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Original Article

Sofosbuvir and Ribavirin in Turkish non-cirrhotic chronic hepatitis C patients infected with genotype 2 or 3

Tayibe Bal, Mehmet Cabalak

Department of Infectious Disease and Clinical Microbiology, Hatay Mustafa Kemal University, School of Medicine, Hatay, Turkey

Abstract

Aim: Few studies have evaluated real-world clinical experience with sofosbuvir (SOF) plus ribavirin (RBV) in hepatitis C virus (HCV) genotypes 2 and 3 infections from Turkey. Thus, this study aimed to investigate the results of sofosbuvir plus ribavirin therapy in genotype 2 and 3 cases followed in an infectious disease clinic at a university hospital in Hatay, southern Turkey.

Material and Methods: In this single-centre, retrospective, observational study, 58 eligible patients treated with SOF/RBV (400 mg of SOF plus weight-based RBV) therapy between October 2016 and February 2019 were examined. Forty-three patients who had completed the duration of treatment and had known virological response status were evaluated for treatment outcomes.

Results: SOF/RBV achieves a sustained virological response (SVR) rate of 96.3% and 100% in the HCV genotype 2 and 3 groups, respectively, with treatment duration of 12-24 weeks. No patient experienced a virologic breakthrough while only one experienced virologic relapse after the completion of therapy. The incidence of adverse events was 25.5% (11/43) while the most common (11.6%) adverse event was ribavirin-related hemolytic anemia.

Conclusion: The current study revealed that the SOF/RBV therapy achieved excellent response rates with a good safety profile in non-cirrhotic Turkish patients infected with HCV genotype 2 or 3.

Keywords: HCV; genotype 2; genotype 3; ribavirin; sofosbuvir; Turkey

INTRODUCTION

Approximately 2.8% of the world population is thought to be infected with hepatitis C virus (HCV) (1). In Turkey, HCV genotypes 2 and 3 are less prevalent than genotype 1 infection, being present in 2.2%, 4.9% to 91.8% of patients with chronic hepatitis C (CHC) patients (2). However, in recent years the change in genotype distribution by increasing risky behavior especially who use injection drugs, the prevalence of non-1 genotypes is increasing (3,4). Furthermore, as the injection drug users nowadays, at the center of the hepatitis C epidemic, increasing our knowledge of treatment outcomes in non-1 genotypes including genotype 2 and 3 infections is essential (5).

Sofosbuvir (SOF)/ ribavirin (RBV) therapy no more widely recommended as a first-line treatment option for CHC patients infected with genotype 2 and 3, maybe because of the low response rates in Western patients (6). However, there is a growing body of literature that shows SOF/RBV regimen resulted in higher sustained virological response (SVR) rates in Asian patients compared with non-Asian patients, supporting the importance of understanding the effect of racial/ethnic differences on outcomes following direct-acting antiviral (DAA) therapy (7,8). Therefore, it is essential to report national experiences in this area to improve DAA therapies.

Up to now, there have been few studies assessing the efficacy and safety of SOF/RBV combination in the treatment of genotype 2 or 3 CHC patients in Turkey (9,10). Thus, this study aimed to investigate the results of SOF/RBV regimen in genotype 2 and 3 cases followed in an infectious disease clinic at a university hospital in Hatay, southern Turkey

MATERIALS AND METHODS

In this single-centre, retrospective, observational study, the data of 58 patients who were infected with HCV genotype 2 or 3 and treated with 400 mg of SOF + weight-based RBV therapy between October 2016 and February 2019 were examined. Forty-three patients who had completed the duration of treatment (12 weeks for genotype 2 and 24 weeks for genotype 3) and had known virological response status (HCV RNA [HCV ribonucleic acid] level at 4 weeks

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Corresponding Author: Tayibe Bal, Department of Infectious Disease and Clinical Microbiology, Hatay Mustafa Kemal University, School of Medicine, Hatay, Turkey **E-mail:** dr.tayibal@gmail.com

of treatment and post-treatment week 12) were evaluated for treatment outcomes.

Baseline demographic data of the patients, including age, gender, comorbidities, previous HCV treatment experience, chronic medications (to prevent possible drug-drug interactions) were recorded before the initiation of treatment. Abdominal sonography (the evidence of cirrhosis or portal hypertension) and liver biopsy results (if available), HCV viral load (HCV RNA level at 4 weeks of treatment and at weeks 12 post-treatment) and HCV genotype results, the side effects seen during therapy and how the ribavirin-related anemia had been managed were retrieved from the electronic database of the Hatay Mustafa Kemal University Hospital retrospectively.

The initial dose of RBV was ranging from 1000 mg/day (≤ 75 kg) to 1200 mg/day (> 75 kg) and divided into two doses. During the treatment process, if the hemoglobin fell to ≤10g/dL, the dosage of RBV was decreased by 200mg/day while the RBV was discontinued if the hemoglobin level fell to ≤ 8.5 g/dL.

Rapid virological response (RVR) was defined as undetectable HCV RNA at treatment week 4, while SVR was defined as undetectable HCV RNA at 12 weeks after cessation of therapy.

Virological relapse was defined as undetectable HCV RNA in serum at the end of treatment, followed by detectable HCV RNA during follow-up while virological breakthrough was defined as an increase in serum HCV RNA level during treatment.

Patients co-infected with hepatitis B virus (HBV) or human immunodeficiency virus (HIV), who had clinical, radiological, histological evidence of cirrhosis, who had previously taken a DAA therapy were excluded from this analysis.

HCV genotype and plasma HCV RNA levels were determined by a real-time PCR assay, using the Bosphore HCV Quantification Kit V2 (Anatolia Geneworks, Turkey) with a detection limit of 25 IU/mL.

Approval for the study was granted by the Ethics Committee of Hatay Mustafa Kema University Hospital (Decision date: 31/10/2019 number: 2)

Statistical analysis

Efficacy analysis was conducted with a per-protocol (PP) population. SPSS for Mac 23.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analyses. No normally distributed continuous variables are expressed as the medians (IQR: interquartile ranges). Categorical variables were demonstrated as number and percentages and compared with Chi-square or Fisher Exact test when appropriate. P <0.05 was considered statistically significant.

RESULTS

Patients' demographics

Of the 43 patients whose treatment outcomes could be evaluated, 20 (46.5%) were female, and 23 (53.5%) were male. The median age of patients was 56 (IQR:28-66) years, and thirteen (30.2%) patients were ≥65 years of age. While 16 (37.2%) of these cases were infected with genotype 3, the majority of cases (n=27, 62.8%) were infected with genotype 2. All of these cases were non-cirrhotic, 9.3% of who had experienced interferon-based antiviral therapy. Among the participants, 32.6% were a prisoner, and 9.3% were addicted to multiple substances. Only six of the patients had at least one comorbidity. Table 1 shows the baseline characteristics of the patients and their response to therapy, according to genotype.

Primary outcomes

Among 43 patients who had completed the treatment duration and who's SVR12 could be evaluated, only one (2.3%) patient relapsed at posttreatment week 12, and there was no patient with viral breakthrough or non-response during the treatment period.

In PP analysis, SVR rates were high in patients with genotype 2 and genotype 3 infections (96.3% and 100%, respectively).

Secondary outcomes

The incidence of adverse events was 25.5% (11/43). The most common (11.6%) adverse event was ribavirin-related hemolytic anemia which was more common among patients aged ≥ 65 years than those aged less than 65 years (23.1% vs 6.7%); however, this difference was not statistically significant (p=0.153). RBV dose reduction was required in 6.9% (3/43) of the patients, and the rate of RBV discontinuation due to anemia was 4.6% (2/43). Less common adverse events were fatigue, pruritus and nausea/vomiting (6.9%, 4.6% and 4.6%, respectively).

There was no all-drug discontinuation secondary to drug-related adverse events. Chest pain was the only severe adverse event. Details of adverse events and management of the anemia, according to genotype, are summarized in Table 2.

During the treatment and follow-up period, none of the patients required liver transplantation or developed hepatocellular carcinoma (HCC) or had severe hyperbilirubinemia.

DISCUSSION

There is little published information on the efficacy and safety of SOF/RBV regimen for the treatment of HCV genotype 2 or 3 in real-world clinical practice from Turkey (9,10). The current study revealed that the SOF/RBV combination achieved excellent response rates with a good safety profile in non-cirrhotic Turkish patients infected with HCV genotype 2 or 3.

The results of this retrospective real-world study show that SOF/RBV achieves a SVR rate of 96.3% and 100% in the HCV genotype 2 and 3 groups, respectively, with treatment duration of 12-24 weeks. Although it is possible that these high SVR rates were influenced by the low

Table 1. Baseline characteristics of the patients and virological response to SOF plus RBV therapy according to genotype

	GT2 cases (n=27)	GT3 cases (n=16)
Variables	61(56-72)	25 (21.2-34.5)
Age (years)		
Gender	16 (59.7)	4 (25)
Female	11 (40.7)	12 (75)
Male	4 (14.8)	0 (0)
Treatment experienced	13 (48.1)	0 (0)
Aged ≥65 years	19 (70.4)	6 (37.5)
HCV RNA ≥800.000 IU/mL*	2 (7.4)	12 (75)
Prisoner	2 (7.4)	2 (12.5)
Drug abuser	5 (18.5)	1 (6.2)
Comorbidities	2 (7.4)	0 (0)
DM	2 (7.4)	0 (0)
HT	1 (3.7)	0 (0)
COPD	0 (0)	1 (6.2)
Psychosis	1 (3.7)	0 (0)
RCC		
Virological response	21 (77.8)	14 (87.5)
RVR	26 (96.3)	16 (100)
SVR	41.75±3.34	47.50±4.41
Day 10*	47.75±5.46	54.00±3.94

Data are expressed as n (%) or median (IQR); *Viral load at baseline;
IQR: interquartile range. GT: genotype; DM: diabetes mellitus; HT: hypertension; COPD: chronic obstructive pulmonary disease; RCC: renal cell carcinoma; SVR: sustained virological response; RVR: rapid virological response

Table 2. Adverse events and management of anemia according to genotypes

	12 weeks SOF + RBV for GT2 (n=27)	24 weeks SOF + RBV for GT3 (n=16)	Total (n=43)
Variables			
Patients with any AEs	7 (25.9)	4 (25)	11 (25.5)
Common AEs			
Anemia (Hb<10 g/dL)	5 (18.5)	0 (0)	5 (11.6)
Fatigue	3 (11.1)	0 (0)	3 (6.9)
Pruritus	1 (3.7)	1 (6.2)	2 (4.6)
Dyspepsia	0 (0)	1 (6.2)	1 (2.3)
Nausea/vomiting	2 (7.4)	0 (0)	2 (4.6)
Alopecia	0 (0)	1 (6.2)	1 (2.3)
Vertigo	1 (3.7)	0 (0)	1 (2.3)
Headache	1 (3.7)	0 (0)	1 (2.3)
Serious AEs			
Chest pain	0 (0)	1 (6.2)	1 (2.3)
Death	0 (0)	0 (0)	0 (0)
Management of anemia			
RBV dose reduction	3 (11.1)	0 (0)	3 (6.9)
Discontinuation of RBV	2 (7.4)	0 (0)	2 (4.6)

Data are expressed as n (%); SOF: sofosbuvir; RBV: ribavirin; AEs: adverse events; Hb: hemoglobin

number of patients in the current study, similar favorable SVR rates were seen in a recent multicenter study from Turkey, too (9). Furthermore, those SVR rates are much higher than those reported from most western countries but similar to those reported in Asian populations (7,11-13). These results are in line with recent studies indicating that the differences in ethnicity may affect rates of sustained virological response to DAA regimens (14,15). Nevertheless, to clarify whether the better response was linked to ethnicity need to be studied further.

The HCV genotypes 2 and 3 mostly grouped together in treatment guidelines and even in clinical studies (16,6). Maybe it is because they have responded well to interferon-based therapies with higher SVR rates compared with other genotypes (17). However, with the introduction of new DAA agents (SOF/RBV combination was the first DAA approved in 2014), it is clearly understood that they differ in response to therapy and HCV genotype 3 infections labelled as the most difficult-to-treat genotype (18,19). Furthermore, HCV genotype 3 infection is known to be an essential risk factor for treatment failure among non-genotype 1 infections (20). However, surprisingly the PP_SVR rates among patients with HCV genotype 3 infections were (100%) as high as the rates among those with HCV genotype 2 infections (96.3%) in the current study. However, among the patients with genotype 3 infection in the current study, there were no subjects who had the evidence of cirrhosis or aged over 50 years which have been considered potential predictors of poor outcome in previous studies (18,6). More research is required to determine the efficacy and safety of SOF/RBV therapy in cirrhotic Turkish patients.

No patient experienced a virologic breakthrough while only one experienced virologic relapse after the completion of therapy in the current study. The small size of the dataset in our study makes it difficult to draw definite conclusions. However, similar breakthrough rates (0 to <1%) were observed in large-scale studies from different countries, too (21,8,11,22). These results are accord with recent studies indicating that sofosbuvir has a high genetic barrier to resistance (6).

In our real-life experience, the adverse-event rate was 25.5% [11/43], which was considerably lower than that (60-90%) with interferon and ribavirin combination therapy (23). Nevertheless, this rate was similar to that reported in previous studies conducted in HCV genotype 2 and genotype 3 infected patients who received SOF/RBV therapy (24-26). In accordance to the literature in the current study all patients experienced mild adverse events while only one patient reported a severe adverse event (chest pain), however, it is not clear whether this event depended on the antiviral therapy (27,11). Furthermore, there was no discontinuation of the therapy due to adverse events. To conclude, these results suggest that possibly in the absence of interferon, the adverse events of RBV are not as much as we are concerned.

Consistent with the previous findings, the most common adverse event was RBV induced anemia (11.6%) in the present study which was more common among patients aged ≥65 years than younger adults (23.1% vs 6.7) with low rates of RBV dose reduction and discontinuation (6.9% vs 4.6%) (26,28). However, in contrast to earlier findings, there were no significant differences in the frequency of severe anemia during treatment with SOF/RBV among those who received 12 and 24 weeks of therapy (7,25). This unexpected result might be explained by the fact that patients with genotype 3 infection (who received 24 weeks of therapy) are considerably younger than with genotype 2 (who received 12 weeks of therapy). Taken together, these results support previous literature reports which showed a link between older age and RBV induced anemia (28,26).

These findings are limited by the small sample size and single-centre retrospective nature. Nevertheless, the present results might provide helpful information for the development of new DAA drugs against the HCV genotypes 2 and 3 infections.

CONCLUSION

In conclusion, according to the results of the current study, it was suggested that SOF/RBV regimen is effective and safe in non-cirrhotic Turkish adults who are infected with HCV genotype 2 and 3.

Conflict of interest: The authors declare that they have no competing interest.

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