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ORIGINAL ARTICLE

Effect of Acute Versus Gradual Dosing Of Atorvastatin Regarding Liver Enzymes In Chronic Renal Patients

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ABSTRACT

Keyword: atorvastatin, chronic kidney disease, CKD, liver enzyme, ALT, AST.

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Background and Aim: Chronic kidney disease (CKD) progression is related to poor outcomes, elevated CVD complications, kidney failure, and early death. Atorvastatin is the primary therapy for preventing atherosclerosis and cardiovascular disease (CVD) by reducing hypercholesterolemia. This study evaluates the effect of acute versus gradual atorvastatin dosing on liver enzymes in chronic kidney disease cases. **Methodology**: Conducted from March to October 2023, the study included 102 patients divided into two groups (fifty-one each). Group (A) received an immediate high dose of atorvastatin (eighty milligram), while Group (B) started at 5 mg, increasing by 10 mg every four weeks. The study lasted six months from the maximum tolerated dose. Group (A) continued high-intensity atorvastatin for six months. **Results**: Among 102 patients (sixty-one men, 59.8 percent, & 41 women, 40.2 percent), mean age 58.25 ± 10.34, liver function (ALT, AST) showed a significant distinction among groups (P = 0.007, 0.000, respectively). **Conclusion**: Gradual atorvastatin initiation is Better tolerated in comparison with immediate high-dose treatment in cases with CKD. These findings support initiating treatment with a low dose and progressively elevating it to enhance tolerance and preserve hepatic function.

INTRODUCTION

Chronic kidney disease is defined by kidney abnormalities continuing for more than three months, indicated by a glomerular filtration rate (eGFR) below sixty millimeters per minute /1.73 m^2, and a progressive decrease in kidney function, demanding renal replacement therapy, including transplantation or dialysis. [1, 2].

CKD is one of the few non-communicable diseases (NCDs) that has exhibited an elevation in death over the past two decades, emerging as a predominant cause of death globally [3]. Hypertension and diabetes are the primary etiologies of chronic kidney disease; however, other factors such as glomerulonephritis, infections, and environmental exposures are prevalent in Asia and developing countries. Genetic risk factors, including sickle cell trait and two APOL1 risk alleles, may elevate the possibility of chronic

kidney disease in cases of African descent. Additionally, a familial history of renal failure, age of sixty years or older, tobacco use, obesity, nephrolithiasis, and CVD are significant risk factors; nevertheless, viral, autoimmune, genetic, obstructive, and ischemic injuries are all common causes. [1, 4].

Chronic kidney disease may be one of the outcomes of cases with CVD or vice versa. CKD patients are at a greater possibility for developing CVD than those with existing coronary heart disease. Hyperlipidemia is prevalent in CKD and It is expected to exceed forty percent in cases with renal failure [5]. The lowest levels of HDL-C have been correlated with a greater possibility of renal failure; however, no association has been identified between NHDL-C, TC, or TG and kidney failure [5].

Chronic kidney disease cases with Lipid abnormalities have showing elevated triglycerides, diminished high-density lipoprotein cholesterol, elevated apolipoprotein B concentrations, and reduced apolipoprotein A1 concentrations. Patients with nephrotic syndrome exhibit greater concentrations of low-density lipoprotein cholesterol (LDL-C). In cases with mild CKD and without nephrotic syndrome, the lipid profile reveals reduced HDL-C concentrations ,normal LDL-C concentrations and increased triglycerides [6].

Atorvastatin medications is utilized in the controlling and treatment of hypercholesterolemia Clinical trials indicate that statins are becoming recognized as a 1ry treatment for the prevention of atherosclerosis and CVD in both 1ry and 2ry settings [7]. A recent study indicates that atorvastatin medication, in contrast to standard care, lowered the relative possibility of initial CVD occurrence by twenty-eight percent in cases with chronic kidney diseases and by eleven percent in those without chronic kidney disease [8].

Dyslipidemia resulting from renal dysfunction is the predominant consequence in individuals with CKD, exacerbating damage of kidney and the reduction of kidney function. The prompt initiation of lipid controlling medication in cases with chronic kidney disease is essential and well-accepted [9].

Statin-induced liver impairment is often dose- & time-dependent and may resolve with withdrawal of the medication; hence, the possibility of chronic hepatitis is minimal. [10, 11]. epidemiological investigations indicate a correlation among increased liver enzyme concentrations and coronary heart disease (CHD). The population-based Hoorn investigation in the Netherlands indicated that elevated baseline serum ALT concentrations forecast an augmented possibility for coronary heart disease. Hyperlipidemic cases exhibiting mildly-to-moderately raised ALT concentrations could receive larger advantages from rigorous statin therapy compared to those with normal ALT concentrations [12].

Our objective is to assess the impacts of acute versus gradual statin dose introduction in cases with chronic kidney disease, specifically examining the effects on the muscles and liver to enhance protection of the kidneys and CVD.

SUBJECTS AND METHODS

This prospective investigation has been conducted at Aswan University Hospital in Aswan, Egypt. The Institutional Review Board (IRB) at the Faculty of Medicine, Aswan University received ethical permission for the present investigation. Before inclusion in the investigation, the goals and characteristics of the investigation, together with the associated hazards, have been explained to the cases, & written informed consent has been collected from all participants. The identification details of all subjects have been preserved in confidentiality and preserved from public access.

From March 2023 to October 2023, 100 and 2 cases were chosen from the outpatient clinics of Internal Medicine Department at Aswan University Hospital. The calculation was performed utilizing Open Epi software, with a confidence concentration of 95% and a power of ninety percent. This related to the frequency of major adverse cardiac events (MACE) among cases who have CKD, with a rate of 25.2 percent among those receiving statins compared to 58.1 percent in the general CKD population. Cases not administered statins [13].

All cases have been evaluated for baseline characteristic, involving sex, age, BMI, and history of DM and hypertension. Certain laboratory assessment, including liver profile (ALT, AST).

Cases with CKD having medical treatment with statins have been involved in the investigation, while those on long-term lipid-lowering therapy prior to admission, who died through hospitalization, who had end-stage renal disease demanding peritoneal dialysis or hemodialysis, or who presented with cardiogenic shock, hemodynamic instability or acute ST-segment elevation myocardial infarction (STEMI) have been excluded.

Cases have been divided into two groups, each comprising fifty-one cases. Group (A) has been received an elevated dose of atorvastatin (eighty milligrams) from beginning. Group (B) has been received a low beginning dose of atorvastatin (five milligrams), which has been subsequently raised every four weeks. Participants received either high-dose statins (atorvastatin eighty milligrams), considered safe by the American Journal of Cardiology, or a reduced dose (five milligrams), with increases in the dose occurring every four weeks. The monitoring period was six months, beginning from the administration of the highest tolerable statin dose. The up-titration approach included enhancing the statin dose by ten milligrams weekly. The high-intensity statin group has been treated for a duration of six months from the start.

Statistical Analysis:

Categorical and continuous data have been reported as number (%) & mean ± standard deviation (SD), with t-tests utilized for parametric variables and Wilcoxon tests for non-parametric variables to evaluate group differences (CKD vs CAD + CKD). The test of Chi-square has been utilized to compare categorical variables. The rate of long-term event-free has been assessed utilizing Kaplan-Meier curves, & the test of log-rank has been utilized to recognize significant distinctions in survival rates among the 2 groups. A univariate Cox regression model has been utilized to determine the relevant factors affecting the frequency of CVS events. A multivariate Cox regression analysis has been done to identify the independent factors. Hazard ratios and their related ninety five percent confidence intervals have been utilized to determine the extent of the possibility of cardiovascular events. All statistical analyses have been done as two-tailed tests. A P-value under 0.05 has been considered statistically significant. All statistical analyses have been conducted utilizing SAS 9.1 (SAS Institute, Cary, USA, NC).

RESULTS

The current investigation has 100 and 2 participants, consisting of sixty-one males (59.8 percent) and forty-one women (40.2 percent), with a mean age of 58.25 ± 10.34 years and a mean BMI of 25.32 ± 3.37. The participants were classified into two groups; Group A comprised 62.7 percent males, with an

average age of 60.92 ± 13.80 & a mean body mass index of 24.75 ± 3.23. In Group B, 56.9 percent of cases were men, with an average age of 56.22 ± 4.14 years and a mean body mass index of 25.89 ± 3.45. No statistically significant distinctions exist among the two examined groups according to gender, age, and body mass index (P-values equal to 0.086, 0.545, 0.087, respectively). **(Table 1).**

Table (1): Comparative analysis among both groups with h regard to demographic data.

	Total (number=102)	**Group (A) (number=fifty one)**	**Group (B) (number=fifty one)**	**Test**	**P value**
Age (years)				2.021	0.086
Mean ± standard deviation	58.25 ± 10.34	60.92 ± 13.80	56.22 ± 4.14		
Min - Max	26 – 85	26 – 85	49 – 62		
Sex				0.367	0.545
Male	61 (59.8%)	32 (62.7%)	29 (56.9%)		
Female	41 (40.2%)	19 (37.3%)	22 (43.1%)		
Body mass index (kg/m^2)				-1.728	0.087
Mean ± standard deviation	25.32 ± 3.37	24.75 ± 3.23	25.89 ± 3.45		
Min - Max	18.6 – 32.8	18.6 – 32.8	19.4 – 32.8		

T: Two-Sample Independent t-Test X^2: Chi-square test, p-value above 0.05: nonsignificant, p-value under 0.05 significant.

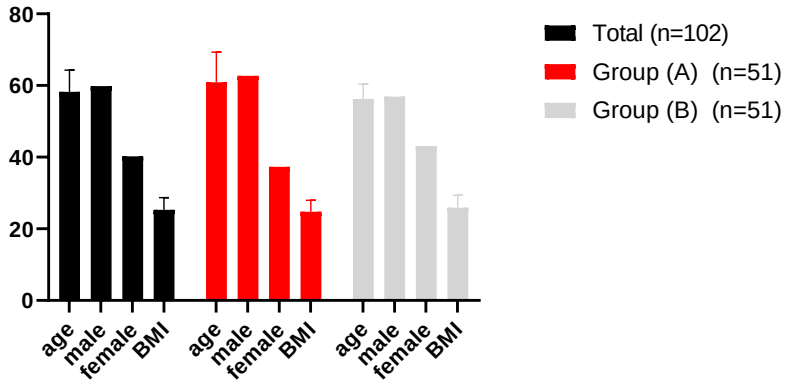
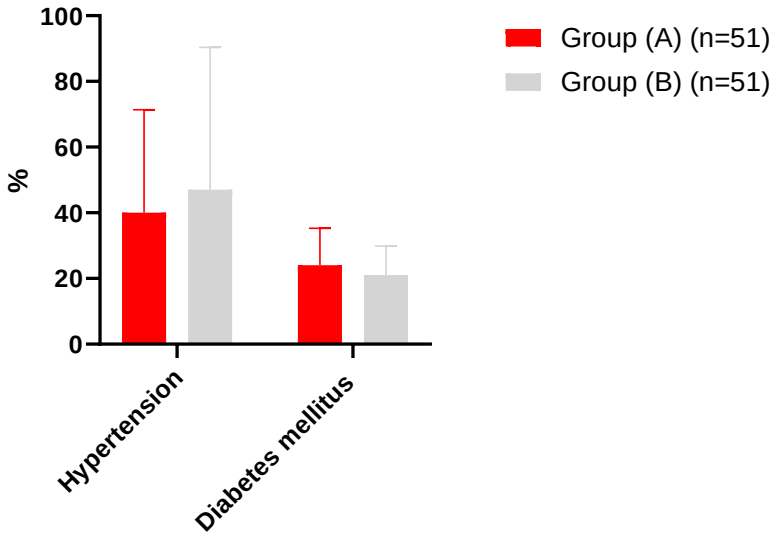


Figure (1): Comparison between both groups as regards demographic data.

Regarding comorbidities, 78.4 percent of group A had hypertension & 47.1 percent had DM, but in group B, 92.2 percent had hypertension & 41.2 percent had DM. There is statistically insignificant distinction in comorbidities among the two examined groups (P-values = 0.060, 0.550, respectively) **(Table 2)**.

Table (2): Comparative analysis among both groups according to medical data.

	Group (A) (number=fifty one)	**Group (B) (number=fifty-one)**	**Test**	**P value**
Hypertension	40 (78.4 percent)	47 (92.2 percent)	3.830	0.060
Diabetes mellitus	24 (47.1percent)	21 (41.2 percent)	0.358	0.550



Figuer(2): Comparison between both groups as regards medical data.

In group A's liver function test findings, the mean ALT was 26.58 ± 21.45, & mean AST was 31.67 ± 22.63. In group B, mean ALT was 32.27 ± 2.73, & the mean AST was 31.78 ± 4.83. A statistically insignificant distinction has been observed between the two examined groups for baseline liver function (P-values equal to 0.063, 0.972, correspondingly) (Table 3). Concerning the monitoring profile, in group A, the mean ALT was 54.59 ± 21.41, & the mean AST was 57.83 ± 17.89. In group B, the average ALT was 45.78 ± 7.33, & the mean AST was 46.06 ± 7.96. A highly statistically significant distinction exists between the two examined groups for liver profile monitoring (P-values equal to 0.007, 0.000, respectively). **(Table 4).** In compare between the baseline of the study and regards the follow-up profile after 6 months, there were a significant elevation ALT and AST in the both group **(Table 3, 4)**.

Table (3): Comparative analysis among both groups according to baseline hepatic function.

	Group (A) (number=fifty-one)	**Group (B) (number= fifty-one)**	**Test**	**P value**
ALT (U/L)			- 1.882	0.063
Mean ± standard deviation	26.58 ± 21.45	32.27 ± 2.73		
Min - Max	4 – 143	27 – 37		
AST (U/L)			- 0.035	0.972
Mean ± standard deviation	31.67 ± 22.63	31.78 ± 4.83		
Min - Max	8.3 – 132	22 – 41		

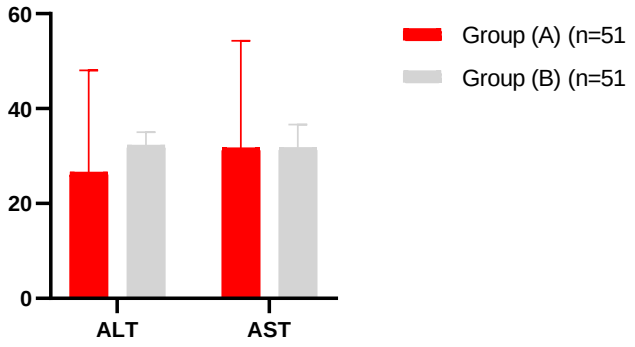


figure (3): Comparison between both groups as regards baseline liver function.

Table (4): Comparative analysis among both groups according to monitoring liver profile.

	Group (A) (number= fifty-one)	**Group (B) (number= fifty-one)**	**Test**	**P value**
ALT (U/L)				
Mean ± standard deviation	54.59 ± 21.41	45.78 ± 7.33	2.778	0.007
Min - Max	12 – 97	33 – 62		
AST (U/L)				
Mean ± standard deviation	57.83 ± 17.89	46.06 ± 7.96	4.294	0.000
Min - Max	16 – 110	33 – 64		

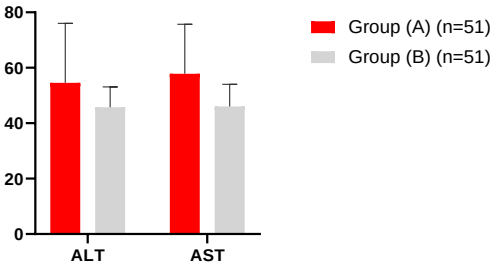


Figure (4): Comparison between both groups as regards follow-up liver profile.

DISCUSSION

Common risk factors for cardiovascular disease & chronic kidney diseases involve age, DM, hypertension, tobacco use, dyslipidemia, family history, and male gender. Hypertension, elevated

glucose and cholesterol levels, along with tobacco consumption, can be effectively altered. Toxic metabolites generated by uremia in chronic kidney disease, together with disorders that disrupt the metabolism of elements like calcium and phosphorus, contribute to the elevated CVD in cases with chronic kidney disease, classified as non-traditional risk factors [14].

A linear correlation exists among the cardiovascular protective impact of statins and the degree of atorvastatin medication. The effectiveness & safety of high-intensity statin therapy in cases with CKD remain uncertain, garnering significant attention from clinicians globally [15]. Current meta-analyses have examined the influence of statins on cases who have chronic kidney diseases and found that statin medication can diminish death and CVS events in chronic kidney disease cases, excluding those undergoing hemodialysis [16].

At baseline in our investigation, there was statistically insignificant distinctions in liver enzymes (ALT and AST) among the two groups examined. After a six-month follow-up, the aminotransferase levels (ALT and AST) exhibited a highly significant distinction among the two examined groups. Furthermore, there is a notable elevation in the liver profile in both analyzed groups when comparing the baseline of the study to the follow-up after six months.

In a post-hoc analysis of the trial, cases have been categorized into two groups: those with moderate increase in baseline aminotransferase concentrations and those with normal baseline aminotransferase concentrations. The decrease in cardiovascular events linked to statin medication was shown to be more significant in cases with moderate baseline elevations in aminotransferase concentrations than in those with normal baseline liver enzyme concentrations [12].

The findings of our investigation, as previously discussed, contradict a prior meta-analysis that assessed the safety of high against low-dose atorvastatin therapy. The authors determined that patients undergoing high-dose atorvastatin therapy had a greater possibility of experiencing transaminase elevates than those on low-dose atorvastatin [17].

It also conflicts a comprehensive investigation and meta-analysis by Yan et al., which demonstrated an insignificant distinction among non-intensive statin therapy and high-intensity statin therapy or placebo for sustained elevation of liver enzymes. Cases with CKD are deemed more susceptible to intensive or high-dose pharmacotherapy compared to the general population. Nevertheless, their analysis revealed no significant distinctions in any of the safety assessment among high-intensity statin medication and control groups [18].

All statins are metabolized by the liver, and the rate of elimination is contingent upon the lipophilicity of each statin. Conversely, when high-intensity lipophilic statins such as atorvastatin have been compared to low-intensity statins, no correlation with elevated transaminases has been observed [19].

Liver harm induced by atorvastatin is infrequent according to postmarketing data. The Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm indicated no variation in hepatic adverse effects among 5,168 hypertension cases administered atorvastatin ten milligrams per day over a duration of 3.3 years. No idiosyncratic drug-induced liver injury (DILI) associated with atorvastatin has been identified in the experiment examining the association among the daily dose of various statins and drug-induced hepatic injury. Asymptomatic increases of liver enzymes are the predominant side effects of liver related to atorvastatin, which may not essentially show liver damage [20].

Retrospective data indicate that the frequency of sustained increases in blood transaminases is 0.5 percent among atorvastatin-treated population [17].

Nonetheless, many adverse effects have been observed with atorvastatin, involving cholestatic damage, hepatocellular damage, a mixed pattern of atorvastatin-related hepatocellular and autoimmune-type reactions, cholestatic damage, and fulminant liver failure [21].

Others observed that the interval from atorvastatin exposure to manifestation of liver toxicity may vary, with an average duration of 9.4 weeks and a vary from one to fifty-two weeks. Most transaminase elevations occurred within the initial sixteen weeks of statin therapy and have been deemed dose-dependent, which corresponds slightly with our investigation. No cases of substantial ALT increases have been observed immediately following statin use. The increase of serum transaminases is frequently self-limiting and can be associated with changes in the hepatocyte membrane, leading to enzyme leakage rather than direct hepatic cell damage [22].

CONCLUSION

Our investigation revealed that the gradual initiation of atorvastatin therapy is more tolerable than the immediate administration of high-dose atorvastatin in cases with CKD. Despite comparable baseline characteristics among the two groups, cases administered high-dose atorvastatin eighty milligram from the outset (Group A) showed significantly greater increase in hepatic enzymes (AST & ALT) at monitoring than those who underwent gradual up-titration from five milligrams over four weeks (Group B). To enhance atorvastatin tolerance and protect the liver in cases with chronic kidney disease and cardiovascular CVD, these findings suggest initiating treatment with reduced-dose statins and progressively elevating the dose above 1 month to achieve a balance among heart protection and safety.

We suggested for further investigation utilizing a significant case group to substantiate our findings, hence enhancing outcomes and satisfaction levels.

Ethics approval and consent for participation:

This investigation obtained ethical permission from the Institutional Review Board of the Faculty of Medicine, Aswan University, & secured signed informed permission from all participants prior to their registration in the investigation. All subjects' identification information has been maintained under confidentiality and protected from public access.

Conflict of interests: The authors has no conflicts of interest to declare.

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REFERENCES

1- 1. Chen, T.K., D.H. Knicely, and M.E. Grams, *Chronic Kidney Disease Diagnosis and Management: A Review.* Jama, 2019. **322**(13): p. 1294-1304.

2- 2. Vaidya, S.R. and N.R. Aeddula, *Chronic kidney disease*, in *StatPearls [Internet]*. 2022, StatPearls Publishing.

3- 3. Kovesdy, C.P., *Epidemiology of chronic kidney disease: an update 2022.* Kidney Int Suppl (2011), 2022. **12**(1): p. 7-11.

4- 4. Webster, A.C., et al., *Chronic kidney disease.* The lancet, 2017. **389**(10075): p. 1238-1252.

5- 5. Chawla, V., et al., *Hyperlipidemia and long-term outcomes in nondiabetic chronic kidney disease.* Clinical Journal of the American Society of Nephrology, 2010. **5**(9): p. 1582-1587.

6- 6. Hu, P.-J., et al., *Effect of statins on renal function in chronic kidney disease patients.* Scientific reports, 2018. **8**(1): p. 16276.

7- 7. Verdoodt, A., et al., *Do statins induce or protect from acute kidney injury and chronic kidney disease: an update review in 2018.* Journal of translational internal medicine, 2018. **6**(1): p. 21-25.

8- 8. Sarnak, M.J., et al., *Chronic kidney disease and coronary artery disease: JACC state-of-the-art review.* Journal of the American College of Cardiology, 2019. **74**(14): p. 1823-1838.

9- 9. Schlackow, I., et al., *Cost-effectiveness of lipid lowering with statins and ezetimibe in chronic kidney disease.* Kidney international, 2019. **96**(1): p. 170-179.

10- 10. Alanazi, N.S., T.S. Alenazi, and K.A. Alenzi, *Hepatotoxicity induced by fluvastatin: a reversible acute cholestatic liver injury.* The American Journal of Case Reports, 2021. **22**: p. e931418-1.

11- 11. Wang, H., et al., *Fatal hepatic failure following atorvastatin treatment: A case report.* Medicine, 2023. **102**(19): p. e33743.

12- 12. Tikkanen, M., et al., *Effect of intensive lipid lowering with atorvastatin on cardiovascular outcomes in coronary heart disease patients with baseline elevations in alanine aminotransferase levels.* European Heart Journal, 2013. **34**(suppl_1): p. P679.

13- 13. Natanzon, S.S., et al., *Statin therapy among chronic kidney disease patients presenting with acute coronary syndrome.* Atherosclerosis, 2019. **286**: p. 14-19.

14- 14. Vallianou, N.G., et al., *Chronic Kidney Disease and Cardiovascular Disease: Is there Any Relationship?* Curr Cardiol Rev, 2019. **15**(1): p. 55-63.

15- 15. Mills, E.J., et al., *Intensive statin therapy compared with moderate dosing for prevention of cardiovascular events: a meta-analysis of> 40 000 patients.* European heart journal, 2011. **32**(11): p. 1409-1415.

16- 16. Zhang, X., et al., *Effect of statins on cardiovascular events in patients with mild to moderate chronic kidney disease: a systematic review and meta-analysis of randomized clinical trials.* BMC Cardiovascular Disorders, 2014. **14**: p. 1-12.

17- 17. Newman, C., et al., *Comparative safety of atorvastatin 80 mg versus 10 mg derived from analysis of 49 completed trials in 14,236 patients.* The American journal of cardiology, 2006. **97**(1): p. 61-67.

18- 18. Yan, Y.-L., et al., *High-intensity statin therapy in patients with chronic kidney disease: a systematic review and meta-analysis.* BMJ open, 2015. **5**(5): p. e006886.

19- 19. Dale, K.M., et al., *Impact of statin dosing intensity on transaminase and creatine kinase.* The American journal of medicine, 2007. **120**(8): p. 706-712.

20- 20. Liu, Y., et al., *Atorvastatin-induced acute elevation of hepatic enzymes and the absence of cross-toxicity of pravastatin.* International journal of clinical pharmacology and therapeutics, 2010. **48**(12): p. 798.

21- 21. Bhardwaj, S.S. and N. Chalasani, *Lipid-lowering agents that cause drug-induced hepatotoxicity.* Clinics in liver disease, 2007. **11**(3): p. 597-613.

22- 22. Clarke, A. and P. Mills, *Atorvastatin associated liver disease.* Digestive and liver disease, 2006. **38**(10): p. 772-777.