# FREQUENCY OF SUSTAINED VIROLOGIC RESPONSE IN HEPATITIS C POSITIVE, TREATMENT NAÏVE PATIENTS ON SOFOSBUVIR AND DACLATASVIR

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***ABSTRACT***

***OBJECTIVES***

*To measure the frequency of sustained virologic response in Hepatitis C positive, treatment naïve patients on Sofosbuvir and Daclatasvir.*

***METHODOLOGY***

*This descriptive study was conducted in the Department of Medicine, Khyber Teaching Hospital Peshawar from 15th May 2020 to 14th November, 2020. A sample size of 93 was calculated by using sustained virologic response in 96% patients using Sofosbuvir and Daclatasvir with the confidence level as 95% and 4% margin of error under WHO formula for sample size determination in health studies. Consecutive non probability sampling technique was used in the study.*

***RESULTS***

*Ninety Three treatment naïve hepatitis C patients were included in the study containing 53 males (57%) and 40 females (43%) with mean age of 43 ± 0.23. 84 (90%) patients were in Child A class according to Child Pugh score. Overall 89 (95.7%) patients showed sustained virologic response following 12 weeks treatment of naïve HCV patients with combination of sofosbuvir and daclastavir. 5 patients developed side effects to the drugs; 2 patients developed anemia with one patient having anemia severe enough to require blood transfusion. 4 patients did not respond to the treatment regime in terms of sustained virologic response for 12 week treatment and were continued for 24 weeks on the same regime.*

***CONCLUSION***

*This study concludes that combined sofosbuvir and daclatasvir for 12 weeks appear to have sustained virologic response in treatment naïve HCV patients. Child score has statistically significant correlation to sustained virologic response with Child A class showing SVR in all patients. Patients in Child class C did not show SVR. Thrombocytopenia has direct and negative affect on SVR.*

***KEYWORDS:*** *Hepatitis C, Sofosbuvir, Daclatasvir, Treatment Naïve, Sustained Virologic Response*

## INTRODUCTION

Chronic Hepatitis C is a chronic liver disease caused by a small, enveloped, single stranded RNA virus referred to as Hepatitis C virus. It is a major cause of liver pathology leading to liver injury, cirrhosis and ultimately hepatocellular carcinoma (HCC). Chronic infection with hepatitis C virus is the major contributing factor to the development of HCC with approximately 71 million individuals affected worldwide. Statistics from all over the world estimate 184,000,000 individuals affected with HCV making it a global public health problem.[1] In Pakistan, HCV is the major health issue with a ranking of 134th among 174 countries according to the Human Development of Index of the United Nations with gross prevalence of 11.5% in adults; 10.10% in blood donors; 4.65% in pregnant women; 1.6% in children; 24.97% in patients with different diseases and 51% in intra-venous drug abusers. With the prevalence of 63.45%, HCV genotype 4 ranks the highest.[2] The principal route of transmission to the host is mainly through blood transfusions, unsterilized surgical instruments (medical, surgical, dental), use of illicit drugs through injections, acupuncture as well as sexual transmission. Approximately 20% of the patients suffer from lethal liver injury and cancer.[3] Owing to increased anti-viral potency and safety index, oral direct acting anti-viral drugs (DAA) have changed the treatment of HCV drastically.[4] These drugs on the basis of mechanism of action are divided into NS3/4A protease inhibitors (e.g., boceprevir, telaprevir, simeprevir, asunaprevir, and paritaprevir boosted by ritonavir), NS5A replication complex inhibitors (e.g., daclatasvir, ledipasvir, and ombitasvir), and NS5B polymerase inhibitors (sofosbuvir and dasabuvir).[5] Until recently, the standard treatment regimen for HCV in United States and Europe has been pegylated interferon (PegIFNa) with

ribavirin (RBV) for 24 to 48 weeks depending on virologic response; treatment-naïve patients receiving this regimen had sustained virologic response of 43%-70% , however, advanced liver care was not financially feasible and this drug combination had modest success rate, poor tolerability and difficult administration.[6] New drug therapy involving usage of DAAs for genotype 4 HCV drastically improved sustained virologic response in treatment-naïve patients as indicated by the efficacy of SOF-based treatment regimens evaluated in phase II and phase III trials demonstrating SVR rate reaching 96%.[7] The development of interferon-free regimen for HCV infection has the potential to significantly impact incidence, prevalence and overall burden of Hepatitis C virus. The introduction of new HCV treatment combination has marked the beginning of new era in HCV therapy. However, the real life results concerning the efficacy and safety of this therapy regarding genotype 4 HCV is still scarce. This study aims to assess the clinical effectiveness of sofosbuvir based therapy in combination with daclatasvir and measure the frequency of patients treated in terms of SVR. It will help us gather local data on the efficacy of DAAs and also enable us in determining any outcome differences that may be attributable to genetic differences in our population from the western population.

## METHODOLOGY

This cross sectional study was conducted in the department of Medicine, Khyber Teaching Hospital, Peshawar over a period of 6 months from 15th May 2020 to 14th November, 2020. Sample size was calculated as 93 by using sustained virologic response in 96% patients using sofosbuvir and daclatasvir.[8] The confidence level was 95% and margin of error 4% under WHO formula for sample size determination in health studies. Sampling was done using consecutive non probability sampling technique. The study included patients with age more than 18 years and less than 70 years; patients having positive HCV antibodies confirmed with a positive polymerase reaction (PCR) for HCV-RNA (>25Iu/ml); treatment-naïve patients, while pregnant females , patients with renal impairment (serum creatinine>2.5mg/dl and estimated glomerular filtration rate <30 ml/min/1.73m2),patients with hepatocellular carcinoma and patients with hepatitis B virus or human immunodeficiency virus (HIV) co infection were excluded. The above exclusions were made on the basis of history, clinical examination, hematological, radiological investigations and past medical record. These will act as confounders and if included in study, will produce bias. After ethical approval from hospital ethical committee, the study was conducted and data was collected from the patients fulfilling the inclusion criteria visiting outpatient department. A written informed consent was taken from all patients included in the study and were subjected to thorough history taking, clinical examination and investigations including complete blood count (CBC), liver function tests (aspartate transaminase, alanine transaminase, serum bilirubin, serum albumin, and international normalized ratio), serum creatinine, HCV antibody, HBs-Ag, α-fetoprotein, and abdominal ultrasound. Estimation of HCV RNA level was done by Cobas Ampli Prep/Cobas TaqMan HCV-RNA assay (Roche Diagnostics; Pleasanton, CA, USA) with a threshold of detection 15 IU/mL. Patients received 12 weeks treatment with 400mg sofosbuvir and 60mg daclatasvir combination therapy with once daily dosing and post treatment HCV RNA were checked for sustained virologic response. The outcome measure was Sustained virologic response defined as patients with undetectable HCV RNA at completion of treatment. Patients were categorized as treated if SVR was less than or equal to 25IU/ml, and untreated if greater than or equal to 25IU/ml. Frequency of treated patients was calculated among total patients. All data was recorded in form of charts and tables. Confounders were controlled by strictly following exclusion criteria. Data was stored and analyzed by statistical software SPSS version 17. All the quantitative variables like age, liver function tests, and platelet counts were analyzed by mean +/- standard deviation. Frequencies and percentages were calculated for qualitative variables like sex, Child Class, treatment side effects and sustained virologic response. SVR was stratified among age and gender, platelet count, adverse effects and child class to see effect modifications. All the results were presented in tables and graphs.

## RESULTS

A total of 93 naïve patients of HCV were enrolled in the study with 53 males (57%) and 40 females (43%). The mean age of patients received was 43$\pm$ 0.23 years. The study included 23.7% patients of 18 -30 years age; 18% of 31-40 years; 28% of 41-50 years; 16.1% of 51-60 years and 14.01% of 61-70 years. The mean platelet count was $220.17x10^3$ cells/dL. 84 patients (90%) were in Child A class according to child pugh score. Over all 89% patients (95.7%) showed sustained virologic response following 12 weeks treatment of newly diagnosed, treatment naïve HCV patients with the regimen of sofosbuvir and daclatasvir. Data analysis showed only 5 percent developed side effects to the drugs; 2 percent developed anemia and one patient with anemia severe enough to require blood transfusion. 4 patients including 3 males and 1 female did not respond

to the treatment regime in terms of SVR and were referred to advance hepatology center for further management. The study showed no significant correlation of SVR with gender and age. Child score demonstrated significant statistic correlation with SVR with patients of Child A class having SVR in all patients. Patients belonging to Child C class showed insignificant correlation (p=0.46). In addition to child score, thrombocytopenia also has direct effect on sustained virologic response. Platelet count of less than $50x10^3$ did not respond well to treatment regimen. The correlation was statistically significant (p=0.05).Table 1 demonstrates distribution of patients with respect to Child Class.

**Table 01: Distribution of Patients with Respect to Child Class**

| | F | %age |
|---|---|---|
| **Child A** | 84 | 90.3 |
| **Child B** | 06 | 06.5 |
| **Child C** | 03 | 03.2 |

Table 2 describes the distribution of side effects among study sample.

**Table 02: Distribution of Side Effects**

| Adverse Effects | F | %age |
|---|---|---|
| **Yes** | 05 | 06 |
| **No** | 88 | 94 |

The distribution of SVR among patients is described in Table 3.

**Table 03: Distribution of SVR**

| SVR | F | %age |
|---|---|---|
| **Yes** | 89 | 95.7 |
| **No** | 04 | 04.3 |

Table 4 elaborates the stratification of gender and age with respect to SVR.

**Table 04: Stratification of Gender and age w.r.t Sustained Virologic Response**

| Gender | Sustained Virologic Response Yes | No | Total |
|---|---|---|---|
| **Male** | 50 | 03 | 53 |
| **Female** | 39 | 01 | 40 |
| **Age** | **Sustained Virologic Response Yes** | **No** | **Total** |
| 18-30 years | 21 | 01 | 22 |
| 31-40 years | 17 | 00 | 17 |
| 41-50 years | 26 | 00 | 26 |
| 51-60 years | 14 | 01 | 15 |
| 61-70 years | 11 | 02 | 03 |

Table 5 has stratified platelet count, Child Pugh Class and side effects from anti-viral therapy with respect to SVR.

**Table 05: Stratification of Platelet Count, Child Pugh Class and Side Effects with Respect to Sustained Virologic Response**

| Platelet count (x $10^3$/cmm) | Sustained Virologic Response Yes | No | Total |
|---|---|---|---|
| <60 | 13 | 03 | 16 |
| 61-120 | 15 | 01 | 16 |
| 121-150 | 09 | 00 | 09 |
| >150 | 53 | 00 | 53 |
| **Child Class** | **Sustained Virologic Response Yes** | **No** | **Total** |
| Child A | 81 | 03 | 84 |
| Child B | 6 | 00 | 06 |
| Child C | 02 | 01 | 03 |
| **Type of Side Effects** | **Sustained Virologic Response Yes** | **No** | **Total** |
| Diarrhea | 1 | 0 | 1 |
| Anemia | 2 | 1 | 3 |
| Myalgia | 1 | 0 | 1 |
| Fatigue | 1 | 0 | 1 |

## DISCUSSION

The treatment scenario for HCV has undergone a major progress in the last few years with the introduction of new effective therapeutic regimens. This study focuses on the usage of combined regimen of Sofosbuvir and Daclatasvir for 12 weeks in naïve HCV patients. 89(97.5%) subjects showed successful eradication of HCV with SVR of 95.7%. Only small number of patients (6.5%) faced the adverse effects of the combined regimen with fatigue in 01 patient, anemia in 2 patients, headache in one patient and myalgia in one patient. The results of our study are in accordance with a study conducted by Fontaine et al who concluded that combination of sofosbuvir and daclatasvir was associated with a high rate of SVR in treatment naïve HCV positive patients.[9] The statistical analysis of this study by Fontaine et al has enrollment of 47 patients of HCV genotype 4 and received a combination of this regimen with or without ribavirin for 12 or 24 weeks respectively. The overall SVR was 86-100% according to patients' baseline characteristics and therapeutic regimen. In our study, we did not do genotyping of HCV positive patients due to financial constraints. But keeping in view high prevalence of genotype 3 among HCV positive patients in Pakistan, we presumed majority of our patient sample being genotype 3, HCV positive.[10] Another study conducted in Egypt including >18,000 patients with HCV infection, showed that about 95% achieved SVR in12 weeks.[11] This study concluded that 92.67% patients achieved successful eradication of HCV. SVR in treatment-naïve and treatment experienced patients was 94.12% and 87.01% respectively. With regards to adverse effects, people were categorized as 59% patients with minor illnesses, 27% with fatigability complaints, anemia in 5.67% patients , headache in 4%

patients and insomnia in 2.3% patients.[11] Our study results were also in accordance with Ahmed et al who come to the conclusion that combined regimen of Sofosbuvir and Daclatasvir was associated with high rate of SVR in treatment of HCV genotype 4 with overall SVR of 92.6%, thus supporting the results of our analytical study.[12] Currently with the most recent generations of pan-genotypic oral DAAs, there are increased rates of SVR and hence the aforementioned predictive factors might not have the same importance and strength as they did before. The results of our study revealed that older age, Child Pugh Class B and C and low platelet counts are the predictors of non-response associated with Sofosbuvir and Daclatasvir therapy for HCV positive patients. This might be attributed to the fact that most of the patients with older age and/or low platelet count in our study were associated with chronicity at presentation likely caused by a longer duration of HCV infection. With regards to age factor, few studies showed the relation of older age to SVR rates using all oral DAA regimens because elderly patients were often excluded from clinical trials. However little difference in SVR rates were observed between elderly and young patients.[13,14] With regard to liver status, Ferenci et al reported that the severity of hepatic dysfunction appeared to affect the response rate to DAA, with higher SVR in patients with chronic hepatitis or Child A liver cirrhosis than in those with Child B or C liver cirrhosis.[15] Few other local studies have also concluded that the anti-viral combination is very effective in eradication of hepatitis C and is available in many centers of Pakistan free of cost. This regimen is pan genotypic with very good response seen in genotype 3 which is the most prevalent genotype in Pakistan.[16,17,18]

## LIMITATIONS

One limitation of our study was that genotyping had not been done for our patients. We might have received different responses to sofosbuvir and daclatasvir combination among HCV positive patients of different genotypes, which we could have compared to study results from other parts of the world. Another limitation of our study was that SVR was checked after 12 weeks; some resistant cases do achieve SVR at 24 weeks and we might have missed those cases.

## CONCLUSIONS

With the final impression and results analysis from this study as well as available literature, combined sofosbuvir plus daclatasvir for 12 weeks appears to have sustained virologic response in treatment naïve HCV positive patients having a high rate of SVR and safety profile. Older age, Child–Pugh class B/C and low platelet count are independent risk factors of treatment failure. Sofosbuvir plus daclatasvir regimen should be considered in the treatment of naive HCV-infected patients. Moreover, this study effectively analyzes the role of combined regimen of oral DAA in treatment-naïve HCV patients.

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