Comparing Daclatasvir Plus Sofosbuvir, With or Without Ribavirin, for Hepatitis C Virus Genotype 3 Management.

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ABSTRACT... Objectives: to evaluate the sustained virology response rate of Daclatasvir (DCV) + Sofos (SOF) with and without Ribavirin (RBV) for 12 and 24 weeks in patients presented with advance liver disease. Study Design: Randomized control trial. Setting: Department of gastroenterology, Services hospital, Lahore. Period: January 2018 to January 2019. Material & Methods: Patients advance hepatitis genotype 3 infection was enrolled through non probability consecutive sampling technique. Main outcome variable is sustained virology response rate. SPSS version 23 was used for data analysis. Mean and standard deviation and frequency percentages were calculated for numerical and qualitative data respectively. P value ≤0.05 was considered as significant. Results: One way ANOVA was used to check the differences between four groups, while chi-square test was used for categorical variables. Overall SVR12 rates and causes of treatment failure for the primary (actual duration) for patients who received DCV+SOF for 24 weeks, overall SVR12 (mITT) was 64.4% with RBV and 11.9% without RBV and treatment failure was found 31.3% without RBV and 28.1% with RBV. Sensitivity analyses (duration initially considered), SVR12 in terms of mITT for 24 weeks treatment is 58.4% and without RBV and 15.6% with RBV. Treatment failure is 47.1% without and 23.5% with RBV. Conclusion: Daclatasvir with sofosbuvir is an effective treatment for hepatitis C genotype 3 infections as it achieved high sustained virology response rate in patients of advance liver disease or cirrhotic patients. Without addition of ribavirin this treatment is effective when given for 24 weeks.

Key words: Advance Liver Disease, Daclatasvir, Sofos, Ribavrin, Sustained Virology Response.

INTRODUCTION
Hepatitis C is an inflammatory and infective disease of liver which develops after getting infection with hepatitis C.¹ Hepatitis C may be acute or chronic in nature. Genotype 3 of hepatitis C virus is a most common and prevalent genotype in the world that associated with fibrosis and accelerated progression.² In this genotype there are greater risk of hepato cellular carcinoma and steatosis which is the main cause of hospital stay and mortality of liver infected patients as compared to other genotype.³

In cases of the genotype 3 infection safe, effective and urgent treatment should be provided.³ Oral regimes of hcv have greater safety and improved efficacy relative to treatment with ribavirin and pegylated interferon (peg IFN), but some of these oral agents have limited results against genotype 3.⁴ Daclatasvir is an inhibitor of non structural protein 5A, and sofosbuvir is an inhibitor of non structural protein 5B. Both these drugs have potent activity against genotype 3 of hepatitis being a pan genotypic oral antiviral for hcv.⁵

12 weeks treatment of DCV plus SOF gives 96% successful results in non fibrotic patients of hepatitis genotype 3 infection.⁶ According to the American association for the study of liver disease, European association for the study of liver is recommended this regimen as a gold standard for the treatment of non cerotic infection of genotype 3 but in the cerotic patients genotype 3 of hepatitis C is more difficult to treat with
combination of DCV plus SOF plus RBV in third phase for 12 to 16 weeks of treatment.\textsuperscript{7,8}

In several guidelines combination of DCV plus SOF for 24 weeks recommended for the treatment of genotype 3 infection. Early access and awareness programmes about hcv allow the new drugs for their authorization and marketing purpose.\textsuperscript{9,10} In this study we access the result of daclatasvir plus sofosbuvir with or without combination of ribavirin in patients of hepatitis genotype 3.

**MATERIAL & METHODS**

The study was conducted in Department of gastroenterology, Services hospital, Lahore.in one year duration from January 2018 to January 2019. The study was started after the approval from the ethical board and informed written consent was obtained from the patients after detailed information and purpose of the study.

Adult patients with cirrhotic HCV infection were included in the study without any alternative treatment indication like HCV reoccurrence after liver transplant, advanced liver disease or indication of liver or renal. Patients were divided into two groups. One group was given treatment for 12 weeks and other group was given treatment of 24 weeks with or without addition of ribavirin. DCV 60mg plus SOF 400mg once daily was recommended treatment for 24 weeks, RBV was added in some patients.

**RESULTS**

One hundred and twenty patients were included in this study, both gender. The patients were divided into two groups as obese and non-obese. Overall SVR12 rates and causes of treatment failure for the primary (actual duration) for patients who received DCV+ SOF for 24 weeks, overall SVR12 (mITT) was 64.4% with RBV and 11.9% without RBV and treatment failure was found 31.3% without RBV and 28.1% with RBV. Sensitivity analyses (duration initially considered), SVR12 in terms of mITT for 24 weeks treatment is 58.4% and without RBV and 15.6% with RBV. Treatment failure is 47.1% without and 23.5% with RBV.

In 12 weeks treatment primary analysis give SVR12 in terms of mITT is 21.8% without RBV and 2% with RBV, sensitivity analysis give SVR12 in terms of mITT 20.7% without and 51.9% with combination of RBV+DCV+SOF. Treatment failure is 37.5% with and 3% without RBV in primary analysis and in sensitivity analysis 29.4% without and 0% with RBV (Table-II). Status of these SVR 12 in terms of mITT and sensitivity duration independently in cirrhotic and non cirrhotic patients was given in Table-III.

One way ANOVA was used to check the differences between four groups, while chi-square test was used for categorical variables. P-values considered as significant at ≤0.005.

**DISCUSSION**

Hepatitis C genotype 3 viruses are more difficult to treat with oral antivirals drugs as compare to other genotypes. Hazode C et al\textsuperscript{11} conducted a study on this topic with treatment of advance liver disease with DCV plus SOF in combination with Ribavirin and without Ribavirin. After 24 weeks he observed SVR12 rate of 89% without RBV and less success rate 82% with RBV. This study is identical to our study in terms of treatment regimens and duration of treatment (12 weeks and 24 weeks).

Another study was conducted by Nelson DR et al\textsuperscript{12} on non cirrhotic patients presented with F3 fibrosis. Patients treated with DCV plus SOF with and without RBV but treatment given for 12 weeks and 24 weeks. SVR12 rate was 96% in this group that is similar to 12 weeks treatment in non cirrhotic with SOF plus DCV alone.

In another study Lorey V et al\textsuperscript{13} also reported similar results, he treated non cirrhotic patients with DCV and SOF with and without RBV but duration of treatment were 12 and 16 weeks. All these patients diagnosed F3 fibrosis cases. He concluded that treatment with DCV plus SOF without RBV for 12 weeks is effective and safe treatment for F3 patients.
| Variable                                      | DCV+SOF 12 Weeks | DCV+SOF+RBV 12 Weeks | DCV+SOF 24 Weeks | DCV+SOF+RBV 24 Weeks | P-Value |
|----------------------------------------------|------------------|---------------------|------------------|----------------------|---------|
| **Age (years)**                              | 46.77±6.88       | 50.33±4.32          | 46.93±6.66       | 44.75±9.94           | 0.516   |
| **Gender**                                   |                  |                     |                  |                      |         |
| Male                                         | n=20 (50%)       | n=5 (83.3%)         | n=40 (60.6%)     | n=6 (75%)            | 0.292   |
| Female                                       | n=20 (50%)       | n=1 (16.7%)         | n=26 (39.4%)     | n=2 (25%)            |         |
| **HCV- RNA at day 0, ≥6 log10 IU/mL**         | n=26 (65%)       | n=2 (33.3%)         | n=22 (33.3%)     | n=3 (37.5%)          | 0.948   |
| **HCV- RNA ≥6 log10 IU/mL**                  | n=19 (47.5%)     | n=1 (16.7%)         | n=25 (37.9%)     | n=3 (37.5%)          | 0.486   |
| **Advanced fibrosis (F3)**                   | n=7 (17.5%)      | n=1 (16.7%)         | n=13 (19.7%)     | n=2 (25%)            | 0.963   |
| **Cirrhosis**                                | n=33 (82.5%)     | n=6 (100%)          | n=59 (89.4%)     | n=8 (100%)           | 0.356   |
| **Child- Pugh class**                        |                  |                     |                  |                      |         |
| A                                            | n=26 (65%)       | n=0 (0%)            | n=28 (42.4%)     | n=3 (37.5%)          | 0.007   |
| B                                            | n=6 (15%)        | n=0 (0%)            | n=6 (9.1%)       | n=1 (12.5%)          |         |
| C                                            | n=8 (20%)        | n=6 (100%)          | n=32 (48.5%)     | n=4 (50%)            |         |
| **MELD category at day 0**                   |                  |                     |                  |                      |         |
| <10                                          | n=22 (55%)       | n=0 (0%)            | n=22 (33.3%)     | n=3 (37.5%)          | 0.001   |
| 10 to <15                                     | n=13 (32.5%)     | n=0 (0%)            | n=15 (22.7%)     | n=1 (12.5%)          |         |
| ≥15                                          | n=5 (12.5%)      | n=3 (50%)           | n=29 (43.9%)     | n=4 (50%)            |         |
| Hepatocellular carcinoma                     | n=1 (2.5%)       | n=2 (33.3%)         | n=1 (1.5%)       | n=3 (37.5%)          | 0.000   |
| Extrahepatic manifestations                  | n=4 (10%)        | n=3 (50%)           | n=4 (6.1%)       | n=2 (25%)            | 0.257   |
| Without F3 or F4 fibrosis                    | n=3 (7.5%)       | n=3 (50%)           | n=14 (21.2%)     | n=3 (37.5%)          | 0.028   |
| Post- liver transplant HCV recurrence         | n=2 (5%)         | n=1 (16.7%)         | n=2 (3%)         | n=3 (37.5%)          | 0.001   |
| Preliver/renal transplant                    | n=19 (47.5%)     | n=5 (83.3%)         | n=49 (60.6%)     | n=6 (75%)            | 0.210   |
| Treatment experienced                        | n=3 (7.5%)       | n=1 (16.7%)         | n=8 (12.1%)      | n=2 (25%)            | 0.529   |
| SOF experienced                              | n=4 (10%)        | n=3 (50%)           | n=17 (25.8%)     | n=2 (25%)            | 0.080   |
| Co- infection with HIV/HBV                   | n=4 (10%)        | n=1 (16.7%)         | n=10 (15.2%)     | n=1 (12.5%)          | 0.888   |
| **Laboratory test results at TAR**            |                  |                     |                  |                      |         |
| Platelets, ×10^9/L                           | 126.38±1.77      | 125.93±2.01         | 126.12±1.83      | 127.21±1.37          | 0.882   |
| Albumin, g/L                                 | 38.04±0.92       | 37.75±0.95          | 37.94±0.98       | 38.39±0.785          | 0.559   |
| ALT, IU/L                                    | 84.38±3.81       | 82.88±6.08          | 83.72±4.54       | 84.06±5.74           | 0.831   |
| AST, IU/L                                    | 80.15±2.13       | 80.67±2.03          | 80.32±2.10       | 80.79±1.87           | 0.848   |
| Total bilirubin, μmol/L                      | 13.09±1.26       | 12.62±1.36          | 12.86±1.29       | 11.23±1.52           | 0.748   |
| Gamma GT, IU/L                               | 116.94±2.34      | 117.87±2.21         | 117.29±2.29      | 115.24±2.11          | 0.772   |
| **Laboratory abnormalities at day 0**         |                  |                     |                  |                      |         |
| Platelets <50×10^9/L                         | n=6 (15%)        | n=2 (33.3%)         | n=4 (6.1%)       | n=3 (37.5%)          | 0.024   |
| Albumin <35 g/L                              | n=6 (15%)        | n=1 (16.7%)         | n=7 (10.6%)      | n=1 (12.5%)          | 0.481   |
| ALT >175 IU/L                                | n=6 (15%)        | n=2 (33.3%)         | n=0 (0%)         | n=0 (0%)             | 0.729   |
| AST >200 IU/L                                | n=3 (7.5%)       | n=0 (0%)            | n=4 (6.1%)       | n=3 (37.5%)          | 0.019   |
| Total bilirubin >60 μmol/L                   | n=5 (12.5%)      | n=0 (0%)            | n=11 (16.7%)     | n=2 (25%)            | 0.831   |
| Gamma GT >90 (women) or >140 (men) IU/L      | n=12 (30%)       | n=1 (16.7%)         | n=15 (22.7%)     | n=0 (0%)             | 0.816   |

Table-I. Demographic characteristics.
| Variable                  | DCV+SOF 12 Weeks | DCV+SOF+RBV 12 Weeks | DCV+SOF 24 Weeks | DCV+SOF+RBV 24 Weeks | Total |
|--------------------------|------------------|----------------------|------------------|----------------------|-------|
| **Primary analysis (actual treatment duration)** |                  |                      |                  |                      |       |
| mITT                     | n=25 (20.8%)     | n=2 (2%)             | n=72 (6%)        | n=18 (15%)           | 120   |
| Observed values          | n=21 (19.3%)     | n=3 (3%)             | n=69 (63.3%)     | n=16 (14.7%)         | 109   |
| **SVR12, n (%)**         |                  |                      |                  |                      |       |
| mITT                     | n=22 (21.8%)     | n=2 (2%)             | n=65 (64.4%)     | n=12 (11.9%)         | 101   |
| Observed values          | n=21 (23.3%)     | n=1 (1.1%)           | n=60 (66.6%)     | n=8 (8.8%)           | 90    |
| Treatment failure, n     | n=12 (37.5%)     | n=1 (3%)             | n=10 (31.3%)     | n=9 (28.1%)          | 32    |
| Virological breakthrough  | n=2 (8.7%)       | n=2 (8.7%)           | n=12 (52.2%)     | n=7 (30.4%)          | 23    |
| Relapse                  | n=5 (41.6%)      | n=0 (0%)             | n=1 (8.3%)       | n=6 (50%)            | 12    |
| Undefined virological failure | n=3 (60%)   | n=0 (0%)             | n=2 (40%)        | n=0 (0%)             | 5     |
| Non- virological failure | n=6 (66.6%)      | n=1 (11.1%)          | n=1 (11.1%)      | n=1 (11.1%)          | 9     |
| **Sensitivity analysis (treatment duration initially considered in TAR)** |                  |                      |                  |                      |       |
| mITT                     | n=20 (16.6%)     | n=10 (8.3%)          | n=65 (54.2%)     | n=25 (20.8%)         | 120   |
| Observed values          | n=18 (16.8%)     | n=6 (5.6%)           | n=56 (52.3%)     | n=18 (16.8%)         | 107   |
| **SVR12, n (%)**         |                  |                      |                  |                      |       |
| mITT                     | n=16 (20.7%)     | n=4 (51.9%)          | n=45 (58.4%)     | n=12 (15.6%)         | 77    |
| Observed values          | n=12 (23.1%)     | n=2 (3.8%)           | n=32 (61.5%)     | n=6 (11.5%)          | 52    |
| Treatment failure, n     | n=5 (29.4%)      | n=0 (0%)             | n=8 (47.1%)      | n=4 (23.5%)          | 17    |
| Virological breakthrough  | n=4 (30.8%)      | n=1 (7.7%)           | n=6 (46.2%)      | n=2 (15.4%)          | 13    |
| Relapse                  | n=3 (42.8%)      | n=0 (0%)             | n=3 (42.8%)      | n=1 (14.3%)          | 7     |
| Undefined virological failure | n=1 (33.3%) | n=0 (0%)             | n=1 (33.3%)      | n=0 (0%)             | 3     |
| Non- virological failure | n=1 (25%)        | n=1 (25%)            | n=1 (25%)        | n=1 (25%)            | 4     |

Table-II. Sustained virological response and treatment failure.

| Variable                  | DCV+SOF 12 weeks | DCV+SOF+RBV 12 weeks | DCV+SOF 24 weeks | DCV+SOF+RBV 24 weeks | P-value |
|--------------------------|------------------|----------------------|------------------|----------------------|---------|
| **Patients without cirrhosis** |                  |                      |                  |                      |         |
| mITT                     | n=15 (35.7%)     | n=1 (2.4%)           | n=23 (54.8%)     | n=3 (7.1%)           | 42      |
| **SVR12**                |                  |                      |                  |                      |         |
| mITT                     | n=12 (41.2%)     | n=1 (3.4%)           | n=14 (48.3%)     | n=2 (6.8%)           | 29      |
| Treatment failure, n     | n=1 (33.3%)      | n=0 (0%)             | n=1 (33.3%)      | n=1 (33.3%)          | 3       |
| Virological breakthrough  | n=0 (0%)         | -                    | n=1 (100%)       | n=0 (0%)             | 1       |
| Relapse                  | n=0 (0%)         | -                    | n=0 (0%)         | n=0 (0%)             | 0       |
| Undefined virological failure | n=1 (100%)  | -                    | n=0 (0%)         | n=0 (0%)             | 1       |
| Non- virological failure | n=1 (100%)       | -                    | n=0 (0%)         | n=0 (0%)             | 1       |
| **Patients with cirrhosis** |                  |                      |                  |                      |         |
| mITT                     | n=22 (61.1%)     | n=3 (8.3%)           | n=5 (13.8%)      | n=6 (16.6%)          | 36      |
| Observed values          | n=13 (68.4%)     | n=1 (5.2%)           | n=3 (15.8%)      | n=2 (10.5%)          | 19      |
| Treatment failure, n     | n=12 (41.4%)     | n=3 (10.3%)          | n=6 (20.7%)      | n=8 (27.6%)          | 29      |
| Virological breakthrough  | n=0 (0%)         | n=1 (25%)            | n=2 (50%)        | n=1 (25%)            | 4       |
| Relapse                  | n=2 (25%)        | n=3 (37.5%)          | n=2 (25%)        | n=1 (12.5%)          | 8       |
| Undefined virological failure | n=2 (33.3%) | n=2 (33.3%)          | n=1 (16.6%)      | n=1 (16.6%)          | 6       |
| Non- virological failure | n=2 (50%)        | n=1 (25%)            | n=0 (0%)         | n=1 (25%)            | 4       |

Table-III. Sustained virological response and treatment failure by cirrhosis status (primary analysis: actual treatment duration).
Welzel TM et al\textsuperscript{14} conducted a study on HCV patients treated with DCV+ SOF with or without RBV and didn’t observe any significant difference among groups regarding sustained virological response rate, as 89% response rate with RBV and 88% without RBV. In two similar studies conducted by Ioannou GN et al\textsuperscript{15} and Feld JJ et al\textsuperscript{16} sustained response rate was observed 81% and 82% respectively. It was also reported in these studies that 12 weeks treatment with SOF and Ledipasvir give less 65% SVR12 rate. Jacobson IM et al\textsuperscript{17} concluded that treatment with RBV and SOF for 13 weeks give 29% sustained virology response rate. SVR is not satisfactory after 12 weeks of treatment with this combination. Similar combination of regimens was given for 16 weeks in study by Foster GR et al\textsuperscript{18} and reported 50-60% response rate in genotype 3 cirrhotic patients. ZeuzemS et al\textsuperscript{19} also conducted a study with same combination but for 24 weeks and reported 60-75% response rate of sustained virology.

Here is another study conducted by Zanaga LP et al\textsuperscript{20} on treatment of genotype 3 infection of hepatitis C in which he observed treatment with SOF+PegInf in combination with ribavirin for 12 weeks have 83-100% SVR without any significant difference in cirrhotic and non cirrhotic patients. Same treatment with similar regimen for 24 weeks have 82-96% SVR rate.

**CONCLUSION**

Daclatasvir with sofosbuvir is an effective treatment for hepatitis C genotype 3 infections as it achieved high sustained virology response rate in patients of advance liver disease or cirrhotic patients. Without addition of ribavirin this treatment is effective when given for 24 weeks. Beyond this observational study more observation and cohort studies required.

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| Variable                              | DCV+SOF 12 weeks | DCV+SOF+RBV 12 weeks | DCV+SOF 24 weeks | DCV+SOF+RBV 24 weeks | Total |
|---------------------------------------|------------------|----------------------|------------------|----------------------|-------|
| Patients with ≥ 1 AE                 | n=8(6.6%)        | n=12(10%)            | n=20(16.6%)      | n=11(9.2%)           | 120   |
| Patients with ≥ 1 serious AE         | n=9(7.5%)        | n=15(12.5%)          | n=2(1.6%)        | n=7(5.8%)            |       |
| Discontinuation because of AEs (excluding death) | n=4(3.3%)        | n=2(1.6%)            | n=13(10.8%)      | n=5(4.2%)            |       |
| Deaths                               | n=3(2.5%)        | n=2(1.6%)            | n=5(4.2%)        | n=2(1.6%)            |       |

Table-IV. On- treatment safety summary by derived regime.
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AUTHORSHIP AND CONTRIBUTION DECLARATION

| Sr. # | Author(s) Full Name | Contribution to the paper | Author(s) Signature |
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| 1     | Yasir Mahmud        | Conceptualized & Designed the study, Collected data. | [Signature] |
| 2     | Mahmood Ahmad       | Collected data. Data interpretation & Data analysis. | [Signature] |
| 3     | Sidra Rasheed       | Collected data. | [Signature] |
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