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A REVIEW ON RISKS INVOLVED IN STATIN THERAPY

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ABSTRACT

There is a controversy going on statins concerning their safety in patients, since their introduction in 1987. Statins known to show a lot of beneficial effects in treatment. However, there are number of risks associated with statin therapy such as elevated blood sugar and enzyme levels, memory impairment, myopathy, rhabdomyolysis and congenital abnormalities. The diabetes risk should be taken into account only if statin therapy is considered for patients at low CV risk, the risk of diabetes mellitus was found to be minor when compared to cardiovascular benefits. Cognitive impairment such as memory loss was found from high dose use of statins and resolves on discontinuation of therapy. In statin therapy muscle toxicity is rare however creatine kinase (CK) levels should be monitored. It is advisable to avoid statins during pregnancy. Finally, overall benefits of statin therapy takes advantage over the risks.

Keywords: Statins, Cardiovascular disease, Risk, Cholesterol, Rosuvastatin

INTRODUCTION

Cardiovascular disease is one of the main leading cause of death in industrialized countries [(1)].The prevention and control of cardiovascular diseases is mainly depends on therapy with lipid-lowering agents, most commonly achieved with 3-hydroxymethyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) [(2)]. Statins, are a class of drugs particularly used to lower cholesterol levels, and most commonly prescribed medications in the world. The most common adverse effects of statins include myopathies, elevations of liver enzymes, and very rarely, rhabdomyolysis. Reduction of dose or discontinuation of drug usually leads to resolution of these adverse effects. There is a debate ongoing for past many years, whether statins are surely as safe as described in clinical trials. Recently, warning details of the label for all statins has exposited by U.S food drug administration. The FDA concluded serious liver injury with statins is uncommon and unpredictable in individual patients. For detecting and preventing serious liver injury and that routine periodical supervision of liver enzymes does not appear to be effective. Therefore, labels were drummed to remove the need for routine periodical supervision of liver enzymes [(3)]. The main risks of statins include memory loss, risk of diabetes, potential muscle damage and rarely liver injury. Adverse effects depends upon the dose, and health risks are exaggerated by a number of factors, such as Drug interactions that increase statin potency, Metabolic syndrome, Thyroid disease, Other genetic mutations linked to mitochondrial dysfunction.

Classification and Mechanism:

Usually statins are obtained by 2 ways

1. Fungal fermentation: lovastatin, pravastatin, simvastatin
2. Synthesis: fluvastatin, atorvastatin, cerivastatin.

Cerivastatin was withdrawn from world pharmaceutical market in 2001, as 31 patients died by acute renal failure caused by rhabdomyolysis. Cholesterol esters from LDL molecules are hydrolyzed in liver to free cholesterol. The liver also produces cholesterol by de novo synthesis by a pathway involving formation of mevalonic acid by the enzyme hydroxymethylglutaryl co-enzyme A-reductase (HMG-CoA reductase). Statins inhibit this rate limiting enzyme resulting in decrease in hepatic cholesterol synthesis, leading to increased synthesis of high affinity LDL receptors (up regulation) of the surface of liver cells leading to increased clearance of cholesterol-rich plasma LDL. This causes reduction in plasma LDL cholesterol. The hypolipidemic effect is dose dependent and is observed in 10 days. Full effect is usually observed in 6 weeks. Whereas simvastatin and atorvastatin, in addition, raise HDL level in some patients and lower the triglyceride levels.

The risk of diabetes: Generally Diabetes occurs due to the defects in the body's mechanism to produce or use insulin—which is a hormone, required to convert food into energy. If the pancreas are not in a position to produce enough insulin or if cells do not respond in a proper manner to insulin, blood sugar levels in the blood gets highly elevated, which may leads to serious health problems. From many review of findings, combined dose show that statins mostly elevates blood sugars levels. Diabetes mellitus was found to be more in patients with statin therapy when compared to those not on statin therapy. Although patients on statins have a greater risk of getting diabetes mellitus during the studies, simultaneously they also experience a substantial decline in cardiovascular outcome. Even though Diabetes mellitus was diagnosed in 27% of patients with statin therapy (rosuvastatin), the chances of getting heart attack was lowered by 54%, stroke by 48%and death from any other cause by 20% when compared to patients receiving placebo (medication without active ingredient). Risk and benefit must be considered at the same time on use of statins. Recent meta-analysis studies proposes that statin therapy might be related with a 9 percent growth in the risk of new onset of diabetes in comparison to placebo. Atorvastatin 80 mg reduced the number of CVD events both in patients at low and high risk for NOD in equivalence with low-dose statin. Gathering information from the 225 patients on statin use from different individual studies, one new extra case was found in 4 year study whereas 5.4 cardiovascular events were prevented. Regardless of statin use the other factors like older age, increased weight, higher blood sugar levels contribute in developing diabetes mellitus[4]. In patients without diabetes mellitus and receiving statin therapy, fasting blood sugar levels were increased by 3 mg/dl when compared to those not on statins[5]. Both atorvastatin and rosuvastatin increases haemoglobinA1c level by 0.3% in patients with DM [6]. Another study by Enas A. Enas. demonstrates that statin therapy provides overall remarkable benefit in primary prevention of events there by cardiovascular events and mortality largely depends on the decrease in the level of LDL-C The advantages of statin therapy far outweigh any possible serious adverse effects, even in people at very low risk of CVD events [7]. The risk of diabetes mellitus was found to be minor when compared to cardiovascular benefits which involves with reduction in heart disease and risk factors.

Risk of neurological impairment: FDA has been investigating numerous reports of cognitive impairment on use of statins for several years [5]. Based on international guidelines it was conclusive that statins are recommended for primary prevention of cardiovascular diseases and in secondary prevention of stroke also suggested to measure the cardiovascular risk in order to investigate the effectiveness of statins for primary prevention [7]. In a cohort of 4731 stroke patients on an randomized treatment with atorvastatin 80 mg/day or placebo with regardless of cholesterol level indicates who attained >50 percent of LDL-C (low density lipoprotein – cholesterol) has doubled the risk of ischemic stroke without any significant increase in hemorrhagic stroke. Pravastatin and rosuvastatin are hydrophilic statins which may less likely to impart cognitive impairment [8]. In patients with a history of intracerebral hemorrhage use of statins was cautioned. On use of statins several case reports and case series reveals that symptoms include short-term and long-term memory loss, behavioral changes, impaired concentration and attention, paranoia, and anxiety. Usually the cholesterol synthesis is required for the normal function of neurons, whereas statins inhibits cholesterol synthesis which results in neurocognitive effects [7]. In 2003 FDA released information regarding 60 case reports of memory loss on use of statins which was short term memory loss that happens on start of therapy or at high doses and resolves on discontinuation of therapy [9]. From the study Jukema et al. states out of 9 observational studies found Four studies exhibits beneficial effects, 3 studies shows no effect on cognitive function and 2 studies noticed an increased risk of cognitive impairment associated with statin use [10]. The meta-analysis results of 12 randomized clinical trials (RCT) shows a conclusive evidence that 9 RCT doesn't show any improvement in cognitive function

only 1 RCT shows a detrimental effect of statin use on cognitive function and 2 other studies shows a beneficial output in cognitive function. In view of the benefit of statins for reduction of cardiovascular events by 25% to 45%, cardiovascular benefit is outweighed by the small increase in relative risk, therefore, clinical practice for statin therapy should not be modified for patients with high or existing CVD risk. However, the newly identified diabetes risk should be taken into account only if statin therapy is considered for patients at low CV risk or for patient groups for which CV benefit has not been proven [(10)].

Risk of hepatotoxicity: Statins drugs work on liver to reduce the production of cholesterol, they are used in the treatment of chronic liver disease Even though there are no prominent studies of which reveals use of statins in chronic liver disease, physicians are cautioned about their use of statins in patients with liver disease. Serious liver damage is extremely rare, and Moderate asymptomatic hepatic transaminase elevations are common among patients with statin treatment. In all non-statin lipid-lowering therapies asymptomatic elevated levels of transaminase are common and believed to be as an outcome of lowering LDL-C and gets resolved with continued statin treatment. [(7)]. Commonly used statins like atorvastatin and fluvastatin found established elevations in aminotransferases within the first 12 weeks of therapy and reaches normal after discontinuation of therapy. In dyslipidemia patients about 50 per cent are having coexisting nonalcoholic fatty liver disease (NAFLD) – a condition well known for fluctuating transaminase levels. The post-hoc analysis of the GREACE trial explains that statin therapy is not only safe but also improves liver tests and reduces CVD morbidity in patients with mild-to-moderately abnormal liver enzymes that are potentially attributable to NAFLD [(11)]. A study which was conducted on 437 patients with moderate abnormal liver function (227 with statin therapy and 210 with non-statin), states that the liver enzymes levels were found to be significantly improved in patients with statin therapy and elevated liver enzyme levels were found in non-statin therapy. Amongst the patient with abnormal liver enzymes, 10 percent of CVD events occurred in patients with statin therapy and 30 percent of CVD events were occurred in patients with non-statin therapy. In comparison to people with normal liver function, the CVD risk reduction by 68% was considerably high in statin therapy patients [(7)]. Statin therapy should be avoided in conditions like cirrhosis, detoriating liver function, acute liver failure, alcoholic liver disease and heavy alcohol consumption. Liver damage and serious liver failure happens at a rate of one per million person-years, which is similar to the incidence in the normal population. No deaths have been reported to date due to liver failure despite the fact that more than a billion statin prescriptions have been filled all over the world during the past 26 years [(12, 13)]. The Food and Drug Administration (FDA) has finally recommends that liver damage is rare with statins and liver enzyme tests are to be performed before the statin treatment and then if any liver damage symptoms occur.

Risk of muscle damage:

Statins are the class of drugs that increases the tone of muscle injury called myopathy, characterized by unexplained muscle weakness or pain. In some middle aged and geriatric people muscle pain, creatine kinase levels are usually elevated even though statins are not in use [(14, 15)]. On use of statins fatigue with or without pain has also complained. However muscle toxicity is rare during the statin use [(16)]. While on administering statins in patients with myalgia creatine levels should be monitored. In most cases CK elevation may occur asymptomatically without myalgia. The term" myopathy" generally refers to a disorder of skeletal muscle which causes muscle weakness, with Difficulty in a raising arms above the head [(13)].Duration of statin therapy and the onset of myopathy may varies from a few weeks to more than 2 years [(14)]. Statin related myopathy shows a broad spectrum of disorders ranging from mild muscle aches to severe pain followed by restriction in mobility, and also raise in creatine kinase levels [(13)]. In statin clinical trials myopathy incidence was reported as low i.e., 0.1-0.2% [(13)]. Generally myopathy occurs in 10% of patients in clinical practice and 5 % of patients in clinical trials those who are treated with statins. It was observed that on patients with statin monotherapy severe myopathy is very rare [(13)]. A study provides an evidence that Patients receiving concomitant therapy with gemfirozil, niacin or cyclosporine, the incidence of myopathy with gemfirozil and lovastatin was 0.15% which then eventually increase to 2%, 5% and 28%. Myopathy risk varies in between high and low potency statins such as high risk with simvastatin and low risk with atorvastatin. The prevalence of myopathy in 250000 patients was 240 per million, nonetheless comparing 80 mg of atorvastatin daily by randomizing the patients with several standard regimens of statins or placebo [(19)]. National Lipid Association (NLA) recommends to measure the creatine kinase levels to those who are at high risk. [(20)]. "Rhabdomyolysis" is the breakdown of muscle tissue that leads to the release of muscle fiber contents into the blood. These substances are harmful

to the kidney and often cause kidney damage. Rhabdomyolysis is the severe form of myopathy and is very rare which is associated with statin therapy. As per the accordance to NLA definition, the condition of rhabdomyolysis when CK is >10xULN (upper limit of normal).is >2000 units [(20)]. Risk of rhabdomyolysis varies with different statins. With comparison to the increased risk of myopathy FDA has withdrawn the simvastatin 80 mg and approved rosuvastatin 80 mg dose. Apart from this, simvastatin doses was highly restricted by FDA [(13, 16, 20)]. If any symptoms of rhabdomyolysis occurs statin therapy should be immediately discontinued. About 90 percent of cases of patients gets fully recovered in few weeks and 10 percent is usual mortality rate. If a specific interaction has been entailed, it is better to start stain therapy again excluding the interacting drugs. Or else a lower dose or an alternate statin can be tried with monitoring patient closely [(22)].

Risk in pregnancy: There is fewer clinical and laboratory data available concerning the unexpected exposure of satins in human pregnancy [(23)]. In between 1987 and 2001 FDA identified 178 case reports of spontaneous exposure of pregnant women to statins, including 52 cases in first trimester out of which 20 reports of malformations followed by 4 reported cases with CNS defects and 5 cases of unilateral limb deficiencies [(24)]. Pharmacovigilance reports from Merck pharmaceutical company shows that statin exposure particularly lovastatin or simvastatin in pregnancy, identified 477 reports subjected to statin exposure only 225 cases were recorded. Out of 225 reports 154 were healthy infants followed by 49 were elective abortions, 18 were spontaneous abortions and 4 are fetal related deaths. Apart from these 6 congenital abnormalities were observed. Although the number of reports was relatively small, there was no evidence of an increase in congenital anomalies in children born to women exposed to simvastatin or lovastatin compared with the general population [(25)]. Although information to date is not about to conclude it is advisable to avoid statins during pregnancy and pregnant women exposed to cholesterol –lowering drugs to be monitored very closely.

Conclusion: Statins are a class of drugs particularly used to treat the cardiovascular diseases by lowering the cholesterol levels in the body. Likewise the other drugs statins also produce some adverse effects on long-term use, which are considered as the minimal effects when compared to the lifesaving beneficial effects of statins in patients with cardiovascular diseases. There are complaints of raised blood sugar levels and developing of type 2 diabetes should be considered and outweigh the risk benefit ratio on use of statins. Blood levels should be monitored before initiating therapy. The reports about memory loss and confusion are reversible with in few weeks after discontinuing statin therapy. Statins are not much hepatotoxic drugs and liver enzyme levels are monitored if such symptoms exist, or before the statin therapy. Creatine kinase (CK) levels should be monitored before starting therapy to high risk patients. If Rhabdomyolysis is noticed statin therapy should be discontinued immediately. Although reliable information is not available it is advised to avoid statins during pregnancy. Outweighing the risk and benefits of statins, statins are a good choice in lowering the cholesterol levels. Finally, statins are advantageous over their risks, it is highly suggested to use statins according to the requirement.

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