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**Original Article**

# Sustained Virological Response (SVR) and Safety of Two Direct Acting Anti-Viral (DAA) Combination Therapies in Chronic Hepatitis-C Infected Patients of Lahore, Pakistan. A Randomized Controlled Trial

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## ABSTRACT

Chronic Hepatitis C (HCV) is a deadly infection affecting > 185 million people worldwide and led to liver cirrhosis, hepatocellular carcinoma, or liver failure. Recently, treatment regimens of chronic HCV have entered the era of direct acting anti-virals (DAAs). Sustained virological response (SVR) rate is one of the best available tools to evaluate the efficacy of DAA treatments. **Objective:** To compare SVR rate and safety of two combinations of DAA treatments (Sofosbuvir and Daclatasvir vs Sofosbuvir and Velpatasvir) in chronic HCV infected patients of Lahore, Pakistan. **Methods**: Present randomized controlled trial was conducted at Mayo Hospital, Lahore, Pakistan and recruited 76 chronic HCV infected patients according to Consort guidelines. Registered patients were allocated in two groups by lottery method. Group A received sofobuvir with daclatasvir (SOFO + DCV) while group B received sofobuvir with velpatasvir (SOFO + VEL) treatment for 12 weeks. Response to therapy was evaluated in terms of SVR after 24 weeks and safety profile of the drug. **Results:** Both treatment groups showed high SVR 24 weeks after the completion of therapy. Group A (SOFO + DCV) presented 92% SVR while group B showed 97% SVR rate. Both DAA combination therapies presented good efficacy and safety profile. Few contraindications noted during the treatment included fatigue, arthritis, headache, loss of appetite and anemia. **Conclusions:** The efficacy of both DAA combination therapies was comparably high with > 90% SVR rate. Group A proved safer as compared to group B. Studied DAA combinations are effective treatment options for chronic HCV treatment planning.

## INTRODUCTION

Hepatitis C infection is the leading cause of death in the United States, affecting more than 185 million people representing 2.8% global estimated prevalence. More than 60% of worldwide estimated cases belonged to Asia with 71.9 million active HCV replication cases [1, 2]. Chronic hepatitis C infection frequently leads to the development of liver cirrhosis, hepatocellular carcinoma, liver failure or death. HIV positive patients experience even worse condition during anti-retroviral therapy [3]. Since 2014, treatment of chronic hepatitis C infection has entered in the new regime by introduction of highly effective direct acting anti-virals (DAAs) which have shown complete cure in more than 90% patients. DAAs treatment includes 1-3 tablets per day for 8-12 weeks. Very few studies reported the side effects associated with the treatment. Pakistan has been the ranked as second highly prevalent HCV

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infected country and is among the list of low/middle-income countries cannot afford the highly expensive DAAs treatments at high level. Therefore, generic versions of DAA combination therapy are available in Pakistan to treat the highly transmissible disease. Sustained virological response (SVR) is one of the best available tools to evaluate the effectiveness of any anti-viral treatment of HCV infection. SVR is defined as "an absence of detectable HCV RNA in the serum with use of an assay having a sensitivity of at least 50 IU/ml 12-24 weeks after therapy is complete". It measures the extent to which any treatment can clear the viral infection and what proportion of infected people achieve SVR. It varies from 80-90% using different combinations of direct anti-viral agents (DAA) with pegylated interferons (pegIFN) and ribavirin [4-7]. Combination of two DAAs have shown the SVR rate of up to 99% (8, 9). SVR has been reported as robust and clinically meaningful therapeutic endpoint to evaluate the success of any anti-viral therapy (10). Clinical research in chronic Hepatitis C treatment regimens is now advancing rapidly and reported studies used SVR 12 as well as 24 weeks post treatment as primary endpoint indicator of the therapy. However, Phase III clinical trials of boceprevir and telaprevir have used SVR 24 weeks post treatment as primary indicator of the endpoint [11, 12]. Another study conducted by FDA assessed the concordance of SVR12 and SVR24 by combining data from fifteen clinical trials (n-12,000) and results revealed 98% patients with SVR 12 also had SVR 24; thus proving the efficacy of SVR12 equally well with SVR24 [13]. Improved SVR rates can therefore lead to decrease the currently excessive prevalence and transmission rates of HCV. There are 9 different variants of HCV and most of the DAAs were designed against genotype 1 which raise questions about the efficacy of these treatments on other genotypes. Till now very limited data is available on assessment of SVR 12 in different combinations of sofosbuvir (SOF) with daclatasvir (DCV) or valpatasvir (VEL) in most frequent genotypes of Pakistan. The objective of the present study was to compare the SVR in a group taking sofosbuvir and daclastasvir combination with second group taking sofosbuvir and valpatasvir in chronic HCV patients of Lahore, Pakistan. The results of the study will help medical professionals and general physicians to prioritize the line of management based on sound knowledge in this dynamic era of HCV treatment and finally, to manage the patients who are suffering from disease. Clinician will also be able to delineate the satisfactory treatment outcome of therapy that will help to reduce the concerns of the patient and his family.

## METHODS

This randomized controlled trial was approved by institutional review board of King Edward medical university, Lahore after considering the safety and efficacy of the drugs and was carried out according to the ethical guidelines involving human subjects. Chronic HCV infected patients visiting the gastroenterology outdoor department of Mayo Hospital, Lahore were recruited in the study after taking written informed consent. Convenient sampling technique was used for sample collection. Chronic HCV patients of both genders with 18-60 years' age, history of positive anti-HCV antibodies followed by positive HCV RNA by qualitative test were included in the study. Patients with liver cirrhosis, co-infection, diabetes mellitus, CKD, NAFLD/NASH, drug addiction or liver transplant plan, serious illness or consent refusal were excluded from the study. Patients with contraindications to therapy like severe anemia, malabsorption, ischemic heart disease, arrhythmias, jaundice, pregnancy, lactation, infertility, malignancy, severe depression, and psychosis were also excluded. The details of selection of study subjects following the consort guidelines are given in Figure 1.

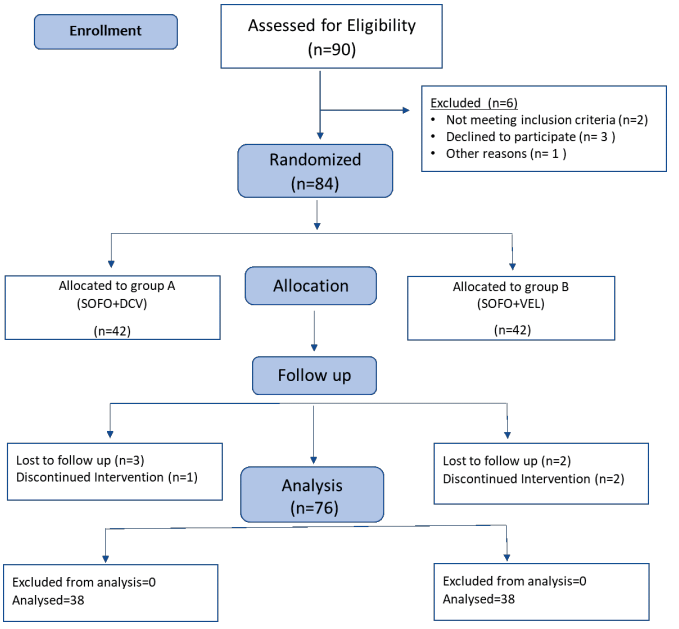


**Figure 1:** Consort for selection of study subjects

Enrolled patients were allocated in two equal groups by lottery method (computer generated technique). Group A received sofosbuvir (400mg) and daclatasvir (60mg) (SOF + DCV) treatment while group B received sofosbuvir (400mg) and velpatasvir (100mg) (SOF + VEL) treatment for 12 weeks. SVR was measured 24 weeks after completion of treatment (HCV RNA<100compies per ml). Drug side effects of both groups were noted on follow up visits based on history and clinical examination. Data were recorded into Microsoft Excel and statistical analysis was carried out using SPSS version 21.0 (IBM Corp., Armonk, USA). Normally distributed quantitative data were presented as mean ± standard deviation (S.D.), and non-normally distributed

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data was represented as median. In cases where the association between two qualitative parameters was evaluated, data was presented as proportions and the Chi-squared test used. A p-value ≤ 0.05 was considered statistically significant

## RESULTS

This randomized controlled trial initially enrolled 90 chronic HCV patients visiting Gastroenterology outdoor of Mayo Hospital, Lahore, Pakistan after taking written informed consent from each patient. Selection of study subjects was carried out by using standard consort guidelines. Briefly, 84 chronic HCV infected patients were selected after applying the inclusion criteria. Selected 84 patients were randomized by lottery method in two equal groups as group A (n=42) received sofobuvir and daclatasvir and group B (n=42) received sofobuvir and velpatasvir anti-viral treatment for 12 weeks. 4 patients in each group discontinued intervention or failed to follow up therefore excluded from final analysis. Both study groups thus included 38 study subjects each and were treated in the same hospital setting for 12 weeks. Demographics of study subjects are given in the table 1.

| Characteristics | No. |
|---|---|
| Subjects Enrolled | 76 |
| Mean Age ± SD | 42 ± 10 |
| Group A (Sofo + Dcv) | 38 |
| Group B (Sofo + Vel) | 38 |
| Average Viral Load Before Intervention | 127 8483 |

**Table 1:** Demographic characteristics of study subjects

Gender distribution of enrolled patients is given in Figure 2. 24 weeks after the completion of therapy SVR was noted for both groups to check the efficacy of both treatments.

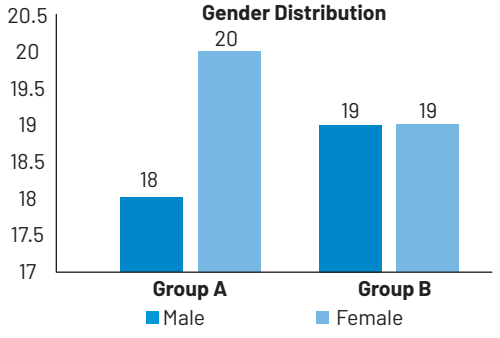


**Figure 2:** Gender distribution in both intervention groups

Interestingly, both groups showed good SVR as measurable amount of viral RNA was detected only in 8% patients (3/38) of group A and 3% patients (1/38) of group B representing 92% and 97% SVR respectively in both groups (Figure 3). There was no statistically significant difference in the treatment efficacy of both groups (p=0.307).

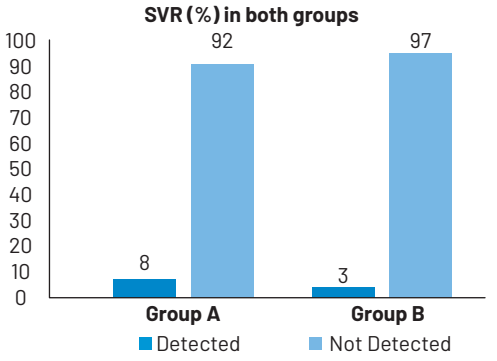


**Figure 3:** SVR (%) in group A (92%) and group B (97%)

Side effects were compared among both treatment groups. Fatigue was most common side effect present in 60.5% patients in Group A and 65.8% in Group B (p=.634). Arthritis was present in 52.6% in Group A and 55.3% in Group B (p=.818). Alopecia was present in 5.3% in Group A and 44.7% in Group B and was statistically significant (p=.040). Loss of appetite was present in 29.8% in Group A and 55.3% in Group B and was statistically significant (p=.040).

| Side Effects | Group A (Sof + Dac) | | Group B (Sof + Vel) | | p-value |
|---|---|---|---|---|---|
| | No | Yes | No | Yes | |
| | N(%) | N(%) | N(%) | Frequency | |
| Fatigue/Weakness | 15(39.5%) | 23(60.5% | 13(34.2%) | 25(65.8%) | .634 |
| Headache | 22(57.9%) | 16(42.1%) | 23(60.5%) | 15(39.5%) | .815 |
| Insomnia | 35(92.1%) | 7.9%) | 27(71.1%) | 11(28.9%) | .018 |
| Dementia | 38(100.0%) | 0 (0.0%) | 38(100.0%) | 0(0.0%) | *– |
| Fever | 36(94.7%) | 2(5.3%) | 32(84.2%) | 6(15.8%) | .135 |
| Nausea | 26(68.4%) | 12(31.6%) | 19(50.0%) | 19(50.0%) | .102 |
| Vomiting | 37(97.4%) | 1(2.6%) | 36(94.7%) | 2(5.3%) | .558 |
| Diarrhea | 38(100.0%) | 0(0.0%) | 34(89.5%) | 4(10.5%) | .040 |
| Alopecia | 36(94.7%) | 2(5.3%) | 21(55.3%) | 17(44.7%) | .000 |
| Skin Rash | 35(92.1%) | 3(7.9%) | 34(89.5%) | 4(10.5%) | .692 |
| Oral Ulcer | 38(100.0%) | 0(0.0%) | 37(97.4%) | 1(2.6%) | .314 |
| Arthritis | 18(47.4%) | 20(52.6%) | 17(44.7%) | 21(55.3%) | .818 |
| Dyspnea | 34(89.5%) | 4(10.5%) | 36(94.7%) | 2(5.3%) | .395 |
| Cough | 37(97.4%) | 1(2.6%) | 37(97.4%) | 1(2.6%) | 1.000 |
| Loss of Appetite | 27(71.1%) | 11(28.9% | 17(44.7%) | 21(55.3%) | .020 |
| Anemia | 31(81.6%) | 7(18.4%) | 26(68.4%) | 12(31.6%) | .185 |
| Neutropenia | 38(100.0%) | 0(0.0%) | 36(94.7%) | 2(5.3%) | .152 |
| Thrombocytopenia | 38(100.0%) | 0(0.0%) | 35(92.1%) | 3(7.9%) | .077 |

*= Cannot be computed variable is static

**Table 2:** Comparison of side effects in both treatment groups

## DISCUSSION

Therapeutics of chronic HCV infection has entered the next era of DAAs which have achieved higher SVR rates as compared to interferon therapy in no time. Spengler found that DAAs had shown potential to restrain the development of liver cirrhosis in chronic HCV infected patients. Therefore, modern treatment of HCV is now shifting towards the DAAs around the globe [14]. Hill et al., found that DAAs were costly but the availability of generics in developing countries has revolutionized the therapy but require careful analysis of side effects and efficacy [15].

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The European association for study of liver (EASL) has recommended the addition of ribavirin with Sofobuvir and daclatasvir or sofobuvir and velpatasvir combination therapy depending upon the presence or absence of liver cirrhosis in the patients [16]. Likewise, Chung et al., recommended the addition of ribavirin in patients with cirrhosis along with Sofobuvir and daclatasvir or sofobuvir and velpatasvir treatment [17]. This study was conducted to compare the efficacy, SVR and side effects of two combinations of DAAs. Study subjects (n=76) were randomized in two equal groups as groups A received sofobuvir & daclatasvir treatment whereas group B received sofobuvir and velpatasvir treatment for 12 weeks. All patients were treated in the same hospital setting and were followed up 24 weeks after the completion of therapy for assessment of SVR24 and careful analysis of side effects. Study results report the good SVR rates in both groups as in group A only 3 patients (8%) were detected with viral RNA after 24 weeks of therapy representing the 92% SVR rate. Whereas in group B only 1 patient (3%) detected viral RNA representing the 97% SVR rate. Our results are in concordance with previously published data where combination of sofobuvir and velpatasvir was shown to achieve the higher SVR in clinical trials [18]. Belperio et al., reported the comparable results of sofobuvir with daclatasvir and sofobuvir with velpatasvir therapy in HCV genotype. Omar et al., study reported the data from different geographical locations with different ethnicities [19, 20]. Present study carefully analyzed the SVR, and side effects caused by the therapy in both groups and found fatigue/weakness as most frequent side effect appeared in both treatment groups (60% group A and 65% group B) which was followed by arthritis (52% group A and 55% group B), headache (42% in group A and 39% group B) and loss of appetite (28.9% group A and 55.3% group B).

## CONCLUSIONS

Study concluded that comparable SVR rate was achieved for both study groups where sofobuvir and velpatasvir treatment group achieved higher SVR as compared to sofobuvir and daclatasvir group. Both treatments were effective to clear the viral load but when compared for side effects group A (sofobuvir and daclatasvir) experienced fewer side effects as compared to group B. Moreover, fatigue, arthritis, headache, loss of appetite and anemia were found to be the most frequent side effects of the therapy.

### Conflicts of Interest

The authors declare no conflict of interest

### Source of Funding

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