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Statin Use is Associated with Reduction in Fibrosis and Cirrhosis in a Predominantly African American Urban Population with Hepatitis C

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Abstract

Background: Statins are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors which have the potential to modify HCV host cell lipid metabolism and thus could have an impact on outcomes of viral infection. Epidemiologic studies of the association between statin use and worsening of liver disease parameters such as fibrosis and the incidence of Hepatocellular Carcinoma (HCC) have generated inconsistent results. In addition, most studies have been of small sample size and few studies have included significant numbers of African American (AA) participants who were not on anti-viral therapy (i.e natural history cohort). Our objective was to investigate the impact of statins upon fibrosis, cirrhosis and HCC in our predominantly African-American population. Methods: The EMR of the largest health care provider in Southeast Michigan and its associated multi-specialty group were use to identify all the patients with HCV who had at least one visit over a period of 1 year (2015). Patients who were on treatment were included if pre-treatment data was available. Stratification was into 2 groups based on the presence of prescriptions for statins in their 2015 EMR records. HIV and Hepatitis B co infected patients were excluded. Liver fibrosis was defined by APRI [(AST/ AST normal)/ Platelet ×100] and FIB-4 [(Age × AST)/(Platelet × √ALT)] scores. Cirrhosis was defined by a combination of laboratory data and imaging studies. HCC was diagnosed by imaging and/or biopsy.

Results: From a data set of 459 patients with HCV, we identified 150 patients who were prescribed statins and compared them to 309 patients who were not. Patients were similar in gender, race and BMI. Statin use was associated with significantly lower Fibrosis defined by APRI (0.6 vs 0.9; P<0.005) and Fib 4 (2.1 vs 2.8; P<0.05). Patients on statins also had lower cirrhosis than those who were not (12% vs 21%; p< 0.05) by Fischer's chi square test. Although not statistically different patients on statins were less likely to develop HCC (2 pts vs 7 pts) .

Conclusion: In a predominately AA patient population with chronic HCV, statin use is associated with reduced fibrosis, cirrhosis and with a decrease in HCC risk. Given that statins are underutilized by many primary care providers, these results provide additional evidence that statins use is beneficial in preventing liver disease progression in patients with Hepatitis C infection.

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Introduction

In 2012, an estimated 26% of US adults were on the lipid-lowering class of medications known as statins for the primary benefit of lowering atherosclerotic disease [1]. That was also the year when the FDA decided that the risk of clinically significant hepatotoxicity was so exceedingly rare that use of these medications no longer warranted routine monitoring of liver enzyme levels. With in three short years of that decision, our entire initial view of statin use in chronic liver disease was reversed and subsequent evidence has only further confirmed this trend. The current consensus is that statins have a beneficial role in multiple steps along the natural history and pathogenesis of liver disease, from early inflammation and fibrosis through late stage cirrhosis and even development of Hepatocellular carcinoma (HCC) [2-4]. Although intuition may dictate that statin use would have the most benefit in Nonalcoholic Fatty Liver Disease (NAFLD), most of the literature showing benefit has been focused on chronic Hepatitis C virus (HCV)-related cirrhosis [2,5]. A landmark VA study published in Gastroenterology found a 40% reduction in death and decompensation of HCV-associated cirrhosis in patients with statin use [6]. A more recent large study out of Taiwan, compared three distinct etiologies of cirrhosis and revealed a significantly reduced risk of

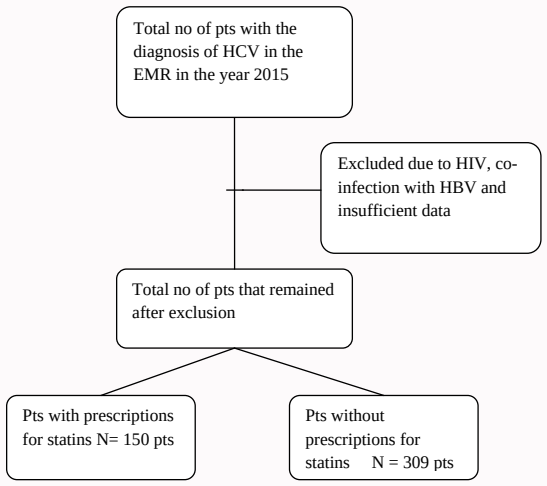

Figure 1: Study Flow Sheet.

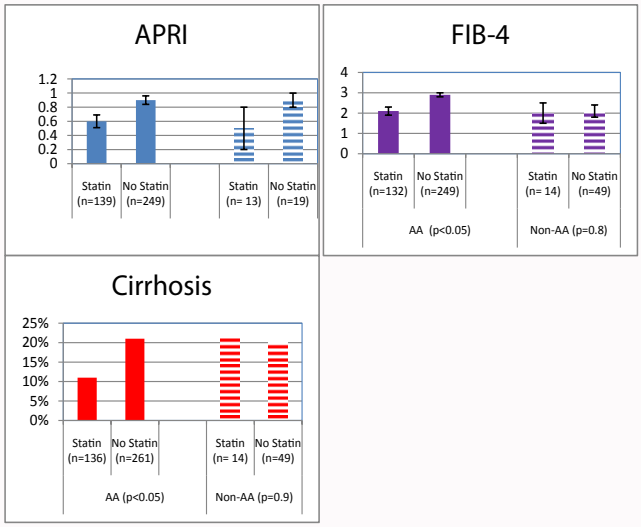

Figure 2: Patients were classified by race and statin use. Results are presented as mean +/- SEM or %. The number of patients in each group is indicated in the parenthesis. Significance was defined by t-test or Chi-Square analysis.

decompensation in HCV-associated cirrhosis with statin usage [7]. While the former VA study relied on the VA Clinical Case Registry, which consisted of a patient population that is predominantly white (approx. 50%), almost exclusively male (approx. 98%), and contains a disproportionate amount of certain comorbidities including dyslipidemia, alcohol, drug abuse, and hypertension, the later Taiwan study, although more gender-balanced, was again limited by a population that has significantly less obesity and comorbidities [6,7].

Goal

The goal of the current study was to retrospectively examine the benefit of statin usage among chronic HCV patients in a large urban medical center.

Methods

Patients

The source of data was the electronic health record of Wayne State University Physician Group, a large multi-disciplinary health care provider in Southeast Michigan. All patients with the ICD9/10

Table 1: Statin vs. Non-Statin in all included HCV patients.

	Statin (n=150)	No Statin(n=309)	P value
Age	63.4 ±1.3	61.3 ± 0.9	0.01
Males	95 (63%)	181 (58%)	
Females	55	127	
AA (%)	91%	85%	0.068
BMI	27.4 ± 1.1	29.4 ± 0.8	0.12
AST	43.0 ± 6.5	56.9 ± 4.6	0.0006
ALT	48.9 ± 6.6	60.9 ± 4.6	0.003
Albumin	3.7 ± 0.1	3.7 ± 0.1	0.75
Platelets	218.9 ± 11.8	209.9 ± 8.3	0.21
APRI	0.6 ± 0.2	0.9 ± 0.1	0.003
FIB 4	2.1 ± 0.5	2.8 ± 0.3	0.02
Cirrhosis	12%	21%%	0.015
Fibrosis (Fibrospect)	60%	63%	0.51
HCC	2	7	0.49

diagnosis of Hepatic C virus (HCV) with at least one clinic visit over a period of 1 year in 2015 were identified. Demographics including race, sex, and body mass index, along with clinical evidence of liver disease including serologic and radiologic markers of liver disease were collected. Hepatocellular carcinoma (HCC) was confirmed by imaging + serological tumor marker (AFP), and/or biopsy. Statin usage was determined based on whether the patient was or was not on statin therapy at the time the data was collected. Patients with Human Immuno Deficiency Virus (HIV) or Hepatitis B Virus (HBV) co-infections were excluded. Patients treated for HCV were excluded unless the data was available prior to treatment.

Definitions

Liver fibrosis was determined using serologic markers to calculate APRI [(AST/ AST normal)/ Platelet × 100] and FIB-4 [(Age × AST)/ (Platelet × √ALT)] scores. Cirrhosis was defined by a combination of laboratory and radiographic findings.

Outcomes

Our primary outcome measures were progression of liver fibrosis as measured by APRI or FIB-4 score. Development of cirrhosis is defined as >1,7 by APRI or >3.5 by FIB-4. Incident HCC was based on the patients EMR and search by ICD-9/ICD-10 codes.

Statistical analyses

Stratification was into 2 groups based on documentation of prescriptions for statins use in their 2015 electronic health record. Characteristics values were calculated in the overall sample size, in AA compared to non AA, and males vs. females among AA, by using ANOVA or Student's t-test for continuous variables and Chi-Square Pearson analysis for character variables using JMP (SAS) software.

Regulatory approvals

The study was approved by the institutional review board at Wayne State University, Detroit.

Results

As shown in the (Figure 1) flow chart, 459 patients were available for analysis with a 2:1 ratio of non-statin to statin using patients. In 2015 the age, gender, and BMI were similar between the two groups. Significantly less liver disease was noted in the statin group compared

Table 2: Statin vs Non-Statin and Gender for African American (AA) vs. Non-AA.

	AA			Non AA		
	Statin (n= 136)	**No Statin (n=260)**	**p value**	**Statin (n=14)**	**No Statin (n=49)**	**p value**
Age	63.4 ± 0.5*	62.7 ± 0.3	p ≤ 0.2	62.2 ± 3.4	54 ± 1.8	P ≤ 0.03
Males	85	150		10	32	
Females	51	110		4	17	
BMI	27.2 ± 0.5	28.3 ± 0.3	p ≤ 0.07	29.4 ± 1.9	29.1 ± 1	p ≤ 0.9
AST	44.3 ± 3.4	56.4 ± 2.4	p ≤ 0.004	29.9 ± 10.5	59.2 ± 5.8	p ≤ 0.02
ALT	50.2 ± 3.3	58.4 ± 2.3	p ≤ 0.04	35 ± 13.8	75.9 ± 7.7	p ≤ 0.01
Albumin	3.6 ± 0.05	3.6 ± 0.03	p ≤ 0.9	3.7 ± 0.1	3.8 ± 0.06	p ≤ 0.4
Platelets	221.8 ± 6.2	209 ± 4.5	p ≤ 0.1	189.6 ± 18.5	209 ± 10.3	p ≤ 0.3
APRI	0.6 ± 0.09	0.9 ± 0.06	p ≤ 0.009	0.5 ± 0.3	0.9 ± 0.1	p ≤ 0.06
FIB 4	2.1 ± 0.2	2.9 ± 0.1	p ≤ 0.02	2 ± 0.5	2.1 ± 0.3	p ≤ 0.8
Cirrhosis	11%	21%	p ≤ 0.01	21.40%	20.40%	p = 0.93
Fibrosis (Fibrospect)	62%	64%	p ≤ 0.57	30%	59%	p ≤ 0.11
HCC	2	6	p ≤ 0.78	0	1	p ≤ 0.59
* ± sem						

Table 3: Statin use in African American patients with HCV, Female vs. Male.

	Female			Male		
	Statin (n=51)	No Statin (n=110)	p value	Statin (n=85)	No Statin (n=151)	p value
Age	63.9 ± 2.2	61.9 ± 1.5	0.13	63.2 ± 1.1	63.3 ± 0.9	0.92
BMI	27.3 ± 1.9	29.8 ± 1.3	0.03	27.1 ± 1.3	27.4 ± 1.0	0.76
AST	42.7 ± 13.0	59.6 ± 8.9	0.03	45.3 ± 7.6	54.2 ± 5.7	0.06
ALT	44.0 ± 9.3	55.4 ± 6.3	0.04	54.0 ± 9.1	60.7 ± 6.8	0.24
Albumin	3.6 ± 0.1	3.5 ± 0.1	0.33	3.7 ± 0.1	3.8 ± 0.1	0.4
Platelets	222.4 ± 21.1	205.7 ± 14.5	0.2	221.5 ± 15.4	212.9 ± 11.6	0.37
APRI	0.7 ± 0.2	1.1 ± 0.1	0.03	0.61 ± 0.2	0.81 ± 0.1	0.08
FIB 4	2.3 ±1.1	3.4 ± 0.8	0.09	2.1 ± 0.5	2.6 ± 0.4	0.12
Cirrhosis	18%	22%	0.54	7%	21%	0.006
Fibrosis (Fibrospect)	63%	67%	0.67	62%	66%	0.96
HCC	1	0	0.14	1	6	0.22

to the non-statins Table 1. Statistically significant differences were found in AST, ALT, APRI, FIB-4 and cirrhosis. Fibrosis by FIBROspect assay, Albumin and Platelet values were not significantly different. There were fewer cases of HCC in the statin group (2 vs 7) but the difference was not statistically significant. Since a large number of patients were AA (85-91%), the effect of statin use was also evaluated by race (AA vs non-AA). The same improved liver functions were statistically significant in the AA population, consistent with their being the dominant population in the overall group Table 2. Given the small number of non-AA patients, the majority of the liver relevant parameters although improved did not achieve significance.

Gender differences were also evaluated in the AA population Table 2. Patients who were using statins, had improved liver relevant parameters, but the reduction in the number of patients resulted in a reduction in statistical significance. Of note was the APRI and FIB-4 achieved significance in females and the incidence of cirrhosis which was higher in men, was significantly improved in the patients in the statin group.

Discussion

Our understanding of the pharmacology and physiology leading to the beneficial effects of statins in HCV and cirrhosis has continued to grow exponentially. Undoubtedly a part of the mechanism is directly related to inhibition of HMG-CoA reductase, the rate-limiting step of the cholesterol synthesis pathway. The lipid lowering effects in the liver can influence HCV replication and subsequent lipoprotein particle assembly; with each step, heavily relying on the lipid environment [2,5].Studies performed with interferon and ribavirin prior to direct acting antiviral agents becoming readily available, showed a significant reduction in the clearance and Sustained Virologic Response (SVR) among patients who are on concomitant statin therapy [2,8,9]. In addition to the antiviral effects in HCV infection, statin use also benefits individuals with liver disease regardless of underlying etiology and at all stages, through its documented anti-inflammatory and anti-contractility effects. These effects include up regulation of hepatic endothelial nitric oxide (eNO) and the inhibition or reduction of hepatic stellate cell activation.7,8,9 Anti-fibrotic effects of statins were first well characterized in relation to cardiac pathology and has shown similar evidence in the liver [2,4,10]. Lastly, statins have also been shown to induce tumor apoptosis and mitotic arrest, which likely correlate with the previously described reduction in HCC among statin users [2,5,6,8,11,12].

Our study is the first to examine HCV liver disease and statin usage specifically at a predominantly urban medical center in the US which has a large AA population. The findings in the current study are consistent with the recent narrative that statin use is associated with improved outcomes in patients with chronic liver disease, especially from HCV infection. Statin usage has been shown in prior studies to statistically reduce HCC occurrence, which is also supported by our findings.

The importance of the focus on specific patient demographics should not be underestimated. One obvious factor is race, as 85% of our patients were African American. Ethnicity is closely linked to a host's genetic immunology. Numerous studies examining chronic viral hepatitis B and C infections have discovered racial predominance in specific interleukin genetics, including single nucleotide polymorphisms. The effects of these differences are linked to viral infectivity as well as pro-inflammatory impact of cytokines, which is ultimately linked to fibrosis and progression to cirrhosis and even HCC [13,14,15]. Other distinctions of an urban population are perhaps more closely linked to socioeconomic differences. The rate of metabolic syndrome and average BMI is notably higher in this population than the average patient, raising the risk for coexisting steatohepatitis [16,17]. Prior studies have shown decreased progression of fibrosis and cirrhosis decompensation in NASH-associated cirrhosis [18]. Additionally, although alcohol and drug abuse were not specifically recorded in our current study, this patient population typically has higher than national rates of both [17,19,20]. Statin usage has shown a dose-responsive effects in reducing the rate of cirrhosis decompensation in prior studies. However, this effect is to a lesser degree compared to other common etiologies of liver cirrhosis, presumably due to repeated insult from continued alcohol consumption and liver damage [7].

Our findings while consistent with those posed by other studies, did have several limitations. The study population was smaller than some but not all previously published studies such as those using national databases such as those of United States VA system or the national Taiwanese health system. Another limitation of the study included that the statin intensity, the duration of therapy, nor the statin start and end time could be confirmed. On the other hand, despite the smaller population and statin compliance issues, statistically significant lower liver disease results were still obtained. Co-morbidities and life style choices including drug and alcohol use were also not part of the analysis. While biopsy was not used to determine the status of liver disease, standard practice indirect means were used including serology and radiography.

Conclusion

Statin usage has a benefit in HCV-associated fibrosis, cirrhosis, and HCC reduction in African-American patients.

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