RESEARCH PAPER | Medical Science | Volume : 3 | Issue : 1 | January 2013 | ISSN - 2249-555X

A study on Statin use and Hepato-damaging effects

KEYWORDS

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ABSTRACT The beneficial role of Statins in primary and secondary prevention of coronary heart disease has resulted in their frequent use in clinical practice. However, safety concerns, especially regarding hepatotoxicity, have driven multiple trials, which have demonstrated the low or moderate incidence of statin-related hepatic adverse effects. The most commonly reported hepatic adverse effect is the phenomenon known as transaminitis, in which liver enzyme levels are elevated in the absence of proven hepatotoxicity. This class effect is usually asymptomatic, reversible, and dose-related. However, the increasing incidence of chronic liver diseases, including nonalcoholic fatty liver disease and hepatitis C, has created a new challenge when initiating Statin treatment in patients with high cardiovascular risk. These diseases result in abnormally high liver biochemistry values, discouraging Statin use by clinicians, fostering treatment discontinuation, and leaving a large number of at-risk patients untreated. In this study the CVD patients with and without history of liver disease were studied, who are Statin users. This review supports the use of Statin treatment in patients with high cardiovascular risk whose elevated aminotransferase levels should be closely monitored, while taking this medicine.

Introduction-

Ischemic heart disease and stroke are the predominant causes and are responsible for>80% of CVD deaths. The Global Burden of Disease study estimate of age-standardized CVD death rate of 272 per 100 000 population in India is higher than the global average of 235 per 100 000 population. India will soon bear the largest burden of heart disease globally: In India, out of the estimated population of more than 1.27 billion dispersed across various geographical regions, about 45 million people suffer from coronary artery disease. 'According to current estimates, India will soon have the highest number of cases of cardiovascular disease in the world,' says Dr Nikhil Kumar, Director, Cardiology, Fortis Memorial Research Institute, Gurgaon. It is estimated to account for 35.9% deaths by the year 2030.Heart disease is more prevalent in the younger generation: Heart disease has escalated among the younger generation with a significant risk in both males and females. 'More and more number of young Indians are suffering from coronary artery disease, owing to their poor lifestyle, and if this continues the future looks even more dangerous,' says Dr Kumar. 'Five years ago, we hardly saw young patients with heart problems. Now, we get many cases where people in the 25-35 age group are diagnosed with heart disease' said Dr Ajay Chaurasia, head of cardiology department, BYL Nair Hospital stated in the Saffola Life study.

Doctors often prescribe statins for people with high cholesterol to lower their total cholesterol and reduce their risk of a heart attack or stroke.

In high-risk cardiac patients, with dislipedemia and higher serum Cholesterol levels Statin therapy has become the standard of care. In fact, statins are the most efficacious drugs for decreasing low-density lipoprotein cholesterol levels; they reduce both primary and secondary cardiovascular risk in the general population. Statins are inhibitors of hydroxymethyl-glutaryl coenzyme A reductase, the enzyme that catalyzes the rate-limiting step of the cholesterol biosynthetic pathway. As a class, statins are among the most frequently prescribed drugs worldwide. Lovastatin was the first statin introduced (in 1987); since then, simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin, and pitavastatin (Livalo, Kowa) have been used clinically.

Clinical trials have shown that statin use has been associated with elevations in serum alanine aminotransferase (ALT) levels in approximately 23% of persons who take the drugs. Also enzymatic profiles of other enzymes are also observed disturbed due to use of drugs of Statin family and hampers the liver functioning capacity of the users.Also some other side effects were observed in some previous studies.

Hypothesis-Based on these findings I have designed one study to observe and analyze the effect of taking Statin as Serum lipid correcting drug on hepatic enzymatic profile and Liver function capacity (LFC) of some selected statin users. The users are divided in to two groups – one who were already prone for hepatic problems ,and who are started Stain for cardiac protection, and other group who were not having any hepatic problem initially before taking Statin.

Study Design-It was a case-control multicentre study.
Control- Statin Users, without any hepatic problem initially -20 patients
Experimental Subjects –With some history of hepatic problems and having marginally abnormal hepatic enzymatic profile.20 patients.
Duration of Study-8-12 weeks
Area- Bilaspur city and outskirt area.
Time- Sep 2012-Dec 2012.
Dose- Rosuvastatin, 10-20 and above 20 mgs/day
Methodology- The demographic data of all the subjects and controls were collected.

- The blood sugar of all the related persons were analyzed by using NYCOCARD.
- The Blood tests were done to assess the serum level of the following enzymes-

Volume : 3 | Issue : 1 | January 2013 | ISSN - 2249-555X

- Aspartate aminotransferase (AST or SGOT)
- Alanine aminotransferase (ALT or SGPT)
- Alkaline phosphatase, 5' nucleotidase,
- Gamma-glutamyl transpeptidase (GGT)
- LDH (Lactate dehydrogenase)

Biochemical Auto-analyzer Star 21 was used for the serum level analysis of these enzymes. The estimation kits of Span Diagnostics were used for the quantative analysis.

- Estimation of Coagulation panel (prothrombin time or PT), it was done by using Ink Spot method.
- Estimation of serum C-peptide level by using Method of Akita Aba.
- Estimation of serum Bilirubin level was done by using Autoanalyser –Star 21 model.
- Platelet count was done, by using Total Hematology chamber, DT 5000 of Mindrey company.

Observations-

TABLE-1 Hepatic Profile of both the Groups

Sr	Parameters	Controls with no History of Hepatic Illness	Participated	Experimentals with history of hepatic illness	Participated	Significant Difference
1.	Daily Statin Dose	**10 -15 mg**	20	**> 20 mg**	20	1.98
2.	Aspartate aminotransferase (AST or SGOT)	**139 Units /L**	20	**165 units /L**	20	1.322
3.	Alanine aminotransferase (ALT or SGPT)	**143 Units/L**	20	**229 /L**	20	8.066
4.	ALT/AST Ratio	**1.73 ± 1.31**	20	**2.84 ± 0.33**	20	2.09
5.	Alkaline phosphatase	**119 U/L**	20	**256 U/L.**	20	1.81
6.	gamma-glutamyl transpeptidase (GGT)	**81 U/L**	20	**99 U/L.**	20	4.41
7.	LDH (Lactate dehydrogenase)	**188 U/L**	20	**237 U/L**	30	1.005
8.	Prothrombin time	**21 Seconds**	30	**31 seconds.**	30	6.93
9.	Total Albumin	**2.2 g / dL**	30	**1.9 g/dL**	20	4.56
10.	serum Bilirubin	**3.4 mg/dL**	20	**4.18 mg/dL**	20	1.90
11.	Total Platelet Count	**228,000 /µL**	20	**167,000 /µL**	20	2.09
12.	CT	**computed tomography showed mild necrosis**	5	**computed tomography showed moderate necrosis**	5	--
13.	Ultra sound	**Grade -1 to 2 damage**	11	**Grade -3 to 4 damage**	9	--

TABLE-2 Correlation among Daily Statin Dose and different factors related to Liver Malfunctioning

Serial	Factors	Degree of correlation
1.	SGPT	0.7039
2.	GGT	0.6451
3.	Serum Albumin Level	-0.7089
4.	Serum Creatinine Level	0.4303
5.	Serum Bilirubin	0. 6612
6.	Platelet count	-0.7021
7.	Prothrombin time	-0.561

Other Side Effects

Serial No	Statin dose / Day	Effects	Percentage of studied persons affected
1.	20 mg	Muscular Pain	89%
2.	15-20 mg	Mental Confusion / memory Loss	74%
3.	15 mg - 30mg	Increased Blood Sugar Level	82%
4.	20 mg	C-Peptide level	72%
5.	30 mg	Serum Creatinine level	43%
6.	20 mg	Platelet count	39%
7.	20 mg	Prothrombin time	54%
8.	20 mg	Digestive upsets	67%

Factors related with Increased Risks of Side Effects

1.	Taking multiple medications to lower cholesterol
2.	Being female
3.	Having a smaller body frame
4.	Being age 65 or older
5.	Having kidney or liver disease
6.	Drinking too much alcohol

Discussion-In this study the higher dose of Statin has adverse effect but the dose limited to 10-15 mg /day is found almost safe. The elevation of hepatic enzymes is seem in almost all users, but became asymptomatic in low dose users, in patients with history of hepatic malfunctioning before the use of Statin affected more adversely. Apart from enzymatic profile of Liver , other parameters of LFT were also affected as serum Albumin level platelet count and clotting factors .Serum glucose level was found moderately elevated, showed the involvement of Statin with type –II Diabetes and serum C-peptide level was also elevated , showed Insulin resistance in users. The serum Creatinine level was observed high, showed that kidneys are also affected in users. Also females, aged patients, taking multiple therapy are precipitating factors for more severe side effects. The parallel use of other antibiotic, antifungal and some immunosuppressant medications have also added complications. The use of other mild forms of Statin are advised by clinicians to reduce the severity of complications as Lovostatin or Fluvostatin. Faced with the dilemma of managing the care of patients who have multiple comorbid conditions and who are receiving multidrug therapy, the primary care physician must customize treatment to each patient. Statin use and the associated decrease in levels of LDL cholesterol are of extreme importance for the primary and secondary prevention of CHD. In light of the significant reduction in the risk of life-threatening cardiovascular events that Statins provide, primary care physicians should not withhold Statin therapy from patients whose transaminase elevations , But close LFT monitoring is strongly recommended..

Volume : 3 | Issue : 1 | January 2013 | ISSN - 2249-555X

Thus, Clinical trial findings indicate that the overall risk of hepatotoxicity with Statins is moderate to severely high and it is dose and type of Statin related. A more detailed study community based study is required to conform the conclusions.

REFERENCES 1. Grundy SM, Cleeman JI, Bairey CN, et al. Coordinating Committee of the National Cholesterol Education Program, Endorsed by the National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, and American Heart Association Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines [published correction appears in Circulation.2004;110(6):763] Circulation 2004;110(2):227-239. |2. Pedersen TR, Kieksus J, Berg K, et al. Scandinavian Simvastatin Survival Study Group Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344(8934):1383-1389. |3. Stein EA. The power of statins: aggressive lipid lowering. Clin Cardiol. 2003;26(4)(suppl 3):III25-III31. |4. Forrester JS, Libby P. The inflammation hypothesis and its potential relevance to statin therapy. Am J Cardiol. 2007;99(5):732-738. |5. Argo CK, Loria P, Caldwell SH, Lonardo A. Statins in liver disease: a molehill, an iceberg, or neither?Hepatology 2008;48(2):662-669. |6. Bhardwaj SS, Chalasani N. Lipid lowering agents that cause drug induced hepatotoxicity. Clin Liver Dis.2007;11(3):597-613. |7. Chang CY, Schiano TD. Drug hepatotoxicity. Aliment Pharmacol Ther. 2007;25(10):1135-1151. |8. Tolman KG. The liver and lovastatin. Am J Cardiol. 2002;89(12):1374-1380. |9. Dujovne CA. Side effects of statins: hepatitis versus "transaminitis"–myositis versus CPKitis. Am J Cardiol. 2002;89(12):1411-1413.