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Outcome Analysis with Directly Acting Antiviral Agents in Chronic Hepatitis C Patients in Relation to Clinical, Laboratory and FibroScan Parameters in a Tertiary Care Centre of North Bengal

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Abstract

***Introduction:** Hepatitis C virus (HCV) infection, one of the most prevalent viral diseases responsible for mortality throughout the world, particularly for its dreaded chronic hepatic complications, is now considered highly amenable to be treated successfully with the very effective antiviral drugs available. Direct-acting antiviral (DAA) agents are receiving discernible attention as a treatment of chronic Hepatitis C because of its improved clinical outcome, sustained virological response (SVR) and reversibility of liver fibrosis.*

***Background and objectives:** There are sparse data regarding rapidity of liver fibrosis regression following HCV eradication. Here we want to establish the reversibility of clinical outcomes, SVR and FibroScan parameters within an established timeframe.*

***Methods:** Total 100 patients with serologically proven HCV infection excluding patients with concomitant Hepatitis B and HIV infection, chronic kidney disease and chronic alcoholics attending North Bengal Medical College and Hospital, both in-patient and out-patient, during a 1.5 years period were enrolled in a prospective, observational, longitudinal study. Post-treatment outcomes with DAA were measured in terms of fibrosis markers (APRI, Median stiffness and METAVIR score by FibroScan), sustained virological response, lab parameters and features of portal hypertension.*

***Results:** Significant clinical improvement was noted both clinically and objectively. Signs of portal hypertension like ascites reduced from 11% to 1%, melena reduced from 16% to 4%, and haematemesis from 6% to 3% after treatment completion. HCV RNA was reduced from baseline mean of 3816581.9 to 9.9 (SD 3.1) which corroborated with the regression of liver fibrosis by reduction of non-invasive parameters like APRI score from baseline mean of 1.3 to 1.0 and median stiffness in FibroScan from mean of 8.76 kPa to 6.70 kPa. Also, there was 64% regression in METAVIR fibrosis stage after completion of DAA.*

***Conclusion:** 12 weeks treatment with DAA led to reduction of features of portal hypertension, and regression of liver fibrosis which was corroborated with achievement of SVR.*

***Key words:** Chronic Hepatitis C, DAA, FibroScan, HCV RNA quantitative assay.*

***Abbreviation:** SOF = Sofosbuvir, DCV = Daclatasvir, VEL = Velpatasvir, DAA = Direct acting antiviral, AST = Aspartate Transaminase, APRI = AST to Platelet Ratio Index.*

Introduction

Hepatitis C virus (HCV) is a leading cause of liver-related morbidity and mortality worldwide. An estimated 71 million people are affected globally by chronic hepatitis C infection[1-3]. HCV accounts for roughly 0.7 million deaths per year across the globe[4]. The estimated prevalence of HCV infection is as high as 5.2% depending on the geographical area[5]. The development of direct-acting antiviral agents (DAA) has been the most significant scientific development for treatment of HCV infection[6]. Prior to the advent of DAAs, because of the progressive and perceived irreversible hepatic fibrosis, HCV infection accounted for more than 70% of chronic liver disease related morbidity and mortality, particularly in nations with a high HCV burden[7]. This perception of irreversibility of hepatic fibrosis has changed as there is evidence of regression in fibrosis stage after successful DAA treatment[8]. The purpose of our study was to investigate post-treatment outcomes with DAA in chronic hepatitis C patients in this part of the country with respect to clinical improvement, sustained virological response, and reversibility of liver fibrosis.

Aims

1. Effectiveness of antiviral regimen for sustained virologic response (SVR).

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2. Improvement of clinical and laboratory parameters after completion of antiviral treatment (DAA).
3. Improvement of FibroScan parameters following treatment.

Material and Methods

This study enrolled chronic HCV patients at North Bengal Medical College and Hospital, Darjeeling between 1st April 2021 and 30th September 2022. It was an observational, prospective, longitudinal study, which enrolled 100 patients of Hepatitis C infection, excluding patients with concomitant Hepatitis B and HIV infection, chronic kidney disease and alcoholic liver disease (patients with liver disease having history of significant amount of alcohol intake, i.e., more than 2 drinks per day for women and more than 3 drinks per day for men for 10 years or more [1 drink equals ~14 g of ethanol, which is 1 beer, 4 oz of wine, or 1 oz of 80% spirits]) and other causes (e.g., Wilson's disease, etc.). HCV infection was confirmed by HCV-RNA quantification assay in all patients. Cirrhosis was diagnosed by experienced radiologists in the Radiology Department, based on the results of imaging modalities such as ultrasonography (USG) and FibroScan (LOGIQ P9 GE MAKE shear wave transient Elastography). Seven patients with massive ascites in whom FibroScan was difficult to perform, were excluded. Clinical outcomes and other laboratory parameters (i.e., complete blood count, liver function tests, etc.,) were evaluated in all patients. AST to platelet ratio index (APRI) score, a useful non-invasive method of assessing liver fibrosis, was also evaluated.

APRI score calculation

APRI score = (AST/ULN) x 100)/platelet count (10^9/L)

For APRI, ULN signifies the upper limit of normal for AST which was taken as 40 U/L in our study.

APRI score greater than 0.7 and greater than 1.0 was used for predicting significant hepatic fibrosis and cirrhosis respectively[9].

Table I: Liver FibroScan.

Liver Fibrosis staging	METAVIR score	Median stiffness (kPa)
Normal-Mild	F1	6.48 - 6.60
Mild-Moderate	F2	6.60 - 8.07
Moderate-Severe	F3	8.07 - 9.31
Cirrhosis	F4	>9.31

Table I shows Optimal LOGIQ S8 shear wave elastography cut-off values in terms of shear wave speed (m/s) and Young's Modulus (kPa) for classifying fibrosis stage in the patient population under evaluation. Data was acquired using R3.1.9 equivalent software and the C1-6-D probe.

Treatment with DAAs

Standard treatment protocol was followed as per the National Viral Hepatitis Control Programme guidelines[10]:

- Non cirrhotic: Sofosbuvir + Daclatasvir (400/60 mg) for 12 weeks.
- Cirrhosis without decompensation: Sofosbuvir + Velpatasvir (400/100 mg) for 12 weeks.
- Cirrhosis with decompensation: Sofosbuvir + Velpatasvir (400/100 mg) for 24 weeks.

Patients were evaluated 12 weeks post-treatment (i.e., at 24th week and 36th week in non-cirrhotic, compensated cirrhosis and decompensated cirrhosis, respectively) compared to baseline data.

Statistical analyses

Variables were reported as mean ± SD. Categorical variables were compared by Chi-squared test. Continuous variables were compared by Student's t-test. Statistical analyses were performed using IBM SPSS software, version 21 with p value < 0.05 considered statistically significant.

Results

Characteristics of patients

A total of 100 patients, ranging from 19 to 70 years of age, 60 (60%) patients were in the age bracket of 35 to 54 years and the mean age at diagnosis was found to be 41.9 (± 11.2) years. Majority of the infected people were male (78%) *versus* female (22%). 15% of patients had a definite history of IV drug abuse. 13% patients had pedal oedema, 11% patients had icterus, and only 2% patients had fever.

Among 100 patients, 57 were non-cirrhotic, whereas 43 were cirrhotic (20 were compensated and 23 were decompensated).

As a complication of portal hypertension in decompensated cirrhosis, melena (16%) was more common at presentation compared to haematemesis (6%). During baseline clinical evaluation, splenomegaly was more prevalent compared to hepatomegaly (27% vs 7%), and 11% patients had clinical ascites.

Baseline biochemical parameters were recorded as mean ALP 103.3 IU/L, mean SGPT 77.3 IU/L, mean SGOT 79.5 IU/L. Pre-treatment mean platelet count was 1.70,000/mm^3.

Mean HCV RNA was 3816581.9 copies/ml. 12 weeks post-treatment, overall mean HCV RNA was reduced to 9.9

copies/mL.

The number of patients with melena was reduced from 16 to 4 patients, haematemesis was reduced from 6 to 3 patients, and ascites was reduced from 11 to 1 patient as compared to baseline *versus* post-treatment.

APRI score

For Daclatasvir receiving patients (n = 57) mean APRI of 0.71 was reduced to 0.66 (Fig. 1). Before treatment, there were 10 patients with APRI score >1 which was reduced to 6 patients. Similarly, patients with APRI score ≤0.7 rose from 32 to 37 following Daclatasvir treatment.

For Velpatasvir receiving patients (n = 43), pre-treatment APRI score of 2.15 was reduced to 1.49 post-treatment (Fig. 2). Patients with APRI score >1 were 30, which was reduced to 23, and patients with APRI score ≤0.7 rose from 4 to 11 after Velpatasvir treatment. Overall, the pre-treatment mean APRI score of 1.33 was reduced to 1.01 post-treatment.

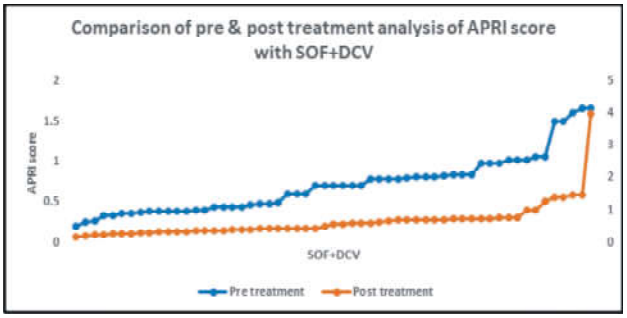

Fig. 1: *Comparison of APRI score in patients treated with Sofosbuvir (SOF) and Daclatasvir (DCV).*

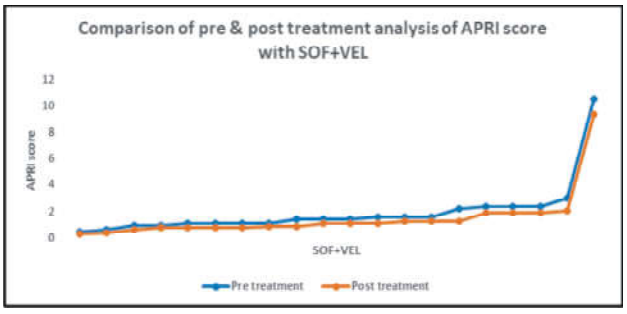

Fig. 2: *Comparison of APRI score in patients treated with Sofosbuvir (SOF) and Velpatasvir (VEL)*

FibroScan

Among Daclatasvir treated patients, pre-treatment liver stiffness of 6.88 kPa was reduced by 10.47% to 6.16 kPa (Fig. 3); for Velpatasvir, it was reduced by 34.13%, from 11.25 kPa to 7.41 kPa (Fig. 4). Overall baseline median stiffness of 8.76 kPa was reduced to 6.70 kPa (-23.52%) after treatment.

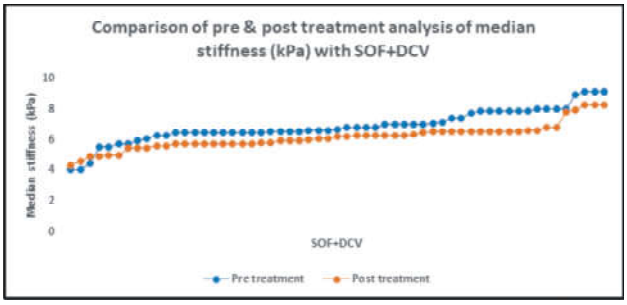

Fig. 3: *Comparison of median stiffness in patients treated with Sofosbuvir (SOF) and Daclatasvir (DCV).*

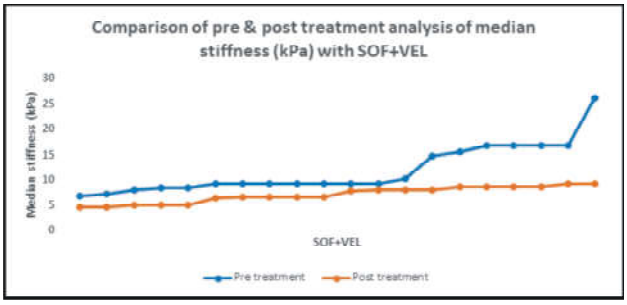

Fig. 4: *Comparison of median stiffness in patients treated with Sofosbuvir (SOF) and Velpatasvir (VEL).*

Discussion

Donahue *et al* reported that the HCV prevalence in Baltimore, Maryland, was 85% for IDUs (Injection drug users)[10]. Quite interestingly, only 15% of patients had a definite history of IV drug abuse in our study. This points to the fact that other modes of viral transfer in adults like unsafe medical practices (of repeated syringe use), occupational exposure, sexual exposure, using same razor for multiple people in saloons and many others are yet to be thoroughly explored at the community level. This study found that history of melena was more common at presentation compared to haematemesis (16% vs 6%), only 2% patients had fever, 11% patients had icterus and 13% patients had pedal oedema. During baseline clinical evaluation, splenomegaly was more prevalent compared to hepatomegaly (27% vs 7%), and 11% patients had clinical ascites. All this baseline clinical evaluation depicted the fact that signs and symptoms of portal hypertension contributed to the most significant presenting complications of HCV infection where splenomegaly was the most consistent sign followed by a history of melena and ascites.

Ascites was reduced to 1% (down from 11% at baseline,

Chi square 8.173, p value 0.002). Only 4% patients reported melena (compared to 16% at baseline, Chi square 21.875, p value <0.001) and 3% reported haematemesis (compared to 6% at baseline, Chi square 48.454, p value <0.001) after 36 weeks of starting DAA. Similar improvement was noticed in platelet count as well, with a baseline mean of 1.70,000/mm^3 (SD 0.6) to 12 weeks post-treatment mean value of 1.90,000/mm^3 (SD 0.6) (p value <0.001).

In our study, the most dramatic change was noticed in HCV RNA status where a baseline mean of 3816581.9 (SD 775582.8) was reduced to a mean of 9.9 (SD 3.1) with a t value of 4.921 and a p value of <0.001 after 12 weeks of treatment completion. This data re-establishes the excellent sustained virologic response (SVR) after giving DAAs for treating HCV infection.

APRI score was improved following treatment, which was statistically significant (from a baseline mean of 1.3, (SD 1.6) to post-treatment mean of 1.0, (SD 1.3), t value 3.933, p value <0.001). But one patient had a deterioration of APRI score from 0.26 to 4 which also corresponded to the deterioration of median stiffness value from 6.49 to 7.82.

FibroScan revealed that the mean baseline median stiffness improved from 8.76 (SD 3.9) to 12-week post-treatment median stiffness of 6.70 (SD 1.2) with a p value of <0.001. In a previous study, it was found that 61.9% patients had regression in METAVIR fibrosis stage after successful DAA treatment[8]. However, in our study we found 64% regression in METAVIR fibrosis stage, while a deterioration of 6% in METAVIR fibrosis stage.

Ascites, being a hindering factor while performing transient elastography, posed a challenge while performing liver stiffness. As a result, data from the excluded patients with ascites could not be assessed. Real time elastography could yield better results in such cases and leaves a path for further studies[11].

Genotype evaluation was not done in this study as pan genotypic regimen was used in our patients. There is very limited data available globally showing variability in the effect of existing treatment upon different genotypes[12,-14].

However, the data in this study further strengthens the impact of DAAs in HCV infection while preventing hepatic complications which is probably explained by regression of fibrosis, intra-hepatic blood flow and the function of hepatocytes perhaps improves and leads to improvement in hepatic outcomes.

Conclusion

We conclude that those who were infected with hepatitis C mostly presented in the 4th to 5th decade and were diagnosed either incidentally or after a complication, mainly in the form of signs and symptoms suggesting portal hypertension. So, it is a mandatary to perform hepatitis C serology along with HCV RNA quantitative assay in all such patients. Patients who had SVR (sustained virological response) after receiving DAAs therapy displayed a substantial Fibro Scan value decline, which correlated with the regression of the validated fibrosis score APRI except one patient whose APRI score and fibrosis measurement value deteriorated; though we did not really know the exact reason in this patient; there was a possbility of effect of confounding factors (co-morbidities). Whether the improvement of these non-invasive parameters in the form of APRI score and METAVIR score represent a real fibrosis regression or merely a resolution of chronic liver inflammation with subsequent improvements in FibroScan value and laboratory parameters have to be investigated by histopathological sampling or better correlation between non-invasive and invasive methods. Again, a longer follow-up is needed to monitor long-term effect of DAAs while curing an HCV infection and its chronic complications. Moreover, the present study was a single centre study and the sample size was too small to extrapolate the conclusions to the entire population.

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