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Original Research Article

Efficacy and safety of sofosbuvir plus ribavirin in treatment-naive chronic hepatitis c genotype 3 patients of South Punjab, Pakistan

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ABSTRACT

Background: To evaluate the efficacy and safety of sofosbuvir (SOF) plus ribavirin (RIB) in naive patients with chronic HCV genotype 3. The study design was open label, quasi experimental study. The study was conducted at Medical Outpatient Department of Medical Unit-1, Bahawal Victoria Hospital, affiliated with Quaid e Azam Medical College (QAMC), Bahawalpur, from April 2016 to June 2019.
Methods: A total of 627 treatment-naive patients, aged above 18 years, with chronic Hepatitis C virus (HCV) genotype 3 infection were enrolled. SOF as 400 mg once a day plus weight-based RIB (1000 mg/day <75 kg and 1200 mg/day >75 kg) was given to all the study participants for 24 weeks. Qualitative polymerase chain reaction (PCR) for HCV ribonucleic acid (RNA) were done at 4 weeks to note the rapid virological response (RVR) whereas end of treatment response (ETR) was recorded at 24 weeks and sustained virological response (SVR) was noted 3 months after completion of treatment.
Results: By 4th week, PCR of 524 (83.6%) patients was available, out of which, 492 (93.9%) had undetectable HCV RNA. By the end of treatment (24 weeks), PCR of 401 (64.0%) patients was available, out of which, 393 (98.0%) had undetectable HCV RNA. Data of 291 (46.4%) patients was available for SVR, 274 (94.1%) had undetectable HCV RNA. Weakness and fatigue turned out to be the commonest side effects, observed in 236 (37.6%) patients.
Conclusions: Sofosbuvir was found to have good efficacy and safety in the local population of South Punjab having treatment-naïve chronic HCV genotype 3 infection.

Keywords: Efficacy, Hepatitis C virus infection, Sofosbuvir, Ribavirin, PCR

INTRODUCTION

More than 200 million people are estimated to be affected by hepatitis C virus (HCV) around the globe and it is considered to be the leading cause of chronic liver disease and decompensated liver disease especially in developing countries.[1,2] Amongst various genotypes globally, genotype 1 has an overall share of 46% while genotype 3 accounts for nearly 22% of the cases. In Pakistan, the burden of HCV seems to involve more than 10 million individuals and the numbers are growing every day.[3] In Pakistan, the prevalence of HCV is about 6.7% while genotype 3 is involved in around 79% of the cases.[4]

It has been well documented that as much as 85% of the HCV cases remain permanently infected once they contain acute hepatitis C infection.[5] Since 1986, interferon revolutionized the HCV treatment and up till recent years combination of pegylated interferon α along with ribavirin for 48 weeks for genotype-1 while 24 weeks for genotype 2 and 3 became the standard mode of treatment. These treatments accompanied undesired side effects whereas

sustained viral response (SVR) was also not up to satisfaction.[6,7]

After getting Food and drug administration (FDA) of the United States approval, direct-acting antiviral (DAA) agents modernized the much needed HCV treatment. Sofosbuvir (SOF) is a nucleotide analogue inhibitor of HCV non-structural protein 5 B (NS5B) polymerase which became the 1st DAA to get the FDA approval in 2013 and since then, has been one of the most popular choices in treating chronic HCV infection for clinicians around the globe.[8,9] SOF is usually used in combination with different drugs, most commonly ribavirin and has been shown to achieve superb results in comparison to its ancestor treatments for HCV. The famous VALENCE study from Europe went on to show the rapid virologic response (RVR) of 99% with the use of SOF plus RIB while the same study got SVR as 85%.[10]

Not much work enquiring about the efficacy and safety of SOF plus ribavirin (RIB) is published in Pakistan while studies from around the world pose variable results. So, this will be the 1st study from South Punjab evaluating efficacy and safety of SOF plus RIB in chronic HCV genotype 3 naïve patients.

METHODS

This was an open label, quasi experimental study, conducted at MOPD of Medical Unit-1, BVH, affiliated with Quaid e Azam Medical College (QAMC), Bahawalpur, from April 2016 to June 2019. Approval from institutional Ethical and Research committee was taken for this study.

A minimum sample size of 470 was considered using World Health Organization (WHO) sample size calculator, by taking anticipated SVR as 99% in genotype 3 according to VALENCE trial10 while absolute precision was considered as 0.9% along with 95% confidence interval. Six hundred and twenty seven treatment-naïve patients (who did not have any history of HCV treatment) of either gender aged above 18 years, with chronic HCV genotype 3 infection as demonstrated by detectable HCV ribonucleic acid (RNA) of genotype 3 on qualitative polymerase chain reaction (PCR) were enrolled during the study period. All non-responders, relapsers and cirrhotic patients having detectable HCV RNA on PCR were excluded from the study. Informed consent from all the study participants was sought. Baseline evaluation and investigations were done in all the patients. SOF as 400 mg once a day plus weight-based RIB (1000 mg/day <75 kg and 1200 mg/day >75 kg) was given to all the study participants for 24 weeks. PCRs were done at 4 weeks to note the RVR whereas end of treatment response (ETR) was recorded at 24 weeks and SVR12 was noted 3 months after completion of treatment.[4]

Statistical package for social sciences (SPSS) version 20 was used for data handling and analysis. Comparison of age, hemoglobin levels, alanine transaminase levels (ALT), platelet counts and total leukocyte counts (TLC) were done by using independent sample t test between patients who achieved negative PCR or remained PCR positive for HCV RNA by the end of study intervals. For qualitative variables like gender, area of residence, side effects, marital status and comorbidities, chi square test by taking p value <0.05 as of statistical significance was applied to note the significance.

RESULTS

Out of a total of 627 patients, 299 (47.7%) were male and 328 (52.3%) female. The overall mean age was 40.26±12.4 years. Majority of the patients, 512 (81.7%) belonged to rural areas and 563 (89.8%) were married.

Table 1: Serological response in comparison to study variables.

	PCR at week 4 (n=524)			PCR at week 24 (n=401)			PCR at 12 week post treatment (n=291)		
	Undetected (n=492)	**Detected (n=32)**	**P value**	**Undetected (n=393)**	**Detected (n=8)**	**P value**	**Undetected (n=274)**	**Detected (n=17)**	**P value**
Mean age (years)	41.32±8.1	41.71±7.7	0.79	43.18±8.5	41.74±9.1	0.64	41.66±9.4	43.62±9.6	0.40
Mean Hb (gm/dl)	12.87±2.5	12.37±2.4	0.27	12.74+2.7	11.76+2.7	0.31	12.76±2.7	12.52±2.6	0.72
Mean ALT (IU/l)	66.21±63.2	82.72±62.6	0.15	48.39±34.6	74.37±64.1	0.04	44.52±32.5	68.53±52.7	0.04
Mean TLC	7473.33±5331.7	7188.37±4724.7	0.76	7630.17±5718.0	7245.88±5801.6	0.85	7562.49±5861.8	7382.14±5546.7	0.90
Mean Platelet Count	231229.32±125201.8	224470.59±116427.1	0.77	189762.38±54701.7	174744.26±43382.5	0.44	158301.17±36731.9	156671.42±41543.8	0.86

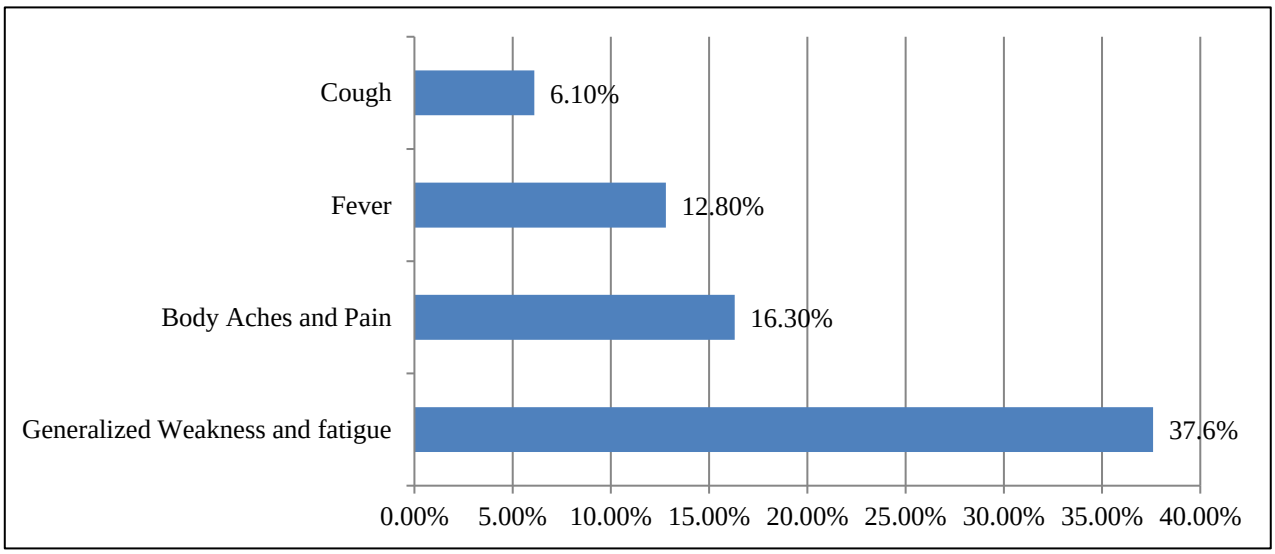

Figure 1: Common side-effects of treatment among all the patients.

There were 325 (51.8%) cases with body mass index (BMI) <25, 178 (28.4%) with 25-30 124 (19.8%) as >30.

By the 4th week, PCR of 524 (83.6%) patients was available, out of which 492 (93.9%) had undetectable HCV RNA. By the end of treatment (24 weeks), PCR of 401 (64.0%) patients was available, out of which, 393 (98.0%) had undetectable HCV RNA. Data of 291 (46.4%) patients was available for the evaluation of SVR, 274 (94.1%) had undetectable HCV RNA.

Table 1 shows findings of the various study variables of patients like age, haemoglobin levels, ALT, TLC and platelet count compared at different study intervals (4th week, 24th week, 12 weeks post treatment) to find out any significance between patients who achieved negative PCR or remained PCR positive for HCV RNA by the end of study intervals but no statistical significance was noted ($p>0.05$) as except ALT at 24 weeks and 12 weeks post treatment.

Overall, side effects were noted in 251 (40.0%) patients while generalized weakness and fatigue turned out to be the commonest, observed in 236 (37.6%) whereas body aches and pains in 102 (16.3%), fever in 80 (12.8%) and cough in 38 (6.1%) as shown in figure 1.

DISCUSSION

Direct acting anti-virals (DAA) have provided a new dimension to treatment of HCV. Around the world, efficacy of SOF in various genotypes has been studied quite often in the last few years. Although studies like FISSION, FUSION, POSITRON, ALLY-3 and BOSON have analyzed and found excellent effectiveness of SOF in genotype 3 but local data in this regard is scarce to say the least.[11-15]

In the current study, we noted rapid virologic response (RVR) in about 94% patients, ETR in 98% and SVR in 94% patients. A local study from Rawalpindi in 2016, evaluating the effectiveness of SOF plus RIB, found RVR in about 92% treatment naive patients, ETR in 93.8% and SVR in 83.3% in the same group of patients.[4] The relatively better ETR and SVR success rate in our study may be explained on the basis of difference in selection criteria of teartment-naïve patients. The Rawalpindi study included cirrhotic treatment-naïve patients in the treatment naïve group, while we had excluded cirrhotic patients from the current study. RESiP, a multicenter trial having more than 5000 patients from Pakistan, conducted predominantly on HCV genotype 3 patients (94%) has also shown better SVR success rate in non-cirrhotic patients (97%) as compared to cirrhotics (89%) on sofosbuvir and ribavirin based treatment.[16] On the other hand, in VALENCE trial it is concluded that there is no significant difference in achievement of SVR amongst non-cirrhotic treatment naïve patients (95%) versus cirrhotic treatment naïve patients (92%), but the sample size for cirrhotic patients in this trial was quite low (only 13).[10] Sarwar et al has also documented sub-optimal treatment out come in cirrhotic patients (75.4%) especially in those with decompensation as compared to non-cirrhotic patients (93%) treated with sofosbuvir based regimen.[17] In general the results of present study are comparable with various national and international studies.[10,21,22,23] To the best of our knowledge this is perhaps the first reported experience of sofosbuvir in southern Punjab population of Pakistan, hopefully it will strengthen confidence regarding use of sofosbuvir in clinical practice in this region.

Before the introduction of SOF, hepatitis C was treated with interferon and RIB. The response rate of this regimen was not satisfactory (SVR ranging between 58% to 75%).[23] These results were further declined to nearly 27% in those patients who had failed earlier IFN therapy.[24] Moreover, the patient also had to face many side effects of

those drugs for a long time due to prolonged therapy durations. The addition of SOF in the antiviral therapy regimen has not only dramatically improved the SVR rate but has also minimized the side effects.

We did not notice any serious side effects of the studied regimen, while complaints of generalized weakness, body aches and pains, fever and cough were observed. SOF plus RIB therapy has been depicted to be safest antiviral therapy in local as well as international studies in the recent years.[1,4,12,13,14] All the side effects with this regimen are manageable and possess low threat as compared to previously available treatments.[25]

CONCLUSION

Sofosbuvir was found to have excellent efficacy and safety profile in the local population of South Punjab having treatment-naive HCV genotype 3 infection. The minor side effects observed during study were easily manageable.

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