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Chronic Hepatitis C

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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/uL, 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[1]. 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[1]. 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[2]. 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 decompensated chronic liver disease while 470,000 were related to hepatocellular carcinoma[1]. 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%[3]. In 2016, the Global Health Sector Strategy, by World Health Assembly aimed to eliminate viral hepatitis as a threat to public health by 2030[1]. 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

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low pill burden, higher genetic barrier to resistance and fewer drug interactions but also have fewer side effects, so better tolerability and compliance. The ultimate end result is off course better viremic control in the long term[4]. While newer medications for hepatitis C treatments are emerging at a rapid pace, it's not always possible, especially in the resource poor countries to get access to these newer treatment regimens for various reasons, most important of which remains the financial constraints. Considering the enormous burden to the health care set up posed by the hepatitis, physicians are at times forced to give older medications, till the time newer regimens are freely available at affordable prices in the local market. Hereby, we report our experience of treatment of chronic hepatitis C, comprising predominantly of genotype 3, with both dual as well as triple therapy.

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 genotype; 1, 3 and 4, were selected using non-probability 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 haemoglobin 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 international normalized ratio and reduced platelet count), biochemical (raised bilirubin, low albumin 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 triple regimen fell 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 willingness 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 treatment duration and availability of pegylated interferon at reduced price. Out of 158 patients with genotype 3, 121 were treated with NS5B polymerase inhibitor sofosbuvir and ribavirin combination (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 therapy 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 adjusted 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.

Statistical Analysis

Rapid virological response (RVR) was defined as undetectable HCV RNA by PCR at week 4 of treatment[5]. 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[5]. Non responder was defined as a person, who failed to have an undetectable HCV RNA at the end of the therapy[5]. 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 99 (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 35 (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.

Table-I: Demographic characteristics of the sample (N=182).

Parameters	Total patients (182)	Genotype 1 (21)	Genotype 3 (158)
Mean age (years) SD	44.9 11.96	42.76 10.78	45.16 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) SD	0.82 0.68	0.64 0.27	0.84 0.72
Mean AST IU/ml (range) SD	64.5 (15-233) 40.39	52.76 (27-134) 40.38	66.27 (15-233) 41.73
Mean ALT IU/ml (range) SD	68.56 (10-625) 56.78	54.71 (18-116) 56.77	70.72 (10-625) 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)

Table-II: Response rate with dual therapy among patients.

Parameters	Total Number of Patients	Dual Therapy				
		No. of Patients	ETR	NR	SVR 12	LTF
Overall	182	129	109 (96.5%)	4 (3.5%)	107 (94.7%)	16
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 (16.66%)	10 (83.3%)	4
TN, non-cirrhotic	82	63	58 (96.6%)	2 (3.33%)	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 relapsers 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 inter-feron, 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	-	1	-
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 relapser 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[4,17,18,20].

Two subsequent trials Positron and Fusion again elaborated the same fact regarding sofosbuvir based treatment. Positron confirmed that 12 weeks of therapy with SOF/RIB was not quintessential for genotype 3, with an SVR 12 of 68% (n=57/84) in patients without cirrhosis that further dropped to 21% (n=3/14) in those with cirrhosis, making this an unacceptable treatment option in cirrhotic patients[18].

Considering the limitations of SOF/RBV treatment regimen in particularly difficult to treat genotype 3 patients, BOSON trial was designed, which included treatment experienced cirrhotic patients with genotype 2 and both treatment naïve as well as experienced patients with genotype 3. Three patients who were on 24 weeks of treatment with dual therapy had virological failure during treatment. The response rate were lower in both treatment naïve and treatment experienced cirrhotic, with being 82% (n=18/22) and 76% (n=26/34) with 24 weeks of SOF/RBV while it was 91% (21/23) and 86% (n=30/35) with SOF/PEG/RBV respectively. IL 28B non CC allele and male sex were associated with relapse in both 16 and 24 weeks of SOF/RBV treatment regimens. Cirrhosis was associated with relapse in SOF/PEG/RBV and 16 weeks of SOF/RBV treatment but not with 24 weeks of SOF/RBV. This study established that SOF/PEG/RBV was significantly superior as compared to other two treatment regimens, with all subgroups achieving SVR 12 >90%, with the exception of cirrhosis where SVR 12 was 86% although it still outmatched others. It was also established that dual therapy with SOF/RBV remains an alternative acceptable treatment option for patients who are unwilling or cannot take interferons for various reasons[19].

Lonestar-2 trial substantiated that triple therapy was the most effective treatment regimen for interferon eligible patients till that time with SVR 12 of 83% in treatment experienced patients with genotype 3, both with and without cirrhosis[20]. Considering the efficacy of triple therapy all our interferon eligible patients were given its choice. 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 naïve 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[21]. 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)[4]. 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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