# Sofosbuvir Adverse Events Profile in a Subset of Pakistani Population

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## ABSTRACT

**Objective:** To determine frequency and pattern of adverse events reporting in a subset of Pakistani population being treated for chronic hepatitis C with sofosbuvir combination therapy.

**Study Design:** Descriptive study.

**Place and Duration of Study:** Department of Medicine, Gastroenterology Division, Shalamar Hospital, Lahore, from September 2015 to May 2016.

**Methodology:** Patients who were offered sofosbuvir therapy for treatment of chronic hepatitis C were randomly enrolled. The study subset included both treatment naïve as well as retreatment groups. Patients were screened for subjective as well as objective evidence of adverse events at regular intervals. Frequency was determined.

**Results:** Among 196 patients with chronic hepatitis C, 192 patients received dual therapy consisting of ribavirin and sofosbuvir. The most frequent complaints in these subjects were fatigue, fever, myalgias and nausea accounting for 55%, 42%, 44.2% and 50%, respectively. Twenty-seven percent of patients reported with drop in hemoglobin of >2g/dl, while absolute neutropenia and moderate to severe thrombocytopenia was observed in 3% and 5% of patients, respectively. One patient died as a result of severe pancytopenia. Later derangements were all observed in patients with decompensated disease.

**Conclusion:** Sofosbuvir showed less severe adverse effects in terms of symptomatology and less frequent neutropenia and thrombocytopenia as compared to previous regimens. Careful monitoring is required, especially in those with decompensated liver disease.

**Key Words:** *Sofosbuvir. Chronic hepatitis C. Direct acting antiviral drugs. Sofosbuvir adverse events.*

## INTRODUCTION

Treatment of chronic hepatitis C had always been challenging, continuously undergoing new trials and tests with an objective to achieve better SVR rates. Previously conventional interferon was the standard treatment for chronic hepatitis C with several limitations and less than adequate SVR rates. With the advent of new direct acting antiviral drugs, the above targets have been achieved in a much improved manner.

DAA are divided into four categories, i.e. NS3/4A protease inhibitors, NS5A protease inhibitors, NS5B nucleoside type polymerase inhibitors and NS5B non-nucleoside type polymerase inhibitors. This group of drugs is not indicated as monotherapy and is always recommended to be given in combination with pegylated interferon and ribavirin to minimize resistance rates. Combination regimens containing protease and polymerase inhibitors have achieved SVR rates of upto 95% and 99%, respectively.[1-8]

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Sofosbuvir belongs to class 3 direct acting antivirals. It is actually a prodrug, metabolized into direct acting antiviral metabolites that inhibit HCV NS5B RNA-dependent polymerase, which is required for viral replication. Sofosbuvir has activity against genotypes 1, 2, 3 and 4.[9] On the other hand metabolites of sofosbuvir do not have inhibitory effects on human DNA or RNA polymerases, which probably is the reason for better safety profile.[10] Majority of the drug is excreted through kidneys, hence limitation of its use in patients with advanced renal disease and a scarce data availability in this aspect. Above all, studies conducted in western population have proven to be far safer when using sofosbuvir combination therapy as compared to interferon-based regimen, particularly neuropsychiatric symptoms and bone marrow suppressive effects.[11,12]

The purpose of this study was to analyze the adverse events related to sofosbuvir in Southeast Asian population and to compare it with western data whether the two sets of populations differ in their representation which may be further related to different metabolic rates and renal excretion in widely separate ethnicities.

## METHODOLOGY

The study was carried out in the Department of Medicine, Gastroenterology Division, Shalamar Hospital, Lahore from September 2015 to May 2016. It was a prospective

observational study. Patients of chronic hepatitis C who were visiting the gastroenterology outpatient department and started on sofosbuvir combination therapy were enrolled by simple convenient sampling. Equal number of male and female patients were selected. Study group included both treatment-*naïve* and patients undergoing retreatment, majority being treatment-*naïve*.

Patients were followed at baseline, i.e. before start of treatment and thereafter at 4-week, 12-week and 24-week, respectively. A questionnaire comprising of a set of symptomatology was introduced and asked each time they reported on proposed visit. The subjects were enquired about these complaints either not present previously or reported as aggravation of previous symptoms. Similarly, patients were also directed to mark severity of symptoms as mild, moderate or severe, mild being not limiting daily life activities and severe as a consideration to discontinue treatment. Patients were serially screened for cytopenias, derangements in liver and renal functions on each visit. Documentation of a new or worsening of already existing co-morbid major organ dysfunction was done by thorough clinical examination. Patients were also screened for HCV genotype as well as status of underlying liver disease. Those with comorbid conditions were directed to give complete information regarding other medications they were currently taking. Patients with end-stage renal disease (ESRD) were excluded from the study.

Data was entered and analyzed in SPSS version 20. Mean and standard deviation was calculated for age. Percentages and frequencies were described for subjective complaints. Frequency of absolute neutropenia ANC <1500/mm$^3$, marked thrombo-cytopenia <50,000/mm$^3$, drop in hemoglobin >2 g/dl, rise in ALT >2 times UNL and bilirubin elevation >2 mg/dl that developed during therapy was also described. Number of deaths resulting from above complications were noted. P-value was calculated using test for two populations propotions, any value of $\leq$0.05 was taken as significant.

## RESULTS

A total of 200 patients with chronic hepatitis C receiving sofosbuvir-based regimen were enrolled in the study. Initially, equal number of males and females were selected. Out of these, three female and one male patients were lost to follow-up. The mean age was 46 ± 10 years. One hundred and two (52%) patients were treatment-naïve, while rest of individuals (94%) were on retreatment either because of non-responder status or relapse of HCV. Fifty-seven (29%) patients had decompensated liver disease. Four (2%) patients received triple therapy consisting of sofosbuvir, ribavirin, and peg INF; while rest of patients received dual therapy. All the study patients were of genotype 3 except 2% of patients receiving triple therapy who had genotype 1.

**Table I:** Comparative analysis of subjective symptoms.

| Symptom | Ribavirin+ Sofosbuvir[a] (n=250) | Ribavirin+ Sofosbuvir[b] ( n=192) | p-value |
|---|---|---|---|
| Fatigue | 75 (30%) | 106 (55%) | <0.0001 |
| Myalgia | 22 (9%) | 85 (44.2%) | <0.0001 |
| Fever | 10 (4%) | 81 (42%) | <0.0001 |
| Chills | 5 (2%) | 27 (14%) | <0.0001 |
| Flu | 15 (6%) | 4 (2%) | 0.044 |
| Headache | 75 (30%) | 72 (37.5%) | 0.096 |
| Insomnia | 40 (16%) | 98 (51%) | <0.0001 |
| Asthenia | 52 (21%) | 40 (20.8%) | 0.992 |
| Nausea | 32 (13%) | 96 (50%) | <0.0001 |
| Rash | 22 (9%) | 32 (16.6%) | 0.012 |
| Pruiritis | 67 (27%) | 65 (33.8%) | 0.107 |
| Diarrhoea | 30 (12%) | 15 (8%) | 0.149 |

*Comparison done between study groups receiving similar regimens; a=data from Gilead Sciences, December 2013[10]; b=data from study at Shalamar Institute of Health Sciences.*

**Table II:** Comparative analysis of hematological parameters.

| Parameters | Ribavirin$^+$ Sofosbuvir[a] (n=250) | Ribavirin$^+$ Sofosbuvir[b] (n=192) | p-value |
|---|---|---|---|
| Fall in hemoglobin | | | |
| >2 g - 5g/dl | 15 (6%) | 53 (27.6%) | <0.0001 |
| >5 g/dl | 2 (0.8%) | 5 (3%) | 0.131 |
| Neutropenia | | | |
| <1500/mm$^3$ | 0% | 6 (3%) | 0.004 |
| <500/mm$^3$ | 0% | 1 (0.52%) | 0.254 |
| Thrombocutopenia | | | |
| <50,000/mm$^3$ | 2 (0.8%) | 10 (5%) | 0.004 |
| <25,000/mm$^3$ | 0% | 1 (0.52%) | 0.254 |

*Comparison done between study groups receiving similar regimens; a=data from Gilead Sciences, December 2013[10]; b=data from study at Shalamar Institute of Health Sciences.*

Subjective symptoms like fatigue, myalgia, fever, insomnia and nausea were more frequent. On comparative analysis with a similar study group, a p-value of <0.0001 was recorded; while less common symptoms were flu, diarrhea and rash (Table I). However, none of the symptoms were severe enough to warrant discontinuation as reported by the patients. Among hematological parameters, anemia was the most frequent abnormality developed during treatment. Drop in hemoglobin was seen in 147 (75%) patients (p=0.001), whereas severe anemia having Hb fall >5 g/dl was seen in 8 (4%) of total patients. Absolute neutropenia and thrombocytopenia was noted in 8 (4%) and 12 (6%) individuals, respectively. In later case, all patients were with decompensated cirrhosis. Among these, one patient taking sofosbuvir and ribavirin died due to severe pancytopenia after two months of treatment. Since majority of the study group received dual therapy, so further break up and comparative analysis of this subgroup was done (Table II). No worsening of any of comorbid condition was noted.

## DISCUSSION

Treatment of chronic hepatitis C, one of the major burdens of infectious diseases and associated with life

threatening complications, is undergoing continuous research process with an aim to achieve an optimum combination of therapy and minimal or no associated adverse events. Until now, direct acting antiviral drugs have come out with near-desirable results. One of the class of direct acting antivirals has activity against NS5B polymerase, which is essential for viral replication. sofosbuvir is one of them. As already described, it is a prodrug and needs hepatic conversion to active metabolites. Its metabolite uridine analog triphosphate acts as chain terminator. Sofosbuvir has activity against genotype 1, 2, 3 and 4 of hepatitis C. Majority of the agent is excreted via renal pathway and a small percentage may be excreted in feces.[9] Although many studies propose that there is no significant difference in pharmacokinetics of this agent in variant ethnicities, gender, and age groups; but ongoing studies and research process is required to validate it.[13] The purpose of this study was to evaluate adverse events secondary to sofosbuvir-based therapy in a subgroup of Pakistani population.

Chronic hepatitis treatment has always faced challenging side effects with past therapies, especially with interferon and ribavirin. Ribavirin induced anemia could not be off set yet because of its indispensible requirement in chronic HCV therapy until recently, although newer guidelines by American Association of Study of Liver Diseases (AASLD) have recommended treatment regimens containing other newer antivirals in place of ribavirin; but such regimens have limited availability in developing countries at present. However, interferon has been definitely replaced with much more better options.[14,15] Previously, 10-17% of patients turned out with serious adverse events due to interferon. Similarly, 18-27% and 3-4% reported with neutropenia and thrombocytopenia, respectively.[16,17] So apart from neuropsychiatric symptoms, bone marrow suppression was one of the major contributor to pre-mature termination of treatment.

Although among various classes of direct acting antiviral agents, treatment related adverse events are also variable. Still sofosbuvir has been reported to have a better safety profile with very smart SVR rates. Fatigue, headache and nausea have been reported in 30%, 30% and 13% of individuals receiving sofosbuvir and ribavirin for 24 weeks, respectively.[10] The present study reported these symptoms at a frequency of 55%, 37% and 50%, respectively. The percentage of symptomatology rises proportionately on addition of pegylated-INF. Less reported complaints were rash, flu and chills comprising 16%, 2% and 14%, respectively as compared to 6%, 9% and 2% in international studies.[10] Although the study population showed higher frequencies of subjective complaints, however, none of the above symptoms were severe enough which resulted in treatment discontinuation. This reflects that metabolism of sofosbuvir may not be significantly different between these two racial origins, but psychosocial behavior of populations living in underdeveloped countries may vary widely.

The other important area that needs attention is effect on bone marrow and hemoglobin. About 2/3rd of patients receiving ribavirin experience drop in hemoglobin but severe anemia is reported in <1% of individuals.[18] In another study, the percentage of anemia was found to be 6-8% in sofosbuvir-based regimens and 14-23% when peg INF was added.[9] In our study, 27% of patients receiving sofosbuvir and ribavirin combination reported with drop in hb >2g/dl from baseline; out of these, 3% had severe anemia with hb fall >5g/dl. Absolute neutropenia and severe thrombocytopenia were seen in 3% and 5%, respectively. Mild to moderate anemia alongwith neutropenia and thrombocytopenia is more frequent in our population. The last two abnormalities are reported in <1% of patients in studies conducted in the West.[10] However, statistical difference was not significant between two populations when severe cytopenias were analysed. But it has been observed that fall in hemoglobin was more frequent and severe in patients with decompensated cirrhosis as compared to compensated liver disease (hb fall >2g/dl 50% vs. 19%). All cases reporting with severe thrombocytopenia and neutropenia were those with decompensated disease. One of those patients died due to complications as a result of severe pancytopenia during treatment.

There had been no evidence of any untoward effect on various comorbid conditions, 42% of our patients had comorbities, majority being diabetic, hypertensive and a small percentage had ischemic heart disease and hypothyroidism. No worsening of underlying condition was noted.

Sofosbuvir-based regimens have not shown a marked decline in frequency or pattern of symptomatology in this set of population but do reflect improved tolerance and compliance owing to lesser severity of these symptoms. Psychosocial behavior of people living in under-developed countries may be a contributing factor in undue reporting of symptoms. Similarly, ribavirin appears as the major determinant of anemia in this population, again supported by evidence of high percentage of anemia in dual therapy group. In order to further validate these results, larger populations and multicenter studies in this region need to be conducted.

## CONCLUSION

In short, mild to moderate anemia and cytopenias were more frequent in the study population as compared to the West and severe cytopenias should be anticipated, especially in those with decompensated liver disease.

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