# EFFICACY AND BENEFICIAL EFFECTS OF SOFOSBUVIR WITH DACLATASVIR ON LIVER FUNCTIONS OF EARLIER TREATMENT FAILURE PATIENTS INFECTED WITH GENOTYPE 3 OF HEPATITIS C VIRUS

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## ABSTARCT

***Objective***: To evaluate the efficacy of sofosbuvir with daclatasvir and its promising effects on liver functions especially in respect to earlier treatment failure patients to frame an appropriate regimen for them.

***Study Design***: A prospective, observational cohort study.

***Place and Duration of Study***: Pak Emirates Military Hospital Rawalpindi, Army Medical College Rawalpindi, from Jan 2018 to Dec 2018.

***Methodology***: A total of 114 patients infected with genotype 3 were segregated into two groups according to their treatment status with 57 patients in each group. They received treatment according to the World Health Organization guidelines to assess the efficacy in terms of sustained virological response upon 12 weeks of completion of treatment (SVR 12) and to evaluate changes in serum alanine aminotransferase (ALT), total bilirubin, albumin and prothrombin time (PT). The results were comparatively analyzed between the groups.

***Results***: The percentage of patients attaining SVR 12 was nearly same in both the groups (94.7% vs 93%). Improvement in ALT, total bilirubin, serum albumin and prothrombin time was highly significant ($p$<0.001). When all the parameters were statistically compared, no substantial difference in the results was obtained.

***Conclusion***: This study exhibited that the regimen consisting of sofosbuvir and daclatasvir is equally effective and beneficial for newly diagnosed and earlier treatment failure patients by eradicating the virus and improving liver function parameters which ultimately result in improved quality of life.

**Keywords**: Chronic hepatitis C, Daclatasvir, Genotype 3, Sofosbuvir, SVR 12.

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## INTRODUCTION

Pakistan ranks second amongst the hepatitis C prevalent countries[1]. A meta-analyses identified that prevalence rate of chronic hepatitis C (CHC) infection in Pakistan is 6.2%[2]. The biggest dilemma of our CHC infected patients is that they are confronting with the most difficult to treat genotype of the hepatitis C virus (HCV) which is the genotype[3]. It is an important cause of substantial increase in liver related mortality. Direct consequences of genotype 3 related infection include development of liver fibrosis, rapid progression into cirrhosis and hepato-cellular carcinoma[3].

In the years of direct antiviral agents (DAAS), the agony of earlier treatment failure patients infected with genotype 3 is real and the management of such patients is a major challenge for our clinicians because the existing recommendations do not specify the treatment for earlier treatment failure patients. These treatment failure patients are those who either relapsed/did not respond to the antiviral therapy earlier, either with interferon or sofosbuvir with ribavirin, or withdrawn treatment due to intolerability. Likewise, the beneficial effect of the above mentioned combination on clinical consequences and biochemical parameters of liver function is still to be proven[4].

Discovery of DAAs has remarkably evolved the treatment of CHC infection. The nucleotide analogues sofosbuvir and daclatasvir are newly approved DAAS. Sofosbuvir is NS5B polymerase inhibitor which acts by means of a defective substrate inside the virus; therefore inhibits the synthesis of viral ribonucleic acid (RNA)[5]. It is the

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first ever marketed NS5B nucleoside inhibitor[6] and is the basis of nearly every CHC treatment combination. Daclatasvir is NS5A polymerase inhibitor resulting in inhibition of viral RNA replication and translation[7]. It is always combined with other DAAS in various regimens[8]. Presently, the regimen consisting of sofosbuvir and daclatasvir with or without ribavirin is one of the highly endorsed treatment regimen having pangenotypic activity[9]. But the facts and figures regarding the efficacy of this combination in geno type 3 infected Pakistani patients especially those who are earlier treatment failure, is not available up till now.

We especially conducted this study to gather the real world data of Pakistani patients regarding the efficacy of a new combination of sofosbuvir with daclatasvir to suggest an optimum treatment regimen for earlier treatment failure patients, and also to institute the degree of improvement in the biochemical parameters of liver function. Hence, we will be able to formulate our own guidelines depending on our patient's statistics to help the clinicians, to get better results and to save cost.

## METHODOLOGY

It was a prospective, observational cohort study conducted in gastroenterology department of Pak Emirates Military Hospital (PEMH), Rawalpindi after sanctioning by ethical review boards of PEMH and Army Medical College (CREAM) Rawalpindi. The study was carried out agreeing to the current Good Clinical Practices, certified with the Helsinki Declaration. We conscripted a total of 114 patients in the study without gender discrimination. The sample size was calculated by keeping the level of confidence 95% and power of study 80% considering the prevalence rate 6.2%. Purposive sampling technique was applied in the study. Patients were distributed into two groups on the basis of their treatment status, having 57 patients in each group (group 1=treatment naïve,group 2=earlier treatment failure patients) who fulfilled the inclusion criteria: (1) age of the patients between 18 to 65 years, and (2) positive cases of genotype 3, who were diagnosed positive by quantitative and qualitative polymerase chain reaction (PCR). Exclusion criteria were as follows: (1) patient age less than 18 or more than 65 years, (2) history or presence of any hepatic or extrahepatic malignancy, (3) co-infection with hepatitis B or human immunodeficiency virus (HIV), (4) any other liver related illness or renal problem with eGFR <30 mL/min, (3) lactating mothers or pregnant women, (4) patients on anti-epileptics, (5) any contraindication associated with ribavirin (baseline risk of severe anemia).

Sofosbuvir was given to all the patients in a dose of 400mg once a day and daclatasvir in a dose of 60 mg per day for 12 weeks in non-fibrotic patients and for 24 weeks with the addition of ribavirin in those patients who had clinical, laboratory or radiological evidence of fibrosis/ cirrhosis. Dose of ribavirin was calculated according to the weight of the patient. It was given as a dose of 1000 mg per day for patients weighing ≤75kg and 1200mg per day for patients weighing >75kg[10].

Patients were regularly followed up and considered for end of treatment response (ETR) and sustained virological response after 12 weeks of completion of the treatment (SVR 12) by quantitative Polymerase chain reaction (PCR) which was carried out via Sacace HCV real-time quantitative kit. SVR 12 is a sign of successful eradication of HCV and is defined as persistent absenteeism of viremia in blood stream 12 weeks afterwards completion of treatment[9]. Those patients who attained SVR 12 were subjected to evaluation of the beneficial effects on liver function parameters including alanine aminotransferase (ALT), total bilirubin, serum albumin by using a fully automated chemistry analyzer (Roche), and prothrombin time (PT) by using biorad kit. The results were compared amongst the groups.

Statistical analysis was completed by entering whole data on SPSS version 22. Mean and SD were imaged for elucidation of numerical

variables. Independent t-test and paired sample t-test were used for revelation of the comparison. Qualitative variables were reflected by frequencies and percentages, and chi square and Mc Nemar tests were applied for comparison. *p*-value was considered significant if it appeared to be less than or equal to 0.05.

## RESULTS

A total of 57 patients were included in group 1 with the mean age of 49 ± 13.08 years amongst them 30 (52.6%) patients were males and 27 (47.4%) were females. Of 57 patients in group 2, 24 (42.1%) patients were males and 33 (57.9%) were females. The mean age of the patients in group 2 was 50 ± 12.6 years. Both the groups were comparable in respect to their demographic profile ($p$>0.05).

In group 1, ETR was attained by majority of patients with the percentage of 94.7% (N=54) and all of them achieved SVR 12. Overall baseline serum ALT level in group 1 was 86.04 U/L, total bilirubin 12.86 µmol/L, serum albumin 40.05 g/L and PT was prolonged in 75.4% (N=43). After achieving SVR 12 average serum ALT level and total bilirubin level were reduced to normal in considerable number of patients which were 23.64 U/L and 3.62 µmol/L respectively. Average serum albumin was 45.89 g/L which was significantly raised to fall in the normal range. PT remained prolonged only in 14.03% (N=8) of patients after attaining SVR 12 (table-I & fig-1).

In group 2, 93% (N=53) patients attained ETR reflecting the majority of patients, and all of them achieved SVR 12. Overall baseline serum ALT level in group 2 was 77.68 U/L, total bilirubin 12.42 µmol/L, serum albumin 38.96 g/L and PT was prolonged in 82.5% (N=47). After achieving SVR 12 average serum ALT level and total bilirubin level were significantly reduced which were 35.47 U/L and 4.37 µmol/L respectively. Average serum albumin was found as 44.15 g/L which was raised to normal in considerable number of patients. PT remained prolonged only in 22.8% (N=13) patients after achieving SVR 12 (table-I & fig-1).

Excitingly, the improvement in all the parameters of liver function came out to be highly significant in both the groups after SVR 12 ($p$<0.001) irrespective of their treatment status.

**Table-I: Mean value of variables at different times.**

| Variables | | Group 1 (n=57) | Group 2 (n=57) |
|---|---|---|---|
| ALT (U/L) | Pretreatment | 86.04 ± 68.77 | 77.68 ± 58.21 |
| | After SVR 12 | 23.64 ± 13.13 | 35.47 ± 65.45 |
| | *p*-value | <0.001 | 0.001 |
| Total Bilirubin (µmol/L) | Pretreatment | 12.86 ± 7.04 | 12.42 ± 7.05 |
| | After SVR 12 | 3.62 ± 2.82 | 4.37 ± 4.77 |
| | *p*-value | <0.001 | <0.001 |
| Serum Albumin (g/L) | Pretreatment | 40.05 ± 6.47 | 38.96 ± 7.29 |
| | After SVR 12 | 45.89 ± 5.38 | 44.15 ± 5.01 |
| | *p*-value | <0.001 | <0.001 |
| Prolonged PT n (%) | Pretreatment | 43 (75.4%) | 47 (82.5%) |
| | After SVR 12 | 8 (14%) | 13 (22.8%) |
| | *p*-value | <0.001 | <0.001 |

**Table-II: Comparison of variables between the groups after achieving SVR 12.**

| Variables | Group 1 (n=57) | Group 2 (n=57) | Significance (*p*-value) |
|---|---|---|---|
| Positive PCR cases n(%) | 3 (5.3%) | 4 (7%) | 1.000 |
| ALT (U/L) | 23.64 ± 13.13 | 35.47 ± 65.45 | 0.18 |
| Total Bilirubin (µmol/L) | 3.62 ± 2.82 | 4.37 ± 4.77 | 0.3 |
| Serum Albumin (g/L) | 45.89 ± 5.38 | 44.15 ± 5.01 | 0.08 |
| Prolonged PT n (%) | 8 (14%) | 13 (22.8%) | 0.2 |

Striking consequences of the study were found when two groups were compared (table-II, figure). No significant difference was found in any parameter after comparison, proving that this regimen is equally effective for both the newly diagnosed cases and old treatment failure cases.

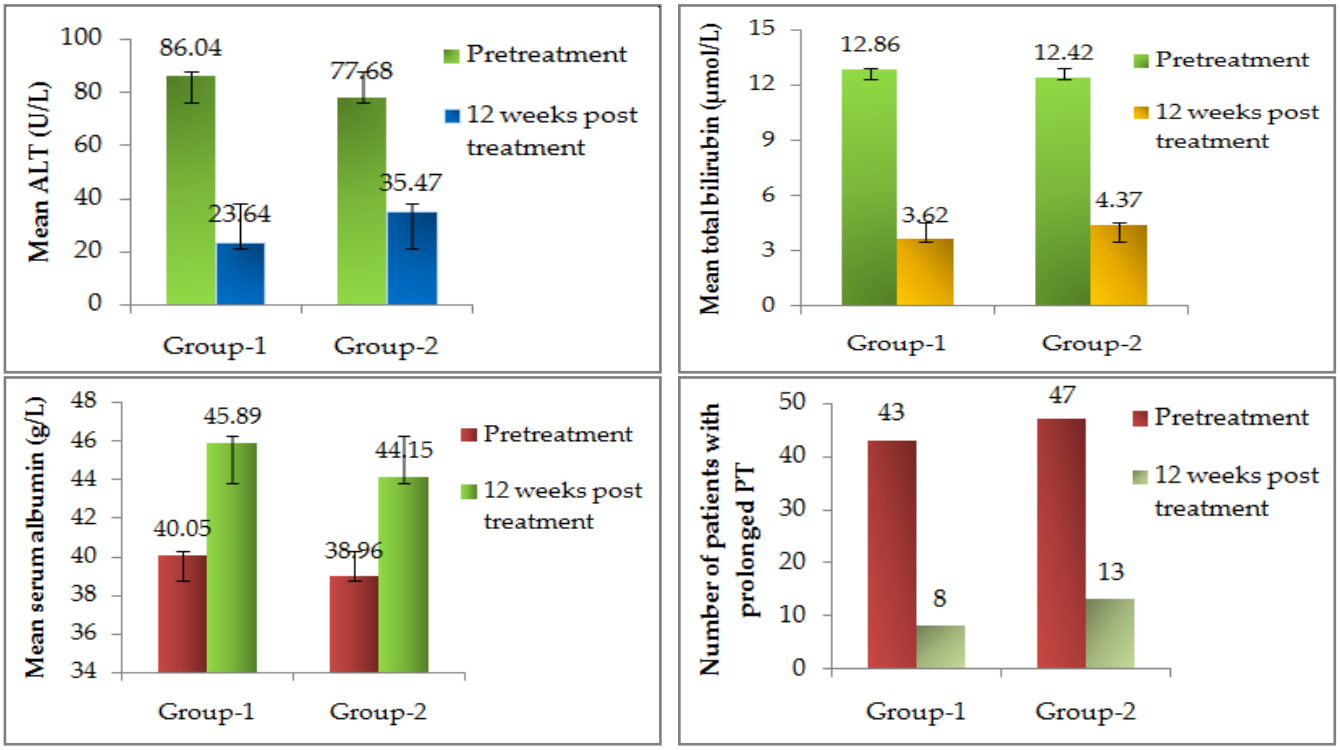


**Figure: Progressive alterations in serum ALT, total bilirubin, albumin and number of patients with prolonged PT and their comparison between the groups.**

## DISCUSSION

Evaluation exposed outstanding SVR 12 rates which was the endpoint of study and the hallmark of effective HCV treatment. The ETR and SVR 12 rates for earlier treatment failure patients were analogous to those of the treatment naïve group (94.7% vs 93%), buttressing the previous opinions[11,12]. Though slightly more number of patients maintained SVR 12 in group 1 as compared to the patients in group 2 but statistically significant difference was not observed ($p$=1.000), verifying the above mentioned combination as an optimum treatment regimen for earlier treatment failure patients. One of the prospects could be that adding daclatasvir to the regimen results in knocking out the remaining variants of HCV which persistently lowered than the range of detection in non-responders or relapsers[13]. Another study stated rather lesser SVR 12 rates depicting 86% in earlier treatment failure group[14]. But the central difference is that Nelson's study was a phase III clinical trial while a real life cohort signified our study. Cohorts from real life practices have the lead over clinical trials as it subjugates the confines of trials and is a real test of efficacy of a drug[15]. Result of the efficacy which we found in earlier treatment failure group was in consonance with a research conducted by Leroy and colleagues[16]. Large sample size proved to be the strength of our study which was smaller in Leroy's work. This emphasized that the combination of sofosbuvir and daclatasvir lead to greater and parallel SVR 12 rates in both treatment naïve and earlier treatment failure patients.

It is a buttoned-down reality that liver functions improve after eradication of HCV[17] but to what extent they improve after achieving SVR 12 with DAAS, is still to be known. The hallmark of hepatocellular necrosis, serum ALT, was also

analyzed in this study. Insult to hepatocytes or their inflammation causes ALT leakage into the bloodstream more than usual. It is a renowned fact that level of liver enzymes drops to normal when inflammation settles but clinically most important finding was that ALT levels also normalized in earlier treatment failure group without any significant difference with the newly diagnosed group. The same results were also obtained by Omar *et al*. From their study on a genotype 4 infected cohort[15].

The substantial decrease in average serum bilirubin was comparable among the groups, backing the findings from victims of other liver problems comprising autoimmune type[18] and alcoholic type of hepatitis where hepatic functions reestablished after an effective treatment.

Remarkable improvement in serum albumin levels in both the groups strengthens the impression that reduced synthetic ability of liver is a direct consequence of hepatocytes inflammation and that abating inflammation can revive synthetic role of liver to certain level[19]. This kind of improvement in liver synthetic function was also observed with interferon therapy earlier to the discovery of DAAS but it used to take longer period to rebuild liver synthetic function, while our study evidenced the improvement within 12 weeks of viral eradication. Hence, certifying the beneficial effects of sofosbuvir and daclatasvir in improving patient's quality of life not only in treatment naïve but also in earlier treatment failure patients.

We highlighted a considerable improvement in PT in both the groups, which is another parameter reflecting liver synthetic function and an indirect sign of portal hypertension/cirrhosis. This inference authenticate the insight that liver is the leading place for production of clotting proteins and that prolonged PT is a gauge of significant damage in the ability of liver to produce clotting proteins. This observation is underpinning the results of trial encountered by Mohamed and colleagues with daclatasvir and asunaprevir (NS3 protease inhibitor) suggesting the likelihood of reinstatement of synthetic capacity of liver after successful antiviral treatment in CHC patients[20].

## CONCLUSION

This study exhibited that the regimen consisting of sofosbuvir and daclatasvir is equally effective and beneficial for newly diagnosed and earlier treatment failure patients by eradicating the virus and improving liver function parameters which ultimately result in improved quality of life.

## CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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