



## EFFICACY OF SOFOSBUVIR IN INTERFERON TREATED PATIENTS OF HEPATITIS C INFECTED WITH 3A GENOTYPE.

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**ABSTRACT... Objectives:** Hepatitis C is a blood borne infection primarily disrupting the functional and architectural integrity of liver and has a considerable share in worldwide mortality and morbidity. Treatment strategies against the causative RNA-based virus has widely evolved over time with newer Direct Acting Antivirals (DAA) being recently introduced. This study serves to assess the efficacy of Sofosbuvir (DAA) in patients of HCV genotype 3a with prior treatment with interferon. **Study Design:** An Open label, Prospective Quasi Experimental Study. **Setting:** Mayo Hospital, Lahore. **Period:** September 2016 to December 2017. **Material and Methods:** 212 patients with genotype 3a who had been previously treated with interferon (INF). They were treated with Sofosbuvir 400mg once daily and Ribavirin 400mg thrice daily. The treatment duration was 24 weeks following which the end of treatment response (ETR) was determined by quantifying viral load by Polymerase Chain Reaction (PCR). **Results:** Of the 212 patients enrolled, 50 patients did not give follow up either due to availability issues or due to non-compliance. 13 patients left the treatment due to comorbidities. 149 patients completed the treatment out of whom 131 patients showed positive response (87.9%). Nine patients with high viral load showed relapse while nine patients were non-responders. **Conclusion:** In interferon experienced patients of HCV genotype 3a, Sofosbuvir has shown to reach sublimure rates which may serve to obviate conventional treatment strategies owing to their longer treatment duration and significant adverse effects. As demonstrated by this study, the modest safety profile coupled with an enhanced therapeutic efficacy of Sofosbuvir is expected to revolutionize treatment strategies against Hepatitis C limiting the spread and hence the incidence of disease.

**Key words:** Genotype 3a, Hepatitis C, Interferon Treated Patients, Sofosbuvir.

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## INTRODUCTION

Hepatitis C, a disease that causes destruction of the structural and functional capacity of the liver, is caused by a virus belonging to family Flaviviridae, genus Hepacivirus and species Hepatitis C virus; it has six genotypes with 3a being most common in Pakistan.<sup>1,2,3,4</sup> Hepatitis C can be acute, chronic or self-resolving in 15-45% of cases.<sup>5</sup> It is transmitted mainly through body fluids along with vertical transmission during pregnancy as well.<sup>6,7</sup> Hepatitis C exhibits mutation in its nucleotide, genotype and sub-genotypes with rates being 1-5%, 30-50 and 15-30% respectively.<sup>8</sup> The reasons for mutation may be various, with lack of proofreading and rapid rate of replication being noteworthy.<sup>9</sup> Genome of HCV contains structural

proteins(core proteins: E1, E2) and nonstructural proteins (NS1-5) out of which NS5A possesses a region known as interferon-alpha sensitivity determining region (ISDR) that helps to develop resistance to interferon through repression of PKR Protein kinase.<sup>10,11,12,13,14</sup> Acyclovir(an anti-viral) was initially tried for the treatment of hepatitis, but with little success.<sup>15</sup> INF-alpha(an antiviral cytokine), when given for 24 weeks, showed positive response with an SVR of 6%- this doubled with the doubling of treatment duration.<sup>16,17,18</sup> Ribavirin, an antiviral agent approved by WHO in 1972, was previously used as monotherapy to treat hepatitis C, but it happened to lower ALT level but not viral load.<sup>19,20,21</sup> Ribavirin, when used with INF-alfa for 24 weeks, showed an improved SVR

of 24% which was doubled by doubling therapy duration.<sup>22</sup> FDA approved this combination of drugs and duration for genotype 3a in 1998.<sup>23</sup> The factors that determine the efficacy of INF-based treatment of HCV patients are cirrhosis, hepatic steatosis, host's genetic variation in IL28B, gender, obesity, non-response to previous interferon-based therapy, age, ethnicity, insulin resistance, HCV genotype, HCV load and co-infection with HIV.<sup>24</sup> Since the duration of this therapy was long and hard to tolerate, dosage for INF-alfa was decreased by increasing its half-life through pegylation (INF + Inert compound) which showed a higher SVR than before (39%) which later proved to be 54 to 56% after combining it with ribavirin for 48 weeks.<sup>25</sup> This combination was approved by FDA for genotype 3a for 24 weeks.<sup>26</sup> In the next step direct acting antivirals (DAA) were used which proved to be comparatively safer and more effective. These were Simeprevir (HCV Protease Inhibitor), Declatasvir (HCV NS5A Inhibitor), and Sofosbuvir (HCV NS5B Polymerase inhibitor).<sup>27,28</sup> Sofosbuvir is a nucleoside analogue and inhibits replication of HCV RNA.<sup>29</sup> FDA approved it with ribavirin for 24 weeks for genotype 3a.<sup>30</sup> Feld et al found SVR for genotype 3a with Sofosbuvir to be 88% in non-cirrhotic pretreated patients.<sup>31</sup> VALENCE study of Europe found SVR of 85% for genotype 3a.<sup>32</sup> A recent study in Pakistan at Rawalpindi showed an SVR of 96.5% with SOF+RBV for genotype 3a.<sup>33</sup> Another study named RESiP in Pakistan involving 94% 3a patients showed an SVR of 86% in INF experienced patients.<sup>34</sup> There is lack of data on the efficacy of Sofosbuvir in 3a genotype especially for those who have been already treated with INF. Here our study provides an evidence of its efficacy which will be very useful for its future use in INF experienced patients of HCV.

### AIMS AND OBJECTIVES

1. Analyzing the efficacy of Sofosbuvir in HCV patients infected with 3a genotype who have had interferon treatment.
2. To study different factors that affect the efficacy of Sofosbuvir

## MEHODOLOGY

### Study Design

Open label, Prospective Quasi Experimental study.

### Setting

Mayo Hospital, Lahore.

### Study Duration

September 2016 to December 2017.

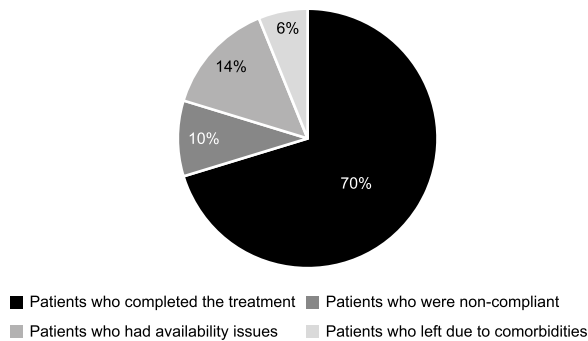
Patients of age b/w 20 to 70 years infected with HCV genotype 3a who had previously been treated with INF and did not have decompensated chronic liver disease (confirmed by USG-Abdomen and signs and symptoms of decompensation) were included. HIV negative Pakistani nationals were enrolled after taking informed consent. All patient infected with HCV genotype other than 3a or age greater than 70 or less than 20 or with DCLD or HIV positive patients or patients of HCV 3a having foreign nationality were excluded. Serum AST and ALT levels of the patients were determined at the start of study by measuring the rate of consumption of NADH in their respective reactions spectrophotometrically. Commercially made kits were used for this purpose. Serum creatinine level was also determined based on Jaffe's method which measured rate of formation of orange yellow creatinine-picric acid complex, the concentration of which was proportional to creatinine in serum sample at beginning of study. Real Time Quantitative PCR and PCR Genotype were also done at the start of treatment. Patients were followed up for 24 weeks of treatment for any adverse event and to ensure compliance and a quantitative PCR was also performed at the end of 24 weeks in order to determine response of therapy at the end (end of treatment response i.e. ETR). History to probe cause of HCV was taken. Patient was asked about history of blood transfusion, IV drug abuse or family history of his/her partner being HCV positive. Co-morbidities if present in any patient were recorded as well. All patients were given Sofosbuvir 400mg one tablet in a day and Ribavirin 400mg one tablet three times a day. Data was analyzed using SPSS 20.

**RESULTS**

In this study 212 patients infected with genotype 3a were enrolled in which 50 patients left and did not give follow up for following reasons: 30 patients belonged to far off outskirts of the country and were not able to report back while 20 patients were non-compliant. 162 patients continued the therapy out of which 13 patients discontinued due to comorbidities and 149 patients completed the therapy i.e. 24 weeks.

Results of this study came out to be: 131/149 (87.9 %) patients showed positive response out of which 51 (38.9 %) were males and 80 (61 %) were females.

Summary of patients enrolled

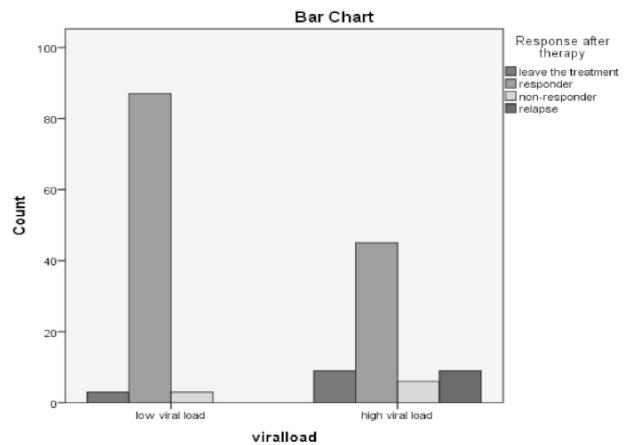


Considering  $8 \times 10^5$  IU/ml or above as high viral load, nine patients showed relapse and all had high viral load. One patient relapsed at 6 weeks, two of them after 8 weeks and six after 12 weeks. The reason of their relapse was not identified but it was thought that it might be due to mutation in NS5B polymerase.

There were nine patients who were non-responders. Two of them had low viral load while rest of them had high viral load. Two patients showed features of decompensated chronic liver disease (DCLD) on USG. Five patients were non-compliant. Two patients were non-responders with the reason being unknown.

8 patients discontinued the treatment due to fatigue, myalgia, marked pallor and weight loss. One patient left the therapy due to congestive heart failure. Two patients discontinued due to cancer. One known diabetic and hypertensive

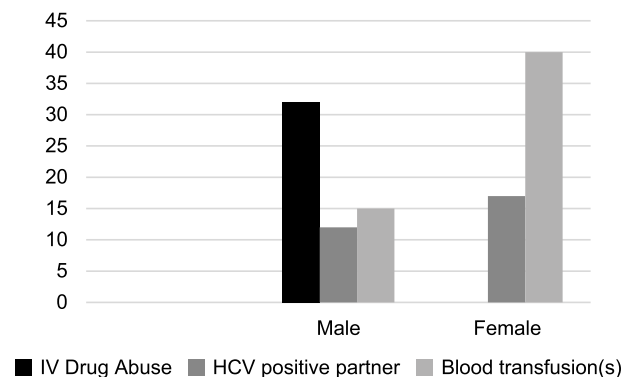
patient discontinued the treatment due to pedal edema and pallor. One diabetic patient left the treatment due to chronic kidney disease (CKD) and anemia.



**P-value came out to be significant (<0.005).**

Average of all patients' age, ALT, AST, viral load and creatinine level were 46.54 ( $\pm 9.59$  years), 72.28 ( $\pm 42.73$  IU/l), 78.01 ( $\pm 50.23$  IU/l), 15146523 ( $\pm 5205719$  IU/mL) and 0.8 ( $\pm 0.3$  g/dL) respectively. History of the patients revealed that 32 (19.7 %) patients were drug abusers and all were males. 29 (17.9%) had HCV positive partner in which 12 (7.4%) were males and 17 (10.5%) were females. 55 (33.9 %) patients had a history of blood transfusion in which 15 (9.24%) were males and 40 (24.66%) were females.

Prior History Highlights



**DISCUSSION**

HCV, a threat to the globe, mainly affects liver and has led millions to death with mortality rate still on the rise necessitating the need to devise effective treatment. After trying acyclovir

and ribavirin as monotherapy, the problem was somewhat catered with by using INF and RBV in combination. The treatment was further improved by use of pegylated INF. Still side effects of this combination were a much bigger problem hampering patients' compliance. DAA revolutionized the treatment of hepatitis C out of which the one primarily used was pan-genotypic polymerase inhibitor, Sofosbuvir.

SOF, approved by FDA in 2013, proved to be very effective for HCV. Efficacy of Sofosbuvir against genotype 1 was abundantly documented in Western population but its activity against genotype 3 (common in the East) was only proven in a few trials the notable ones being FISSION, FUSION, POSITRON, ALLY-3 and BOSSON trial. The results of these trials proved it to be very effective both in treatment-naïve and INF experienced patients.<sup>35-39</sup> VALENCE trial showed an SVR of 77% in INF experienced patients of genotype 3a. An important study of Pakistan RESiP trial that involved 94% of patients of 3a showed an SVR of 86% in INF experienced patients. In our study, 162 patients were included of which 149 completed therapy (24 weeks). The response after therapy was 87.9% %. Results of previous studies were very close to it. There were 9 patients who showed relapse. Relapse was due to mutation or reinfection by HCV with no role of INF resistance in it since it did not seem to be related to non-structural proteins.<sup>40</sup> There were 9 patients who were non-responders the precise reason of which was not known.

Various studies indicated that INF treated female patients of age 50 or greater showed high SVR than male patients due to gender disparity. So in this study similar results were found.<sup>41,42</sup>

There were 13 patients who discontinued the therapy. Discontinuation of therapy was mainly due to either side effects of the drugs or any other co-morbidity that imposed additional stress on the patient and led to inability to tolerate the therapy. So, in order to improve the compliance of the patient, acute events and side effects need to be managed properly along with patient's education.

SOF proved to be very effective for HCV in combination with other DAA. A recent study showed that 86% efficacy of SOF plus Declatasvir for 12 weeks in INF experienced patients of 3a (37). Another result for this regimen was 89% SVR in another trial.<sup>43</sup> SVR could be increased by increasing duration of treatment. The use of SOF and other DAA and their therapy duration was not well known for HCV GT-3a patients. So, it was an unsolved issue and needed more work on it. Another issue was relapse of INF treated patients after taking complete therapy of SOF plus RBV. Through this research, we have tried to reflect on both the issues and give an insight on the expected outcome.

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Sr. #	Author-s Full Name	Contribution to the paper	Author's Signature
1	Saroosh Zahoor	Drafting manuscript.	
2	Sarmad Zahoor	Writing and analyzing the data.	
3	Samreen Hameed	Reviewed the article and helped analyzing data.	
4	Syed Maaz Abdullah	Data collection and editing.	
5	M. Sohail Afzal	Supervised and reviewed the study.	
6	Uzma Butt	Strongly reviewed the article.	