Original Article

# Evaluation of Atorvastatin Safety on Liver Function Tests, a Prospective Study

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## Abstract

**Background:** Although lipid lowering agents as statins are used frequently in hyperlipidemic patients as well as patients with cardiac disease, they could have major hepatic side effects, the aim of this study is to evaluate the safety of statins mainly atorvastatin on liver as estimated by liver aminotransferase assay.

**Materials and Methods:** Patients with indication of atorvastatin were included the study. As a before and after study all the patients underwent serum level measurement of aminotransferases at the beginning and after three month of taking the drug.

**Results and Conclusion:** HMG-COA reductase as atorvastatin should be safe in different doses 20,40 and 80 mg in patient with hyperlipidemia with and without cardiac disease without significant hepatotoxicity.

**Keywords:** HMGG-COA reductase, hepatotoxicity statins, atorvastatin

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## Introduction

There are multiple cardiovascular risk factors that among them hypercholestrolemia as well as diabetes and hypertension are increasing in many populations[1]. In patients with obesity and metabolic syndrome there would be increase in fat deposition in the liver producing fatty liver. Non-alcoholic fatty liver disease (NAFLD) encompasses a wide spectrum of liver injury. Currently, there are no proven effective therapies available. Atorvastatin is a new 3-hydroxy-3-metylglutaryl coenzyme a reductase inhibitor that reduces lipid serum levels[2]. In both situations due to increased risk of cardiovascular disease and liver damage,lipid lowering agents should be prescribed to correct the lipid abnormalities. Statins are highly effective in lowering serum cholesterol concentrations and preventing ischemic heart disease[3]. Statins, ezetimibe, and bile acid-binding resins can be used individually or in combination for lowering lowdensity lipoprotein cholesterol (LDL-C) levels. Statins are the most potent drugs for lowering LDL-C and are well tolerated in most patients. Drug induced hepatotoxicity is understimated in many parts of the world, and lipid lowering agents are among the list of the culprits.Since 2001, an ALT level of >3 x ULN and a total bilirubin level of >2 x ULN has been used in combination to define clinically-significant abnormal liver function, with confirmation required by additional clinical and laboratory data[4]. *P* Hence, an isolated elevated level of transaminases does not necessarily indicate hepatotoxicity, and an increase of 3 x ULN may not be a sufficient biochemical criterion of hepatic lesion because of the considerable capacity of the liver to withstand damage[5,6]. *P*Consumption of 3-hydroxy-3-

methylglutaryl coenzyme A reductase (HMG-CoA) inhibitors, known as statins, has been associated with elevated transaminase levels but rarely with acute hepatitis. Recently, several cases of acute hepatitis secondary to atorvastatin therapy have been published[7-12]. They reported a case of a 72-year-old man who developed acute cholestatic hepatitis after reinitiatingtreatment with atorvastatin at a higher dose than that previously prescribed. After treatment discontinuation, the patient made a full recovery, with normalization of clinical and laboratory findings[13]. The aim of this study was to evaluate any possible injury to the liver by using HMG CO-A reductase inhibitors as determined by biochemical measurement.

## Methods

We conducted the study in 250 patients with hypercholestrolemia and cardiac disease in cardiology ward or clinic of Modarres hospital. All the patients with clear indication for HMG-COA reductase took atorvastatin and after three months the level of aminotransferases were measured. Patients with history of alcohol use,known liver diseases, like hepatitis,decompensated heart failure or hemodynamic instability, taking medications with the elevation of liver enzymes as their side effects like valproate, were excluded. We also excluded patients with prior elevated liver enzymes, but giving another class of lipid lowering agent due to ethical consderation. It was a before and after study that the serum level of transaminases were measured both before and after taking atorvastatin.

**Statistical Analysis**

All analysis were performed by SPSS version sixteen.

We used student t–test for evaluating the relationship among quantitative variables of the study and Chi2 square of qualitative ones.

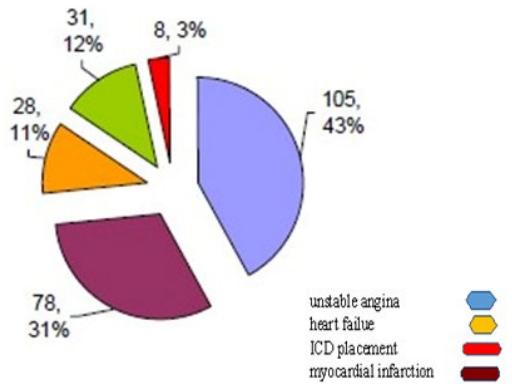


**Figure 1. The frequencies of patients with different cardiac disease taking Atrovastatin**

## Results

The incidence of increased aminotransferase level in patients on atorvastatin was 18 percent. It was 3.6 and 10 percent respectively in our patients taking 20, 40 and 80 mg of atorvastatin. Ten patients from all of 250 patients (4%) had more than 3 times increase in liver transferases that the medication was discontinued. Two percent for patients taking less than 80 mg atorvastatin and 5 percent of patients on 80 mg of the drug had more than 3 times elevation in aminotransferase level but the difference was not statistically significant (p=0.4). Age distribution of the patients was between 40 to 80 years old in 86.6%. Age and sex had no impact on atorvastatin induced elevation of transaminases.

## Discussion

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or statins are potent inhibitors of cholesterol biosynthesis.The overall clinical benefits observed with statin therapy appear to be greater than what might be expected from changes in lipid profile alone, suggesting that the beneficial effects of statins may extend beyond their effects on serum cholesterol levels[14]. Bader et al. described the significance of statins in treatment of hyperlipidemic patients and they found that elevated aminotransferases with statins was dose dependent a base line LFT may be done before starting statins and that is even not necessary for asymptomatic patients without a history of liver disease using lovastatin[15]. However, these guidelines may seem to be optional as there is no evidence that monitoring reduces the rate of hepatotoxicity[16-23]. Chalasani et al. retrospectively evaluated the hepatotoxicity risk in subjects treated for at least 6 months with atorvastatin,simvastatin or fluvastatin. Drawn from the pharmacological registry of an insurance company, the subjects were segregated into two groups: one group with elevated transaminases before treatment (cohort I; n=342) and another group with normal levels of transaminases (cohort II; n=1435)[24-32].

The frequency of elevated aminotransferase is <1% for low-to-moderated doses (40mg) and reaches 3% for high doses (80 mg). Therefore, the risk of suffering

from liver failure as a consequence of this class of drugs, is low i.e. approximately about 1 per million, according to notification to regulatory authorities [33]. In a meta-analysis of randomized clinical trials (RCTs) of fluvastatin, pravastatin, lovastatin and simvastatin at low or moderate doses (<40 mg oral), the prevalence of elevated transaminases >3 x ULN was similar in the active treatment groups compared to the placebo groups, but only slightly higher in two studies of fluvastatin versus placebo (1.13% vs. 0.39%, p=0.04)[35]. However, atorvastatin despite being the mostprescribed statin had not been included in this meta-analysis. When analyzing large-scale RCTs where high-dose atorvastatin was used (80 mg oral), the prevalence of asymptomatic elevations of transaminases >3 x ULN was slightly higher (3%) compared to placebo, or with another statin at moderate dose. Statin use is associated with a significant reduction in the risk of HCC among patients with diabetes. Patients with hepatitis c as well as autoimmune hepatitis may be confounding for liver aminotransferase level evaluation, so excluded from the study.

In this trial we also exclude patients with baseline elevation of aminotransferase level but Vuppalanchi et al, showed that significant hepatotoxicity from lovastatin was very infrequent in this study, and individuals with elevated baseline liver enzyme levels did not have higher frequency of lovastatin hepatotoxicity than those with normal liver enzyme levels. Lucena et al. showed that neither old age nor female sex had now influence on severity of drug induced liver injury as our study .Cohen et al showed that there is no evidence that statin therapy should be altered or discontinued solely on the basis of elevated aminotransferase levels in an asymptomatic patient. Should more objective evidence of hepatic dysfunction be identified, such as hepatomegaly, clinical evidence of jaundice,elevated direct bilirubin, or increased prothrombin time, discontinuation of statin therapy ought to be considered. Our study again showed that atorvastatin use in patients with cardiac disease would be safe and in comparison to literature reviews, aminotransferase elevation to more than 3 times occurred in 4 percent of our patients. In conclusion this study showed that use of statins at high dose in patients with cardiac disease would be safe.

# References


1. Justin L. The Increasing Incidence of Coronary Artery Disease and Cardiovascular Risk Factors among a Southwest Native American Tribe. ARCH INTERN MED. 2002;162-5.
2. Parra JL, Reddy KR. Hepatotoxicity of hypolipidemic drugs. Clin Liver Dis. 2003;7:415-33.
3. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review.
4. Cder-phrma. AASLD Conference 2000: clinical white paper on drug-induced hepatotoxicity.
5. Hardisty JF, Brix AE. Comparative hepatic toxicity: prechronic/ chronic liver toxicity in rodents. Toxicol Pathol. 2005;33(1):35-40.
6. Navarro VJ, Senior JR. Drug-related Hepatotoxicity. N Engl J Med. 2006;354:731-9
7. Cohen DE, Anania FA, Chalasani N. An assessment of statin safety by hepatologists. Am J Cardiol. 2006;97:77-81.
8. Hou R, Goldberg AC. Lowering low-density lipoprotein cholesterol: statins, ezetimibe, bile acid sequestrants, and combinations: comparative efficacy and safety. Endocrinol Metab Clin North Am. 2009;38:79-97.
9. Pugh AJ, Barve AJ, Falkner K, et al. Drug-induced hepatotoxicity or drug-induced liver injury. Clin Liver Dis. 2009;13:277-94.
10. Wilson JP, Omar MA و Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. Ann Pharmacother. 2001;35(9):1096-107.
11. Talbert RL. Safety issues with statin therapy. Journal of the American Pharmacists Association: JAPhA. 2006;479(2):46-9.
12. Nakad A, Bataille L, Hamoir V, Sempoux C, Horsman Y. Atorvastatin-induced acute hepatitis with absence of cross-toxicity with simvastatin. Lancet 1999;353(9166):1763–4.
13. De Castro ML, Hermo JA, Baz A, de Luaces C, Perez R, Clofent J. Acute cholestatic hepatitis after atorvastatin reintroduction. Gastroenterologia y Hepatologia. 2006;29(1):21–4.
14. Gershovich OE, Lyman AE. Liver function test abnormalities and pruritis in a patient treated with atorvastatin: case report and review of the literature. Pharmacotherapy. 2004;24(1):150–4.
15. Jimenez-Alonso J, Osorio JM, Guierrez-Cabello F, de la Osa AL, Leon L, Garcia JDM. Atorvastatininduced cholestatic hepatitis in a young woman with systemic lupus erythematosus. Archives of Internal Medicine. 1999;159(15):1811–2.
16. Takemoto M, Liao JK. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors, Arterioscler Thromb Vasc Biol. 2001;21:1712-19.
17. Jones PH, Davidson MH, Stein EA, Bays HE, Miller E, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). Am J Cardiol. 2003;92:152.
18. Aviram M, Dankner G, Cogan U, et al. Lovastatin inhibits LDL oxidation and alters its fluidity and uptake by macrophages: in vitro and in vivo studies. Metabolism. 1992;41:229–35.
19. Chen L, Haught WH, Yang B, Saldeen TG, Parathasarathy S, et al. Preservation of endogenous antioxidant activity and inhibition of lipid peroxidation as common mechanisms of antiatherosclerotic effects of vitamin E, lovastatin and amlodipine. J Am Coll Cardiol. 1997;30:569–75.
20. Kimura M, Kurose I, Russell J,Granger DN. Effects of fluvastatin

on leukocyteendothelial cell adhesion in hypercholesterolemic rats. Arterioscler Thromb Vasc Biol. 1997;17;11521–6.
21. Lehr HA, Seemuller J, Hubner C, Menger MD, Messmer K. Oxidized LDL-induced leukocyte/endothelium interaction in vivo involves the receptor for platelet activating factor. Arterioscler Thromb. 1993;13:1013–18.
22. Saito Y, Yoshida S, Nakaya N, Hata Y, Goto Y. Comparison between morning and evening doses of simvastatin in hyperlipidemic subjects. A double-blind comparative study. Arterioscler Thromb. 1991;11:816.
23. Bader T. Liver tests are irrelevant when prescribing statins. Lancet. 2010;376:1882-3.
24. Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology. 2013;144:1419-25.
25. Björnsson E, Jacobsen E, Kalaitzakis. Hepatotoxicity associated with statins: Reports or idiosyncratic liver injury post-marketing. J Hepatol. 2012;56:374-80.
26. El-Serag HB, Johnson ML, Hachem C, Morgano RO. Statins are associated with a reduced risk of hepatocellular carcinoma in a large cohort of patients with diabetes. Gastroenterology. 2009;136:1601-8.
27. Lucena MI, Andrade RJ, Kaplowitz N, García-Cortés M, Fernández MC, RomeroGómez M, et al. Phenotypic characterization of idiosyncratic drug- induced liver Injury: The influence of age and sex. Hepatology. 2009;49:2001-9.
28. Andrade RJ, Lucena MI, Fernández MC, Peláez G, Pachkoria K, García-Ruiz E, et al. Drug-induced liver injury: An analysis of 461 incidences submitted to the Spanish Registry over a 10-year period. Gastroenterology. 2005;129:512-21.
29. FDA Guidance for Industry, Drug-induced liver injury: Premarketing Clinical Evaluation (Issued July2009).
30. Chalasani N. Statins and hepatotoxicity: focus on patients with fatter liver.Hepatology. 2005;41:690-5.
31. Cueto R, Valdivielso P, Lucena MI, García-Arias C, Andrade RJ, González-Santos P.Statins: Hepatic disease and hepatotoxicity risk. Open Gastroenterol J. 2008;2:18-23.
32. Russo MW, Scobet M, Bonkovsky. Drug-induced liver injury associated with Statins.Semin Liver Dis 2009;29:412-22.analysis. BMJ. 2003;326:1423.
33. Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol. 2006;97(8A):52C-60C.