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REVIEW ARTICLE

Atorvastatin Pleiotropism: Role in Cardioprotection

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ABSTRACT

The 3-hydroxymethyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, known as statins, are known to be the prime and most effective therapy for reducing blood cholesterol levels and hence, significantly reduce cardiovascular morbidity and mortality. Moreover, statins possess a wide range of beneficial biological effects apart from lipid lowering commonly referred to as the pleiotropic effects. Atorvastatin, a member of statins, has been used for lowering blood cholesterol levels by inhibiting HMG-CoA reductase. Atorvastatin has been well reported to be an effective drug therapy for the treatment of dyslipidemias alongwith prevention of various cardiovascular diseases. The present review article summarizes about the numerous pleiotropic effects exhibited by atorvastatin in affording cardioprotection.

Key Words: Statins, Atorvastatin, Cholesterol, Cardiovascular

INTRODUCTION

Cardiovascular disease associated with dyslipidemia is the leading cause of morbidity and mortality worldwide and its prevelance has continuously increased over the past few decades [1,2]. The HMG-CoA reductase inhibitors commonly known as statins, possess multiple beneficial effects above and beyond that of cholesterol lowering in affording cardioprotection [3]. Randomized controlled trials have significantly demonstrated that statin therapy has been the most effective therapy in patients suffering from cardiovascular disease [4]. Atorvastatin, sold by Pfizer under the trade name Lipitor, is a potent member of the statins class, inhibits HMG-CoA reductase enzyme found in liver that plays a key role in production of cholesterol in the body [5]. Atorvastatin was firstly synthesized in the year 1985 by Bruce Roth while working at Parke-Davis Warner-Lambert Company (now Pfizer). In the year 2008, Lipitor became the top-selling branded pharmaceutical in the world [6,7]. Atorvastatin has been well reported to lowering blood cholesterol levels. Additionally, it also has been noted to stabilize plaque and prevent strokes through its anti-inflammatory and other mechanisms. Atorvastatin has been widely employed to prevent hypercholesterolemia and mixed dyslipidemia to reduce total cholesterol, low density lipoprotein (LDL) cholesterol, apo-B, triglycerides and C-reactive protein (CRP) levels [8,9,10,11]. Moreover, atorvastatin treatment has been used in the treatment of various cardiovascular diseases and multiple risk factors associated with myocardial infarction, stroke, unstable angina and revascularization [12,13,14]. The present review article discusses about various pleiotropic effects demonstrated by atorvastatin in the course of affording cardioprotection.

PHARMACOLOGY OF ATORVASTATIN

Atorvastatin is chemically (3R, 5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)- 1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid. Like all other statins, atorvastatin is a competitive inhibitor of HMG-CoA reductase and is a completely synthetic compound. HMG-CoA reductase catalyzes the reduction of HMG-CoA to mevalonate, which is considered as the rate-limiting step in hepatic cholesterol biosynthesis [15]. The inhibition of the enzyme HMG-CoA reductase reduces the de novo cholesterol synthesis thereby increasing expression of low-density lipoprotein receptors on

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hepatocytes. This further causes the increases in LDL uptake by the hepatocytes and decreasing the amount of LDL-cholesterol in the blood. Additionally, atorvastatin reduces triglycerides levels in blood and increases the levels of HDL-cholesterol. In various clinical trials, it has been observed that the drugs that block cholesterol uptake like ezetimibe combine with the cholesterol biosynthesis inhibitors like atorvastatin or simvastatin and lower the cholesterol levels or targeting levels of LDL [15, 16]. However, precautionary steps must be when treating with atorvastatin as it may lead to rhabdomyolysis and myopathy [17, 18]. Moreover, atorvastatin therapy is strictly contraindicated during pregnancy as it is likely to cause harm to fetal development because of the importance of cholesterol and various products in the cholesterol biosynthesis pathway for fetal development including steroid synthesis and cell membrane production. In addition, nursing mothers are not recommended to take atorvastatin due to the possibility of adverse reactions in nursing infants as experiments with rats indicate that atorvastatin is secreted into human breast milk [6,7].

ATORVASTATIN AND CARDIOPROTECTION: THE POTENT ANTIOXIDANT

Numerous studies have documented atorvastatin to be a potent antioxidant that has a vital role in affording cardioprotection. Atorvastatin treatment has been noted to produce endothelium-dependent vasodilation and improve endothelial function by decreasing oxidative stress [19, 20]. Moreover, atorvastatin treatment reduced thiobarbituric acid reactive oxygen substances (TBARS) levels and lipid peroxidation levels, the oxidative stress markers, which further evidenced its antioxidant action [21]. Myocardial injury has been documented to be associated with increased oxidative stress involving NADPH oxidase. Treatment with atorvastatin has been reported to reduce vascular and cardiac free radical formation, normalize the expression of the NADPH oxidase and thus show anti-oxidative properties [22]. Moreover, administration of isoproterenol produced severe myocardial damage and oxidative stress in rats. Atorvastatin treatment reduced myocardial infarction in rat hearts as assessed in terms of improvement in serum parameters and reduction in oxidative stress. The lipid-independent anti-oxidative and anti-inflammatory effects of atorvastatin involve extracellular regulated kinase-nuclear factor kappa B (ERK1/2/NF-κB) pathway that is noted to afford cardioprotecion [23]. Moreover, the decrease in oxidative stress in subjects with metabolic syndrome was also noted with atorvastatin treatment that further evidenced the antioxidant potential of it in affording cardioprotection [24]. Atorvastatin has been reported to induce a significant decrease in TNF-α, IL-6 and MDA alongwith a significant increase of SOD activity that accounts for its cardioprotective and antioxidant action [25]. Furthermore, recent studies have demonstrated that atorvastatin inhibited homocysteine-induced NADPH oxidase activation, ROS accumulation and apoptosis through p38MAPK dependent mechanisms that contribute to atorvastatin-mediated cardioprotective effects [26, 27].

PLEIOTROPISM WITH ATORVASTATIN

Numerous long-term, randomized trials have well reported that statins significantly decrease the risks of myocardial infarction, stroke and vascular death thereby decreasing cardiovascular mortality and morbidity. In contrast, atorvastatin has been conferred to show an early clinical benefit in the lipid-lowering trials by documenting its pleiotropic effects. It has been reported that patients on atorvastatin had significantly decreased platelet activity compared with patients administered with other statins or those taking no statins. Moreover, treatment with atorvastatin has shown protective effects against membrane lipid peroxidation at various pharmacological concentrations that account for its pleiotropic effects that translate into early clinical benefits on cardiovascular disease [28]. Increased oxidative stress has been considered as a common feature in chronic heart failure that has been associated with inflammation, endothelial dysfunction and extracellular matrix degradation. Treatment with atorvastatin therapy decreased inflammation and extracellular matrix remodeling and improved both endothelial function and exercise capacity accounting for its potential role in heart failure [25]. Additionally, atorvastatin treatment improved endothelial function and decreased the expression of proinflammatory cytokines and adhesion molecules. Moreover, it improved the balance between endothelium-derived thrombotic or fibrinolytic molecules in patients with conjestive heart failure which suggest that statins are beneficial for patients with heart failure by improving endothelial function and modifying inflammatory and thrombotic mechanisms [29].

Further, it has been found that long-term effects of atorvastatin include decrease in plasminogen activator inhibitor type-1, significant alterations in LDL subfractions and improvement of endothelial function apart from early reversal of hypercholesterolemia [30]. Furthermore, atorvastatin has been noted to suppress intimal hyerplasia and assist in intimal regeneration by lowering blood lipids and intimal smooth muscle cell accumulation accounting for its potential role in vascular intimal hyperplasia [31]. In addition, accumulating evidence supports that atorvastatin is able to modify the composition of atherosclerotic plaques and their inflammatory status through a series of effects involving tissue factors [32]. Hyperglycaemia has been known to increase oxidative stress and thereby resulting in endothelial dysfunction. Administration of atorvastatin significantly improved endothelial function by reducting inflammatory cytokines and other markers of oxidative stress [33]. Atorvastatin therapy in patients with nonischemic heart failure has been noted to improve left ventricular ejection fraction and attenuate adverse left ventricular remodeling thereby evidencing its potential in patients with nonischeic heart failure [34]. Additionally, it has been documented that the development and progression of atherosclerosis comprises of various processes that include endothelial dysfunction, chronic inflammation, thrombus formation and lipid profile modification. Atorvastatin has been reported to significantly reduce LDL levels, platelet P-selectin levels and interleukin-6 (IL-6) levels thereby finding a potential role in preventing the development and progression of atherosclerosis [35].

In addition, statistics from various primary prevention studies such as ALLHAT-LLT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack, Lipid-Lowering Therapy), ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial, Lipid-Lowering Arm), CARDS (Collaborative Atorvastatin Diabetes Study, WOSCOPS (West of Scotland COronary Prevention Study) demonstrates that atorvastatin show a protective effect in reducing stroke. Moreover, a number of secondary prevention studies such as GREACE (GREek Atorvastatin and Coronary-heart-disease Evaluation), HPS (Heart Protection Study) and SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) confirm the ability of atorvastatin in reducing stroke risk [36]. Further, a number of clinical trials have demonstrated that treatment with atorvastatin resulted in significant reductions in cardiovascular events in patients with and without cardiovascular diseases [37, 38]. In a study of diabetic patients, atorvastatin showed decreased occurrence of acute cardiovascular events, coronary revascularizations and stroke [38]. Moreover, atorvastatin has been found to be effective in reducing nonfatal myocardial infarctions and fatal cardiovascular events in hypertensive patients. The high-dose administration of atorvastatin has been noted to be effective in reducing risk of recurrent stroke in patients with preceding cerebrovascular events [38]. Atorvastatin has been shown to benefit patients suffering from recent acute coronary syndrome and to slow cognitive decline in preliminary studies of patients with azheimer's disease. The cardioportective potential of atorvastatin was further confirmed by the fact that atorvastatin treatment reversed hypertension-induced cardiac remodeling in rats by down-regulating PKD and myocyte enhancer factor which may serve as a novel therapeutic target for atorvastatin in treating hypertensive patients [39,40].

CONCLUSION

Cardiovascular diseases persist to be the leading cause of mortality and morbidity. Over the past few years, statins by aggressively lowering LDL-cholesterol has significantly decreased cardiac events as evident from the majority of the studies using statin therapy.

The data from various randomized controlled trials strongly recommend atorvastatin as a new strategy for the treatment of patients with cardiovascular events. Atorvastatin inhibit HMG-CoA reductase competitively and thereby reduce LDL and triglycerides levels in hypertriglyceridemic patients more than other cholesterol-lowering drugs. Furthermore, throughout its dose range, atorvastatin has been found to be safe and well tolerated therapy. Moreover, the pleiotropic effects exhibited by atorvastatin makes it as an effective medication for secondary prevention of stroke and other cardiovascular events in patients with or without history of cardiac diseases. Further large-scale randomised trials are needed to explicate the exact utility of atorvastatin alone or in combination with other antioxidants in prevention of various cardiovascular diseases.

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