https://doi.org/10.36570/jduhs.2020.3.856

JDUHS

SHORT COMMUNICATION

# Sofosbuvir and Ribavirin in Chronic Hepatitis C Virus Patients with No Response or Relapse with Interferon Therapy

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## ABSTRACT

To determine the response rate to sofosbuvir and ribavirin in chronic Hepatitis C Virus (HCV) patients who did not respond or relapsed with interferon therapy. A case series study was performed at Jinnah Postgraduate Medical Centre (JPMC), Karachi from January 2017- January 2019. HCV RNA positive were initiated in eligible patients with sofosbuvir 400mg once daily and ribavirin 400mg orally according to body weight for six months. Rapid viral response (RVR) [normal/undetectable ALT and AST level or very low HCV RNA at 4-6 weeks]. HCVRNA, CP, ALT were checked after 3 months of stopping treatment to confirm sustained virologic response (SVR). Of 100 cases, 16 (16%) were non-responders while relapse was observed in 84 (84%) patients. Among the 13 cirrhosis patients, 11 (84.6%) achieved SVR. Females had a significantly higher response rate as compared to males (p value 0.034). The sustained virological response rate in interferon treated chronic hepatitis C patients retreated with sofosbuvir and ribavirin was found satisfactory.

**Keywords:** Sofosbuvir, chronic hepatitis C, Sustained virological response, non responder, relapse, ribavirin.



## INTRODUCTION

Chronic Hepatitis C virus (HCV) is an important public health problem. Approximately 130-175 million people worldwide are affected with HCV.[1] Pakistan has the 2nd largest pool of HCV patients in the world.[2] Common sequelae to chronic infection include cirrhosis and hepatocellular carcinoma. Previously the optimum therapy for HCV was the combination of interferon and ribavirin therapy. In Pakistan genotype 3 is most prevalent (>80%)[3] whose response to interferon was 60-70% only.[4]

Once treated with interferon, about 30-40% patients would show a disease relapse on stopping therapy (relapsers) while a small percentage would not show any response (non-responders).[5]

The advent of Direct Acting Antivirals (DAAs) i.e. oral nucleoside analogues has revolutionized treatment of HCV. In addition to ease of administration, the advantage of oral route these drugs also boast of a better response rate and side effect profile. These include drugs like sofosbuvir, ledipasvir, simeprevir etc. They are given in different combinations depending on the genotype.[6] Presently only sofosbuvir, daclatasvir and velapatasvir are available in Pakistan.

Sofosbuvir (SOF) is the most commonly used nucleoside analogue which is safe and can be used to treat patients of all disease stages and HCV genotypes. It was first approved in 2014. A combination of sofosbuvir and ribavirin for 24 weeks or a combination of pegylated interferon, sofosbuvir and ribavirin for 12 weeks is recommended for the treatment of HCV.[7] The response rate of sofosbuvir in combination with other drugs is more than 90% in untreated and 87% in retreated patients.[8] The Boson study showed similar response rate.[9] whereas the Resip study reported a much higher response rate.[10] Studies in Pakistan show large variation in results. A study showed a response rate of 79.4% in interferon treated cases.[11] A much better response rate (99.34%) was reported by Iqbal et al.[12]

As mentioned above sofosbuvir is a miracle drug which has now become the first line therapy for chronic HCV. But most studies conducted in this regard are from the western world. The studies from Pakistan have large variation in terms of response rate i.e 79.4% vs 99.34%.This prompted us to undertake this study to determine the response rate at our centre.

## METHODS

A case series study was conducted at Outpatient department Pakistan Health Research Council (PHRC) Research Centre of Jinnah Post graduate Medical Centre (JPMC) Karachi from January 2017-January 2019.

Ethical approval was taken from the Ethics Review Committee (ERC) of Jinnah Postgraduate Medical Center Karachi (Ref No.F.2-81/2019-GENL/21152). After taking written informed consent chronic HCV positive patients who had relapsed or did not respond to previous interferon therapy were assessed for any signs of decompensation or low hematological values. Patients with co infections such as hepatitis B and HIV were excluded from the study.

All patients over the age of 18 years who had a detected HCV RNA after stopping interferon and ribavirin therapy with haemoglobin ≥11grams/dl, platelets over 50,000/Ul were treated with sofosbuvir 400mg once daily and ribavirin 400mg orally according to body weight (800mg ≤ 70kg, 1200mg ≥ 70kg) for six months were included in the study. Side effects of the treatment such as body aches, fever, and diarrhea were recorded in a proforma designed for this purpose.

Response to treatment was assessed through blood tests like CP (complete blood count) and ALT (Alanine aminotransferase) which were done every 1-2 months during treatment, while HCV RNA (qualitative) was done between 4-6 weeks to determine the rapid virological response (RVR). A patient was said to achieve RVR if the ALT and AST levels became normal and undetectable or very low HCV RNA at 4-6 weeks. HCVRNA, CP, ALT were checked after 3 months (12 weeks) of stopping treatment to confirm sustained virological response (SVR) i.e. viral eradication.

Data were analyzed on SPSS (Statistical packages of social sciences) version 24. The demographics and clinical characteristics of patients were summarized as frequencies and percentages (for qualitative variables i.e. gender, symptoms, physical examination). Moreover, RVR and SVR to see the response of treatment (outcome). Whereas mean ±SD were calculated for quantitative variables like age, weight and height. Statistical comparison between non responders /relapsers to interferon and ribavirin therapy treated with sofosbuvir and ribavirin (outcome) was performed by chi-square test/Fisher's exact test. p-value ≤0.05 was considered significant.

## RESULTS

Out of 100 cases, 60 (60%) were males and 40 (40%) were female. The age ranged from 16 years to 62 years. The mean age was 41.5 ± 9.92 years. Majority of the patients (80%) had history of IFN conventional therapy. There were 16 (16%) responders and 84 (84%) were relapse patients (Table 1).

Mean haemoglobin level at baseline was 13.8 ±1.57mg/dl, during treatment was 11.5mg/dl ±1.73. While mean Hb drop was 2.3 ± 1.38 mg/dl i.e Hb dropped by 17% during treatment.

The relationship between SVR and general characteristics of patients treated with DAAs are shown in table 2. It was found that females had a significantly better chance of achieving SVR 38 (95%) as compared to males 48 (80%) (p- value 0.034).

Most common side effects encountered during treatment include anaemia (3 patients 3%), bodyaches (15 patients 15%), pain epigastrium (7 patients 7%) and diarrhea (1 patient 1%).

## DISCUSSION

This study aimed to determine the response rate of sofosbuvir and ribavirin in patients who were non-responders /relapsers to interferon and ribavirin treatment. Majority of the patients in the study i.e 80% were non responders/ relapsers who had been treated previously with conventional interferon. The reason may be that as mentioned above genotype 3 is the most prevalent genotype in Pakistan. The recommended treatment for this genotype was conventional interferon.

In this study the response rate was found to be 86% which is similar to previous studies. A study conducted in 2015 with predominantly genotype 4 patients showed similar results.[13] The Boson study reported a response rate of 94% in treatment experienced patients without cirrhosis having genotype 3 which was much higher as compared to the present study. However, the SVR rate was reduced to just 77% in patients with cirrhosis.[14]

Previously, age < 40 years was considered an important predictor of response in HCV patients treated with interferon and ribavirin therapy. The present study shows a slightly better response among patients < 40 years of age. This is in contrast to previous studies conducted on patients receiving direct acting antivirals which show that patient's age does not affect the treatment response.[15]

Out of 13 patients in the study who had cirrhosis, 11 (84.6%) patients achieved sustained virological response. Trials Solar 1 and 2 in which decompensated patients were treated with sofosbuvir/ledipasvir showed similar results.[16] Yek e al also reported a response rate i.e 82% among cirrhotic patients.[17] Another study in which patients were treated with sofosbuvir and daclatasvir showed a response rate of just 69% among genotype 3 patients highlighting the fact the importance of adding ribavirin in patients with

**Table 1: Demographic and Past Historyof patients (n=100)**

| | Frequency | Percent |
|---|---|---|
| Gender | | |
| Male | 60 | 60.0 |
| Female | 40 | 40.0 |
| Age group (years) | | |
| Under 40 | 36 | 36.0 |
| 40-49 | 42 | 42.0 |
| 50 & above | 22 | 22.0 |
| Past treatment | | |
| IFN Conventional | 80 | 80.0 |
| IFN Peg Interferon | 20 | 20.0 |
| Status of Past treatment | | |
| Non-Responder | 16 | 16.0 |
| Relapse | 84 | 84.0 |
| Decompensated cirrhosis | | |
| Ascites | 8 | 8.0 |
| Edema | 4 | 4.0 |
| Variceal Bleed (Hematemesis/malena) | 1 | 1.0 |

SVR: Sustained Virological Response
IFN: Interferon

**Table 2: Comparison of treatment response with demographic and clinical characteristics of the patients (n=100)**

| Variables | No. of subjects | SVR | | p-value |
|---|---|---|---|---|
| | | Achieved | Not Achieved | |
| Gender | | | | |
| Male | 60 | 48 (80.0%) | 12 (20.0%) | 0.034* |
| Female | 40 | 38 (95.0%) | 2 (5.0%) | |
| Age group (years) | | | | |
| Under 40 | 36 | 33 (91.7%) | 3 (8.3%) | 0.308 |
| 40-49 | 42 | 36 (85.7%) | 6 (14.3%) | |
| 50 & above | 22 | 17 (77.3%) | 5 (22.7%) | |
| Past treatment | | | | |
| IFN Conventional | 80 | 72 (90.0%) | 8 (10.0%) | 0.051 |
| IFN Peg | 20 | 14 (70.0%) | 6 (30.0%) | |
| Status of Past treatment | | | | |
| Non-Responder | 16 | 12 (75.0%) | 4 (25.0%) | 0.321 |
| Relapse | 84 | 74 (88.1%) | 10 (11.9%) | |
| History | | | | |
| Ascites | 8 | 6 (75.0%) | 2 (25.0%) | - |
| Edema | 4 | 4 (100%) | - | - |
| G.I. Bleeding | 1 | 1 (100%) | - | - |

SVR: Sustained Virological Response, IFN: Interferon
*p-value <0.05

cirrhosis.[18] Feng Su et al reported a much higher response rate 90% in patients with decompensated cirrhosis.[19]

In this study response rate was significantly higher among females than males. A study conducted by Baden et al reports similar findings.[20] The reason may be that females have slower disease progression as compared to males which results in better response to antiviral therapy. This slower progression rate has been attributed to estrogen and estradiol which provide protection from liver fibrosis.

In the present study, 14 patients did not clear the virus after oral therapy. Out of these, two had liver cirrhosis which would explain why they did not respond to treatment. But the reason as to why the 12 other patients did not clear the virus could not be identified, taking into account their age, gender or disease stage. A possible reason could be that genotype of these patients is not known. HCV genotype is an expensive laboratory investigation especially as most patients coming to our outpatient clinic are non-affording.

Side effect profile with DAAs was negligible if we compare it with interferon based therapy. Only side effects encountered with this regimen was due to ribavirin but in very few cases dose reduction was required. HCV genotyping was not performed in the current study which is one of the limitations. Despite of this, present analysis shows the result of DAAs with ribavirin which is more than 85% and is much better than interferon based therapy. Nowadays more antiviral drug combinations are available therefore the addition of more DAAs and new agents is expected to give much better results. More studies will be required to determine the effect of those drug regimens which might not only give better results but also reduce the duration of therapy.

## CONCLUSION

The sustained virological response rate in interferon treated chronic hepatitis C patients retreated with sofosbuvir and ribavirin is 86%.

**ETHICAL APPROVAL:** The study was approved by Institutional Review Board Committee, Jinnah Postgraduate Medical Centre Karachi (Approval No. F.2-81/2019-GEN/21152/JPMC).

**CONFLICT OF INTEREST:** All authors do not have any conflict of interest to declare.

**FUNDING:** No funding was obtained for this study.

Received: November 24, 2019
Accepted: November 20, 2020

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