Efficacy of First Available Direct-Acting Antiviral Agent in Treatment of Chronic Hepatitis C; Results from a Single Centre in Pakistan

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ABSTRACT

Objective: To determine the efficacy of dual (sofosbuvir and ribavirin) and triple therapy (sofosbuvir-ribavirin-pegylated interferon) for treatment of hepatitis C.

Study Design: Comparative cross sectional study.

Place and Duration of Study: Department of Medicine, Combined Military Hospital, Lahore, from Nov 2014 to Mar 2017.

Methodology: A total of 182 consecutive patients with age ≥18 years and positive HCV RNA by polymerase chain reaction were included, while patients with haemoglobin of <10 g/dl, albumin <2 g/dl, platelet count of <100×10^9/L, creatinine clearance of <60 mL/min or liver disease caused by non-hepatitis C related causes were excluded from study.

Results: Total 129 (70.8%) were treated with dual and 53 (29.1%) with triple therapy. Amongst patients with genotype 3 (158/182), the overall sustained virological response at 12 weeks (SVR 12) was 94.4% in patients with dual therapy while it was 97.3% with triple therapy. In non-cirrhotic patients it was 95% in treatment naïve and 100% in treatment experienced group. While in cirrhotic patients with genotype 3, SVR 12 with dual therapy was 83.3% (p=0.331) and 88.9% in treatment naïve and treatment experienced patients respectively, while it was 100% in both groups with triple therapy. SVR 12 for genotype 1 (21/182) was 100%, both for dual as well as for triple therapy. Haematological side effects dominated the clinical picture with 11.5% suffering from anaemia.

Conclusion: Both dual and triple therapy were effective in patients with hepatitis C with acceptable level of side effects, genotype 3 being the most predominant genotype.

Keywords: Hepatitis C virus (HCV), SVR 12.

INTRODUCTION

The global burden of hepatitis is enormous, with approximately 328 million people worldwide suffering either from hepatitis B or C. In 2013, The Global Burden of Disease Study revealed that hepatitis accounted for about 1.45 million deaths worldwide, which was a major increase from 0.89 million in 1990. The morbidity, as measured in disability adjusted life years, also saw an upsurge to 0.87 million from 0.65 million. The highest increase was for hepatitis C, for which Disability adjusted life years (DALYs) raised by 43%. Worldwide, South and East Asia had 52% mortality related to hepatitis, which was the greatest number of hepatitis related deaths in absolute numbers. In global hepatitis report, 2017 by World Health Organization, it was estimated that out of the hepatitis related deaths in 2015, 720,000 were due to complications of de-compensated chronic liver disease while 470,000 were related to hepatocellular carcinoma. In 2017, a meta-analysis revealed that the estimated prevalence of hepatitis C, in the average population of Pakistan was 8.4%, with about 11.55% of the adults suffering from chronic hepatitis C of which genotype 3 a was the most common type, affecting 63.45%. In 2016, the Global Health Sector Strategy, by World Health Assembly aimed to eliminate viral hepatitis as a threat to public health by 2030. The treatment for hepatitis C has witnessed a major change with the advent of newer direct acting antiviral agents. These medications are not only easy to administer with...
low pill burden, higher genetic barrier to resist-
ance and fewer drug interactions but also have
closer side effects, so better tolerability and com-
pliance. The ultimate end result is off course better
viremic control in the long term\textsuperscript{4}. While newer
medications for hepatitis C treatments are emer-
ging at a rapid pace, it’s not always possible,
especially in the resource poor countries to get
access to these newer treatment regimens for vari-
rable reasons, most important of which remains
the financial constraints. Considering the enorm-
ous burden to the health care set up posed by
the hepatitis, physicians are at times forced to
give older medications, till the time newer regi-
mens are freely available at affordable prices in
the local market. Hereby, we report our experi-
ence of treatment of chronic hepatitis C, compris-
ing predominantly of genotype 3, with both dual
as well as triple therapy.

\textbf{METHODOLOGY}

This comparative cross sectional study was
done from November 2014 to March 2017 at
Combined Miliatary Hospital Lahore. A total of
182 patients, with chronic hepatitis C with geno-
type; 1, 3 and 4, were selected using non-proba-
bility consecutive sampling technique and were
analyzed to determine treatment outcomes. The
study was conducted in accordance with the
principles of Helsinki’s declaration and good
clinical practice guidelines and was approved
by institution’s ethics committee (reference No.
247/ERC/CMHLMC). Inclusion criteria included,
evidence of hepatitis C infection, as assessed by
positive anti HCV antibodies by ELISA and
positive HCV RNA by polymerase chain reaction
(PCR) and age ≥18 years while patients with haem-
oglobin of <10 g/dl, albumin <2 g/dl, platelet
count of <100/uL, creatinine clearance of <60
mL/min or liver disease caused by non-hepatitis
C related causes were excluded from study.

The diagnostic criteria of cirrhosis included
consistent clinical, haematological (raised interna-
tional normalized ratio and reduced platelet
count), biochemical (raised bilirubin, low albu-
mun and AST >ALT), radiological parameters
(heterogenous liver parenchyma with irregular
margins, nodular liver or enlarged left hepatic
lobe on ultrasound, fibroscan reading of 12.5 kPa
or above, with or without other markers of portal
hypertension like ascites, dilated portal veins,
collaterals or splenomegaly) or an AST to platelet
ratio index (APRI) of 2 or above.

During the study period interferon based
treatment was defined within the recommended
AASLD and EASL guidelines, 2014. The decision
whether to choose pegylated interferon based
treatment regimen or not was based upon viral
genotype, interferon eligibility, previous side
effects, financial constraints and patient’s willing-
ness to receive injections. At the time of study,
the cost of interferon based therapy was almost
half to that of dual therapy because of short treat-
ment duration and availability of pegylated inter-
feron at reduced price. Out of 158 patients with
genotype 3, 121 were treated with NS5B poly-
merase inhibitor sofosbuvir and ribavirin combi-
nation (dual therapy) while 37 with sofosbuvir,
ribavirin and pegylated interferon combination
(triple therapy). Of the 21 patients with genotype
1; 6 were treated with dual while 15 with triple
therapy. The two patients with genotype 4 were
treated with dual while one was given triple the-
rapy and so was the patient with mixed genotype
3 and 4 infection. Peg-INF α2a was administered
180ug per week subcutaneously, sofosbuvir 400
mg once daily while the ribavirin dose was adjus-
ted according to the body weight. (1000 mg per
day in those with body weight less than 75 kg
and 1200 mg for those with >75 kg. The standard
duration of dual therapy was 24 weeks and that
of triple therapy was 12 weeks.

\textbf{Statistical Analysis}

Rapid virological response (RVR) was def-
inged as undetectable HCV RNA by PCR at week
4 of treatment\textsuperscript{6}. Early virological response (EVR)
as an undetectable or ≥2 log reduction of serum
HCV RNA at 12 weeks of treatment, while end
of treatment response (ETR) was defined as an
undetectable HCV RNA by PCR at the end of the
therapy and sustained virological response (SVR)
as an undetectable HCV RNA at 12 weeks after the end of therapy. Non responder was defined as a person, who failed to have an undetectable HCV RNA at the end of the therapy. SVR was determined using the Pearson method by using statistical package of social sciences (SPSS) version 25 of the windows. Descriptive statistics of quantitative variables were expressed as mean and standard deviation while those of qualitative variables as frequency and percentages.

**RESULTS**

Out of 182 patients, majority were females (54.5%), mean age of study population was 44.9, standard deviation (SD) 11.96 and range was 18-73 years. Out of 182, there were 38 (20.8%) patients with cirrhosis; majority of whom (19.2%) had compensated and there were only 3 (1.65%) patients with decompensated cirrhosis. In addition there were also 3 (1.65%) patients with living donor liver transplant.

| Parameters | Total patients (182) | Genotype 1 (21) | Genotype 3 (158) |
|------------|----------------------|----------------|------------------|
| Mean age (years) | 44.9 | 42.76 | 45.16 |
| SD          | 11.96 | 10.78 | 12.18 |
| Female gender-no. (%) | 99 (54.5) | 13 (61.9) | 85 (53.8) |
| HCV subtypes-no(%) | 182 | 21 (11.5) | 158 (86.8) |
| Mean bilirubin (mg/dl) | 0.82 | 0.64 | 0.84 |
| SD          | 0.68 | 0.27 | 0.72 |
| Mean AST IU/ml (range) | 64.5 (15-233) | 52.76 (27-134) | 66.27 (15-233) |
| SD          | 40.39 | 40.38 | 41.73 |
| Mean ALT IU/ml (range) | 68.56 (10-625) | 54.71 (18-116) | 70.72 (10-625) |
| SD          | 56.78 | 56.77 | 59.73 |
| TN; cirrhotic-no (%) | 24 (13) | 2 (8.33) | 22 (13.9) |
| TN; non-cirrhotic -no (%) | 97 (53.3) | 13 (13.4) | 82 (51.9) |
| TE; cirrhotic-no (%) | 14 (7.7) | - | 14 (8.86) |
| TE; non-cirrhotic-no (%) | 47 (25.8) | 6 (12.76) | 40 (25.3) |

| Parameters | Total Number of Patients | Dual Therapy |
|------------|--------------------------|--------------|
| Overall    | 182                      | 129 | ETR | NR | SVR 12 | LTF |
| Genotype 1 | 21                       | 6 | 3 (100%) | - | 3 (100%) | 3 |
| TN, cirrhotic | 2                       | 1 | 1 (100%) | - | 1 (100%) | - |
| TN, non-cirrhotic | 13               | 3 | 1 (100%) | - | 1 (100%) | 2 |
| TE, cirrhotic | -                      | - | - | - | - | - |
| TE, non-cirrhotic | 6               | 2 | 1 (100%) | - | 1 (100%) | 1 |
| Genotype 3 | 158                      | 121 | 104 (96.2%) | 4 (3.7%) | 102 (94.4%) | 13 |
| TN, cirrhotic | 22*                    | 16 | 10 (83.3%) | 2 (16.6%) | 10 (83.3%) | 4 |
| TN, non-cirrhotic | 82                 | 63 | 58 (96.6%) | 2 (3.3%) | 57 (95%) | 3 |
| TE, cirrhotic | 14                     | 12 | 9 (100%) | 1 (11.1%) | 8 (88.9%) | 3 |
| TE, non cirrhotic | 40                  | 30 | 27 (100%) | - | 27 (100%) | 3 |
| Genotype 4 | 3                       | 2 | 2 (100%) | - | 2 (100%) | - |
| TN, cirrhotic | -                      | - | - | - | - | - |
| TN, non-cirrhotic | 2               | 1 | 1 (100%) | - | 1 (100%) | - |
| TE, cirrhotic | -                      | - | - | - | - | - |
| TE, non-cirrhotic | 1               | 1 | 1 (100%) | - | 1 (100%) | - |

*TN: treatment naïve; TE: treatment experienced; NR: non-responder; LTF: lost to follow up, ETR: end of treatment response; SVR: sustained virologic response, *One TN, cirrhotic was treated with Peg IF and ribavirin
Genotype 3 was the predominant type of viral infection, accordant with the prevalence of hepatitis C in this region, affecting 158 (86.8%) of the patients, while 21 patients (10.95%) had genotype 1 and there were 3 patients with genotype 4 (1.6%). One patient had dual infection with HCV genotype 3 and 4 (Table-I).

One hundred and twenty one (66.5%) patients were treatment naïve, while 61 (33.5%) were treatment experienced. Out of these 61; 29 (15.9%) were relapers and 32 (17.6%) were non-responder to either treatment with combination of standard or pegylated interferon (Peg-IFN) with ribavirin. Eighteen (9.9%) were previously treated with standard interferon and ribavirin, 33 (18.1%) with pegylated interferon and ribavirin combination, 9 (4.9%) had been treated twice; first with standard interferon and ribavirin and later with pegylated interferon and ribavirin; while one was intolerant to interferon, so had incomplete prior treatment.

Of the 53 patients in the triple therapy group, all but one patient achieved ETR while 2 were lost to follow up. Of 129 patients in the dual therapy group, 109 (96.5%) patients achieved ETR, 4 (3.5%) were non responders while 16 patients were lost to follow up during treatment, at variable intervals of time. All four non-responders, were treatment naïve females, with genotype 3 infection. Two of them had cirrhosis. There were no significant co-morbidities apart from ischemic heart disease in one patient. Of the 109

### Table-III: Response rate with triple therapy among patients.

| Parameters            | Total Number of Patients | Triple Therapy |            |
|-----------------------|--------------------------|----------------|-----------|
|                       |                          | No. of Patients | ETR       | NR        | SVR 12 | LTF |
| Overall               | 182                      | 53             | 50 (98%)  | 1 (2%)    | 50 (98%) | 2   |
| Genotype 1            | 21                       | 15             | 13 (100%) | -         | 13 (100%) | 2   |
| TN, cirrhotic         | 2                        | 1              | 1 (100%)  | -         | -       | -   |
| TN, non-cirrhotic     | 13                       | 10             | 8 (100%)  | -         | 8 (100%) | 2   |
| TE, cirrhotic         | -                        | -              | -         | -         | -       | -   |
| TE, non cirrhotic     | 6                        | 4              | 4 (100%)  | -         | 4 (100%) | -   |
| Genotype 3            | 158                      | 37             | 36 (97.3%)| 1 (2.8%)  | 36 (97.3%)| -   |
| TN, cirrhotic         | 22*                      | 5              | 5 (100%)  | -         | 5 (100%) | -   |
| TN, non-cirrhotic     | 82                       | 20             | 19 (95%)  | 1 (5%)    | 19 (95%) | -   |
| TE, cirrhotic         | 14                       | 2              | 2 (100%)  | -         | 2 (100%) | -   |
| TE, non cirrhotic     | 40                       | 10             | 10 (100%) | -         | 10 (100%)| -   |
| Genotype 4            | 3                        | 1 (100%)       | 1 (100%)  | -         | 1 (100%) | -   |
| TN, cirrhotic         | -                        | -              | -         | -         | -       | -   |
| TN, non-cirrhotic     | 2                        | 1 (100%)       | 1 (100%)  | -         | 1 (100%) | -   |
| TE, cirrhotic         | -                        | -              | -         | -         | -       | -   |
| TE, non-cirrhotic     | 1                        | -              | -         | -         | -       | -   |

**TN**: treatment naïve; **TE**: treatment experienced; **NR**: non-responder; **LTF**: lost to follow up; **ETR**: end of treatment response; **SVR**: sustained virological response, *One TN, cirrhotic was treated with Peg IF and ribavirin

### Table-IV: Correlation of SVR 12 and other factors among patients.

| Factors                | Univariate | Multivariate |
|------------------------|------------|--------------|
|                        | Adjusted Odds ratio | p-value | 95% CI      | Adjusted Odds ratio | p-value | 95% CI      |
| Age                    | 0.93       | 0.614        | 0.45-1.93   | 1.02                | 0.53     | 0.84-1.11   |
| Gender                 | 0.73       | 0.315        | 0.63-1.8    | 0.29                | 0.28     | 0.03-2.8    |
| Baseline Viral load    | 1.38       | 0.54         | 0.40-4.73   | 1                   | 0.18     | 1-1         |
| ALT baseline           | 0.28       | 0.826        | 0.5-3.5     | 0.96                | 0.14     | 0.92-1.01   |
| AST baseline           | 0.37       | 0.545        | 0.6-4.2     | 0.98                | 0.15     | 1-1         |

*CI: Confidence Interval
patients with ETR, 107 (94.7%) were successful in achieving SVR, whereas 2 patients relapsed at 12 weeks post-treatment. One of them was an overweight, cirrhotic male patient, with genotype 3, who was treated twice before, initially with standard interferon and ribavirin and later on with pegylated interferon and ribavirin. The reason for treatment with dual therapy was refusal of triple therapy. He did not achieve RVR, however his PCR on 8th week of treatment was negative and he achieved ETR, however could not attain SVR 12. The other was a 45 years old lady with genotype 3; who was treatment naïve with no co-morbidities, who had an early virological response and whose PCR was negative twice during treatment as well as at the end of treatment. She, however relapsed 12 weeks, post-treatment. She had a fatty liver on abdominal ultrasound.

Amongst patients with genotype 3, the overall SVR 12 was 94.4% in patients with dual therapy while it was 97.3% with triple therapy. Subgroup analysis further showed that amongst cirrhotic patients with genotype 3, the SVR 12 with dual therapy was 83.3% and 88.9% in treatment naïve and treatment experienced patients respectively, while it was better with triple therapy, being 100% in both groups, however it did not reach the statistical significance, owing probably to the small sample size in both groups; \( p=0.331 \) and 0.62 respectively. In non-cirrhotic patients it was similar with both treatment regimens, being 95% in treatment naïve and 100% in treatment experienced group. SVR 12 for genotype 1 was 100%, both for dual as well as for triple therapy. However, the sample size of patients with genotype 1, whose SVR 12 could be ascertained was considerably small (16/21), as 5 were lost to follow up (table-I,II).

The main haematological side effect of treatment was anaemia, which required use of erythropoietin in 21 (11.5%) patients, 4 (7.7%) in the triple therapy and 17 (13.2%) in the dual therapy group. Five (23.8%) out of these 21 patients were cirrhotic and 16 (76.2%) were female. One of these patients also required concomitant use of granulocytecolony stimulating factor, due to significant neutropenia of 0.8 at 8/12 week of triple therapy. This was a cirrhotic lady, with genotype 3, who was a relaper after treatment with standard interferon and ribavirin. She was able to complete treatment and was successful in gaining long term viral suppression i.e her PCR remained negative 60 weeks post-treatment.

Univariate as well as multivariate logistic regression analysis revealed no significant correlation between SVR 12 and other variables, including age, gender, level of liver enzymes or viral load of the patient table-IV.

DISCUSSION

Over the years, treatment of hepatitis C has witnessed major changes, with newer medications emerging at a rapid pace. Genotype 3 is predominant genotype in South and Central Asia, representing the 71.6% of the global prevalence.\(^6,7\) It also carries the unique property of increased incidence of steatosis and swift fibrosis, thus increasing the risk for hepatocellular carcinoma.\(^8-12\) In this era of direct acting anti-viral drugs (DAA), genotype 3 has been considered the most difficult genotype to treat.\(^13\) In 2013, Sofosbuvir, an NS5B polymerase inhibitor made the major breakthrough for treatment of genotype 3 infection, and since its approval has remained the backbone for the treatment of hepatitis C.\(^14\) Sofosbuvir gained approval for use in local market in Pakistan in November 2014. The high initial cost and lack of availability in government sector hospitals, was the primary reason for its limited initial prescription. It was not until, October 2015, in a country which is considered to carry the second highest global burden of infection with approximately 8 million people infected with hepatitis C, 14 pharmaceutical companies were allowed to manufacture it locally, leading to a fall in price and easy availability to many.

The patients during our study period were treated with dual or triple therapy according to the recommended AASLD or EASL guidelines at the time of study.\(^15-16\) The four large clinical trials from the West that included the patients with genotype 3 to assess the efficacy of sofosbuvir
and ribavirin combination included the Fission, Fusion, Positron and Valence. In Fission the SVR 12 was only 56% for SOF/RBV versus 63% for PEG/RBV and it further dropped to 47% in patients with cirrhosis. The response rate in our study was quite similar to the above mentioned trials, with an overall SVR 12 of >83% in cirrhotic patients with genotype 3 with dual therapy, which was 83.3% in treatment naive and 88.9% in treatment experienced cirrhotic. In comparison, there was 100% response rate (SVR12) with triple therapy, in both treatment naïve (5/5) and treatment experienced (2/2) cirrhotic.

In treatment naïve patients with genotype 1, 24 weeks of SOF/RBV was found to be ineffective, in single center phase 2, NIH Spare trial, which showed a poor SVR 24 of 68%, which further dropped to 50% in those with advanced fibrosis. Once again the efficacy of triple therapy for genotype 1, 4, 5 and 6 was shown by Neutrino study. The SVR 12 for genotype 1 was 89%; 82% in patients with genotype 1b and 92% for 1a. There was splendid response across other genotypes, with 96% in genotype 4 (n=27/28) and 100% in genotype 5 and 6, though the sample size was quite small for genotype 5 (n=1) and 6 (n=6). Cirrhosis and non-CC IL28B genotype were associated with poor response (80% with cirrhosis and 92% without cirrhosis). Considering the superior response rate with triple therapy, 71.4% of our patients, with genotype 1, who were interferon eligible, were treated with triple therapy. However both triple as well as dual therapy was equally effective in genotype 1, achieving an overall SVR 12 of 100%. Both treatments were equally efficacious in both treatment naïve and treatment experienced patients, as well as in those with or without cirrhosis. However the small sample size of patients with genotype 1 (21/182) remains an important limiting factor, reducing the power of the study to draw substantial conclusions for this type, which may also account for variance in treatment response across this genotype from the literature.

Both dual as well as triple therapy were well tolerated with low overall side effects, seen in
7.7% of patients with triple and 13.2% with dual therapy. However none of the patients experienced any intolerable side effects warranting the need for discontinuation of treatment.

CONFLICT OF INTEREST

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

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