, Mercuri M, Mitchel YB. Lipid-altering efficacy and safety of simvastatin 80 mg/day: long-term experience in a large group of patients with hypercholesterolemia. World Wide Expanded Dose Simvastatin Study Group. Clin Cardiol 2000; 23:39-46.
31. Gentile S, Turco S, Guarino G, Sasso CF, Amodio M, Magliano P, Salvatore T, Corigliano G, Agrusta M, De Simone G, Gaeta I, Oliviero B, Torella R. Comparative efficacy study of atorvastatin vs simvastatin, pravastatin, lovastatin and placebo in type 2 diabetic patients with hypercholesterolaemia. Diabetes Obes Metab 2000; 2:355-62.
32. Davidson MH, Ose L, Frohlich J, Scott RS, Dujovne CA, Escobar ID, Bertolami MC, Cihon F, Maccubbin DL, Mercuri M. Differential effects of simvastatin and atorvastatin on high-density lipoprotein cholesterol and apolipoprotein A-I are consistent across hypercholesterolemic patient subgroups. Clin Cardiol 2003; 26:509-14.
33. Liu ST, Liu ZH, Zong XM, Lu ZS, Sun HC, Xiaohui RF. Effect of simvastatin on the function of MG63 cell line. Shanghai Kou Qiang Yi Xue 2010; 19:658-62.
34. Krysiak R, Okopień B. Lymphocyte-suppressing effect of simvastatin in mixed dyslipidemic patients but not impaired glucose tolerance patients. Pharmacol Rep 2011; 63:95-101.
35. Kubatka P, Zihlavniková K, Kajo K, Péc M, Stollárová N, Bojková B, Kassayová M, Orendás P. Antineoplastic effects of simvastatin in experimental breast cancer. Klin Onkol 2011; 24:41-5.
36. Rashidi B, Abediasl J, Tehraninejad E, Rahmanpour H, Sills ES. Simvastatin Effects on Androgens, Inflammatory Mediators, and Endogenous Pituitary Gonadotropins Among Patients With PCOS Undergoing IVF: Results From a Prospective, Randomized, Placebo-Controlled Clinical Trial. J Investig Med 2011; *in press*.
37. Sakamoto K, Osaki M, Hozumi A, Goto H, Fukushima T, Baba H, Shindo H. Simvastatin suppresses dexamethasone-induced secretion of plasminogen activator inhibitor-1 in human bone marrow adipocytes. BMC Musculoskelet Disord 2011; 12:82.
38. Li W, Zhang Y, Bouley R, Chen Y, Matsuzaki T, Nunes P, Hasler U, Brown D, Lu HA. Simvastatin Enhances Aquaporin 2 Surface Expression and Urinary Concentration in Vasopressin Deficient Brattleboro Rats through Modulation of Rho GTPase. Am J Physiol Renal Physiol 2011; *in press*.
39. Hoppe C, Kuypers F, Larkin S, Hagar W, Vichinsky E, Styles L. A pilot study of the short-term use of simvastatin in sickle cell disease: effects on markers of vascular dysfunction. Br J Haematol 2011; *in press*: doi: 10.1111/j.1365-2141.2010.08480.x.
40. Liu ZQ, Liu B, Yu L, Wang XQ, Wang J, Liu HM. Simvastatin has beneficial effect on pulmonary artery hypertension by inhibiting NF-κB expression. Mol Cell Biochem 2011; *in press*.
41. Krysiak R, Gdula-Dymek A, Okopień B. Hemostatic effects of simvastatin in subjects with impaired fasting glucose. Pharmacol Rep 2010; 62:1090-8.
42. Mannheim D, Herrmann J, Bonetti PO, Lavi R, Lerman LO, Lerman A. Simvastatin preserves diastolic function in experimental hypercholesterolemia independently of its lipid lowering effect. Atherosclerosis 2011; *in press*.
43. McDowell SA, Ma Y, Kusano R, Akinbi HT. Simvastatin is Protective During Staphylococcus aureus Pneumonia. Curr Pharm Biotechnol 2011; *in press*.
44. Zhang S, Rahman M, Zhang S, Qi Z, Herwald H, Thorlacius H. Simvastatin regulates CXC chemokine formation in streptococcal M1 protein-induced neutrophil infiltration in the lung. Am J Physiol Lung Cell Mol Physiol 2011; *in press*.
45. Altintas ND, Atilla P, Iskit AB, Topeli A. Long-term Simvastatin Administration Attenuates Lung Injury and Oxidative Stress in Murine Acute Lung Injury Models Induced by Oleic Acid and Endotoxin. Respir Care 2011; *in press*.
46. Cáceres M, Romero A, Copaja M, Díaz-Araya G, Martínez J, Smith PC. Simvastatin alters fibroblastic cell responses involved in tissue repair. J Periodontal Res 2011; *in press*: doi: 10.1111/j.1600-0765.2011.01360.x.
47. Miller T, Yang F, Wise CE, Meng F, Priester S, Munshi MK, Guerrier M, Dostal DE, Glaser SS. Simvastatin stimulates apoptosis in cholangiocarcinoma by inhibition of Rac1 activity. Dig Liver Dis 2011; 43:395-403.
48. Melo L, Caldas IS, Azevedo MA, Gonçalves KR, da Silva do Nascimento AF, Figueiredo VP, de Figueiredo Diniz L, de Lima WG, Torres RM, Bahia MT, Talvani A. Low doses of simvastatin therapy ameliorate cardiac inflammatory remodeling in Trypanosoma cruzi-infected dogs. Am J Trop Med Hyg 2011; 84:325-31.
49. Sicouri S, Gianetti B, Zygmunt AC, Cordeiro JM, Antzelevitch C. Antiarrhythmic effects of simvastatin in canine pulmonary vein sleeve preparations. J Am Coll Cardiol 2011; 57:986-93.
50. Lee DS, Kim YK, Jung YW. Simvastatin, sildenafil and their combination in monocrotaline induced pulmonary arterial hypertension. Korean Circ J 2010; 40:659-64 .