Determination of Real-world Single-center Experience with Direct-acting Antivirals for Improvement of Liver Fibrosis after Chronic Hepatitis C Treatment

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Authors’ contributions
This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

ABSTRACT

Background and Aims: Chronic Hepatitis C virus is the leading cause of morbidity and mortality. Conversion to liver fibrosis and decompensated liver cirrhosis is common if left untreated. Direct-acting Antiviral agents (DAA) may help in liver fibrosis associated burden. Considering the fact, this study aims to determine the comparative effect of combination therapy (Sofosbuvir and Daclatasvir vs. Sofosbuvir and Ribavirin) on liver fibrosis improvement using noninvasive marker AST platelet ratio index (APRI) score.

Methods: A retrospective cross-sectional study was conducted on secondary data of patients who visited a private gastroenterology clinic during the year of 2017 and 2018 in Karachi, Pakistan. Our sample comprised of a total of 300 patients who presented for the first time to the clinic from various provinces.
Results: Among all, 163 (54.3%) patients were treated with Sofosbuvir and Daclatasvir while 137 (45.6%) treated with Sofosbuvir and Ribavirin. The overall mean age and SD of patients was 41.1 ± 13.4 years and among them 64.6% (n = 194) were males. In both groups, treatment response showed negative HCV viral load after treatment, p <0.001. Levels of hemoglobin were significantly reduced in patients treated with Sofosbuvir and Ribavirin, 12.8gm/dL (11.5-14.2) vs. 11.4gm/dL (10.8-12.8), p value 0.03. Levels of total bilirubin significantly improved in patient received Sofosbuvir and Daclatasvir, 1.2mg/dL (0.4 - 1.8) vs. 0.6mg/dL (0.2 - 0.6), p value 0.001. Patients who treated with Sofosbuvir and Daclatasvir had significant improvement in APRI score (pre-treatment 1.26±0.17 vs. post-treatment 0.63±0.09, p value <0.001) in comparison with who treated with Sofosbuvir and Ribavirin (pre-treatment 0.92 ± 0.07 vs. post-treatment 0.43 ± 0.05, p value <0.06).

Conclusion: In present study, we report that the value of APRI improved significantly after treatment with DAA particularly those who treated with Sofosbuvir and Daclatasvir, which may indicate that regression of fibrosis is achievable after removal of the causative agent.

Keywords: Chronic hepatitis C treatment; direct acting antivirals; hepatic fibrosis regression; APRI score.

1. INTRODUCTION

Hepatitis C Virus (HCV) infection is a cause of significant burden on health care globally with approximately 71 million people currently infected around the world with more than 1.5 million new cases diagnosed each year [1]. If left untreated, HCV infection may lead to the development of liver fibrosis, by mechanisms that are direct as well as indirect, leading to subsequent chronic inflammation that progresses to liver cirrhosis in up to 50% infected, which may still be further complicated by hepatic failure or hepatocellular carcinoma [2]. Liver fibrosis assessment is therefore critical for management of patients with chronic hepatitis C. It is also helpful in monitoring their prognosis and making decisions for antiviral treatment.

Sustained viral response achieved in HCV treatment is found to be associated with significant improvement in liver histology seen by taking a tissue from the liver to be examined under microscope in liver biopsy [3,4]. However, there are negative aspects of liver biopsy, such as its invasive nature, high cost, inter or intra-observer variability, and sampling error, all limit its utility [5,6]. For that reason, non-invasive methods have been developed to predict severity of liver fibrosis, amino transferase-platelet ratio index (APRI) being one of them [7,8]. APRI is considered to be the preferred noninvasive test for assessing the presence of cirrhosis in resource-limited settings as it is a simple, inexpensive test with acceptable diagnostic accuracy. It uses routine lab parameters, AST and platelet count which are significantly associated with liver fibrosis [9]. The APRI score’s cutoff value is set by the meta-analysis of more than 40 clinical studies in which researchers concluded that an APRI score has more 70% sensitivity and specificity if it is greater than 1.0 and sensitivity & specificity increases for predicting advance liver fibrosis as APRI score become lower than 1.0. [10].

Since the approval of direct acting antivirals (DAA), several studies have confirmed their remarkable impact on HCV infection prognosis [11]. In 2013 the approval of direct acting antiviral agents (DAAs) i.e. Sofosbuvir and Daclatasvir represented a revolution in the management of chronic hepatitis C virus infection and are affective against 6 major types of HCV infection and achieve more than 90% of sustained virologic response (SVR) even in the presence of compensated liver cirrhosis [12].

A study conducted by Asselah T and colleagues [13] has shown that addition of Daclatasvir in the treatment regime of patients relapsed after previous treatment with Sofosbuvir and Ribavirin therapy resulted in 94% SVR after 24 weeks. A study conducted in Pakistan has suggested Sofosbuvir and Ribavirin therapy to be highly effective, safe, and cost effective for patients of Hepatitis C [14].

Pakistan stands second in the world with a huge burden of Hepatitis C with recent estimates suggesting a prevalence of around 6.8% [10]. Direct Acting Antivirals are gaining popularity in the treatment of chronic hepatitis C in Pakistan yet data regarding the efficacy of DAA in treating
liver fibrosis is still lacking. Although previous studies conducted in various parts of the world have depicted a significant improvement of liver fibrosis in patients given DAA [15], no such study has conducted in Pakistani population to analyse the changes in noninvasive liver fibrosis markers such as APRI score after treatment with DAA. Hence the aim of our study is to assess if fibrosis regression occurs in patients that have been chronically infected with HCV through indirect noninvasive markers like APRI score.

2. PATIENTS AND METHODS

This study is a retrospective cross-sectional study performed on secondary data of patients who visited a gastroenterologist’s clinic during the years of 2017 and 2018. A total of 300 Patients belonging to both gender and adult age groups (age >18 years), infected with HCV (confirmed by a PCR or ELISA), who presented for the first time to the clinic from various provinces of the country, patients who’s LFTs, required for assessing Aminotransferase to Platelet Ratio Index (APRI) score were available, and along with complete data required for the study, were included.

The data collection tool used in obtaining information for this survey was mainly Out-Patient Department (OPD) records filled by the doctor attending the patients. The records were then divided into sections. First included biodata questions and were based on demographic information of the participant including gender, age, area of residence, education status, ethnicity, and marital status. Second section consists of clinical parameters such as laboratory investigations (i.e. complete blood count values (CBC), liver function tests (LFTs), and tests to assess liver synthetic function such as serum albumin, and alpha fetoprotein levels). The last section included treatment plan that was followed by the patient throughout the course of their disease and interestingly, all of the enrolled patients came for follow-ups and no one has mentioned severe adverse effects for which treatment could be halted.

A standard method was used in our study to calculate the degree of liver stiffness, the APRI score, which is calculated by including the baseline upper limit values of AST (IU/L) and the baseline liver stiffness, the APRI score. We set cutoff values for advanced fibrosis as lowest (APRI score 1) and highest (APRI score 2) [10]. We sought informed consent due to study’s retrospective design. Age of patients were grouped as <40 years and ≥40 years. Based on patient’s liver status, patients were categorized into cirrhosis and non-cirrhosis. We followed European Society for the Study of the Liver Disease (EASL) recommendations on treatment of HCV infection [16] and patients were divided into two groups based on the treatment they received, 1) Sofosbuvir (400mg x once daily) and Ribavirin (400mg x twice daily) for 12 weeks and Sofosbuvir (400mg x once daily) and Daclatasvir (60mg x once daily) for 12 weeks in non-cirrhosis while 6 months in patients with liver cirrhosis. HCV RNA was evaluated before and 12 weeks after the end of treatment.

The data relevant to our study i.e. APRI score and other general variables were categorized and analysed using SPSS 22. Frequencies and percentages were used to see the impact of various treatment approaches on APRI score. Student’s t-test was used to find an association between the data. All the tests were significant at p <0.05.

3. RESULTS

A total of 300 patients were treated among them 163 (54.3%) patients were treated with Sofosbuvir and Daclatasvir while 137 (45.6%) treated with Sofosbuvir and Ribavirin. The overall mean age and SD of patients was 41.1 ± 13.4 years and among them 64.6% (n = 194) were males. While females were older than males, 43.2 + 11.77 years vs. 39.9 ± 14.14 years, respectively. Most of the study subjects were urban dwellers (72.6%, n = 218). Sixty-four patients (21.3%) had diabetes mellitus and 84 (28.3%) had hypertension. Twenty-nine patients (9.6%) were currently smoker. The most common presenting clinical manifestation was presence of edema (9.8% in males and 7.5% in females) and ascites (8.8% in males and 7.5% in females). Further description is shown in Table 1.

Table 2 shows response of laboratory parameters among HCV patients before and after treatment with DAA. In both groups, treatment response showed negative HCV viral load after treatment, p <0.001. Levels of hemoglobin were significantly reduced in patients treated with Sofosbuvir and Ribavirin, 12.8g/dL (11.5-14.2) vs. 11.4g/dL (10.8-12.8), p value 0.03 while there was no significant change in hemoglobin levels in patients treated with
Sofosbuvir and Daclatasvir, 13.9gm/dL (11.9-15.1) vs. 13.4gm/dL (11.7-15.0), p value 0.08. Levels of total bilirubin significantly improved in patient received Sofosbuvir and Daclatasvir, 1.2mg/dL (0.4 - 1.8) vs. 0.6mg/dL (0.2 - 0.6), p value 0.001. In both groups, levels of AST and ALT significantly improved after treatment with DAA, p value <0.05.

Table 1. Comparison of baseline and clinical characteristics with respect to gender (N = 300)

| Baseline Characteristics | Total (n=300) | Male (n=194) | Female (n=106) | P-value |
|--------------------------|--------------|--------------|----------------|---------|
| Age in years             |              |              |                |         |
| ≤40                      | 139 (46.3%)  | 100 (51.5%)  | 39 (36.8%)     | 0.020   |
| >40                      | 161 (53.7%)  | 94 (48.5%)   | 67 (63.2%)     |         |
| Range, Mean ± S.D        | 41.1 ± 13.4  | 39.9 ± 14.14 | 43.2 ± 11.77   | 0.040   |
| Presenting complaint     |              |              |                |         |
| Ascites                  | 25 (8.3%)    | 17 (8.8%)    | 8 (7.5%)       | 0.884   |
| Edema                    | 27 (9.0%)    | 19 (9.8%)    | 8 (7.5%)       | 0.661   |
| PSE                      | 4 (1.3%)     | 2 (1.0%)     | 2 (1.9%)       | 0.616   |
| G.I. bleeding            | 5 (1.7%)     | 3 (1.5%)     | 2 (1.9%)       | 1.000   |
| Decompensate Liver       | 31 (10.4%)   | 21 (10.9%)   | 10 (9.5%)      | 0.855   |
| Current treatment        |              |              |                |         |
| Sofosbuvir+Daclatasvir   | 163 (54.3%)  | 117 (60.3%)  | 46 (43.4%)     | 0.019   |
| Sofosbuvir+Ribavirin     | 137 (45.6%)  | 44 (22.7%)   | 34 (32.1%)     |         |

Table 2. Laboratory parameters before and after treatment with daa in hcv patients (N = 300)

| Parameters                  | Sofosbuvir+Daclatasvir (n = 163) | p value | Sofosbuvir+Ribavirin (n = 137) | p value |
|-----------------------------|----------------------------------|---------|--------------------------------|---------|
|                            | Pre-treatment | Post-treatment | Pre-treatment | Post-treatment |
| HCV RNA - log10IU/mL        | 2201000 (288000 - 5400000)       | <0.001  | 2500000 (391000 - 5420000)     | <0.001  |
| Hemoglobin - gm/dL          | 13.9 (11.9-15.1)                 | 0.08    | 12.8 (11.5-14.2)                | 0.03    |
|                            | 13.4 (11.7-15.0)                 |         | 11.4 (10.8-12.8)                |         |
| Platelet - x103/mm3         | 195.4 (110.3 - 217.4)            | 0.71    | 180.8 (109.2 - 205.1)           | 0.34    |
|                            | 191.3 (112.4 - 211.7)            |         | 175.0 (110.1 - 208.5)           |         |
| Total Bilirubin - mg/dL     | 0.8 (0.4 - 1.1)                  | 0.001   | 1.6 (1.2 - 2.0)                 | 0.73    |
|                            | 0.8 (0.4 - 0.9)                  |         | 1.3 (1.0 - 1.3)                 |         |
| Serum Albumin - g/dL        | 3.7 (3.4 - 4.0)                  | 0.47    | 3.4 (2.9 - 3.4)                 | 0.14    |
|                            | 3.8 (3.6 - 3.9)                  |         | 3.3 (3.5 - 3.8)                 |         |
| AST - IU/L                  | 49.1 (36.2 - 80.1)               | 0.001   | 51.1 (35.8 - 71.5)              | 0.001   |
|                            | 31.2 (26.7 - 58.0)               |         | 30.6 (20.2 - 51.4)              |         |
| ALT - IU/L                  | 54.3 (38.1 - 60.7)               | 0.001   | 53.7 (31.2 - 64.9)              | 0.001   |
|                            | 17.4 (15.1 - 45.6)               |         | 15 (12.0 - 41.6)                |         |
Fig. 1. Pre and Post-treatment APRI score comparison to assess liver fibrosis. (a) Changes of APRI, before and after treatment with Sofosbuvir and Daclatasvir. (b) Changes of APRI, before and after treatment with Sofosbuvir and Ribavirin. 

APRI: aspartate aminotransferase/platelet ratio index.

Fig. 2. Pre and Post-treatment APRI score comparison to assess liver fibrosis. (a) Changes of APRI, before and after treatment with Sofosbuvir and Daclatasvir. (b) Changes of APRI, before and after treatment with Sofosbuvir and Ribavirin. 

APRI: aspartate aminotransferase/platelet ratio index.

4. DISCUSSION

Chronic hepatitis C infection if left untreated may lead to liver fibrosis which results in decompensated liver cirrhosis and even Hepatocellular Carcinoma (HCC) hence increasing the liver related mortality. The only treatment is to start the newly available antivirals which may reduce the burden of hepatocellular carcinoma, but sometimes does not eliminate the virus completely even in patients who achieve SVR. Studies suggest that those CHC patients who had advance liver fibrosis are more likely to develop hepatocellular carcinoma [17,18].
Hepatic fibrosis is considered the most important factor for estimating clinical outcome and making therapeutic decisions in patients suffering from chronic hepatitis C, treatment is not necessarily indicated in patients with minimal fibrosis whereas treatment is important for patients with moderate or more severe fibrosis (F≥2) because of the persistent risk of fibrosis progressing to liver cirrhosis or its associated complications [19,20]. Although liver biopsy has long been used by physicians as the rule of thumb for diagnosis of fibrosis, the procedure of biopsy itself is costly, invasive, and requires expertise [21]. Considering the risk of biopsy related complications, other non-invasive techniques such as fibrosis score i.e. APRI, can be used for the diagnosis of liver fibrosis.

In present study we have used APRI score to determine the risk of fibrosis after patients treated with DAA. A previous literature has shown that compared to FIB 4, APRI is found to be a more sensitive, specific and accurate noninvasive test for assessing advanced liver fibrosis in end stage renal disease patients with chronic HCV [22]. In our study, patients treated with Sofosbuvir and Daclatasvir were significantly showed improvement in liver fibrosis as compared to those who were treated with Sofosbuvir and Ribavirin. Consistent findings have been observed in a study conducted by Kurniawan J and colleagues [23]. The difference in both treatment groups could be due to older population with underlying liver cirrhosis fell under regime of Sofosbuvir and Ribavirin.

Our study results also found that patients with decompensated liver markers such as ascites, edema, and portosystemic encephalopathy (hepatic encephalopathy) did not have a significant change in APRI score despite treatment with DAA contrary to patients with non-decompensated liver disease who showed significant improvement in their APRI score post-treatment. This has also been shown by a study conducted in Punjab [24]. This may suggest APRI score does not improve significantly in CHC patients who have fibrosis progression to an extent of decompensated liver disease even with DAA treatment. However, contrary to our study results, another study in Georgia showed reversal of TE scores in 304 patients with advanced fibrosis or cirrhosis after SVR was achieved at a rate similar to that reported by Triedi HD and colleagues [25].

Surprisingly, males were found to be better responders as compared to females in this study. Patients aged <40 years of age were better responders as compared to the patients with >40 years of age. However, APRI score improvement was significant in both males and females and also in both age groups. The better response of younger group patients was also indicated in previous study that revealed that younger group patients with hepatitis C are good candidates to treat [26].

5. STUDY LIMITATIONS AND SUGGESTIONS

Firstly, patients extracted for this study was from the Liver and Hepatology clinic of a private center which lacks the generalization of whole Pakistani population. Secondly, this was a retrospective study hence, variables like, alphafetoprotein levels, child class, patient’s weight, BMI, addiction status, duration of liver disease, and renal status could not be analysed.

Another multicenter study should be conducted in Pakistan to address this crucial disease with an ever rising burden. Further larger and longer follow-up studies at 12 months post DAA treatment should be performed to investigate to the extent to which viral eradication by DAA treatments may improve liver fibrosis and liver functions in long term. Effect on reducing the relative HCC risk should also be evaluated in addition to liver fibrosis.

6. CONCLUSION

In present study, we report that the value of APRI improved significantly after treatment with DAA particularly those who treated with Sofosbuvir and Daclatasvir, which may indicate that regression of fibrosis is achievable after removal of the causative agent.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.
CONSENT
As per international standard or university standard, patients’ written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL
It is not applicable.

COMPETING INTERESTS
Authors have declared that no competing interests exist.

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