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# Daclatasvir-Sofosbuvir Combination Therapy with or without Ribavirin for Hepatitis-C Virus Infection: An Experience from a Tertiary Care Hospital, Pakistan

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## ABSTRACT

***Objective:*** To assess the impact and effectiveness of a pan-genotypic Directly Acting Antiviral (DAA) based regimen for patients with chronic Hepatitis-C (HCV) infection in our setup.

***Study Design:*** Cross-sectional study.

***Place and Duration of Study:*** Departments of Pathology and Medicine, Combined Military Hospital, Malir, Karachi, from Dec 2019 to Jan 2021.

***Methodology:*** Sofosbuvir and Daclatasvir were administered orally at 400mg and 60mg daily, respectively, with or without Ribavirin to treatment-naïve and treatment-experienced adult patients with chronic HCV infection. End-of-treatment response and Sustained virological response were determined among these patients by monitoring viral load using quantitative HCV RNA PCR and various genotypes.

***Results:*** Of the 59 patients, 39(66%) patients received sofosbuvir (SOF)+Daclatasvir (DCV), 12(20.3%) patients were placed on SOF+Ribavirin(Rib) and 8(13.5%) were given triple regime of SOF+DCV+Rib for 12 and 24 weeks respectively. Most of our patients were females, 32(54.23%), with a mean age of 31±17 years. Forty-eight patients (81.35%) were infected with genotype 3, followed by genotype 1 and 2, respectively. The rapid viral response was noted after four weeks of therapy among 27(45.76%) patients. The sustained viral response was noted in 38(64.40%) and 21(35.59%) patients after 12 and 24 weeks, respectively. The end-of-treatment response was observed in 40(67.8%) patients.

***Conclusion:*** Direct-acting antiviral-based regimens have shown favourable results with fewer adverse effects in our patients.

**Keywords:** Direct-acting antiviral therapy, Hepatitis C virus, Polymerase chain reaction, Sustained Viral response.

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## INTRODUCTION

Hepatitis C virus (HCV) is a global health issue and a major triggering factor for hepatic-related mortality and morbqidity.[1] As per the estimate of international data, around 71 million people worldwide are affected with Chronic HCV infection,[2] and every year, around 700,000 people die from HCV-associated liver disease.[3] Pakistan ranks second amongst countries with prevalent HCV infection; ~11 million cases have been reported up till now, and among them, Genotype 3 is most prevalent in our community, followed by Genotypes 1 and 2, along with a significant number of untypeable viral genotypes in the local community.[4]

Previously, treatment modality in practice was mainly interferon-based antiviral regimens. However, many individuals did not show sustained virological response (SVR) either because of infection with non-responder genotypes or extreme side effects and compliance issues.[5] This necessitated interferon-free Direct Acting Antiviral Therapy (DAAT). Now, therapeutic management of HCV has switched from interferon-based therapies to interferon-free oral direct-acting antiviral (DAA) combination regimens.[6] DEATHs revolutionized the management of chronic HCV infection, with better results showing sustained virologic response.[7] Daclatasvir is the first drug in the category of HCV NS5A replication complex inhibitor, and Sofosbuvir is an HCV NS5B polymerase inhibitor, a nucleotide analogue.[8,9]

Although some HCV management trials and relevant epidemiological studies were completed for chronic hepatitis C in some parts of the developing world, data on the epidemiology and treatment response of these antivirals are much more limited.[10] This study assessed the real-world safety and effectiveness of DAA-based therapy, specifically Daclatasvir and Sofosbuvir-based regimens with or without Ribavirin in adult patients with chronic HCV infection.

## METHODOLOGY

The Cross-sectional study was conducted at the Department of Pathology (Microbiology and

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Molecular) in collaboration with the Medical Department, Combined military hospital, Malir Pakistan, from December 2019 to January 2021. The ethical approval was taken from Institutional Review & Ethical Board of Combined Military Hospital (CMH) Malir, Karachi, Pakistan (File no # IRB/17/328). Informed consent was obtained from patients who were enrolled in the study. The sample size was calculated using the WHO calculator, taking the overall prevalence of HCV in Pakistan (6%).[10]

**Inclusion Criteria:** Patients with Chronic HCV infection who were 18 years or older and candidates for oral antiviral therapy, were included.

**Exclusion Criteria:** Pregnant or lactating women, or only serological evidence of HCV but no detectable viremia on PCR were excluded from the study.

The study included all those adults with clinical, radiological and laboratory evidence of infection (detectable HCV viremia on PCR), irrespective of disease stage. Before starting DAA therapy, all patients' baseline tests, including Complete blood count (CBC), Liver function tests (LFTs) and Renal function tests (RFTs), were carried out. Liver fibrosis was assessed using non-invasive tests, e.g. Alanine aminotransferase/Platelet Ratio Index (APRI) score (cut off taken as ≤1 & ≥2) along with ultrasound abdomen to determine the presence of cirrhosis to decide the duration of therapy. The treatment regimens advised according to WHO guidelines as per standard of care.[11]

Sofosbuvir and Daclatasvir were administered orally at 400gm and 60mg once daily, respectively. Ribavirin was given orally twice daily as per body weight where indicated. Sustained virological response 12 weeks after the end of treatment (SVR 12) and failure to respond (non-responder) were observed among these patients. In delayed responders, SVR was assessed after 24 weeks at the end of treatment. Patients were also observed for any adverse event reported while taking these medications.

Serum HCV RNA levels were analyzed with quantitative Qiagen reverse transcriptase quantitative PCR (Artus®HCV RT-PCR-Germany) Kit. The samples, assays and components were stored at –30ºC to –15ºC. The amplified product was detected via fluorescent dyes. The detection range of fluorescence channels was determined according to the fluorescence intensities in the PCR tubes. It allows the detection and quantification of accumulating products without reopening the reaction tubes after the PCR run. The test can quantitative HCV RNA over the range of 65-$1\times10^6$HCVIU/ml. The patient's viral load was monitored at baseline after the end of the treatment period (ETR) and after 12 weeks of the end of treatment to assess for SVR. Adverse effects of DAAT therapy were observed during the duration of therapy. Blood complete picture, coagulation profile, and serum chemistries were performed at baseline and then at scheduled visits throughout the treatment.

Statistical Package for Social Sciences (SPSS) version 25.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Chi-square test was applied to explore the inferential statistics. The *p*-value lower than or up to 0.05 was considered as significant.

## RESULTS

A total of 59 patients diagnosed with chronic HCV patients were enrolled for a based regimen, given in two different combinations. Most of our study populace were females, 32(54.2%), with 23±17 mean age noted among them. Out of the total, 32(54.2%) of them presented without any co-morbid conditions, while 27(45.7%) of them had different comorbidities. 48(81.3%) were infected with Genotype 3 followed by Genotype 1, 2 and mixed cases respectively (Table-I). Among 59 patients, 6(10.2%) had already been treated with an old therapeutic regime, i.e. peg interferon-based regime (relapse or treatment failure), while 53(89.8%) patients were treatment-naive. Of these 59 patients, 39(66%) with APRI score ≤1 received sofosbuvir (SOF)+Daclatasvir (DCV), while 20(34%) with APRI score >2 on triple regime consisted of SOF+DC+Rib for the period of 3(12-weeks) and 6(24-weeks) months as per patients response is shown in Table-II. The overall outcome of patients remained uneventful; only 18(30.5%) patients developed various reversible adverse effects of minor degree, but none of them developed life-threatening conditions that harbour the therapy (Table-III). Treatment response was noted at and after 12 and 24 weeks, respectively. End-of-treatment response (ETR) based on viral load became undetectable at the end of 12 weeks of treatment in 40(67.8%) patients. SVR12 was noted after 12 weeks of the complete course of therapy in 39(66%) patients, along with clinical, radiological and lab parameters improvement, irrespective of their gender, age and genotype distribution. About 19(32.2%) non-responders who failed to show response at the end of 12 weeks of treatment, were given the same regimen for another 3months. In such patients, the therapeutic

response was noted at the end of 24 weeks, labelled as delayed/slow responders. Thus, finally, we successfully achieved SVR 24 in 58(98%) patients. Only 1 (1.7%) Relapse case was observed during this course of study, defined as detectable viral load after therapy stopped when ETR was achieved at 12 weeks (Figure).

**Table-I: Demographic and Clinical details of Patients (n=59)**

| Variables | n(%) |
|---|---|
| **Gender** | |
| Male | 27(45.7%) |
| Female | 32(54.2%) |
| **Age Group** | |
| 20-40yrs | 22(37.3%) |
| ≥41yrs | 37(62.7%) |
| **HCV Genotypes** | |
| Genotype-1 | 7(11.8%) |
| Genotype-2 | 1(1.7%) |
| Genotype-3 | 48(81.3) |
| Mixed | 3(5.1%) |
| **Total Comorbidities** | |
| Midwife home delivery | 27(45.7%) |
| Blood transfusion history | 8(29.6%) |
| Hypertension | 5(18.5%) |
| Diabetes | 3(11%) |
| Ischemic heart diseases | 2(7.4%) |
| Lichen planus | 2(7.4%) |
| *BPH | 1(3.7%) |
| Co-infection with | 1(3.7%) |
| Hepatitis B | 4(14.8%) |
| Tuberculosis | 1(3.7%) |
| No Comorbidities | 32(54.2%) |
| **Ultrasound Findings** | |
| Cirrhosis | 22(37.2%) |
| Spleno-renal varices and | 6(10.2%) |
| Splenomegaly | 4(6.7%) |
| Fatty liver | 8(13.5%) |
| Hepatomegaly | 4(6.7%) |
| Decompensated cirrhosis | NIL |
| **Laboratory Parameters** | |
| Anemia | 14(23.7%) |
| Thrombocytopenia | 6(10.2%) |
| PT/Apttt/INR | 4(6.7%) |
| Increase ALT | 18(30.5%) |

**Benign Prostrate Hyperplasia=BPH, PT= Prothrombin time, INR= International normalized ratio, ALT= Alanine aminotransferase*

**Table II: Comparison of two different Regimen in relation to Duration of Therapy (n= 59)**

| Treatment Regimen | Three Months Duration | Six Months Duration | *p*-value |
|---|---|---|---|
| HCV without cirrhosis Sofosbuvir/Daclatasvir | 27(69%) 39(66%) | 12(31%) | 0.05 |
| HCV with cirrhosis Sofosbuvir/Daclatasvir/Ribavirin | 12(60%) 20(34%) | 8(40%) | 0.05 |

**Table-III: Frequency of Reversible Minor Adverse Effects observed with DAA Therapy (n= 59)**

| Adverse Effects | n(%) |
|---|---|
| Generalized Body Aches | 4(6.7%) |
| Alopecia | 2(3.4%) |
| Headache/Disturbed Sleep | 2(3.4%) |
| Anemia/Arthralgia | 2(3.4%) |
| Myalgias/Numbness | 2(3.4%) |
| Poor Appetite | 2(3.4%) |
| Thrombocytopenia | 2(3.4%) |
| Urticaria | 1(1.7%) |
| Skin dryness | 1(1.7%) |

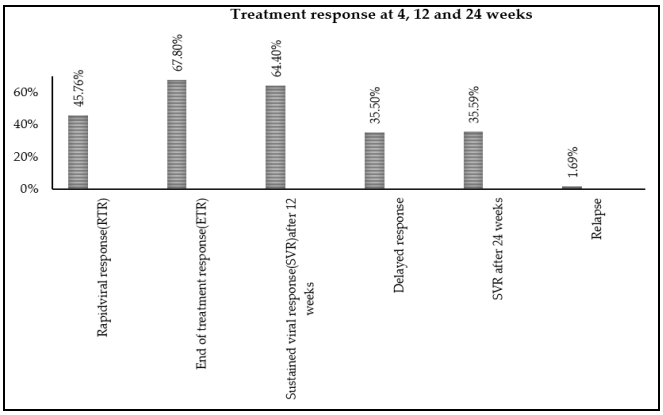


**Figure: DAA therapy response at 12 and 24 weeks observed by a reduction in viral load (n= 59)**

## DISCUSSION

Chronic hepatitis C (HCV) is a single-stranded RNA virus (hepacivirus). HCV infection is one of the most common blood-borne infection infections worldwide and a common cause of end-stage liver disease requiring liver transplant. The rate of fibrosis accelerates after 50 of age.[12] We observed that most of our patients were female (54.2%) of mean age 23±17 years with a history of midwife home deliveries and cesarean sections from some local setups. In others, there was a history of blood transfusion, dental/ interventional procedures and shaving from street barbers. However, none of our patients gave a history of alcohol intake, likely due to our religious constraints.

Over the past ten years, DAAT has revolutionized HCV treatment by increasing the end-of-treatment response rates from less than 50% to more than 90%.[13] Most patients treated with the recommended DAA combinations can be cured, reflected in the achievement of SVR,[14] the same has been observed in our study.

Our findings correlate with the recent phase 3 trials done, which showed that DAA therapy achieved

high SVR rates (more than 90% for genotype-1, 80-90% for genotype-2, 60-70% for genotype-3) for compensated cirrhotic patients, with high tolerance & relatively low rates of adverse effects.[15] In our study, genotype 3(81.3%) was more common, followed by genotype 1(11.8%), with few cases of 2(1.7%) and mixed genotype (5.1%) respectively, when compared to other studies in which genotype 4 cases were also reported.[16,17] In this study, 89.83% of naïve cases while only 10.2% had a previous history of HCV treatment with an interferon based regime, among which 3.38% showed treatment failure and 6.7% relapses. In our study, 17(28.8%) patients showed delayed response with daclatasvir (NS5A protease inhibitor) and sofosbuvir (NS5B nucleotide polymerase inhibitor). SVR was achieved at 24 weeks intervals whereas, in an international study, nonstructural (NS) 3/4 A serine protease inhibitors were shown to suppress HCV RNA by 4 logs 10 in 14 days when used as monotherapy, by 5.5 logs 10 in 14 days when combined with peginter-feron, and suppress to an undetectable level in 12 of 12 patients treated for 28 days when combined peginterferon & ribavirin.[18]

Additionally, there needs to be more data regarding DAA from our part of the world, and we need a more results-based approach to get an exact response of these drugs in our population who have multiple co-morbid along with poor socio-economic conditions. This study will help demonstrate the successful response of DAA-based regimens in this region. Moreover, we need to implement comprehensive strategies at the government level if we want public awareness regarding hepatitis C risk factors, prevention and treatment. This will be achieved by the provision of universal screening with confidential testing for all, the provision of drugs at low cost, and counselling of people to reduce its spread and reinfection, particularly in populations at high risk.[19]

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## CONCLUSION

To conclude, our experience is promising with DAA-based regimens against genotypes 1,2,3 and mixed HCV infection, irrespective of the patient's previous liver status and treatment history. They are safe with very few bearable adverse effects, and ease of oral dosing makes it a favourable choice for clinicians.

**Conflict of Interest:** None.

**Author's Contribution**

Following authors have made substantial contributions to the manuscript as under:

AA: & IR: Data acquisition, data analysis, critical review, approval of the final version to be published.

FS: & SK: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

SY: & AK: Critical review, concept, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately inves-tigated and resolved.

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