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Original Research Article.

To Study the Impact of Direct Acting Antivirals (DAA) Therapy on Liver Fibrosis in Chronic Hepatitis C Infection by Non-Invasive Methods (APRI, FIB-4, Platelet Count and Transient Elastography)

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ABSTRACT

Background: A major complication of Hepatitis C Virus infection is liver fibrosis and its assessment following treatment is a substantial challenge.

Aim: The aim of this study was to study the impact of direct acting antivirals (DAA) on liver fibrosis by non-invasive methods and assess the effectiveness of DAA in patients with Chronic Hepatitis C viral infection.

Methods: A prospective study was conducted on 100 consecutive patients of Chronic Hepatitis C who received a complete course of DAA therapy. The patients were assessed at start of DAA therapy (baseline), at the completion of therapy and Sustained Virologic Response (SVR) i.e. 12 weeks after completion of therapy with non-invasive methods such as APRI, FIB-4, Platelet count and Liver Stiffness Measurement (LSM) using Transient elastography.

Results: In patients who received DAA therapy, the increase in Platelet count and improvement in APRI and FIB-4 values from baseline to SVR 12 were statistically significant ($p<0.001$) but from baseline to completion of treatment were statistically insignificant. The decrease in LSM by TE from baseline to SVR 12 and from baseline to completion of treatment was both statistically significant. The increase in Platelet count and improvement in APRI and FIB-4 values, and decrease in LSM by TE from baseline to SVR 12 were statistically significant among Compensated Cirrhosis and Non-Cirrhosis patients. In patients with decompensated cirrhosis, the decrease in platelet count and the improvement in APRI and FIB-4 were seen but both of these were found statistically insignificant.

Conclusion: There is improvement in non-invasive methods such as APRI, FIB-4, Platelet count and Transient elastography thereby improving clinical outcomes after HCV eradication with DAA thus these non-invasive methods can be used to assess the effectiveness of the antiviral therapy.

Keywords: Chronic Hepatitis C, Liver fibrosis, Direct Acting Antivirals, Sustained Virologic Response, Cirrhosis.

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INTRODUCTION

Hepatitis C virus (HCV) is recognized as a major public health problem. Over 170 million people are infected with the virus worldwide of whom 71 million develops chronic infection.[1,2] The estimated prevalence of HCV infection in India is 0.5-1.5%[3] and in Punjab it is 5.2%.[4] About 60-70% cases of acute hepatitis C virus progress to chronic hepatitis C which develops independent of any identifiable risk factors.[5,6,7]

The goal of Direct Acting Antivirals (DAA) is to prevent disease progression and fibrosis by eradicating the HCV.[8] Currently only SVR 12 (Sustained Virologic Response) i.e. undetectable levels of HCV RNA at 12 weeks after completion of therapy is used to predict eradication of HCV thus prevention of liver fibrosis. Thus liver fibrosis assessment can be used determine the effectiveness of DAA.[9,10] Liver biopsy is the gold standard for staging of liver fibrosis but being invasive in nature[11], non-invasive methods such as Aspartate Transaminase to Platelet Ratio Index (APRI), Fibrosis Index Based on 4 factors (FIB-4), Platelet count and Transient Elastography (TE) are commonly used for liver fibrosis stage assessment.

There have been studies showing that the DAA therapy for HCV infection result in increase in platelet count, lowering of liver enzymes causing improvements in APRI and FIB-4 values and improvement in Liver Stiffness Measurements (LSM) measured by TE.[12-15] Thus estimation of magnitude of decline in liver fibrosis non-invasively after viral eradication with DAA may identify patients likely to be at low risk of liver related complications.[12] In this prospective study, we had aimed to assess the temporal effect of DAA using non-invasive methods and thus the effectiveness of DAA in decreasing mortality and morbidity of Chronic Hepatitis C (CHC) patients.

MATERIALS AND METHODS

Our prospective observational study was conducted on 100 consecutive patients of Chronic Hepatitis C who presented to Medicine OPD/IPD at Rajindra Hospital/Government Medical College, Patiala, a tertiary care hospital in Northern India over a period of 1 year from 1st December 2020 to 30th November 2021. Chronic Hepatitis C patients with age 18-75 years who received a complete course of DAA therapy were included in this study. CHC patients with age <18 years, >75 years, failure to achieve SVR, pregnant and lactating mothers, co-infection with Hepatitis B or HIV, patients with cirrhosis due to other causes of liver disease were excluded. The baseline routine blood investigations like CBC, RFTs, LFTs, PTI/INR, TSP/DSP were done. The normal value of AST and ALT was taken as 0-40 IU/L and the data thus generated was used to calculate APRI and FIB-4 values.

APRI value was calculated with formula: APRI[16] = $\frac{\frac{AST\ level}{AST\ (ULN)}}{Platelet\ Count} \times 100$

APRI < 2: No Cirrhosis (APRI ≤ 1.5: No significant fibrosis and APRI 1.6-1.9: Significant fibrosis) and APRI ≥ 2.0: Cirrhosis.

FIB-4 value was calculated with the formula: FIB-4[16] = $\frac{Age \times AST}{Platelet\ Count \times \sqrt{ALT}}$

FIB-4 < 3.25: No Cirrhosis (FIB-4 ≤ 1.45: No significant fibrosis and FIB-4 1.46-3.24: Significant fibrosis) and FIB-4 ≥ 3.25: Cirrhosis.

Mean value of stiffness was measured in kilopascal (kPa) after screening multiple sections of liver using TE (Fibroscan).

LSM[16] < 12.5kPa: No Cirrhosis (LSM < 8 kPa: No significant fibrosis and LSM 8-12.4 kPa: Significant fibrosis) and LSM ≥ 12.5 kPa: Cirrhosis.

The patients were assessed at the start of DAA therapy (baseline), at the completion of therapy and at Sustained Virologic Response 12 (SVR 12) i.e. 12 weeks after completion of therapy. Outcomes were measured with APRI value, FIB-4 value, Platelet count and Liver Stiffness Measurement using Transient elastography. A detailed clinical history, examination, Ultrasonography, APRI value, FIB - 4 value and LSM using TE were calculated to group the patient into Non-Cirrhosis (NC), Compensated Cirrhosis (CC) and Decompensated Cirrhosis (DC). SVR 12 is taken as the primary endpoint of successful therapy under Mukh Mantri Punjab Hepatitis C Relief Fund (MMPHCRF) and National Viral Hepatitis Control Program (NVHCP).[17]

Data generated from study was analysed using computer software, statistical package for social sciences (SPSS). To describe the descriptive data statistics, frequency analysis and percentage analysis was used for categorical variables and the mean & S.D. were used for continuous variables. Univariate and multivariate analysis was done with t-test and Wilcoxon Signed Ranks Test. p value of less than 0.05 was considered to be statistically significant.

Table 1: Biochemical parameters and LSM at baseline, completion of treatment and SVR 12 of all CHC patients

	AST/SGOT (IU/L)	ALT/SGPT (IU/L)	Platelet Count ($\times 10^9$/L)	APRI	FIB-4	LSM by Transient Elastography(kPa)
Baseline (mean)	102.34	106.90	176.60	1.90	3.57	19.04
Completion of treatment (mean)	95.59	94.73	171.36	1.69	3.32	18.25
SVR 12 (mean)	82.40	79.89	217.62	1.23	2.54	15.67
p value of change from baseline to completion	0.021	0.012	0.574	0.166	0.382	0.001
p value of change from baseline to SVR 12	0.001	0.001	0.001	0.001	0.001	0.001

Table 2: Biochemical parameters and LSM at baseline and SVR 12 of NC, CC and DC CHC patients

		Platelet Count ($\times 10^9$/L)	APRI	FIB-4	LSM by Transient Elastography(kPa)
Non-Cirrhosis (NC) (N=25)	**Baseline (mean)**	203.72	1.18	1.76	8.36
	SVR 12 (mean)	266.24	0.68	1.28	6.63
	p value	0.001	0.001	0.009	0.001
Compensated Cirrhosis (CC) (N=53)	**Baseline (mean)**	163.11	2.49	4.41	21.04
	SVR 12 (mean)	212.85	1.55	2.79	16.36
	p value	0.001	0.001	0.001	0.001
Decompensated Cirrhosis (DC) (N=22)	**Baseline (mean)**	178.27	1.29	3.58	26.38
	SVR 12 (mean)	173.86	1.09	3.39	24.27
	p value	0.783	0.089	0.513	0.074

OBSERVATIONS AND RESULTS

Out of the 100 patients, the majority of patients (n=47) belonged to 31-50 years of age group, with a minimum age of 22 years and a maximum age of 75 years. Sixty four percent of the patients were males and 36% were females. In our study of 100 patients, 75 were cirrhotic out of which 53 patients (70.6%) were of Compensated Cirrhosis and 22 patients (29.3%) were Decompensated Cirrhosis. Rest 25 patients were non cirrhotic.

In our study, the decrease in AST and ALT values from baseline to completion of treatment and from baseline to SVR 12 were both statistically significant. In our study after DAA therapy, the

increase in Platelet count and improvement in APRI and FIB-4 values from baseline to SVR 12 were statistically significant but from baseline to completion of treatment were statistically insignificant. Mean APRI improved from significant fibrosis range at baseline to no significant fibrosis range at SVR 12. Mean FIB-4 improved from cirrhosis range at baseline to significant fibrosis range at SVR 12. In our study, the decrease in LSM by TE from baseline to SVR 12 and from baseline to completion of treatment was both statistically significant. In our study after DAA therapy, the increase in Platelet count and improvement in APRI and FIB-4 values and decrease in LSM by TE from baseline to SVR 12 were statistically significant among Compensated Cirrhosis and Non-Cirrhosis patients. In patients with decompensated cirrhosis, the decrease in platelet count and the improvement in APRI and FIB-4 were seen but both of these were found statistically insignificant.

DISCUSSION

The decline in liver fibrosis following viral eradication with DAA is probably a combination of resolution of hepatic inflammation and regression of fibrosis, with early decline mainly related to resolution of inflammation whereas continued decline after treatment related to fibrosis regression; as has been observed with paired liver biopsy study by Pan et al. [18] Thus detailed prospective studies are warranted to evaluate decline in liver fibrosis by non-invasive methods to assess effectiveness of DAA. In our study, a higher number of males were affected by CHC than females possibly due to the high-risk behavior among males. In our study, 75% of patients were Cirrhotic and 60% of total patients belonged to age group 41-70 years implying that risk of cirrhosis increases with increasing age at time of diagnosis and longer duration of infection.

In our study, the mean value of platelet count was inversely related to severity of disease which is comparable to study done by Dienstag et al.[22] Thus platelet count is related to degree of fibrosis and there is also increase in platelet count after completion of treatment which may be due to increase in Thrombopoeitin caused by decreased necroinflammation of liver thus the improvement in platelet count can be attributed to regression in liver fibrosis thus assessing the effectiveness of DAA. Similar results were seen in studies by Yen-Chun et al[19], Deterding et al[20] and Pons et al.[21]

The improvement in APRI and FIB-4 values were studied by Hsu et[23] al in which there was statistically significant decline within 2 weeks of start of DAA treatment but in our study, there is statistically insignificant decline in APRI and FIB-4 values and statistically significant decline in AST and ALT values from baseline to completion of treatment. This can be attributed to decrease in necroinflammation immediately after start of treatment leading to decrease in AST and ALT values. Thus, APRI and FIB-4 are better markers than AST and ALT to assess effectiveness of DAA as APRI and FIB-4 include age and platelet count also.

Moreover, there was improvement in both APRI and FIB-4 value at SVR 12. Similar results were seen in Hsu et al[23] and Agwa et al.[24] The difference between interpretation of APRI and FIB-4 values i.e. APRI value improved to no significant fibrosis range but FIB-4 value improved to significant fibrosis range might be due to age factor in FIB-4 as 67% of patients in this study were in older age group (41-80 years) leading to high FIB-4 value. These findings are consistent with study done by Mei Lu et al.[25]

Decrease in APRI and FIB-4 values at SVR 12 was statistically significant among Compensated Cirrhosis and Non-Cirrhosis patients but statistically insignificant among Decompensated Cirrhosis patients. Therefore, APRI and FIB-4 are important methods to study fibrosis regression after DAA in Compensated Cirrhosis and Non-Cirrhosis as compared to Decompensated Cirrhosis patients.

We found that there is decrease in LSM by TE during and after treatment and results were comparable to studies done by Knop et al[26] , Lledo et al[27] , Agwa et al[24] and Singh et al.[12] In our study, decrease in LSM by TE was statistically significant among patients with Compensated Cirrhosis and Non Cirrhosis patients and statistically insignificant among Decompensated Cirrhosis patients. Therefore, decompensated cirrhosis appears to regress less than compensated cirrhosis and non-cirrhosis. This is comparable to study by Rockey et al[28] and contrary to study by Singh et al l[12] which showed that there is higher decline in LSM with higher baseline LSM in patient treated with DAA. The mean LSM value is higher for decompensated cirrhosis than compensated cirrhosis thus increase in LSM has clinical implications and high risk of complications. Conversely decrease in LSM post treatment will translate into clinical benefits and will lower the risk of complications thus establishing the effectiveness of DAA.

The limitation of our study includes the small sample size and short term follow up of the patient's following treatment.

CONCLUSION

It can be concluded from the study that after DAA therapy, there is a significant improvement in parameters used in assessing fibrosis such as APRI, FIB-4, Platelet count and Transient elastography. Thus these non-invasive methods can be used to assess the effectiveness of the antiviral therapy and follow up patients after DAA. Considering the high number of CHC patients, early detection and treatment with highly effective DAA evident by improvement in non-invasive methods can prevent further complications and thus improve clinical outcomes by decreasing morbidity and mortality.

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