Available Online at http://www.bjbmr.org

BRITISH JOURNAL OF BIO-MEDICAL RESEARCH

Cross Ref DOI: https://doi.org/10.24942/bjbmr.2020.744 Volume 04, Issue 06, Nov - Dec 2020

ISSN:2456-9739

Review Article

A Perspective Assessment On Statin Associated Adverse Events

Almaja Lekshmi[1], Sowparnika Treasa Sabu[2] and Prof. (Dr). Shaiju S. Dharan[3]

[1]Student, 5th Year PharmD, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences.
[2]Assistant Professor, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences.
[3]Principal, Ezhuthachan College of Pharmaceutical Sciences.

ARTICLE INFO

Article History:
Received on 17th Nov 2020
Peer Reviewed on 28th Nov 2020
Revised on 09th December 2020
Published on 29th December 2020

Keywords:
Statins, pleiotropic effects, adverse effects, alternative therapies

ABSTRACT

Statins are a class of cholesterol lowering agents that act by inhibiting the enzyme HMGCoA reductase which catalyzes the rate limiting step in cholesterol biosynthesis. The first statin to be discovered was named as compactin, but lovastatin became the first statin to be approved within the USA by Food and Drug Administration. Statins are associated with pleiotropic effects like anti-inflammatory, immunomodulatory, endothelial function, antioxidant, antiatherogenic and antithrombotic effects. Even though the benefit outweighs the risk, there are some adverse effects that include statin associated muscle symptoms, liver abnormalities, diabetes, cognitive impairments, cataracts and cancer. Some patients are not able to continue statin therapy due to certain adverse reactions. Alternative therapies are used in such statin intolerant patients that include switching to another statin, using intermittent statin dosage regimen or prescribing statins on alterative days or on once weekly dosage regimen, non statin lipid lowering drugs, new hypolipidemic drugs, mipomersen, microsomal triglyceride transfer protein, life style modifications, LDL apheresis and use of red yeast rice.

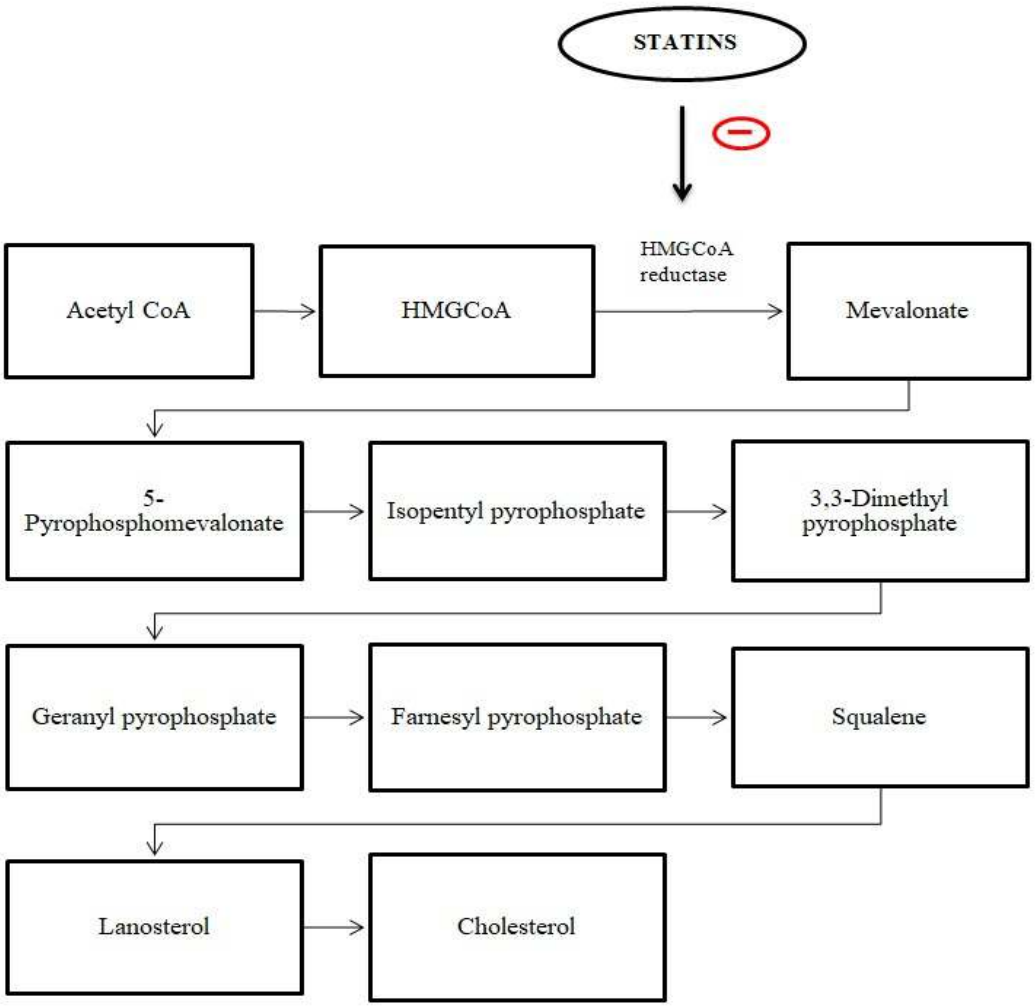
Corresponding Author: *Almaja Lekshmi, Student, 5th Year PharmD, Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences.*

INTRODUCTION

Statins are a class of cholesterol-lowering drugs that are known as the "gold standard" for treating high levels of harmful cholesterol and are one of the most widely prescribed lipid-lowering drug in the world for lowering LDL-C and helps in reducing cardiovascular morbidity and mortality, both in primary and secondary prevention.[1][2] Statins decrease harmful fats in the blood (low-density lipoprotein, cholesterol and triglycerides), while increasing beneficial cholesterol called high-density lipoprotein. Despite of the incredible contributions of statins, they may cause certain adverse effects. Statin users must be made aware of both the statin associated benefits and risks.

Statins block the enzyme in the liver that catalyzes the rate limiting step in cholesterol biosynthesis. This enzyme is known as hydroxy-methylglutaryl-coenzyme A reductase (HMG-CoA reductase). They inhibit the conversion of HMGCoA to mevalonate (Fig.1), and thereby upregulating LDL receptors and lowering LDL- cholesterol. Mevalonate is a substrate for the synthesis of non steroid isoprenoids which serve as the lipid attachments for intracellular signaling molecules that include Farsenyl pyrophosphate, Geranylgeranyl pyrophosphate, Coenzyme Q, Dolichol, Isopentanyl adenosine, heme-A which have major roles in the body and potential relevance to benefits as well as risks of statins.[3]

Fig 1: Inhibition of HMGCoA reductase by statins.



History of Statins

The discovery of statins was done by Akira Endo, a Japanese biochemist, while performing at the Sankyo Company in 1976. Akira Endo isolated a component from the fungus Penicillium citrinum which he identified as a competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase). This was named as compactin or mevastatin and it had been the first statin to be administered that showed to lower plasma cholesterol within the dog, rabbit and monkey. Compactin didn't lower plasma cholesterol in rats, which was subsequently demonstrated to result from massive induction of HMG-CoA reductase in rat liver by inhibitors of the enzyme.[4]

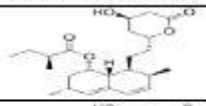
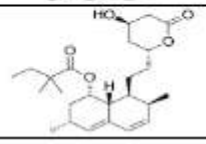
In 1978, Alfred Alberts alongside his colleagues at Merck Research Laboratories discovered a potent inhibitor of HMG-CoA reductase during a fermentation broth of Aspergillus terreus, which was named lovastatin, mevinolin or monacolin K.

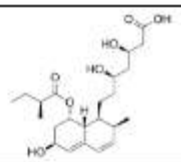
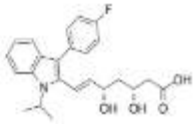
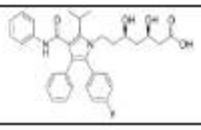
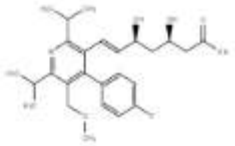
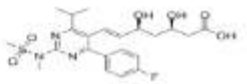
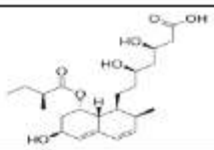
In April 1980, Merck began clinical trials of lovastatin after animal safety studies have shown no adverse effects. In 1983, Merck decided to re-initiate the clinical development programme, initially only in high risk patients with myocardial infarction since additional animal safety studies with lovastatin revealed no toxicity issues believed to be associated with compactin.[4]

On September 1, 1987 lovastatin became the first statin to be approved within the USA by the Food and Drug Administration (FDA). A side-chain ester analog was synthesized by researchers at Merck from lovastatin known as simvastatin with a 2.5 fold better activity in inhibiting HMG-CoA reductase activity, was approved in 1988 for marketing in Sweden. A substituted H-pyrrole compound, atorvastatin which was approximately 3-4 times stronger in rat models as compared to lovastatin was synthesized by investigators at Warner-Lambert.[5]

Statins including pravastatin, fluvastatin, atorvastatin, cerivastatin, and rosuvastatin are synthesized by different pharmaceutical companies.In 2012, the FDA introduced certain changes to the safety information on the labels of statins, including a little increased risk of upper blood sugar levels and eventual type 2 diabetes diagnosis. The statin labels also reports potential cognitive effects like confusion and amnesia experienced by some patients.

Table 1: Types of statins, patented and approval year, origin and its chemical structure.[6]

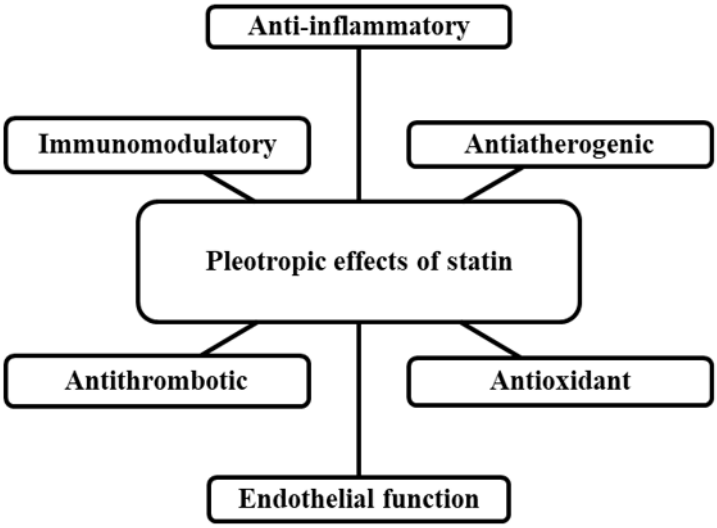
Statins	Patented and approval year	Origin	Chemical structure
Lovastatin	Patented in 1979 and approved for medical use in 1987	Natural	
Simvastatin	Patented by Merck in 1980 and came to medical use in 1992	Semisynthetic	

Pravastatin	Patented in 1980 and approved for medical use in 1989	Natural	
Fluvastatin	Patented in 1982 and approved for medical use in 1994	Synthetic	
Atorvastatin	Patented in 1986 and approved for medical use in the US in 1996	Synthetic	
Cerivastatin	It was marketed by Bayer A G Pharmaceutical Company in 1998. The US FDA announced that the Bayer Pharmaceutical Division had voluntarily withdrawn Baycol from US market due to the severe adverse effect, rhabdomyolysis on August 8,2001	Synthetic	
Rosuvastatin	Patented in 1991 and approved for medical use in US in 2003	Synthetic	
Pravastatin	Patented in 1980 and approved for medical use in 1989	Natural	

Pleiotropic Effects of Statins

The pleiotropic effects of statins may result due to the depletion of the isoprenoids. These effects have beneficial impact on CNS, bone and immune system. Adverse effects may occur in patients with abnormal protein glycosylation due to dolichol shortage, deficiency of coenzyme Q and selenoproteins, and impaired protein prenylation.[7] The pleiotropic effects of statins improve the function of endothelium, enhance the atherosclerotic plaque's stability, reduce the oxidative stress and inflammation, and inhibit the thrombogenic response.The membrane localization and function of the small GTP binding proteins – Rho, Ras, Rac are dependent on isoprenylation. So the inhibition of these small GTP binding proteins plays a major role in mediating the pleiotropic effects.[7]

Fig 2: Pleotropic effects of statins.



Mechanism of statin induced adverse effects

Statins acts by inhibiting the enzyme HMGCoA reductase which is responsible for the conversion of HMGCoA to Mevalonate. The mevalonate is the precursor for cholesterol and also for the non steroid isoprenoids like coenzyme Q 10, heme A, farsenyl pyrophosphate, and geranylgeranyl pyrophosphate.These intermediates have a main role in the benefits and risks of statin. Decreased synthesis of isoprenoid intermediates affects lipidation. The most important proteins affected are GTPases and Lamins. The dysprenylation of GTPases may result in vacuolation of myofibrils, degeneration and swelling of cellular organelles and sometimes cell death.[8] The protein isoprenylation reduction increases the concentration of cytosolic calcium and activation of caspase-3 causing cell death. Coenzyme Q 10 is the most common Coenzyme Q in human mitochondria. It acts as a cofactor in the electron transport chain, in the series of redox reactions that are involved in the synthesis of ATP. Decreased synthesis of Coenzyme Q 10 was associated with statin induced myopathy and the CoQ10 supplementation ameliorated SAMS.[9] Statin toxicity may occur due to reduced sarcolemmal cholesterol level. The skeletal muscle cell membrane stability is impaired and this leads to a reduction in cell proliferation and destabilizes muscle membrane.[10] Dolichols have a major part in the post- translational modification of proteins that are involved in the intracellular signaling. These are important for the cell growth and differentiation, cytoskeletal assembly, protein glycosylation and gene expression. Isopentylpyrophosphate is utilized in the synthesis of selenocysteine. Selenocysteine is required for the synthesis of selenoproteins which have a major role in the maintenance of cell, regeneration of skeletal muscle, thyroid hormone metabolism, oxidative and calcium homeostasis and immune response.[11]

Statin associated muscle symptoms (SAMS)

Based on the use and safety of statins, ACC/AHA/NHLBI clinical advisory divided statin associated muscle symptoms into myopathy, myalgia, myositis and rhabdomyolysis.[12]

- Myopathy: any disease of the muscle.
- Myalgia: the muscle aches or weakness without creatinine kinase elevation.
- Myositis: the muscle symptoms with increased levels of creatinine kinase.
- Rhabdomyolysis: the muscle symptoms with marked creatinine kinase elevations which is greater than 10 upper limit of normal.

Partially reversible mitochondrial myopathy was shown in persons with non-CK-elevating or minimally CK-elevating muscle symptoms on statins in a double-blinded, placebo-controlled, crossover biopsy study.[13] Decreased synthesis

of mevalonic acid from statin use results in decreased energy generation, which can cause muscle injury. Creatine kinase is an important enzyme for muscle function that acts as a marker for muscle damage when found in elevated levels within the blood. Myalgia, myopathy, myositis or at its most severe form of rhabdomyolysis, with some people reporting additional joint and abdominal pain, with blood creatine kinase levels at a minimum of ten times the traditional upper limit is usually defined as statin-induced myopathy.[14]

Skeletal-related side effects include tendon disorders, tendinopathies and arthralgia, although rarely evaluated in large randomized controlled trials.[14]Statins have also been shown to be environmental triggers for anti-HMG-CoA reductase necrotizing autoimmune myositis, a rare disorder characterized by severe muscle fiber death caused by an autoimmune response against the enzyme that statins target. This disorder only develops in individuals with an existing genetic susceptibility, but its severity and wish for immediate treatment with immunosuppressant drugs highlight the importance of familiarity with this disorder.

Rhabdomyolysis

Statins differ within the frequency with which they cause a serious form of myopathy called Rhabdomyolysis, during which muscles are severely damaged. Rhabdomyolysis often begins as muscle pain and may reach loss of muscle cells, renal failure, and death.

When skeletal muscle tissues are damaged, their components are weakened. These components are then released into the bloodstream to be filtered from the body. Of these components, some can cause kidney damage, most common being the protein pigment myoglobin which can block the complex tubing system of the kidney. If blockages become severe, kidney damage and failure can occur. Other cellular enzymes, especially creatine kinase (CK> 40 times the upper limit of normal), also put stress on the kidney. Damaged muscle tissues retain body fluids that cause dehydration and reduced blood flow to the kidney, thereby increasing the danger of organ damage. During statin treatment, rhabdomyolysis was initially reported in cardiac transplantation patients taking lovastatin with concomitant cyclosporine which were unexpected because animal safety studies had not indicated myotoxicity.[15]

Cerivastatin was approved with a maximum dose of 0.3mg per day which was then extended to 0.4mg and 0.8mg. With the post marketing surveillance, the upper doses of Cerivastatin (mainly 0.8mg) were found to possess a better risk of myopathy and rhabdomyolisis than other statins when given alone, but especially together with gemfibrozil because of drug interactions. Also the reduction of LDC-C was approximately 40% with the maximal dose. Although no cases of rhabdomyolysis occurred on cerivastatin in a meta-analysis of randomized trials, it was withdrawn from the market due to excess risk of rhabdomyolysis.[16] Rhabdomyolysis may occur more often in patients taking statins with other drugs that cause rhabdomyolysis or drugs that increase the blood concentration of the statin. Since rhabdomyolysis could also be fatal, unexplained joint or muscle pain that happens while taking statins should be delivered to the eye of a health care professional for evaluation.[17]

Liver abnormalities

Serious liver damage caused by statins is rare. Lovastatin may cause hepatocellular injury in rats and in rabbits it causes liver necrosis. Statins may be associated with mild transaminase elevations less than 3 times the upper limit of normal, sometimes in the context of nonalcoholic fatty liver disease or alcohol use.[15] In prescribing information of all statins, periodic measurement of transaminases were recommended until 2012, then the FDA issued a safety statement recommending transaminase measurement only before starting statin therapy and thereafter when clinically indicated. More often, statins cause abnormalities of liver tests. Abnormal tests usually return to normal when sustaining a statin, but if the abnormal test value is bigger than 3 times the upper limit of normal, the statin usually is stopped. Liver tests should be measured before starting the statin therapy and if

there occurs a medical concern about liver damage.[15]

Diabetes

Statin therapy increases the risk of diabetes and it mainly occurs in patients with pre-existing risk factors for diabetes like elevated HbA1c, elevated body mass index, and impaired fasting glucose.[18] Statins impair the insulin secretion by affecting the calcium channels in the pancreatic beta cells. The important downstream products are decreased due to statins that in turn reduces intracellular signaling. The inhibition of isoprenoids results in decreased glucose transporter-4 expression. Glucose transporter-4 facilitates the glucose uptake within the adipose tissue and skeletal muscles which is initiated by the phosphorylation of insulin receptor tyrosine kinase and recruit glucose transporter-4 from intracellular storage to the plasma membrane.[19] Increased incidence of diabetes was seen in people with elevated levels of high sensitivity CRP and LDL- cholesterol with rosuvastatin diagnosed by physicians in JUPITER (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin).[20]

Cognitive

It still remains a question whether the statins are associated with cognitive impairments or with protective effects. The phase I clinical trial of atorvastatin showed a dose dependent adverse effect on mild, transient, restlessness, euphoria and mental confusion.[21] The phase II and phase III statin clinical trial reported no significant cognitive impairment.[21] Researchers at the University of Bristol, England found that pravastatin and atorvastatin, which are the two commonly prescribed statins has reduced performance of recognition and memory in an animal study. The reported events are non serious and are reversible upon statin discontinuation, and the recurrence of cognitive impairment occurred with statin rechallenge.[22] In 2012, information regarding the potential for reversible cognitive side effects like memory loss and confusion has been added by FDA to the statin labels.[23]

Cataracts

Cataract refers to the clouding of the lens of eyes. Risk of cataracts was higher among the statin users when compared with non users. A research team at the San Antonio Military Center, Texas reported that statin usage increased the risk of developing cataracts by 27 percent.[24] Some of the studies have found the increased risk of cataract formation while some other showed a protective effect with statin use.[25,26]

Cancer

Uncertainty remains about the carcinogenicity of statins. Statins induce the transcription factor forkhead box P3 which leads to the increased number of regulatory T cells that may cause innate and adaptive host antitumor immune response impairment, mainly in elderly and individuals with a history of breast or prostate cancer.[27,28] Some of the clinical evidences suggest the use of statins in the prevention and treatment of cancer as it exerts several antineoplastic properties including reduced tumor growth, metastasis and angiogenesis.[29] Long term clinical trials and vigilant post marketing surveillance for a lot more years are needed to determine whether the statins prove to be carcinogenic in humans.[30]

Alternative Therapy For Statin Intolerant Patients[31]

i) Switching to another statin.
ii) Using intermittent statin dosage regimen or prescribing statins on alterative days or on once weekly dosage regimen. In a study patients intolerant to statins were given rosuvastatin every other day which was tolerated by majority of patients and the LDL-C level was also reduced.[32] Another study suggests the use of once weekly rosuvastatin therapy which might be a better option for patients intolerant to once daily dosing of statins.[33]
iii) Non statin lipid lowering drugs like ezetimibe, fibrates, bile acid sequestrants.
iv) New hypolipidemic drugs: LDL levels can be reduced with this new class of drugs which are expensive than other cholesterol drugs. The PCSK9 inhibitors are recommended for patients with familial cholesterolemia or at risk of developing heart attack or stroke, or

who are intolerant to statins due to severe adverse effects. The two FDA approved medications are alirocumab and evolocumab.[34] Some of the side effects include symptoms of cold/flu, pain and redness at the injection site, back pain.

v) Mipomersen: Antisense oligonucleotide inhibitor apolipoprotein B that reduces LDL and total cholesterol.[35] It is recommended in patients with homozygous familial hypercholesterolemia as an adjunct to diet and other lipid lowering medications. Some of the side effects include increase in liver enzymes and hepatic steatosis.[35]

vi) Microsomal triglyceride transfer protein inhibitor – lomitapide: indicated in homozygous familial hypocholesterolemia to reduce LDL-C, total cholesterol, apo B, and non HDL-C. Within the lumen of endoplasmic reticulum, lomitapide inhibits the microsomal triglyceride transfer protein, preventing the formation of apolipoprotein B, VLDL and chylomicrons and thus results in the reduction of LDL-C. It is contraindicated in pregnancy and in moderate to severe hepatic insufficiency.[34,36]

vii) Intensification of lifestyle modifications: There are several lifestyle changes that can help reduce LDL-C. LDL-C can be lowered with the help of a healthy diet with reduced saturated fat and trans fat, like the Mediterranean diet. The American Heart Association recommends the inclusion of moderate to vigorous exercise for about 40 minutes at least thrice weekly. Weight reduction can help to reduce the risk of vascular events for patients with high triglyceride levels. It is potentially an ideal combination to combining exercise and statin therapy substantially that may reduce the mortality risk in patients.[2]

viii) LDL apheresis: a non-surgical therapy that removes LDL-C from patient's blood by separating cholesterol containing plasma portion of blood which is passed through a machine.[37] The LDL apheresis systems are of five types- cascade filtration or lipid filtration, immunoadsorption, heparin induced LDL precipitation, dextran sulfate LDL adsorption, LDL hemoperfusion.[38]

ix) Use of red yeast rice: a traditional Chinese dietary supplement made by fermenting the yeast, Monascus purpureus, over rice.[39] These contain naturally occurring statin-monacolin K, that may help in the management of mild to moderate hypercholesterolemia in people with no additional cardiovascular risk factors.[40]

CONCLUSION

Even though the benefits of statins outweigh the risks, statin users must be vigilant for the potential adverse effects associated with statin therapy. The purpose of this review was to examine the potential adverse effects of statin and the alternatives for statin intolerant patients.

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How to cite this article:
Almaja Lekshmi, Sowparnika Treasa Sabu and Prof. (Dr). Shaiju S. Dharan *A Perspective Assessment On Statin Associated Adverse Events* Br J Bio Med Res , Vol.04, Issue 06, Pg.1308 - 1317, November - December 2020.
ISSN:2456-9739 Cross Ref DOI : https://doi.org/10.24942/bjbmr.2020.744

Source of Support: Nil **Conflict of Interest:** None declared.