**Original Article**

# Effects on ALT normalization in the first month of treatment by Sofosbuvir/Ribavirin therapy versus Sofosbuvir/Daclatasvir therapy in HCV infected individuals

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## Abstract

**Objective:** To evaluate the effects on ALT normalization in the first month by SOFOS/RIB therapy versus SOFOS/DAC therapy in HCV infected individuals in Pakistan.

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

**Material and Methods:** A cross-sectional analysis was performed in a total of 200 Hepatitis C infected patients, sex, history of diabetes mellitus, prior interferon therapy, decrease in hemoglobin >2 gm/dl in 1st month and rise in serum bilirubin in 1st month was the qualitative variables and the quantitative variables were age, weight, baseline hemoglobin, baseline bilirubin at week 4 of treatment. The statistical relation of the mentioned variables was checked using SPSS version 15 on the basis of data collected.

**Results:** Out of total 200 patients, 47% (94) were males, 53% (106) were females, 28% (56) patients were diabetic & 44.5% (89) patients had history of prior interferon therapy, 28.5% (57) patients were having low hemoglobin levels before starting above mentioned treatment. Both the groups completed the treatments A & B for 24 &12 weeks respectively & collected data showed the superiority of treatment B to treatment A as no decrease in hemoglobin (p=0.000), & no rise in serum bilirubin(p=0.000) during 1st month of treatment while serum bilirubin was 93 % in treatment B and 73 % in treatment A.

**Conclusion:** The results concluded that treatment B (Sofosbuvir / Daclatasvir for 12 weeks) is superior anti-hepatitis C therapy as compared to the treatment A (Sofosbuvir / Ribavirin for 24 weeks) in order to achieve ALT normalization in the first month of therapy in Pakistani population. Ribavirin should be avoided to prevent hemolytic anemia as well.
**Keywords:** Hepatitis C, Alkaline Phosphatase.

## Introduction

The majority of individuals with acute hepatitis C virus (HCV) infection progress to chronic infection [1,2], and are at increased risk of liver fibrosis progression.[3, 4] Several studies have demonstrated that while elevation of alanine aminotransferase (ALT) is an important predictor of the development and progression of liver fibrosis in chronic HCV infection, HCV RNA levels have limited role in this regard.[4,5] This supports a hypothesis suggesting a more important role of intra-hepatic inflammation in the development and progression of liver fibrosis than direct HCV cytotoxicity in HCV infection. This triggered the author to compare the "effects on ALT normalization in the first month by Sofos/RIB therapy versus Sofos/DAC therapy in HCV infected individuals" in order to come to know that if any discrepancy is found in both oral treatment lines, it could be noted.

In certain areas of Pakistan Hepatitis C Virus (HCV) is ruinous to the system of human health; where about 3-13% of population[6] is infected with Hepatitis C viral infection in the country. Decompensated liver cirrhosis together with hepatocellular carcinoma is the most common cause of death associated with chronic HCV infection.[7]

The only known nucleoside analogue is Sofosbuvir that binds directly to the active site of polymerase/NS5B[8] of the hepatitis C virus, so it is highly effective against all genotypes and possesses a high barrier to resistance. While Daclatasvir is an NS5A inhibitor [9], which is also effective against all genotypes. However, it possesses a low barrier to resistance. So, adequate combination partners are required to overcome this resistance.

The result of the antiviral therapy is estimated by sensitive HCV-PCR testing with a lower limit of detection $\leq$ 15 IU / ml.[10] Undetectable HCV-RNA at the end of the therapy, and at 12/24 weeks after the completion of the therapy define End Treatment Response (ETR) and Sustained Virological Response (SVR).[11] Internationally, both SVR 12 and SVR 24 have been accepted as the endpoints for HCV therapy.[12]

Free availability of the above-mentioned drug combination antiviral therapy at some government hospitals plus a very low market rate i.e. at almost Rupees 2000/- made the study cost-effective. The primary goal of chronic HCV infection treatment is to achieve sustained viral response (SVR), characterized by the complete disappearance of the hepatitis C virus from a patient's body. SVR is associated with decreased liver disease mortality rate together with all-cause mortality rate.[13]

## Patients and Methods

This was a cross-sectional comparative study carried out at, Al Rauf Medical and Surgical Hospital Sargodha Region from July to December 2018. A total of 200 patients of chronic hepatitis C aged 18 years and above with positive HCV-RNA were enrolled. The exclusion criteria were patients with decompensated liver disease and child pug score >12, pregnancy, HIV and/or HBV co-infection and renal dysfunction with Creatinine clearance <50 mL /minute.

The enrolled patients were divided into two groups, each consisting of 100 patients. First group patients were treated with a combination of Sofosbuvir and ribavirin for 24 weeks. SOFOSBUVIR was given in a dose of 400mg daily, while ribavirin was given 1000 mg in divided doses for patients weighing less than 70 kg and 1200 mg for those weighing 70 kg and above [14]. Second group patients were treated with a combination of Sofosbuvir and Daclatasvir for 12 weeks. Sofosbuvir was given in a dose of 400mg daily, while Daclatasvir was given in a dose of 60mg daily. The first group was named group A while second as group B. Bio-data including age, sex, weight, history of diabetes mellitus, prior interferon therapy, baseline hemoglobin (Hb), and baseline bilirubin were noted. The change in baseline biochemical and hematological parameters was checked at 4 weeks of therapy. The serum HCV-RNA testing was performed at the end of treatment and 12 weeks after the end of treatment to see for ETR and SVR-12 respectively. During data interpretation, the anemia was defined as a hemoglobin (Hb) level of less than 13.5 g/dl for males and less than 12g/dl for females [15].

The descriptive analysis of the collected data was done using SPSS version 15. Gender, history of diabetes mellitus, prior interferon therapy, decrease in

Hb>2g/dl in 1st month, and rise in serum bilirubin in 1st month were qualitative variables, while age, weight, baseline hemoglobin (Hb), and baseline bilirubin, Hb at 4 weeks of therapy, 4 weeks of therapy and serum bilirubin at 4 weeks of therapy were quantitative variables. Investigational data was interpreted in negative or positive values. For quantitative variables, means and standard deviations were calculated and for qualitative variables, frequencies and percentages were computed. A Chi-square test was applied to find an association of factors at a 5% level of significance. The odds ratio with a 95% confidence interval (CI) was also calculated for each association [15].

## Result

There were a total of 200 patients with a mean age of 44.24 ± 11.20years. Their weight ranged from 38 to 113 kg with a mean value of 73.35 + 13.00 Kg. The mean values of baseline Hb, and bilirubin were 13.04 + 1.68g/dl and 0.98 +0.66 (Table1).

Out of a total of 200 patients, 47% (94) were males and 53% (106) were females. 28% (56) patients were diabetic and 44.5% (89) patients had a history of (H/O) prior to interferon therapy. 28.5% (57) patients were anemic before starting antiviral therapy (Table 2).

100 patients in each of groups A and B completed Sofosbuvir/ribavirin therapy and Sofosbuvir/daclatasvir therapy respectively. The ETR was achieved in 95% and 97 % in groups A and B respectively. The SVR was 93% in group B compared to 73% in group A.

The superiority of group B therapy over group A was observed in statistical figures. No decline in Hb> 2g/dl during the first month of therapy (p=0.000), and no rise in serum bilirubin during the first month of therapy (p=0.000) was significantly seen in the group B patients as compared to group A patients. The decrease in Hb> 2g/dl during the first month of therapy was found in 50% of group A patients while only 9% of group B suffered a decrease in Hb> 2g/dl during the first month of therapy.

The serum bilirubin became elevated than normal value during the first month of therapy in 46% of group A and only 7 % of group B patients. And finally, ALT normalization during the first month of therapy was seen in 51% of group A and 90% of group B patients while 49 % individuals of group A and just 10% of group B failed to achieve the normal ALT levels during the first month of therapy (Table 3).

**Table 1: Descriptive statistics of quantitative variables (n = 200).**

| *Quantitative Variables/ categories* | *Minimum* | *Maximum* | *Mean ± SD* |
|---|---|---|---|
| **Age (Years)** | 19 | 75 | 44.24±11.20 |
| **Weight (Kg)** | 38 | 113 | 73.35±13.00 |
| **Baseline Hb (g/dl)** | 8.9 | 17.3 | 13.04±1.68 |
| **Baseline ALT (IU/L)** | 12 | 623 | 82.02 ±66.27 |
| **Baseline Bilirubin (mg/dl)** | 0.2 | 4.6 | 0.98 ±0.66 |
| **Hb at week 4 (g/dl)** | 6.5 | 16 | 11.77± 1.79 |
| **ALT at week 4 (IU/L)** | 11 | 122 | 26.56±15.58 |
| **Serum Bilirubin at week 4 (mg/dl)** | 0.1 | 5.5 | 0.92± 0.59 |

*WBCs= White Blood Cells; ALT = Alanine Aminotransferase; INR= International Normalized Ratio*

**Table 2: Qualitative variables (n = 200)**

| *Variables/ Categories* | *Treatment offered* | | *Total* |
|---|---|---|---|
| | **SOV+RVB** | **SOV + DAC** | |
| **Gender:** | | | |
| Male | 48 (48%) | 46 (46%) | 94 (47%) |
| Female | 52 (52%) | 54 (54%) | 106 (53%) |
| **H/O Diabetes mellitus** | | | |
| Yes | 28 (28%) | 28 (28%) | 56 (28%) |
| No | 72 (72%) | 72 (72%) | 144 (72%) |
| **H/O Prior interferon therapy** | | | |
| Yes | 45 (45%) | 44 (44%) | 89 (44.5%) |
| No | 55 (55%) | 56 (56%) | 111 (55.5%) |
| **ALT normalization during the first month of therapy** | | | |
| Yes | 51 (51%) | 90 (90%) | 141 (70.5%) |
| No | 49 (49%) | 10 (10%) | 59 (29.5%) |
| **Baseline Hb** | | | |
| Normal | 66 (66%) | 77 (77%) | 143 (71.5%) |
| Low | 34(34%) | 23 (23%) | 57(28.5%) |

**Table 3: Comparison of response to therapy as well as hematological and biochemical parameters (n = 200).**

| *Predictors/Categories* | *Treatment offered* | | *Total* | *p-value* | *Odd ratio with 95% Confidence interval* |
|---|---|---|---|---|---|
| | SOV+RVB (n=100) | SOV + DAC (n=100) | | | |
| **ALT normalization during first month of therapy:** | | | | | |
| Yes | 10 (20%) | 45 (90%) | 90 | 0.799 | 1.000 (0.271-3.694) |
| No | 40 (80%) | 5 (10%) | 10 | | |
| **End Treatment Response (ETR):** | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Achieved | 95 (49.5%) | 97 (50.5%) | 192 | 0.721 | 1.702 (0.396-7.321) | |
| Not-achieved | 5 (62.5%) | 3 (37.5%) | 8 | | | |
| **Sustained Virological Response (SVR) 12:** | | | | | | |
| Achieved | 73 (44%) | 93 (56%) | 166 | 0.000 | 4.914 (2.026-11.918) | |
| Not-achieved | 27 (79%) | 7 (21%) | 34 | | | |
| **Decrease in Hb> 2g/dl during first month of therapy:** | | | | | | |
| Yes | 50 (84.7%) | 9 (15.3%) | 59 | | 0.099 (0.045-0.218) | |
| No | 50 (35.5%) | 91 (64.5%) | 141 | 0.000 | | |
| **Rise in Serum Bilirubin during first month of therapy:** | | | | | | |
| Yes | 46 (86.8%) | 7 (13.2%) | 53 | 0.000 | 0.088 (0.037-0.209) | |
| No | 54 (36.7%) | 93 (63.3%) | 147 | | | |

## Discussion

Sofosbuvir based direct-acting antiviral therapy against HCV is a miracle. The responses to these therapies are excellent. In VALENCE trial [14] on Sofosbuvir/ Ribavirin for 24 weeks duration, ETR was > 90%, while SVR 12 in treatment-experienced cirrhotic patients was only 62%. Similarly, ALLY-3 trial [15] on Sofosbuvir/ Daclatasvir therapy showed both ETR and SVR 12 above 90%. The same combination is now recommended in all HCV genotypes.[5]

In our study, serum ALT Normalization in the first month after starting the antiviral therapy was not achieved well with Sofosbuvir/ Ribavirin therapy (i.e. only 20 % in comparison to 90%). This suggests the more potent Sofosbuvir/ Daclatasvir therapy of 12 weeks duration in our population in achieving serum ALT Normalization in the first month after starting the antiviral therapy in contrast to group A patients. So ALT normalization, during the first month of therapy was seen more in patients treated with Sofosbuvir/ Daclatasvir as compared to Sofosbuvir / Ribavirin therapy (90% versus 51%).

In addition to that many side effects are noted in the patients treated with Ribavirin like hemolysis, anemia, insomnia, pruritis, anxiety, teratogenicity dry cough and hair loss.[15] In the current study, only two parameters were compared in two groups of HCV infected patients. The patients receiving the treatment with Sofosbuvir/ Ribavirin suffered a decrease in Hb> 2 g/dl during the first month of therapy more commonly than patients receiving Sofosbuvir/ Daclatasvir therapy (50% versus 9% only) in addition to that. Similarly, the Sofosbuvir / Ribavirin group had a more rise in serum bilirubin during the first month of therapy (46% versus 7%). Hence a large number of patients suffered hemolytic anemia due to ribavirin in the group who received Sofosbuvir/ Ribavirin for 24 weeks. This whole scenario was suggestive that Sofosbuvir/ Daclatasvir therapy was more efficacious and had fewer side effects in our population. However, larger studies are required to validate these findings.

## Conclusion

In conclusion, this study demonstrated that Sofosbuvir/ Daclatasvir for 12 weeks is a better antiviral therapy for hepatitis C regarding rapid end of injury to hepatocytes due to hepatitis C infection and letting back the ALT levels to its normal levels (hence preventing further decompensating of this culprit disease) as rapid as even first month of starting of antiviral therapy than Sofosbuvir / Ribavirin for 24 weeks in our population. In addition, hemolytic anemia is also a troublesome and serious side effect in half of the patients receiving ribavirin.

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