

# Statins for the Treatment of Liver Fibrosis in Chronic Hepatitis-C Patients

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## Authors' contributions

This work was carried out in collaboration among all authors. Author AA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AKL, AAJ, FM, MKS, MZS and AA managed the analyses of the study and managed the literature searches. All authors read and approved the final manuscript.

## ABSTRACT

**Background:** Hepatitis C virus (HCV) is one of the most common causes of chronic liver disease and the leading indication for liver transplantation worldwide. Chronic hepatitis C (CHC) leads to cirrhosis and hepatocellular carcinoma (HCC). Statins have gained attention for their pleiotropic effects. There is mounting evidence that statins offer chemoprevention against many malignancies. The aim of this was to determine the efficacy of the statin for the treatment of liver fibrosis in chronic hepatitis C patients. **Methodology:** A randomized control trial was conducted at Hepatitis Clinic, People Medical College Hospital, Nawabshah from August 20, 2020, to February 20, 2021. Non-probability, consecutive sampling was adapted. Patients with chronic hepatitis C infection and liver fibrosis were included. Group-A was administered statins in addition to antiviral treatment while Group-B was given anti-viral medications only. Stages of fibrosis were determined by shear wave elastography at the start of the study and after 6 months. All the data were entered and analyzed in Statistical Packages for Social Sciences (SPSS) v25.0. **Results:** There were 73 patients in each group. Fibrosis progression occurred in 7(9.6%) patients in group-A and 23(31.5%) in group-A. The link between the efficacy of the treatment given with

the group-A and group-B was significant with a p-value of 0.001. **Conclusion:** Findings demonstrate a significant reduction in the risk of fibrosis progression among statin users with advanced chronic hepatitis C. These results support a possible role for statins in the prevention of liver disease progression.

**Keywords:** Statins, Liver fibrosis, Hepatitis-C, Nawabshah.

## INTRODUCTION

Hepatitis C virus (HCV) infection causes progressive liver damage and is associated with high morbidity and mortality due to the development of liver cirrhosis and hepatocellular carcinoma<sup>1</sup>. 15-20% of the cases of acute hepatitis are reported to be due to hepatitis C virus and around 50-80% of these patients develop a chronic infection after it lasted for more than six month<sup>2,3</sup>.

According to a recent estimate by World Health Organization (WHO), approximately 71 million people are living with chronic HCV infection across the globe, and out of these approximately 0.4 million people die each year, mostly from cirrhosis and hepatocellular carcinoma<sup>4</sup>. In the USA alone, 3.5 million Hepatitis C virus-infected people<sup>5</sup>. Liver fibrosis is a common complication of chronic hepatitis C infection and is defined as the accumulation of excessive extracellular matrix proteins as a wound healing response to chronic liver injury<sup>6</sup>.

Liver fibrosis is also the common pathway for several liver injuries. Other common predisposing conditions for the development of liver fibrosis include hepatitis B virus infection, human immune-deficiency virus – hepatitis C co-infection, metabolic and toxin-related liver disease, auto-immunity, alcohol abuse, and non-alcoholic fatty liver disease<sup>7</sup>. Liver biopsy has been the gold standard for the diagnosis of fibrosis but is of limited use in advanced disease and periphery settings. These days shear wave elastography has emerged as a non-invasive and easy-to-use method to predict liver fibrosis grades<sup>8</sup>. Direct-acting antiviral therapy has promising results in the successful clearance of the virus from the body. Despite this, the disease may progress in patients with advanced fibrosis thus raising the need for other therapeutic agents<sup>9</sup>.

Moreover, reports on the use of statins in humans have largely been retrospective, based on biochemical markers and without appropriate control groups.<sup>9</sup> Liver fibrosis is associated with significant morbidity and mortality in chronic hepatitis C patients. Antiviral therapy can successfully decrease viral load in the patients but is of little use to stop or reduce the progression of fibrosis in many cases. Deranged lipid profile is the common etiological factor among these patients thus use of statins can be a novel therapeutic strategy to reduce the progression of fibrosis.

In the HALT-C Trial cohort, 543 chronic hepatitis C patients were followed for 3.5 yrs. Fibrosis progression occurred in 3/29 (10%) statin users and 145/514 (29%) non-users.<sup>9</sup> In another systemic review of including many studies and 121,058 chronic liver disease patients, 46% of the

patients were exposed to statins and it was associated with a 46% lower risk of hepatic decompensation.<sup>12</sup>

Limited data is available on the association between the use of statins and reduced progression of liver fibrosis and requires further studies on the subject matter. Early recognition and treatment can significantly reduce the progression of liver fibrosis and can decrease morbidity, mortality in chronic hepatitis C patients.

## METHODOLOGY

A randomized controlled trial was conducted at Hepatitis Clinic, People Medical College Hospital, Nawabshah from August 20, 2020, to February 20, 2021. The Sampling Technique was a non-probability, consecutive sampling. A sample size of 146 (73 in each group) was calculated at 95% confidence level and 90% power of study considering the progression of fibrosis in 10% of the statins users and 29% of control group<sup>9</sup>. The inclusion criteria of our study were Patients of both genders having chronic hepatitis C infection diagnosed as per operational definition and having F2 – F3 stage of liver fibrosis and patients willing to participate and sign written informed consent. The exclusion criteria were the patients having decompensated liver disease or Hepatocellular carcinoma, or have liver disease due to causes other than hepatitis C and the patient already taking statin therapy.

All cases fulfilling the inclusion criteria during the study period were enrolled after written informed consent obtained. The patients were randomly divided into two equal groups using a computer-generated random number table. Group-A was administered with statins in addition to antiviral treatment while Group-B was given anti-viral medications only. Demographic and baseline details of the study subjects were noted and recorded.

Information regarding diabetes, hypertension, smoking, alcohol intake was also recorded. Stages of fibrosis were determined by shear wave elastography at the start of the study and after 6 months. All the data including age, gender, height, weight, BMI, education, duration of disease, child-pugh class, hypertension, diabetes, dyslipidemia, smoking alcohol use, and dose of statin were recorded in predesigned proforma. The efficacy of the drug was labeled.

All the data were entered and analyzed in Statistical Packages for Social Sciences (SPSS) v25.0. Qualitative variables like educational status, obesity, diabetes, hypertension, dyslipidemia, smoking, alcohol use, and obesity were described using frequencies and percentages. Shapiro-Wilk test was used to test the normality of the data while Levene's test was applied to determine the equality of variance in the data. Normally distributed quantitative variables e.g. age, BMI, AST, ALT levels, child-pugh score, duration of hepatitis, and platelet levels were described using mean and S.D, while non-normally distributed variables were described using median (IQR) values. Efficacy was compared between both groups by using chi-square. Effect modifiers such as age, gender, obesity, education, duration of disease, stages of fibrosis, child-pugh class, hypertension, diabetes, dyslipidemia, smoking, and alcohol use were controlled through

stratification. Post-stratification, the chi-square test was used taking p-value  $\leq 0.05$  as statistically significant.

## RESULTS

Total 146 (73 in each group) patients having chronic hepatitis C infection were selected for this study. One of the groups was administered with statins in addition to antiviral treatment (group-A) while the other group (group-B) was given anti-viral medications only. As shown in Table-1, the overall 98 (67.1%) male while 48 (32.9%) females were included in our study. Most of the cases of Hepatitis C infection was found to be in age group  $>45$  having 82 (56.2%) patients. In our study, 70 (47.9%) patients have the infection for the past 1-3 years. 68 (46.6%) patients were classified as Class-A Child-Pugh Class. The frequency of patients having hypertension, diabetes, Obesity and dyslipidemia were 47 (32.2%), 57 (39%), 23 (15.8%), and 24 (16.4%) respectively.

The comparison can be seen in Table-2 between the antiviral medications with and without statins in treating the patients of hepatitis C infection. 66 (90.4%) patients were found to be successfully treated with statins along with antiviral medications while only 7 (9.6%) patients progressed into fibrosis. However, only 50 (68.5%) patients were successfully treated with antiviral medications alone with 23 (31.5%) of them progressing into hepatic fibrosis. The relation of the treatment regimen with the progression into hepatic fibrosis was found to be significant ( $p=0.001$ ).

The stratification can be seen in Table-3 between the group who received statins along with antiviral medications with the group who get only antiviral medications. The prevalence of Stage-F2 and Stage-F3 fibrosis was found to be higher (45 and 21 patients respectively) in the group who received statins as compared to the group who only received antiviral medications (36 and 14 patients respectively).

**Table 1.** Comparison of gender, age, Child=Pugh Class, hypertension, diabetes, Obesity, duration of disease, dyslipidemia, smoking, alcohol use, education status, and stages of fibrosis between groups

Variables	Group-A n (%)	Group-B (%)	Total
<b>Gender</b>			
Female	22 (30.1%)	26 (35.6%)	48 (32.9%)
Male	51 (69.9%)	47 (64.4%)	98 (67.1%)
<b>Age in years</b>			
20-30	18 (24.7%)	19 (26%)	37 (25.3%)
31-45	13 (17.8%)	14 (19.2%)	27 (18.5%)
$>45$ years	42 (57.5%)	40 (54.8%)	82 (56.2%)
<b>Duration of Hepatitis C</b>			
$<1$ year	27 (37%)	30 (41.1%)	57 (39%)
1-3 years	36 (49.3%)	34 (46.6%)	70 (47.9%)

> 3 years	10 (13.7%)	9 (12.3%)	19 (13%)
<b>Child-Pugh Class</b>			
Class-A	32 (43.8%)	36 (49.3%)	68 (46.6%)
Class-B	18 (24.7%)	16 (21.9%)	34 (23.3%)
Class-C	23 (31.5%)	21(28.8%)	44 (30.1%)
<b>Hypertension</b>	25 (34.2%)	22 (30.1%)	47 (32.2%)
<b>Diabetes Mellitus</b>	30 (41.1%)	27(37%)	57 (39%)
<b>Obesity</b>	13 (17.8%)	10 (13.7%)	23 (15.8%)
<b>Dyslipidemia</b>	11 (15.1%)	13 (17.8%)	24 (16.4%)
<b>Smoking</b>	29 (39.7%)	27 (37%)	56 (38.4%)
<b>Alcohol use</b>	7 (9.6%)	5 (6.8%)	12 (8.2%)
<b>Educational Status</b>			
Illiterate	9 (12.3%)	10 (13.7%)	19 (13%)
Primary	15 (20.5%)	16 (21.9%)	31 (21.2%)
Middle	14 (19.2%)	15 (20.5%)	29 (19.9%)
Matric	22 (30.1%)	21 (28.8%)	43 (29.5%)
Bachelor	13 (17.8%)	11 (15.1%)	24 (16.4%)
<b>Stages of fibrosis</b>			
Stage-F2	47(64.4%)	43(58.9%)	90(61.6%)
Stage-F3	26(35.6%)	30(41.1%)	56(38.4%)

**Table 2.** Comparison of efficacy of the treatment given between groups

<b>Efficacy</b>	<b>Group-A</b>	<b>Group-B</b>	<b>Total</b>	<b>P value</b>
Yes	66 (90.4%)	50 (68.5%)	116 (79.5%)	0.001
No	7 (9.6%)	23 (31.5%)	30 (20.5%)	
Total	73 (100.0%)	73 (100.0%)	146 (100.0%)	

**Table 3.** Stratification of efficacy between groups with respect to gender, age, Child=Pugh Class, hypertension, diabetes, Obesity, duration of disease, dyslipidemia, smoking, alcohol use, education status, and stages of fibrosis

<b>Variables</b>	<b>Efficacy</b>	<b>Group-A</b>	<b>Group-B</b>	<b>Total</b>	<b>P value</b>
<b>Gender</b>					
Male	Yes	44 (86.3%)	30(63.8%)	74(75.5%)	0.01
	No	7 (13..7%)	17(36.2%)	24(24.5%)	
Female	Yes	22 (100%)	20(76.9%)	42(87.5%)	0.016
	No	0 (0%)	6(23.1%)	6(12.5%)	
<b>Age in years</b>					
20-30	Yes	17( 94.4%)	14 (73.7%)	31(83.8%)	0.087
	No	1(5.6%)	5 (26.3%)	6(16.2%)	
31-45	Yes	11(84.6%)	11 (78.6%)	22(81.5%)	0.686
	No	2(15.4%)	3 (21.4%)	5(18.5%)	
>45 years	Yes	38(90.5%)	25 (62.5%)	63(76.8%)	0.003
	No	4(9.5%)	15 (37.5%)	19(23.2%)	

<b>Duration of Hepatitis C</b>					
<1 year	Yes	23(85.2%)	20(66.7%)	43(75.4%)	0.105
	No	4(14.8%)	10 (33.3%)	14(24.6%)	
1-3 years	Yes	33(91.7%)	23(67.6%)	56(80%)	0.012
	No	3(8.3%)	11(32.4%)	14(20%)	
> 3 years	Yes	10(100%)	7(77.8%)	17(89.5%)	0.115
	No	0(0%)	2(22.2%)	2(10.5%)	
<b>Child-Pugh Class</b>					
Class-A	Yes	29(90.6%)	24(66.7%)	53(77.9%)	0.017
	No	3(9.4%)	12(33.3%)	15(22.1%)	
Class-B	Yes	17(94.4%)	13(81.3%)	30(88.2%)	0.233
	No	1(5.6%)	3(18.8%)	4(11.8%)	
Class-C	Yes	20(87%)	13(61.9%)	33(75%)	0.055
	No	3(13%)	8(38.1%)	11(25%)	
<b>Hypertension</b>	Yes	22(88%)	15(68.2%)	10(21.3%)	0.098
	No	3(12%)	7(31.8%)	47(100%)	
<b>Diabetes Mellitus</b>	Yes	25(83.3%)	14(51.9%)	39(68.4%)	0.011
	No	5(16.7%)	13(48.1%)	18(31.6%)	
<b>Obesity</b>	Yes	11(84.6%)	6(60%)	17(73.9%)	0.183
	No	2(15.4%)	4(40%)	6(26.1%)	
<b>Dyslipidemia</b>	Yes	7(63.6%)	5(38.5%)	12(50%)	0.219
	No	4(36.4%)	8(61.5%)	12(50%)	
<b>Smoking</b>	Yes	23(79.3%)	16(59.3%)	39(69.6%)	0.103
	No	6(20.7%)	11(40.7%)	17(30.4%)	
<b>Alcohol use</b>	Yes	2(28.6%)	1(20%)	3(25%)	0.735
	No	5(71.4%)	4(80%)	9(75%)	
<b>Educational Status</b>					
Illiterate	Yes	9(100%)	8(80%)	17(89.5%)	0.156
	No	0(0%)	2(20%)	2(10.2%)	
Primary	Yes	13(86.7%)	8(50%)	21(67.7%)	0.029
	No	2(13.3%)	8(50%)	10(32.3%)	
Middle	Yes	12(85.7%)	13(86.7%)	25(86.2%)	0.941
	No	2(14.3%)	2(13.3%)	4(13.8%)	
Matric	Yes	21(95.5%)	15(71.4%)	36(83.7%)	0.033
	No	1(4.5%)	6(28.6%)	7(16.3%)	
Bachelor	Yes	11(84.6%)	6(54.5%)	17(70.8%)	0.106
	No	2(15.4%)	5(45.5%)	7(29.2%)	
<b>Stages of fibrosis</b>					
Stage-F2	Yes	45(95.7%)	36(83.7%)	81(90%)	0.058
	No	2(4.3%)	7(16.3%)	9(10%)	
Stage-F3	Yes	21(80.8%)	14(46.7%)	35(62.5%)	0.009
	No	5(19.2%)	16(53.3%)	21(37.5%)	

## DISCUSSION

We studied the effects of statin use on 146 patients with chronic hepatitis C infection and found out that it effectively slows down the process of progression into liver fibrosis. These similar findings have been shown in the study conducted by Simon et al in a HALT-C trial cohort as well<sup>9</sup>. The use of statins for the management of chronic liver disease globally is quite common. There has been evidence suggesting that its safe in the cases of chronic liver diseases<sup>10,11</sup>. Significant evidence revealed the anti-neoplastic, anti-inflammatory, and antiangiogenic effects and its role as an antiproliferative agent<sup>12-14</sup>. In a nationwide conducted case-control study by Kim et al, 1642 patients with hepatocellular carcinoma(HCC) were evaluated and it was concluded that the use of statins can decrease the risk of fibrosis, which leads to HCC, significantly<sup>15</sup>. The role of statins as an antiviral and immunomodulatory is widely known and is the major mode of action through which statins reduce the risk of progression into liver fibrosis in hepatitis-C patients<sup>16</sup>.

In our study, the efficacy of statins in diabetic patients was found to be 83.3% which is slightly lower as compared to the efficacy in patients without diabetes (95.3%). However, in the study done by Gowtham, poor diabetes control was found to have a poor response of the antiviral agents and a lower sustained virologic response (SVR)<sup>17</sup>. The inclusion of different variables including hypertension, diabetes, smoking, and alcohol use, duration of studies, and the education status helped the results to be analyzed on a broader scale. This was one of the strengths of our study.

The conventional treatment regimen of the Hepatitis C virus is IFN and ribavirin. In one of the randomized control trials conducted in the USA, fluvastatin was included with IFN and ribavirin and its effects were compared with the conventional hepatitis-C virus therapy. It found out that the group with the statins was associated with SVR at a rate higher than its counterpart<sup>18</sup>. It is important to know that not all statins have the same level of effects. A study was carried out to determine the effects of different types of statins on the replication of the Hepatitis C virus. The statins included were atorvastatin, fluvastatin, simvastatin, lovastatin, and pravastatin. It reported Fluvastatin having the most potent anti-HCV activity while lovastatin having the weakest potential of being an anti-HCV<sup>19</sup>. The same study also reported the combined effect of IFN with statins (except pravastatin) to have shown a strongest inhibitory effect on the replication of HCV RNA<sup>19</sup>.

Our study did not test the efficacy of different statins in reducing the progression of HCV infection into fibrosis which is the major limitation of our study. It also included data from the single centre and a very small number of patients were included due to which only limited data has been analyzed. Such studies should be conducted on a broader scale in the future and should include the diversity of patients to get to know the significance of statins in our population in reducing the progression of HCV.

## CONCLUSION

Findings demonstrate a significant reduction in the risk of fibrosis progression among statin users with advanced chronic hepatitis C. These results support a possible role for statins in the prevention of liver disease progression. Further studies with a larger proportion of statin users and pathologic endpoints are warranted. Such analyses will help to define the optimal timing of statin initiation, the ideal duration of therapy, and the impact of statins on those with less severe fibrosis or other etiologies of liver disease.

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