ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

REVIEW ARTICLE

Recent Advances in Statin Therapy

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ABSTRACT

Patients with high cholesterol have more chances of cardiovascular events and mortality rate from vascular disease. Cardiovascular events are reduced by statins in patients suffering from coronary artery disease or who can develop coronary artery disease in the future by reducing cholesterol levels. On the other hand, in chronic heart failure (CHF) patients, low levels of cholesterol can also cause mortality. Statins have an important role in various diseases like acute coronary syndrome, sepsis and inflammation, peri-operative events. Recently, there is demonstrated that vasoconstrictor responsiveness to angiotensin II can be modified by statin treatment in patients with diseased coronary arteries. Also studies have documented that activated matiix metaloprotienase MMPs has an important role in the development of CHF. In experimental studies, production of MMPs was inhibited by statins .Though statins have adverse effects like rhabdomylisis it is proven beneficial in cardiovascular diseases.

Keywords: atherosclerosis, neuohormonal system, matiix metaloprotienase , pleiotropic effects.

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ISSN: 0975-8585

INTRODUCTION

Statins the 3-hydroxy 3-methyl glutaryl coenzyme-A reductase (HMG-CoA) inhibitors are the first choice of drug in hypercholesteromia. The increased level of Low-density lipoprotein cholesterol (LDL) is associated with the development of atherosclerosis. Reduction of lipid is therefore a rational approach towards reducing of cardiovascular risk. The development of statins is a milestone in this field. Statins inhibit intracellular synthesis of cholesterol by preventing the biosynthetic pathway. Statins increase the expression of LDL receptors predominantly in the liver, where the plasma concentration of LDL particles is decreased. Statins posses an HMG-like moiety, may be inactive, after hydroxylation in vivo get activated [1] Table 1 shows the structures of some commonly used statins.

HISTORY

In 1987 the Lovastatin on the first station came to market in the USA. From then statin therapy was widely accepted as well as the relationship between increased cholesterol level and coronary heart disease risk was understood. But at the same time the skeptics did not believe that the reduced cholesterol level would have benefited over mortality, and some even thought that statins have fatal side effects. But clinical trials have repelled these unfounded theories. Now the number of different stations is available in the market. All statins differ from each other pharmacologically. And that's why each of them differ in their performance [2].

CLASSIFICATION OF STATINS

There are many criteria for classification of statins. These different criteria are

Source

Some statins are obtained from the fungus. Eg. Lovastatin, Pravastatin and Simvastatin while Fluvastatin, Atorvastatin are the synthetic statins. Now lovastatin, simvastatin, pravastatin, atorvastatin and fluvastatin are in clinical use [3].

Metabolized in the liver

The liver is a target organ for all statins. The liver retains > 70% of a dose of fluvastatin and lovastatin whereas >80% of simvastatin and 46% of pravastatin [4]. There are no available data for atorvastatin. Lovastatin, simvastatin, atorvastatin metabolized by cytochrome P450 (CYP 3A4) pathway whereas fluvastatin follows the CYP 2C9 pathway, and pravastatin is metabolized differently [5].

Physico-chemical properties

Some statins are hydrophilic, eg. Pravastatin .While some are hydrophobic eg. Lovastatin, simvastatin, atorvastatin . Fluvastatin has intermediate characteristics

MECHANISM OF ACTION

In hepatocytes statins inhibit conversion of HMG-CoA into mevalonic acid, by inhibiting the enzyme HMG-CoA. Statins not only compete with the substrate in the enzyme active site but also alter the conformation of the enzyme after binding to its active site [6]. In this way HMG-CoA reductase cannot attain a functional structure. These drugs are highly effective and specific as they change conformation at the active site. The natural substrate, which has micromolar affinity for HMG-CoA whereas statins shows nanomolar affinity for the same [7].Statins bind to HMG-CoA reductase reversiblely, inhibits of HMG-CoA reductase and reduces intracellular cholesterol. This results in activation of a protease which slices the sterol regulatory element binding proteins (SREBPs) from the endoplasmic reticulum. These SREBPs are translated at the level of the nucleus, and increases the gene expression of LDL receptors. The reduced level of cholesterol in hepatocytes causes an increase in hepatic LDL receptors, which reduces circulating LDL and also its precursors i.e. Intermediate density - IDL and very low density- VLDL lipoproteins[8]. Reduction of LDL cholesterol is dose-dependent[9]. Reduction of triglyceride is proportional to LDL cholesterol reduction[10].

USES OF STATINS

Clinical practice guidelines generally recommend statins for the people who want to reduce their lipid level. Physical exercise and diet with low fats will also help to reduce the cholesterol level [11] .

Primary prevention

Statins are helpful in the reduction of cholesterol in people without other health problems. This is called as primary prevention .There may be benefit over morbidity due to stains. Statins can also improve the quality of life [12].

Secondary prevention

When statins are used in patients having other health problems is called as secondary prevention of statins. Now a day's station is recommended for patients those are susceptible heart disease too. Statins are more useful when taken along with niacin or fibrates for reduction of low density lipoproteins [13].

Atherosclerosis

Beyond lipid lowering property, stations also reduced the progression of coronary atherosclerosis in clinical studies [14], because there is a role of inflammation in atherosclerosis and statins have been recognized to have anti-inflammatory and antioxidant properties. Some studies even demonstrated regression of atherosclerotic plaques with high doses of statins [15].

ISSN: 0975-8585

Inflammation

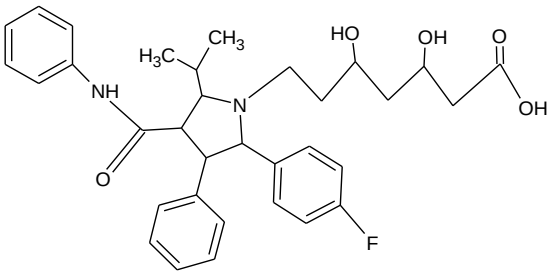
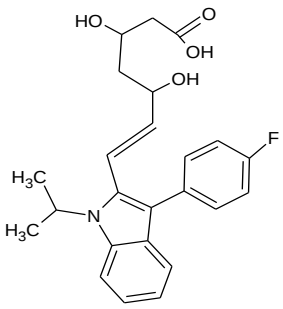
In patients with Cardiac Heart Failure, elevated systemic levels of inflammatory parameters have been extensively documented and associated with progression of CHF and death [16-21]. Several clinical trials have demonstrated the efficacy of statin treatment in reducing C-reactive protein [22] and other inflammatory markers.

ADVERSE EFFECTS OF STATINS

Statin toxicities in adults

The FDA's MedWatch database, health maintenance organization registries and several clinical trials alerts about adverse effects and toxicity of Statins in adults [23]. Generally, statins are tolerable and regarded as safe in adults; however mortality has been reported in association with their use [24]. Even though, statins have many side effects, they are potent hepatotoxic [25-27]. Statins also have potential for teratogenicity [28-30]. Peripheral neuropathy, cognitive adverse effects and a possibility of cancer are other side effects of statins which require additional research.

Table 1- Structure of some statin drug.

Statins	Structure
Atorvastatin	
Fluvastatin	

Statin-Related Hepatotoxicity

In 1% to 3% of patients using statins there is elevation of aminotransaminases level, upto ≥3 times above the normal level on 2 consecutive measurements, which is common, and a "class effect" of statins [31,32]. Generally the elevation of alanine aminotransferase occur ≥90 days after starting the therapy which is asymptomatic [33,34]. The susceptibility for hepatotoxicity may be increased with lipophilic stations when prescribed at a high dose [35].Idiosyncratic fulminant liver failure associated with statin is also rarely reported. The liver-function tests should be routinely monitored. However, no data are able to suggest that this protocol can effectively predict or prevent acute hepatic failure [36-38].

Statin-Related Myotoxicity

Statins cause several muscle complaints like mild myalgias, which may be with or without elevation of Creatine kinase, rhabdomyolysis which may be developed in renal failure and or death [39-40]. Myopathy and rhabdomyolysis are shown by all statins.

Statin-Related Rhabdomyolysis

Cerivastatin (Baycol) was voluntarily withdrawn by its manufacturer in 2001 because it has potential to cause fatal rhabdomyolysis [41]. Later analyses by the FDA also suggested that the rate of fatal rhabdomyolysis of cerivastatin was much greater than that for other stations (nearly 16-80 timeless) [42].All currently approved statins can cause rhabdomyolysis. The mechanism by which statins cause rhabdomyolysis is not exactly known, but it is thought that decreased levels of mevalonate, farnesol, geranylgeraniol, and mitochondrial ubiquinone are responsible [43].

Teratogenicty of Statins

FDA reported that among 214 determined exposures, 31 adverse birth outcomes were recognized, which involve fetal demise, syndromes as well as nonsyndromic limb deformities, and intrauterine growth restriction. (From an uncontrolled case-series analysis of all station exposures during gestation [44]. There are chances of central nervous system and cardiac anomalies with lovastatin- exposed fetuses [45-46]. The teratogenicity due to statins may be because of alterations of sterol-dependent morphogenesis by the lipophilic stations which can cross the placenta.

Statin-Associated Cognitive Effects

There is debate on whether statins particularly that cross the blood-brain barrier can adversely influence cognitive function and or mood. This is an area of ongoing interest [47-48]. Reports of randomized clinical trials performed in adults show adverse cognitive effects of statin [49-50]. Conversely, few random, controlled trials did not find an adverse cognitive effect

of statin treatment [51-52]. There is a ongoing large, randomized trial on statins in which mood, cognition and behavior etc are measured [53].

ROLE OF STATIN IN VARIOUS DISEASES

Statins and cardiovascular disease

Cardiovascular disease and predominantly coronary artery disease are an important cause of morbidity and mortality in developed countries. Statins reduces the cholesterol level and used to prevent mortality in cardiovascular diseases. As earlier mentioned statins have also improved the quality of life in cardiovascular patients.

Acute coronary syndromes

The positive effect of the statin therapy has emerged only recently immediately following ACS occurrence. Comprising myocardial infarction, ST-elevation, non-ST-elevation as well as unstable angina. ACSs often require intensive-care treatment. These patients are at highly susceptible for recurrent coronary events which cause mortality. The stabilization of vulnerable lesions is a critical aspect in preventing these events following ACSs. In spite of significant development in antiplatelet and antithrombotic therapy, these therapeutic options alone do not appear to be adequate in treating the unstable plaque stabilization. Through their cholesterol lowering and pleiotropic effects, statins are found to be important contributors to plaque stabilization [54]. According to number of retrospective and observational studies it is observed that recommendation of starting therapy immediately after an ACS is associated with significant reduction of rate of recurrent coronary events and mortality [54-63].

Peri-operative application of stains

Adverse peri-operative cardiac events are one of the important sources of hospital morbidity and mortality. The overall incidence of peri-operative myocardial infarction among major noncardiac surgery is 2–3%, and among high-risk populations, such as those undergoing vascular surgery, rates as high as 34% have been reported [64]. In many retrospective trials the beneficial role for statins is proved in surgical patients as well as in prospective studies, patients who are subjected to vascular surgery were benefitted with statin therapy. None of the studies found an increased occurrence of adverse effects of statin therapy [65]. Thus patients undergoing vascular surgery, with high risk for cardiac complications, should get statin therapy. The most favorable therapeutic regime with respect to dose and duration of pre-operative and post-operative treatment remains to be determined by further prospective studies as well as the potential benefit for surgical patients with lesser cardiovascular risk. It is important to note that patients with long term statin therapy should continue their therapy post-operatively, and care should be taken that statin therapy is not unintentionally withdrawn in the peri-operative period.

Inflammation and Atherosclerosis

There is an important role of inflammation in the pathogenesis of atherosclerotic coronary disease which has been extensively investigated over the last 15 years. Definitely, there is at least some evidence to implicate inflammation in each step of the atherosclerotic process, from fatty streak formation to plaque progression and rupture. Among the numerous circulating inflammatory biomarkers that have been found to be variably predictive of cardiovascular events, the most widely studied and controversial has been the acute-phase reactant high-sensitivity C-reactive protein. Multiple studies have demonstrated C reactive protein to be an independent predictor of cardiovascular risk. Further, recent laboratory studies of intravenous C-reactive protein infusion in animal models and human volunteers demonstrated increased inflammation and atherosclerosis and activation of coagulation, providing evidence for a direct role of C-reactive protein in the pathogenesis of coronary artery disease. Statins have been recognized to have anti-inflammatory and antioxidant properties, and it has been suggested that these so-called “pleiotropic” effects may account for some benefits of statins beyond LDL-C lowering alone. Recent studies have shown that statins reduce inflammatory macrophage cell growth within atherosclendothelial nitric oxide synthesis [66].

RECENT STATIN THERAPIES

Neurohormonal activation

In human beings, with high levels of cholesterol chances of expression of angiotensin type 1 receptors also increases which in turn results into increased biological effects of angiotensin II [67, 68]. In this consideration, it is of particular interest that increased expression of cardiac angiotensin type 1 receptors is related to reduce myocardial micro vessel density after experimental myocardial infarction. Recently, there is demonstrated that vasoconstrictor responsiveness to angiotensin II can be modified by statin therapy in patients with diseased coronary arteries [69-72]. Oral treatment with statins inhibits rac1-GTPase activity and reduces angiotensin II induced NADPH oxidase activity, and subsequent oxidative stress, and therefore be of particular significance in the ventricles of CHF patients. As well as, statins can inhibit VEGF-induced ACE up regulation in endothelial cells [73] and enhance the efficacy of angiotensin receptor blockers. Besides the renin–angiotensin system, statins can also modify the sympathetic system. β-adrenergic receptor activity and delays the time of onset of cardiac decomposition in pacing-induced dilated β-Adrenergic receptor stimulation of cardiac myocytes leads to apoptosis [74].

Matrix metalloproteinase

Recent studies have documented that activated MMPs have a significant function in the CHF development. In experimental studies, production of MMPs was inhibited by statins. Inhibition of MMP attenuated cardiac fibrosis and failure in murine models. The clinical relevance of all of these potentially beneficial effects remains to be established in clinical studies [75-77].

ISSN: 0975-8585

Pleiotropic effects of statins

Pleiotropic effects are non-lipid lowering effects of statins which include anti-inflammatory property. This reverse endothelial dysfunction was shown by statins due to reduction of LDL oxidation and increase in nitric oxide bioavailability. Their antioxidant actions provide plaque stability, favours coagulation profile, prevent platelet aggregation and normalise sympathetic outflow. Their antiproliferative as well as immunesuppresive properties contribute to the non lipid lowering effects. These pleiotropic effects shown by statin therapy is more advantageous over the routine available drugs for dyslipidemias. These additional benefits not only find therapeutic application in cardiovascular disorder but also in many other disease states [78].

Statin Therapy with Ezetimibe or Niacin in High-Risk Patients

Statin reduce 30-40% of low density lipoprotein in high risk cardiovascular patients. But this is not satisfactory. Many patients continue to be risk so use of Ezitimibe or Niacin may be good alternative. Ezetimibe is the cholesterol absorbing drug .There are ongoing clinical trials on the use of Ezetimibe along with the statins. The second approach is to use Niacin along with statin. Niacin increases the HDL level so this combination is effective one [79].

FUTURE DIRECTION STATIN THERAPY

Now a days in elderly patients statins is prescribed more frequently. Therefore important issues will be drug interactions and polypharmacy . As one cytochrome P450 is major pathways for drug detoxification in the liver, the ideal statin would be metabolized by different metabolic pathway. Recently some statins are available and other statins those under development that possess these properties. Finally, the possibility of statin treatment working through a mechanism other than the reduction of cholesterol should be explored.

CONCLUSION

Statins reduce the cholesterol level as well as they have an important role in acute coronary syndrome, cardiovascular diseases. They prevent mortality and morbidity due high cholesterol level. Statins also have application in peri-operative diseases, inflammation. They also have some side effects like rhabdomyolysis, increased liver enzyme etc. The use of other drugs in combination may be more useful than only statin.

ACKNOWLEDGEMENT

Authors overwhelmingly acknowledge the services provided by our mentor, school of pharmacy, SRTMU, Nanded. Moreover I am deeply indebted to Dr. SG Gattani for his keen interest, all time moral support and suggestions in further improvement of my work.

ISSN: 0975-8585

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