ORIGINAL ARTICLE

EFFECTIVENESS OF SOFOSBUVIR AND RIBAVIRIN IN HEPATITIS C GENOTYPE 3 RELAPSERS

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Background: Combination of DAAs, Sofosbuvir and Ribavirin has been known as an effective treatment for HCV genotype 3. The aim of our study is to assess the efficacy of Sofosbuvir and Ribavirin in relapsed HCV genotype 3 patients. **Methods:** A cross-sectional retrospective analysis of hospital records between January 2015 and December 2016. Data was taken of only those patients who were followed for one year. A total of 193 cases were included in this study who were HCV genotype 3 relapsers and out of these 28 patients failed to be followed. Data was entered and analysed in IBM SPSS software package 23. **Results:** Out of the total 193 cases, 74.1% of cases achieved RVR at 4 weeks of therapy. ETR was achieved by 91.2% cases, while 8.8% of cases were non-responders. There was statistical significance in gender achieving ETR with a *p*-value of .008. 84.5% of cases achieved SVR-12. Statistical significance was noted between haemoglobin levels at presentation and 4 weeks follow-up with a p-value <0.005, and also between 4 weeks and 12 weeks follow-up with a *p*-value <0.005. Statistical significance was also found between age and PCR at 4 weeks (*p*-value of .002), age and PCR at 24 weeks (*p*-value of .051) and between ALT levels and PCR at 4, 12 and 24 weeks follow up (*p*-value <0.005). At 1-year follow-up, 79.3% of cases achieved a negative PCR, 28 patients failed to be followed, 6.2% of cases had a positive PCR. 5.5% of cases of the total 163 SVR cases had a relapse at 1 year. **Conclusion:** HCV genotype 3 patients can benefit from Sofosbuvir and Ribavirin. With the SVR of more than 80%, this combination is cost-effective and safe. Treatment duration should be dependent on RVR and viral load at 4 weeks follow-up.

Keywords: HCV; Sofosbuvir; Ribavirin; Genotype; RVR; SVR

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INTRODUCTION

HCV infection is a significant healthcare problem, with an estimated 170 million people infected globally [(1)]. It is proving to be one of high economic, social, and health burden diseases.[1] Worldwide prevalence of HCV infection highly varies, with the highest disease burden in the Middle East, North African (region including Egypt), and Pakistan.[2] Pakistan is ranked 2nd amongst the countries that account for significant global viremia and with a 6.7% serological prevalence of hepatitis C antibodies.[3] Six major HCV genotypes and various discrete subtypes have so far been identified.[4] It is evident from multiple studies that in Pakistan most prevalent genotype is 3 (79%), more specifically genotype 3a followed by genotypes 1 (7.1%), 2 (4.2%), and 4 (2.2%).[5]

Specific viral markers of hepatitis C infection are used for the detection, evaluation and further management of patients suffering from chronic hepatitis C, including Serum antibodies against HCV (anti-HCV Ab), quantification of viral load (or HCV RNA), HCV genotype.[6] HCV-RNA is the gold standard for the diagnosis of active HCV infection as it is the most reliable marker for HCV viral replication.[7] HCV RNA is also used to evaluate the treatment response (RVR) and sustained virologic response (SVR) at 12 or 24 weeks following completion of the treatment.[7]

The primary aim of HCV treatment is to obtain (SVR), which is generally associated with a decrease in hepatic complications and mortality.[8] In 1991, the conventional treatment for HCV infection was approved to be interferon-alpha therapy (IFN-α therapy), which was having meagre (<20%) sustained virologic response (SVR) rates. Ribavirin (RBV) added to the initial IFN-α regimen in 1998, which shows comparatively higher response rates. Pegylated IFN-α was introduced in 2001, which turned out to be more stable than its predecessor, which further improved the SVR.[9] In the first decade of the 21st century, pegylated IFN- α/RBV combination therapy was the standard treatment, with SVR of 50% for HCV genotype 1.[10] There was a variation in response rates for different genotypes, lower SVR 40–50% for genotype 1 and 4, and a higher SVR of >80% or genotype 2 and 3.[11] As mentioned above around 50–60% of patients infected with HCV either do not

respond or relapse after the therapy.[12] Significant randomized trials relate to RBV having more contribution in preventing relapse.[13] The relapse of HCV infection is defined as having undetectable viral RNA during treatment but suffer a virological relapse within 6 months of cessation of treatment.[13]

Over the past decade, direct acting antiviral drugs (DAAs) which has its action on the non-structural proteins of HCV RNA, has been using for the treatment of HCV infection. These DAAs are well-tolerated and achieve cure rates of above 90%.[14] Sofosbuvir, the first nucleotide analogue from the group of DAAs, inhibits the NS5B polymerase. It is effective in the treatment of genotypes 2 and 3 when co-administered with ribavirin.[15] Sofosbuvir is also a compelling choice of treatment for HCV genotype 3 patients who are relapsers, difficult to treat, or patients who develop liver cirrhosis.[16] In comparison to IFN based therapy, it is associated with fewer side effects.[15]

Although new treatment regimens are showing high cure rates and better tolerability and are expected to reduce morbidity and mortality[17], yet the risk of relapse or reinfection always remains a concern. HCV reinfection is a challenging global health issue. People who are injectable drug users (IDU), high-risk sexual behaviour, co-infection with HIV, or suffering from mental illness, etc. are more prone to HCV reinfection.[18] This study aims to evaluate the response of Sofosbuvir and Ribavirin in the treatment of HCV genotype 3 relapsed patients.

MATERIAL AND METHODS

This study was conducted as a retrospective cross-sectional, in Bilal Medical Trust Hospital, a private hospital in District Buner. Buner is a district in the Malakand division of Khyber Pakhtunkhwa province in Pakistan. This hospital is a trust hospital and provides healthcare to different social classes of people all over Buner. The patient's record register was used to obtain data from January 2015 to December 2016. That data was collected from record registers in which patients were followed for 1 year, even presenting in late 2016.

All HCV genotype 3(3a and 3b) patients who were treated with Interferons and had relapsed within 6 months after completion of treatment, having ages between 25 to 70, were included in the study.

The exclusion criteria is, patients who were newly diagnosed HCV, treatment naïve, and genotypes other than genotype 3. Patients below 18 and above 80 were also excluded from this study. Patients having co-infection with HBV and HIV were excluded from this study as well.

All these patients were given Sofosbuvir once daily 400mg for 12 weeks, and Ribavirin was given as once-daily for 12 weeks. The dose of ribavirin was adjusted according to body weight. For all these patients, baseline investigations were done before the commencement of treatment, including Haemoglobin levels, platelet counts, ALT levels, and total leukocyte counts (TLC). PCR for HCV RNA and genotyping were done as well. Follow-up PCR's were performed at interval of four weeks to assess the RVR (Rapid Virologic Response), at 12 weeks to determine ETR (End of Treatment Response) and 12 weeks post-treatment to determine SVR_{12} (Sustained Virologic Response at 12 weeks). PCR was also done at 24 weeks post-treatment to look for relapse. Alanine transaminase (ALT) and haemoglobin (Hb) levels were also done for these patients in follow-up visits, i.e., at 4 weeks, 12 weeks, 24 weeks, and 1 year.

Rapid virologic response (RVR) is defined as negative serum HCV RNA level at the end of 4 week of treatment. End of treatment response (ETR) is defined as serum HCV RNA level <15 IU/mL after the completion of treatment, and sustained virologic response (SVR) is defined as serum HCV RNA negative status at 12 weeks of follow-up after completion of treatment.

Ethical approval was obtained from the Ethical Review Board of Prime Foundation, Peshawar Medical College, Warsak Road Peshawar. The data was entered and analysed in IBM SPSS software package version 23. Serum haemoglobin levels, serum alanine aminotransferases (ALT), total leukocyte counts (TLC) and serum platelet counts were analysed using descriptive statistics. In addition to this, independent sample t-test was applied at 5% level of significance to compare the age, haemoglobin levels (Hb) and alanine transaminase levels (ALT) of patients who attained negative PCR with those who did not. Serum haemoglobin levels were compared between follow-up visits using paired sample t-test. Chi square test was used to compare significance between patients who attained RVR, ETR and SVR12, based on age, haemoglobin levels and serum alanine transaminase (ALT).

RESULTS

A total of 193 cases were reported and followed in a span of 1 year. Out of the total 193, males were 70 (36.3%), while females were 123 (63.7%).

All cases reported in this study are Genotype 3. Amongst these, Genotype 3a were 180 (93.3%), and Genotype 3b were 13 (6.7%). Their baseline serum profile showed mean haemoglobin level as 12.290 mg/dl (±1.8422mg/dl), mean serum ALT as 94.67IU/L (±25.782 IU/L), mean total leukocyte

count (TLC) as 6400.78 /cmm (±1494.212/cmm) and serum platelet counts as 137891.19/cmm (±43851.116/cmm). The means of haemoglobin level at presentation and 4 weeks follow-up was 1.6378 (±0.9539 SD) at a 95% confidence level, with a *p*-value <0.005. Similarly, the means of haemoglobin levels at 4 weeks and 12 weeks follow up was -1.2254 (±1.0087) at a 95% confidence level, with a *p*-value <0.005. After four weeks of therapy, PCR was compared. 143 (74.1%) cases had a negative PCR, while 50 (25.9%) cases had a positive PCR. End of treatment response (ETR) was achieved in 176 (91.2%) cases, while 17 (8.8%) cases had treatment failure (non-responders). There was statistical significance between gender achieving ETR, i.e., 112 (63.63%) females vs. 64 (36.36%) males, with a *p*-value of .008. 163 (84.5%) cases had achieved sustained virologic response at 12 weeks post-therapy (SVR12), while 30 (15.5%) cases had positive PCR. Response to antiviral therapy and genotype is given in Figure 1. Table 1 shows the comparison between cases who managed negative PCR with those who did not at 4 weeks, 12 weeks, and 24 weeks after the commencement of treatment. A comparison was made between age, haemoglobin levels, and ALT levels. There was statistical significance between age, and PCR at 4 weeks (p-value of .002), age and PCR at 24 weeks (p-value of .051) and between ALT levels and PCR at 4, 12 and 24 weeks follow up (*p*-value <0.005).

At 1-year follow-up, 28 patients failed to be followed as there was no data in record registers. One hundred and fifty-three (79.3%) cases achieved a negative PCR status and were cleared of viral RNA, while 12 (6.2%) cases were still positive for viral RNA. 9 (5.5%) cases of the total 163 cases who achieved SVR had a relapse at 1-year follow-up.

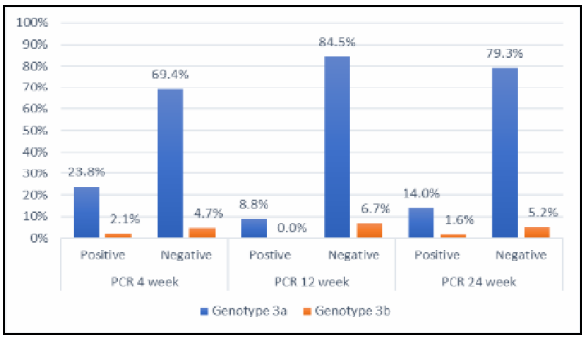

Figure-1: A comparison between Genotype and PCR results at 3 intervals of follow-up

Table-1: Comparison between baseline profile of cases who achieved negative PCR with those who did not after the commencement of treatment

Profile	PCR	PCR at 4 weeks		PCR at 12 weeks		PCR at 24 weeks	
		Mean(±SD)	*p*-value	Mean(±SD)	*p*-value	Mean(±SD)	*p*-value
Age	Positive	58.76(5.702)	.002*	58.24(6.447)	.075	57.03(6.866)	.051*
	Negative	47.72(8.378)		49.84(9.045)		49.39(9.037)	
Hb	Positive	10.076(1.2486)	.409	11.365(1.5894)	.368	-	-
	Negative	10.734(1.3316)		11.830(1.3033)		-	
ALT	Positive	63.28(30.905)	.000*	61.47(19.972)	.000*	66.23(23.428)	.000*
	Negative	30.88(5.614)		34.02(7.902)		35.97(7.548)	

*statistical significance with a *p*-value < 0.05. -no data was available

DISCUSSION

An epoch of oral antiviral regimens has been acquainted with the emergence of direct-acting antivirals. The one to attain universal exposure was Sofosbuvir, an NS5B non-nucleoside polymerase inhibitor, which has got a pan-genotypic effect [15]. Multiple noteworthy studies are done in the western countries that assess the efficacy of sofosbuvir for the different HCV genotypes, but the data is limited for HCV genotype 3 as it dominant in the East[3]. Recently, many cases of relapse have been noticed with patients being treated on INF/RBV regimen. Patients benefit more being on two drug regimens than on a single regimen alone with direct antiviral agents (DAAs), as patients on a single drug regimen has higher frequency of relapse. Maintaining a high level of RBV concentration during treatment as much as possible favours SVR in HCV genotype 3 patients who respond to therapy optimally. Likewise, it is essential to enhance RBV treatment during the entire course of therapy in order to prevent relapse in those patients who cannot boon from a new treatment.[19]

Out of the total 193 cases, males were 70 (36.3%), while females were 123 (63.7%). Correlation between gender and ETR showed statistical significance, 112 (63.63%) females vs. 64 (36.36%) males, with a p-value of .008. These findings are in accordance with the findings reported by Tayyab *et al*. In their study, females had a higher rate of SVR than males, which was statistically significant.[20] In contrast to this, our study had a higher rate of females achieving ETR, which is statistically significant than achieving SVR.

HCV genotype 3 is the most prevalent genotype specific to this region. This study showed that, cases positive for Genotype 3a were 180

(93.3%), while Genotype 3b cases were only 13 (6.7%). Overall, these findings are in accordance with the findings reported by Umer *et al*.; they also concluded that the most prevalent genotype is Genotype 3 (79%) and, more specifically, Genotype 3a followed by Genotype 1, 2 and 4.[5]

In our study, 143 (74.1%) cases had a negative PCR by the end of 4 weeks of treatment, while PCR was positive for 50 (24.9%) cases. 69.4% of Genotype 3a cases out of the total 193 cases were negative, while 4.7% of cases of Genotype 3b were negative. Similarly, 176 (91.2%) cases achieved ETR, while 17 (8.8%) cases were non-responders, i.e., treatment failure. ETR was achieved by 84.5% Genotype 3a cases, while 6.7% of Genotype 3b cases had achieved ETR out of the total 193 cases. Our results demonstrated a statistical significance between gender achieving ETR, i.e., 112 (63.63%) females vs. 64 (36.36%) males, with a *p*-value of .008. About 16 cases were unable to achieve SVR even after achieving ETR. A total of 84.5% of cases had achieved SVR12 in our study. A similar pattern of results was obtained in another study conducted in Pakistan. All the patients were treated with ribavirin and sofosbuvir. In their study, 89% of relapsers had attained RVR, ETR was 100% in relapsers, but SVR was 84.2% in relapsers.[20] In another study, relapsed patients treated with sofosbuvir and ribavirin showed an SVR of 78%; they also concluded that response rates among Genotype 3 were lower than Genotype 2.[15]

We speculate that the low SVR and high relapse rates might be due to the fact that the antiviral therapy duration is suboptimal, which fails to eliminate the viral reservoirs. In case of which patients achieving ETR fails to achieve SVR. According to another study co-chaired by the above mention author, HCV genotype 3 relapsers may benefit from an extended duration of sofosbuvir and ribavirin treatment from 12 weeks therapy to 24 weeks. There were substantially higher SVR and low relapse rates in their study[(21)]. Insulin resistance and disturbance in lipid metabolism are some of the particular characteristics of HCV genotype 3, which are the reasons for the suboptimal response of antivirals.[22]

It is worth mentioning here that we compared variables such as age, Hb levels, and ALT with PCR at 4, 12, and 24 weeks. There was a statistical significance between age and PCR at 4 and 24 weeks with a *p*-value <0.05. Similarly, there was statistical significance between ALT and PCR at 4, 12, and 24 weeks, with a p-value <0.005. The significant haematological side effect of Ribavirin is the haemolysis of red blood cells. It is usually dose-related and self-limiting.[23] Haemoglobin levels were compared, considering the fact, as mentioned above. A statistical significance was found between haemoglobin levels before the initiation of treatment and at 4 weeks follow-up with a *p*-value <0.005. Similarly, there was also a statistical significance between haemoglobin levels at 4- and 12-weeks follow-up, with a *p*-value <0.005.

Another novel finding is that 9 (5.5%) cases of the total 163 cases who achieved SVR had a relapse at 1-year follow-up. The possible explanation for this relapse, as mentioned above, is the reservoirs of viral RNA residing in the tissues of the host, which fails to get eliminated.

According to a review article by Ampuero *et al*., there needs to be a predictor of SVR in HCV genotype 3, which will ease up the situation for clinicians and patients alike. They reviewed a couple of studies, the results of which show that those patients achieving early RVR and having a low viral load (<400000 IU/L) will have early SVR and minimal chances of relapse. This pool of patients will require an antiviral therapy of 12–16 weeks duration. Likewise, those patients who achieve RVR later than 4 weeks and having a high viral load (>800000 IU/L) will have a delayed SVR. This pool of patients will require an anti-viral therapy of 24–72 weeks in order to achieve SVR and have a minimum chance of relapse.[24]

It is clear from the aforementioned arguments; the clinicians need to follow proper guidelines in the management of relapsed HCV genotype 3 patients, especially those who are challenging to treat. One such guideline is EASL guidelines, which take into account baseline viral load, RVR, metabolic irregularities (such as; insulin resistance, metabolic syndrome, and steatosis), advance liver disease, and ETR[(13)]. According to EASL guidelines; 1) patients having low viral load (<400000-800000 IU/L) and RVR should be treated with antivirals for 12–16 weeks, 2) the duration of treatment should not be reduced than 16 weeks, if the patients have advanced fibrosis or metabolic abnormalities despite having low viral load and early RVR, 3) patients whose PCR for HCV RNA is negative at 24 weeks should be treated for 48–72 weeks, 4) patients with positive PCR for HCV RNA and non-RVR at 24 weeks should discontinue therapy.

CONCLUSION

The treatment of HCV genotype 3 relapsed patients opens up new doors of challenges for the clinicians and patients alike. Partly due to the fact that many factors are related to the patients and HCV genotype and partly due to the availability of drugs. HCV genotype 3 relapsed patients can benefit from the

combination of Sofosbuvir and Ribavirin. With the SVR of more than 80%, this combination is cost-effective, and safe in the management of HCV relapsed patients, benefitting younger patients more than older patients. Baseline investigations needs to be done at follow-up visits as haemoglobin and platelets levels are influenced by these drugs.

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AUTHORS' CONTRIBUTION

HAJ: Literature review andformulating introduction. NM: Data collection and literature review. MHK: Methodology, statistical analysis, discussion. MOA: Data collection and data entry. SMAS:Literature review and introduction. MS, HFJ: Data collection and literature review.

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