Published in final edited form as:

Dig Dis Sci. 2010 January ; 55(1): 190–195. doi:10.1007/s10620-009-0959-1.

Statin Therapy and Serum Transaminases Among a Cohort of HCV-Infected Veterans

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Abstract

Background—We sought to determine the effect of statin therapy on serum AST and ALT levels in a cohort of HCV-infected veterans with well-characterized liver disease.

Study—We examined liver biopsy records of consecutive HCV-infected patients and identified 20 patients who were prescribed statins. We matched them on age, stage of fibrosis, and time between HCV diagnosis and statin start dates with up to four HCV-infected patients who did not use statins. ALT and AST values from up to four time points within 1 year of follow-up were abstracted from the medical record. We compared median ALT and AST levels using Wilcoxon–Mann–Whitney tests and assessed changes in ALT and AST over time between the statin and non-statin groups using a non-parametric repeated measures ANOVA model, adjusting for the matching factors, receipt of HCV treatment, BMI, and diabetes.

Results—Patients prescribed statins had higher median BMIs, were more likely to have diabetes, and had higher total cholesterol levels. Median baseline ALT levels were higher among those prescribed statins ($P = 0.04$) while median baseline AST levels were lower among statin users ($P = 0.03$). From baseline to follow-up, the median decreases in both ALT (–13.5 vs. –4.0) and AST (–4.5 vs. –0.5) were significantly larger among statin users compared to non-statin users ($P = 0.03$ and $P = 0.0007$, respectively) even after adjustment.

Conclusions—Among HCV-infected patients AST and ALT levels for those prescribed statins decreased over a 6 to 12-month follow-up period compared to patients not taking statins.

Keywords

Hepatitis C virus; Statins; Transaminases; Veterans

Introduction

Coronary heart disease (CHD) is the leading cause of death in the US [1], accounting for one out of every five deaths [2]. The risk factors for CHD include older age, smoking, overweight/obesity, diabetes, as well as high blood cholesterol [2]. A 10% reduction in total cholesterol levels at the population level is estimated to result in a 30% decrease in the incidence of CHD [3]. The most effective cholesterol-lowering drugs are 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, referred to as statins, which act to block the formation of cholesterol in the liver and also generate additional LDL receptors that absorb LDL-cholesterol from the blood [4]. Clinical trials have shown that the

use of statins reduces LDL-cholesterol levels by 20–45%, which in turn leads to decreases in CHD and all cause mortality [4–6].

Despite the proven benefits of statins, concern with potential hepatotoxicity of statin drugs in patients with liver disease may have resulted in a reduction of statin use in this subset of the population. A meta-analysis published in 2004 reported that the use of statins increased amino-transferase levels by 0.2 to 2.7% in subjects without liver disease [7]. Although one study reported an increase in risk of mild to moderate hepatotoxicity [8], most studies examining AST or ALT levels among patients with HCV infection found no evidence for increased risk of hepatotoxicity [9, 10]. In 2006, the Liver Expert Panel stated that chronic liver disease is not a contraindication for statin therapy [11].

Recently, an HCV-related beneficial effect of statin use among patients with HCV-related liver disease has been suggested. In vitro studies show that high concentrations of statins disrupt HCV replication via depletion of isoprenoid geranylgeranyl pyrophosphate [12, 13]. Statins may thus have antiviral effects through mechanisms not related to lipid metabolism [14, 15]. A pilot study of 31 HCV-infected veterans who were given fluvastatin 20–320 mg/day for 2–12 weeks with weekly monitoring of HCV RNA and liver tests reported modest reductions of viral load [16]. Furthermore, a pharmacoepidemiologic study found that the use of lovastatin was associated with a 40–50% lower incidence of moderate as well as severe liver injury among patients with preexisting liver disease although baseline severity and cause of liver disease could not be adjusted for [17]. Even though prior individual studies examined important aspects of the association between statin and liver disease in HCV-infected patients, these studies either did not adjust for histological severity of liver disease, had generally short follow-up, or did not use control subjects. Clearly, more information is needed about the possible beneficial effect of statins in HCV-infected patients before these medications are considered for an interventional study.

The purpose of this study was to determine the effect of statin therapy on serum levels of AST and ALT in a cohort of HCV-infected veteran patients with well-characterized liver disease.

Materials and Methods

Study Design

We conducted a retrospective cohort study among consecutive patients with laboratory confirmed HCV-infection who had a liver biopsy between Jan 10, 1994, and Nov 26, 2003, at the Michael E. DeBakey VA Medical Center in Houston, TX. Patients were identified through review of the log of liver biopsy records.

We identified 34 HCV-infected patients with liver biopsy who were prescribed statins (simvastatin or lovastatin). We limited our sample to males who had at least two ALT/AST readings during 1 year of follow-up subsequent to statin start date. We excluded one patient who was HIV positive, seven patients with only one recorded ALT/AST measurement, four patients with statin use before HCV ELISA date, and two patients with statin discontinuation prior to their second ALT/AST measurement. Hence, we included 20 HCV-infected patients with liver biopsy who were prescribed statins. We then matched these patients with up to four HCV-infected patients who did not use statins. Patients were matched on age (± 5 years), stage of fibrosis on liver biopsy, and time between HCV diagnosis date (IgG test) date and statin start date. We employed the same exclusion criteria outlined above and identified 64 HCV-infected patients with liver biopsy who were not prescribed statins.

ALT/AST Measurements

For the cohort of 84 HCV-infected patients (20 on statin and 64 not on statin), ALT and AST values from up to four time points within 1 year were abstracted from the medical record. For those prescribed statins, the baseline ALT/AST measurement was the first recorded value prior to the statin start date. In order to have a comparable time frame between HCV diagnosis date and measurement of ALT/AST values for the non-statin group, we computed a time period in which to assess these measurements among the non-statin group. Among those not prescribed statins, the first measurement was taken as the closest reading to the time of the HCV diagnosis date plus the number of days until statin start date for the matched statin user. For both the statin and non-statin groups the second measurement was assessed 4–7 weeks later, the third measurement was taken 8–25 weeks later, and the fourth reading was obtained 6–12 months after the first reading.

Covariates

Covariate information was abstracted from the medical record. Comorbidity data included the presence of diabetes or hypertension. Behavioral information included current and prior alcohol consumption as well as current and prior tobacco use. Patient characteristics included race, ethnicity, and body mass index (BMI) at the time of liver biopsy. Clinical information collected included HCV treatment (within a median of 23 months), HDL-cholesterol, and LDL-cholesterol measurements at baseline.

Statistical Analyses

We compared characteristics of the statin and non-statin groups using Chi-square tests for discrete measures and Wilcoxon–Mann–Whitney tests for continuous measures [18]. To ascertain if differences in transaminase levels in units/liter (U/L) (ALT and AST separately) between the statin and non-statin groups existed at baseline and at 6–12 months, we compared median ALT and AST levels using Wilcoxon–Mann–Whitney tests. Finally, we assessed changes in ALT and AST over time (between baseline and at 6–12 months after baseline) between the statin and non-statin groups using a non-parametric repeated-measures ANOVA model to adjust for the matching factors (age, fibrosis stage on liver biopsy, and time between HCV diagnosis and statin start date), receipt of HCV treatment, BMI, and diabetes. The study was approved by the IRB of Baylor College of Medicine. As a retrospective chart review, individual informed consent was not required.

Results

Characteristics of the HCV-infected cohort by statin use are provided in Table 1. There were no significant differences between 20 HCV-infected patients who received statin therapy and 64 who did not with regard to age, race, ethnicity, HCV genotype, HCV viral load, alcohol consumption, hypertension, tobacco use, fibrosis stage, or receipt of HCV treatment. Of the 20 patients who received statins, most (80%) were prescribed simvastatin, and 15% were prescribed lovastatin. Patients that were prescribed statins had higher median BMIs (30.3 vs. 27.7, $P=0.02$), were more likely to have diabetes (45 vs. 16%, $P\text{ value}=0.02$), and had higher total cholesterol levels (201 vs. 180 mg/dl, $P=0.04$).

Since the majority of statin users did not have AST and ALT readings at the second (4–7 weeks) and third (8–25 weeks) time points, the analyses presented in Table 2 focus on the comparison between measurements taken at baseline and the fourth time point (occurring between 6 and 12 months). In comparing the median AST and ALT levels between the statin and non-statin groups, we found that median baseline ALT levels were approximately 1.4 times higher among those prescribed statins ($P=0.04$) while median baseline AST levels were approximately one-third lower among statin users ($P=0.03$). There were decreases in

both ALT and AST from baseline to follow-up that were significantly larger among statin users compared to non-statin users ($P=0.03$ and $P=0.0007$, respectively). After adjusting for the matching factors, receipt of HCV treatment, BMI, and diabetes, the results were unchanged (data not shown).

Among the 20 statin users, 13 (65%) underwent HCV treatment. Of these, ten had HCV treatment before statin use and three had HCV treatment after statin was started. None of these patients had undetectable virus counts.

The disproportionate declines in AST and ALT median values among statin users seemed to be related to a greater proportion of patients having the decline rather than the magnitude of decline. ALT declined for 13/20 (65%) statin users vs. 37/64 (58%) non-statin users. Among statin users, the smallest decrease was 3% and the largest decrease was 63%. For non-statin users, the smallest decrease was 2% and the largest decrease was 67%. Similarly, AST declined for 11/20 (55%) statin users vs. 32/64 (50%) non-statin users. Among statin users, the smallest decrease was 8% and the largest decrease was 63%. For non-statin users, the smallest decrease was 2% and the largest decrease was 87%.

For those who did not show an ALT decrease, there was no association between race and fibrosis stage ($P=0.5$). Similarly, for those with no AST decrease, there was no association between race and fibrosis stage ($P=0.6$).

Discussion

We found that among HCV-infected patients, patients prescribed a statin medication had larger declines in AST and ALT levels from baseline to follow-up (6–12 months later) compared to those not prescribed statins after matching on age, stage of fibrosis, and time between HCV diagnosis and statin start dates. Further adjustment for receipt of HCV treatment, BMI, and diabetes did not change our findings.

Our results add to the findings of at least five previous studies that examined hepatotoxicity related to statin use among HCV-infected patients (summarized in Table 3). In 2005, Gibson and Rindone [9] reported that the use of statins was not associated with elevations in AST or ALT enzymes in 17 HCV-infected veterans from the Northern Arizona VA Health Care System. A second VA study from the West Palm Beach VA Medical Center evaluated the hepatotoxicity of statins in 146 HCV-infected patients and reported no significant change in ALT levels [10]. These two studies [9, 10] did not use a comparison group of patients not treated with statins so it was unclear how ALT or AST levels among HCV-infected individuals behave in the absence of statins. A subsequent study published in 2006 examined hepatotoxicity from statin use in 166 HCV-infected patients receiving statins compared with two control groups that were matched on age, sex, and BMI—one group consisting of 332 HCV-infected patients not receiving statins and another group comprised of 332 HCV-uninfected patients receiving statins [8]. That study found that compared to HCV-infected patients who were not prescribed statins, HCV-infected patients who were on statin therapy had a decreased risk of severe hepatotoxicity (>10 times ULN, 7 vs. 1%, $P=0.015$) but an increased risk of mild to moderate hepatotoxicity (up to 10 times ULN, 13 vs. 23%, $P=0.009$). In 2008 Bader et al. [16] published results from a trial in which 31 HCV-infected veterans from Oklahoma City were given oral doses of fluvastatin. Bader et al. reported finding no evidence that ALT worsened during treatment with fluvastatin. Additional adjustment for potential confounding factors as identified by medical chart review would enhance the study designs of all four studies. The last study by Lewis et al. was a randomized controlled trial of pravastatin 80 mg or placebo given to large group of patients with compensated chronic liver disease, 81 of whom were HCV-infected. The

subgroup analysis revealed no significant differences in ALT levels before or during statin treatment [19].

Interest in a possible beneficial effect of statins has emerged over the last decade as concerns about hepatotoxicity are being addressed [19–22]. Statins have been shown in vitro to inhibit hepatic stellate cells proliferation and their production of collagens in a dose-dependent manner [23, 24], with the addition of mevalonic acid (the product of HMG-CoA reductase), reversing the effect [23]. Statins may also have an effect specific to HCV. It has been shown that HCV replication depends in part on geranylgeranylation of a host protein and that HCV RNA replication can be disrupted in vitro by high concentrations of statins. This effect was presumably due to severe depletion of mevalonic acid, which led to low cellular levels of geranylgeranyl pyrophosphates, the substrate for the geranylgeranyl-transferase [12, 25]. However, whether these in vitro effects of statins on HCV have any clinical relevance is not known. Last, it is possible that statins reduce hepatic steatosis, which has been implicated as a risk factor for hepatic fibrosis and cirrhosis. Given our preliminary findings of improved LFTs in statin users, future studies need to measure and adjust for steatosis, fibrosis, and viral levels in order to disentangle the mechanism beneficial effect (if any) of statins.

Our study has to be interpreted within its limitations. Since the study is a retrospective cohort study, patients were not randomly assigned to the statin or non-statin group. While we measured several potential confounders and adjusted for these in our models, it is still possible that other unmeasured factors could account for our results. Additionally, the number of HCV-infected veterans in our study was relatively small. Our study could be improved with additional data such as serial measurements of HCV viral load. While the study was adequately powered to detect differences in the average ASL and ALT levels, the estimates are not very precise due to the relatively limited sample size. Due to the retrospective nature of the study and the small sample size, analyzing additional outcomes such as time to cirrhosis is likely to be inaccurate and considerably underpowered.

In conclusion, we found that among HCV-infected patients AST and ALT levels for those prescribed statins decreased over a 6–12 month follow-up period compared to patients not taking statins. These results add to the growing body of evidence that statin use in patients with HCV infection is likely safe. Larger and prospective studies are needed to more definitively evaluate the possible beneficial impact on HCV-related liver disease.

Acknowledgments

The work was partly supported by NIH K24DK078154-03 for Dr. El-Serag, and Public Health Service Grant DK56338, which funds the Texas Medical Center Digestive Disease Center.

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Table 1

Characteristics of the HCV-infected cohort by statin use

Characteristic	Prescribed statins <i>n</i> = 20 # (%)	Not prescribed statins <i>n</i> = 64 (%) # (%)	<i>P</i> -value
Age (years), median	52.0	50.0	0.13
Race			
African-American	10 (50)	39 (61)	0.39
White	10 (50)	22 (34)	
Other/unknown	0 (0)	3 (5)	
Ethnicity ^a			
Hispanic	1 (5)	5 (8)	0.99
Non-Hispanic	19 (95)	58 (92)	
HCV genotype			
1	16 (80)	51 (79)	0.20
2	3 (15)	3 (5)	
3	1 (5)	0 (0)	
4	0 (0)	1 (2)	
Not done	0 (0)	9 (14)	
RNA viral load ^c , median	534,460	553,081	0.99
Alcohol use (current)	13 (65)	53 (83)	0.12
BMI ^a , median	30.3	27.7	0.02
Diabetes	9 (45)	10 (16)	0.01
Hypertension	12 (60)	41 (64)	0.79
Tobacco use (current)	15 (75)	39 (61)	0.30
HDL-cholesterol ^b , median	35.0	46.0	0.04
LDL-cholesterol ^b , median	123.4	109.4	0.06
Total-cholesterol ^b , median	201.0	180.0	0.04
Triglycerides, median	149.0	109.0	0.10
Liver biopsy fibrosis stage			
1	5 (25)	11 (17)	0.95
2	5 (25)	20 (31)	
3	3 (15)	9 (14)	
4	3 (15)	9 (14)	
Unknown	4 (20)	15 (23)	
Received HCV treatment	13 (65)	38 (59)	0.65

^a Ethnicity missing for one non-statin user; BMI missing for one statin user^b HDL missing for seven non-statin users and one statin users; LDL missing for 14 non-statin users and four statin users; Tot Chol missing for five non-statin users and 0 statin users; triglycerides missing for seven non-statin users and one statin user

^cHCV RNA viral load missing for nine statin users and 30 non-statin users

Table 2

Comparison of AST and ALT levels (U/l) by statin use at baseline and at 6–12 month follow-up

	Statin users N = 20	Non-statin users N = 64	P-value
Median serum ALT levels (U/l)			
Baseline	63.5	47.0	0.04
Follow-up	52.5	44.0	0.34
Change from baseline to follow-up	−13.5	−4.0	0.03
Median serum AST levels (U/l)			
Baseline	41.0	63.0	0.03
Follow-up	38.5	58.0	0.01
Change from baseline to follow-up	−4.5	−0.5	0.0007

Table 3

Summary of prior studies examining LFT/statin use among HCV-infected patients

Author, year	Population	Exposure	Outcome	Result
Bader [16]	OK veterans	Baseline to follow-up	Change in ALT	No increase in ALT; non-significant decrease in VL
	31 HCV + statin		Change in viral load	
Gibson [9]	AZ veterans	Baseline to follow-up	Change in ALT or AST	Greatest increase in ALT/AST was 1.5× ULN
	17 HCV + statin			
Khorashadi [8]	Palo Alto veterans	Statin versus no statin; HCV+ versus HCV–	Compare hepatotoxicity b/t statin and non-statin groups	Proportion with hepatotoxicity statin versus non-statin HCV + mild/mod: 23 vs. 13%, $P = 0.009$
	166 HCV + statin		Mild/moderate: up to 10 times ULN	
	332 HCV + no statin		Severe: >10× ULN	Severe: 1 vs. 7%, $P = 0.015$
	332 HCV-statin			
Segarra-Newnham [10]	FL veterans	Baseline to follow-up	Change in LDL	22% LDL reduction, $P < 0.05$ No change in ALT
	146 HCV + statin		Change in ALT	
Lewis [19]	81 HCV infected in a trial of 326 patients	Pravastatin ($n = 38$) or placebo ($n = 43$)	Change in LDL	Significant LDL reduction
			Change in ALT	No difference in ALT change

HCV hepatitis C virus, ALT alanine aminotransferase, AST aspartate aminotransferase, ULN upper limit of normal, P P -value, LDL low density lipoprotein-cholesterol, VL viral load