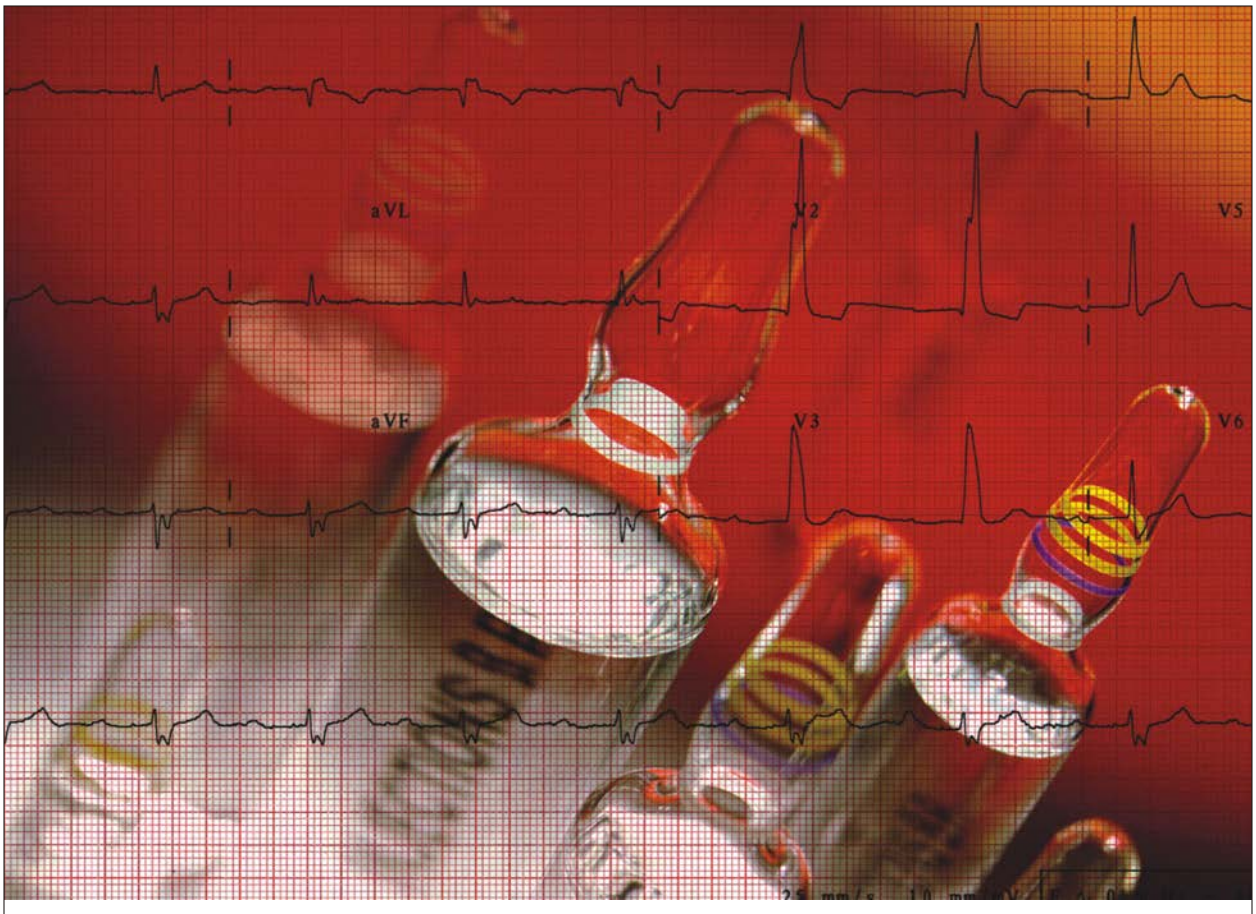

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Mini Review

Pharmacological Effects of Atorvastatin and Cholesterol and Blood Pressure

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Abstract

Cholesterol is a precursor for bile acids and steroid hormones. High concentration of cholesterol in the blood leads to hypercholesterolemia and blood pressure, which may possibly associate with atherosclerotic vascular disease and increased frequency of vascular events. Decreasing of Low Density Lipoprotein (LDL) cholesterol is an important target for the treatment of cardiovascular disease (CVD). Atorvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) inhibitors are the most effective classes of drugs for reducing serum LDL cholesterol level. This review focuses on the pharmacological effects of atorvastatin in lowering cholesterol and control of blood pressure.

Key words: Cholesterol, blood pressure, atorvastatin, HMG CoA reductase

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INTRODUCTION

Cholesterol is the immediate precursor of bile acids, which is essential for fat digestion and steroid hormones for normal functioning of the body[1]. Dietary cholesterol can contribute to changes in serum cholesterol levels, two thirds of the body's cholesterol is synthesized by the liver. Excessive amounts of cholesterol become a significant risk factor for cardiovascular disease (CVD), as demonstrated in clinical trials[2,3].

Hence, the inhibition of hepatic cholesterol biosynthesis has appeared as the target for reducing cholesterol levels in the serum[4]. Certainly, statins have emerged as one of the most effective classes of agents for reducing cholesterol levels by inhibition of 3-hydroxy-3-methylglutaryl co-enzyme A reductase (HMG-CoA) through side chains that bind to the active site of the enzyme's, subsequently blocks the substrate-product transition state of the enzyme[5]. Atorvastatin and rosuvastatin have the highest number of bonding interactions with HMG-CoA reductase[6]. This may reduce the biosynthesis of cholesterol and the complications of vascular diseases[7,8].

This review focuses on the pharmacological effects of atorvastatin in lowering cholesterol and control of blood pressure.

ATORVASTATIN IN CHOLESTEROL

Endo *et al.*[9] isolated the first natural inhibitors of HMG-CoA reductase was mevastatin was isolated from *Penicillium citrinium*. Consequently, a more active fungal metabolite, lovastatin or mevinolin was isolated from *Aspergillus terreus*[10]. Later, several other new statins have become commercially available, both chemically modified and natural statins, including simvastatin, cerivastatin, pravastatin, fluvastatin, atorvastatin and most recently pitavastatin and rosuvastatin[11].

Atorvastatin is one of the most usually prescribed statin in the world. In 2011, the European Society of Cardiology and the European Atherosclerosis Society recommended a target of either LDL cholesterol <70 mg dL^{-1} or $\geq$ 50% reduction in the level of LDL cholesterol in patients with high cardiovascular risk[12]. In Multiple-Intervention-in-type-2-Diabetes. ITaly (MIND.IT) study suggested that, the change in the level of LDL cholesterol seems to be more associated with an increased number of treated patients and a decreased therapy withdrawal than to a right treat-to-target approach[13,14]. The usual doses of atorvastatin and pitavastatin efficiently and safely decrease the elevated concentrations of hepatic enzyme[11]. The SNP rs8192870, located in the first intron of the CYP7A1 gene, may be associated with the LDL level lowering response to atorvastatin[15].

Cholesterol absorption, increased in atorvastatin treated patients by 52.3% in those with the lowest baseline campesterol levels, which may attenuate the effect of LDL cholesterol reduction. In particular, those with the highest lathosterol with the lowest campesterol levels at baseline had considerably less LDL cholesterol reduction than those with the same baseline lathosterol levels with the highest campesterol levels. These results suggest that combined patterns of cholesterol synthesis/absorption markers, relatively than each single marker are potential predictors of the LDL cholesterol lowering effects of atorvastatin in high-risk Coronary Heart Disease (CHD) patients[16].

Atorvastatin lowered P wave dispersion significantly and this finding may be important in the prevention of atrial brillation in hyperlipidemic patients[17]. Treatment responses to atorvastatin and ezetimibe/simvastatin in at-risk patients with the metabolic syndrome were related to age ($\geq$65 years), abdominal obesity and lower baseline high-sensitivity C-reactive protein (hs-CRP)[18]. Atorvastatin and ezetimibe treatment had relatively better lipid-lowering and anti-inflammatory efficiency than treatment with atorvastatin alone[19]. High Density Lipoprotein (HDL) cholesterol is increased by the treatment with atorvastatin or pravastatin (10 mg day^{-1}) by almost the same extent[20].

In CHD patient's serum high mobility group box 1 protein (HMGB1) has been recognized as a novel pro-inflammatory cytokine. HMGB1 levels are increased in hyperlipidemia patients and it could be reduced by atorvastatin[21]. Rodrigues *et al.*[22] study pointed out that APOB rs693 is an independent risk factor for elevated LDL cholesterol levels as well as dyslipidemia. In addition, the variant of CD36 was also associated with dyslipidemia as a risk factor. The response of atorvastatin may possibly predicted by LIPC -514C>T SNP and physical activity.

Wang *et al.*[23] investigated the outcome of atorvastatin treatment on serum hs-CRP and TC levels and the repetition rate of atrial brillation in hypercholesterolemia patients. After 12 months of treatment, the atrial brillation repetition rate in the treatment group was significantly lower than the control group as well as hs-CRP and TC levels were reduced. It supports that atorvastatin is highly effective in reducing serum hs-CRP and TC levels and lowering the recurrence rate of atrial brillation.

Several international multiple-centers, randomized control trials have an incontestable advantage of atorvastatin as it is a lipid-lowering medicine for primary and secondary bar

of CVD. It is also is a reversible and competitive inhibitor HMG-CoA, lowering the *de novo* cholesterol synthesis[24]. The levels of asymmetric dimethylarginine and homocysteine were decreased in hypercholesterolemic patients and the levels of nitric oxide were increased with atorvastatin therapy. It also improved the lipid profiles of the patients and functionality of HDL, oxidative stress and endothelial functions[25].

High-intensity atorvastatin therapy attenuated the natural progression of coronary atherosclerosis in all strata of patients with CHD irrespective of baseline lipoprotein or CRP levels. This result provides added support for the latest United States guideline recommendations for the broad use of high-intensity statin therapy in all patients with atherosclerosis, regardless of baseline lipid status[26]. Recently, Gungoren *et al.*[27] suggested that, lipid levels were reduced significantly after the statin therapy for 24 weeks.

ATORVASTATIN AND BLOOD PRESSURE

Hypertension is demonstrated by endothelial dysfunction, which may responsible for the manifestation of CVD[28]. Saluveer *et al.*[29] observed acute statin effect in hypertension seems to be endothelium-independent as well as related to VSMC function. These actions may provide the benefits and pleiotropic effects of statin treatment. In hypertensive rats, treatment with atorvastatin improved the activity of superoxide dismutase and prevented from glutathione decrement during hypertension[30]. The hypotensive effect of atorvastatin is associated with flow-mediated dilation improvement in hypertensive patients with normal lipid levels. This can be associated with the changes in oxidative stress and endothelial function[31].

Tanaka *et al.*[32] investigated the effects of a single pill of amlodipine (5 mg)/atorvastatin (10 mg) on oxidative stress, blood pressure/lipid control and adherence to medication in patients with type 2 diabetes. These results suggested that combined patterns, relatively than each single pill are potential predictors of hypertension and dyslipidemia in type 2 diabetes patients. Therapy with amlodipine and atorvastatin for 16 weeks have significantly decreased the clinical (blood pressure) level on an average of 45% and also the combination therapy also lowered albuminuria without decline in expected glomerular filtration rate. The results suggest that the combination therapy with amlodipine and atorvastatin exert beneficial effects on renal and vascular damages as well as blood pressure in addition to blood pressure lowering in hypertension with chronic kidney disease patients[33].

Monfared *et al.*[34] investigated the outcome of atrovastatin in the relationship with the plasma total homocysteine levels in renal transplant recipients. Out of 148 about 58.1% of renal transplant recipients were treated with atorvastatin (20-40 mg day^{-1}). The levels of total homocysteine were significantly lower when compared with the non users. It supports that atrovastatin is highly effective in lowering the total homocysteine levels in renal transplant recipients.

The study on effect of a fixed-dose combination of irbesartan-atorvastatin used for treating the patients with hypertension and hyperlipidemia was designed to evaluate the blood pressure-lowering and cholesterol-lowering effect over an 8 week treatment period for a total of 733 patients. Tolerability profiles of therapy showing the incidence rate of 22.27% and resulted that once-daily combination product of irbesartan and atorvastatin provided more compliable treatment for patients with hypertension and hyperlipidemia[35].

The beneficial effects of atorvastatin on the structural remodeling of the lung in ischemic heart failure was studied by inducing pulmonary hypertension in rats by aortic banding divided into four groups including a control group. The rats were treated with atorvastatin at a dose of 10 mg kg^{-1} day^{-1} for 63 days in the AOB63/ATOR63 (an atorvastatin prevention) group showed significant decrease in pulmonary expression of RhoA and Rho-kinase II when compared with AOB63/ATOR50-63 (atorvastatin reversal) group showing an observable improvement in pulmonary vascular remodelling. Pulmonary vascular remodeling was prevented by down-regulating the expression of RhoA/Rho kinase and by inhibiting the proliferation and increasing the apoptosis of pulmonary arterial smooth muscle cells and by attenuating the inflammation of pulmonary arteries[36].

CONCLUSION

Atorvastatin helps in the reduction of cholesterol as well as the control of blood pressure, which enhances the normal lifestyle to the patients with CVD. This is supporting the practice of early introduction of atorvastatin in high-risk patients.

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