Tropical Journal of Pharmaceutical Research January 2022; 21 (1): 151-157
**ISSN:** 1596-5996 (print); 1596-9827 (electronic)


Available online at http://www.tjpr.org
**http://dx.doi.org/10.4314/tjpr.v21i1.23**

**Original Research Article**

# Efficacy of oral combination antiviral therapy in genotype 4 hepatitis C ınfection and the importance of rapid virological response

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*Sent for review: 24 June 2021* *Revised accepted: 18 December 2021*

## Abstract

***Purpose:*** *To evaluate the efficacy and safety of ombitasvir (OMV), paritaprevir (PTV), ritonavir (r), ribavirin (RBV) (OMV/PTVr + RBV), ledipasvir (LDV) and sofosbuvir (SOF) therapies in genotype 4 (GT4) patients, and to determine if the rapid virological response (RVR) observed at 4th week of therapy has a role in predicting sustainability of the response at week 12 (SVR12) post-therapy.*
***Methods:*** *The investigation included 71 subjects with diagnosis of Hepatitis C (HCV) GT4. Some of the patients (40/71) were treated using combination of OMV (25 mg/day), PTV (150 mg/day), ritonavir (r) (100 mg/day), while the others (31/71) were treated using combination of LDV (90 mg/day) and SOF (400 mg/day). Body weight-based RBV was added to both treatment regimens, and the treatments given for a total of 84 days. Viral levels in the patients were evaluated after the 4th and 12th week of drug administration, and at 12 weeks post-administration.*
***Results:*** *The SVR12 responses of the patients on the basis of sub-groups, were 97.5 % for OMV/PTVr + RBV, 96.8 % for LDV/SOF + RBV ($p = 0.6$); 91.3 % for cirrhotic, 100 % for non-cirrhotic ($p = 0.1$); 100 % in untreated, and 95.5 % for treated ($p = 0.33$). While there were numerical differences, these were not statistically significant. The SVR12 response was 100 % in patients with RVR response, and 87.5 % for patients without RVR response ($p < 0.05$). When the patients' aspartate transaminase (AST), alanine transaminase (ALT), platelet (PLT), albumin, creatinine, prothrombin time (PT) and fib4 values before and after treatment were compared, significant difference were observed for all variables ($p < 0.01$), except for PT ($p = 0.3$). there were no dangerous adverse events such as decompensation or death, aside from mild fatigue, with incidence of 19 %.*
***Conclusion:*** *RVR response after OMV/PTVr + RBV and LDV/SOF + RBV treatments show that the treatments can be used safely and effectively in patients with HCV genotype 4. Moreover, RVR might be a suitable determinant of SVR12 response.*

***Keywords:*** ***G****enotype 4 patients, ombitasvir, paritaprevir, ritonavir, ribavirin, ledipasvir, sofosbuvir, efficacy*



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## INTRODUCTION

Hepatitis C disease is a universal public health issue which affects approximately 130 - 185 million people worldwide. Left untreated, it may progress to end-stage hepatic disease and hepatocellular carcinoma [1]. Seven different genotypes and 67 sub-types have been identified for hepatitis C. The prevalence of these genotypes varies with geographical region [2]. Genotype 4 (GT4) is more prevalent in North Africa, Southeast Asia and Middle East, especially in Egypt where GT4 hepatitis C infection accounts for approximately 8 – 13 % of all hepatitis C infections [3], while the frequency of GT4 in Turkey is 3 7.3 % [4].

In recent years, direct-acting antivirals (DAA) have been applied in treating chronic HCV infection. Among the DAAs, non-structural protein 5A inhibitor (NS5A) OMV, non-structural proteinase 3/4A inhibitor (NS3/4A) paritaprevir (PTV), and pharmacokinetic booster ritonavir (r) in combination with RBV (OMV/PTVr + RBV) have been used for cirrhotic, non-cirrhotic, treatment-naive and treatment-experienced patient groups for treating HCV GT4 infection [5-7]. Another DAA combination used for the treatment of genotype 4 hepatitis C is NS5A inhibitor LDV + NS5B polymerase inhibitor SOF (LDV/SOF ± RBV) [8]. Based on whether the patient is treatment-naive or treatment-experienced, it has been recommended that RBV should be added to the treatment of subjects who were not previously treated with DAA [8].

Negative HCV RNA at 4 weeks after the start of hepatitis C therapy is considered a RVR. Previously, RVR has been shown to be a strong predictor for SVR in patients treated using pegylated interferon and ribavirin [9]. There are publications arguing that the RVR obtained during treatment has no effect in predicting SVR [10]. However, RVR has been shown to play a role in SVR12 prediction in patients infected with HCV genotype III [11]. Thus, in all patients treated using DAA, all genotypes should be addressed separately, and the effect of RVR on SVR12 should be determined.

In this study, the effectiveness and safeness of OMV/PTVr + RBV and LDV/SOF + RBV treatments in genotype 4 patients were evaluated. The study was also done to investigate whether RVR outcome has a role in predicting SVR12.

## METHODS

The files of subjects diagnosed with HCV who applied to the gastroenterology polyclinics of the Cumhuriyet University and Kayseri Research and Training Hospital between May 2016 and December 2020, were analyzed. A total of 71 patients (between the ages of 18 and 76) who received DAA therapy were studied (Figure 1). The study received institutional ethical approval and also followed international guidelines for human studies.

Forty (40) patients in OMV/PTVr + RBV group received OMV (25 mg/day), PTV (150 mg/day) and ritonavir (100 mg/day) therapies, while 31 patients in LDV/SOF+RBV group received LDV (90 mg/day) and SOF (400 mg/day) therapy, each for 12 weeks. Body weight-based RBV therapy (1000 mg/day for < 75 kg, and 1200 mg/day for > 75 kg) was added to the treatment of subjects who were earlier given therapy other than DAA. The assessment of virological response was made with HCV mRNA values using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test version 2.0 which has a LOQ of 15 U/L.

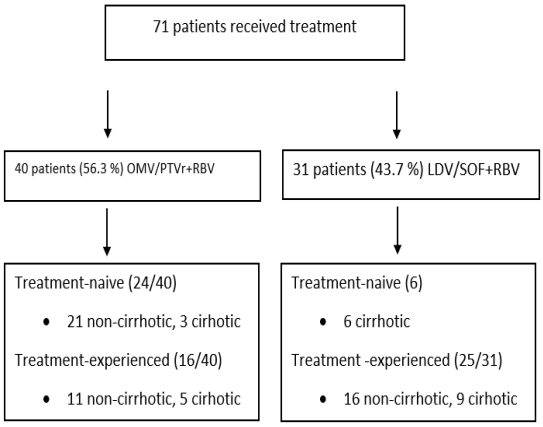


**Figure 1:** Study design

As a baseline, the HCV RNA level was determined at the start of therapy. Then, HCV RNA levels were determined at week 4 of treatment to assess rapid virological response (RVR), at week 12 to evaluate end-of-treatment (EOT) response, and at week 12 post-therapy to assess sustained virological response (SVR12). All subjects were sub-divided based on DAA treatment regimen, RVR response, previous treatment experience, and cirrhosis status.

Hepatic fibrosis stage was determined using liver biopsy or Fib4, where

$$Fib4 = \frac{[Age\ (years) \times AST\ (U/L)\ U/L}{\ldots\ldots\ldots} \quad [12]$$

$$[PLT\ (10^9/L) \times ALT^{1/2}\ (U/L)$$

Fib4 score was considered for treatment-experienced patients, while fib4 and liver biopsy results were used for treatment-naive patients. In patients who underwent liver biopsy, Ishak score (modified Knodell score) [13] was used for fibrosis staging. The fibrosis scores were categorized as follows: 0 = no fibrosis; 1 – 2 = mild fibrosis; 3 – 4 = severe fibrosis; 5 = incomplete cirrhosis, and 6 = cirrhosis. Fibrosis scores > 3.25 are associated with 97% specificity and positive prediction potential of 65 % for late-stage fibrosis [12]. Patients who had nodular and heterogeneous appearance with splenomegaly (spleen size > 130 mm) in liver USG, portal vein (PV) diameter above 13 mm in PV doppler, endoscopy evidence of varicosis, hypoalbuminemia, prolonged coagulation, thrombocytopenia, and fibrosis score of 5 - 6 in liver biopsy, were considered as cirrhotic.

From the laboratory tests in the patient files; bilirubin, AST, ALT, gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), albumin (ALB), prothrombin time (PT), International Normalized Ratio (INR), complete blood count (CBC), serum creatinine, alpha fetoprotein (AFP), and HCV RNA values were determined at baseline, 4$^{th}$ week of treatment, end of treatment, and 12$^{th}$ week after treatment.

Detailed comorbidity status and demographic data such as genetic disease, alcohol use, diabetic state, high blood pressure and coronary artery disease were determined from the anamnesis and physical examination information recorded in the patient files. The files were also checked to see whether the patients experienced common side effects such as headache, fatigue, weakness, arthritis, arthralgia, itching and insomnia during the treatment.

**Statistical analysis**

Data obtained from this investigation were analyzed using SPSS 23.0 software (IBM SPSS Statistics Base 23 V Authorization code: e56444b2255bd0030cf1). Normality of numerical data (interval and ratio scale) was controlled using Kolmogorov-Smirnov test. Since the *p* values were below 0.05, it was determined that the data were not normally distributed. Therefore, the presence of differences between matched subgroups was determined using Wilcoxon test. Differences between categorical data were determined using Pearson Chi-squared, and Fisher Exact tests. Since SVR12 categorical dependent variable is binary, and independent variables (sex, age, body mass index (BMI), fibrosis and treatment regimen) are categorical, the effect of independent variables on dependent variables was determined using logistic regression analysis. Significant difference was assumed at $p < 0.05$.

## RESULTS

A total of 71 patients with genotype IV HCV diagnosis were involved in the study through analyzing their examinations and treatments from their files (Figure I). Forty (40) patients (56.3 %) received OMV/PTVr + RBV, and 31 (43.7 %) received LDV/SOF + RBV treatment regimen for 12 weeks; 48 patients (67.6 %) were non-cirrhotic, 23 (32.4 %) were cirrhotic, 41 (57.7 %) were treatment-experienced, and 30 (42.3 %) were treatment-naive. Among cirrhotic patients, 65.2 % (15/23) were detected to be Child A, and 34.8 % (8/23) to be Child B. When viral kinetics of the patients were checked, RVR rate was 78.9 %, EOT response rate was 100 %, and SVR12 rate was 97.2 %. Clinical, HCV RNA result and demographic characteristics of the patients are summarized in Table 1.

**Table 1:** Treatments received by patients, demographic and clinical characteristics, and rate of virological responses

| Unit | Total (n =71) |
|---|---|
| Sex (male, n (%) | 32 (45.1) |
| Mean age range (years) | 62 (29-82) |
| BMI (kg/m$^2$) | 28.4 ± 3.2 |
| Treatment | |
| *OMV/PTVr+RBV, n (%)* | 40 (56.3) |
| *LDV/SOF+RBV, n (%)* | 31 (43.7) |
| Treatment-naive, n (%) | 30 (42.3) |
| Treatment-experienced [n (%)] | 41 (57.7) |
| Cirhosis [n (%)] | 23 (32.4) |
| Basaline HCV RNA (mean, IU/mL) | 2.21x10$^6$ |
| RVR[a] [n (%)] | 55 (77.5) |
| EOT[a] [n (%)] | 71 (100) |
| SVR12[a] [n (%)] | 69 (97.2) |

*a = undetectable viral load; CTP = Child-Turcotte-Pugh; RVR = Rapid virological response (undetectable HCV RNA at week 4 of treatment); EOT = End of treatment (undetectable HCV RNA at week 12 of treatment); SVR = Sustained virological response (undetectable HCV RNA at week 12 of post-treatment)*

The values of SVR12 were 97.5 % in patients treated using OMV/PTVr + RBV, 96.8 % in patients treated using LDV/SOF + RBV, 91.3 % in cirrhotic patients, 100 % in non-cirrhotic patients, 95.1 % in treatment-experienced patients, and 100 % in treatment-naive patients. Moreover, SVR12 was 100 % in 55 RVR patients with RVR, and 87.5% in 16 non-RVR subjects. When patients with and without RVR were compared with respect to SVR12, there was a

**Table 2:** Biochemical values of hepatitis C subjects treated with DAA (pre- and post-treatment)

| Parameter | Pre-treatment | Post-treatment | *P*-value |
|---|---|---|---|
| Creatinine (mg/dL) (median range) | 0.81 (0.4 - 1.2) | 0.78 (0.42 - 1.1) | |
| AST (U/L), (median range) | 64 (21 – 240) | 27 (12 – 98) | <0,01 |
| ALT (U/L), (median range) | 69 (17 - 310) | 32 (14 - 133) | <0,01 |
| Albumin (g/dL), (median range) | 3.2 (1.9 - 4) | 3.9 (2.5 - 5) | <0,01 |
| PT (sn), (median range) | 9.1 (8 - 12.3) | 9.3 (9 - 13) | >0.05 |
| Platelets (x $10^3$/$mm^3$, (median (range) | 85 (62 - 230) | 115 (79 - 300) | <0,01 |
| Fib4, (median (range) | 3.1 (1.1 - 11) | 1.9 (0.7 – 6) | <0,01 |

statistically significant difference between them ($p < 0.05$; Figure 2).

To determine the predictors for SVR12, the effects of gender, BMI, age, sex, cirrhotic status, therapy experience and baseline viral load parameters on SVR12 were checked using logistic regression analysis. However, the results revealed no statistically significant impacts ($p > 0.05$).

Since SVR12 was higher in patients with RVR, the effects of these same parameters on RVR were checked using logistic regression, and it was observed that only baseline HCV RNA value above 2 U/L had a predictive effect on RVR ($p < 0.05$).

When the pre-treatment AST, ALT, platelet (PLT), albumin, creatinine, PT and fib4 levels were compared with post-SVR12 response values, all variables differed markedly ($p < 0.01$) except for PT ($p > 0.05$; Table 2).

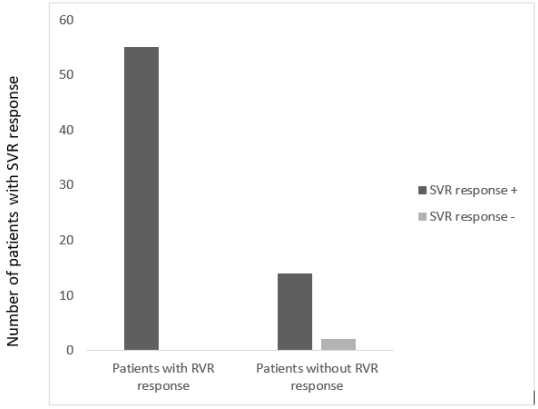


**Figure 2**: SVR12 response was % 100 in patients with RVR response and % 87.5 for a patient without RVR response ($p < 0.05$)

The most common adverse event during treatment was fatigue, with 19.7 % incidence (14/71), followed by headache with 9.9 % incidence (7/71). Diarrhea, pruritus and anorexia were mild adverse events seen less often (Table III). In patients who developed ribavirin-induced mild anemia, no precautions were taken except dose adjustment. Severe anemia causing treatment interruption or ribavirin discontinuation did not occur. The lowest level of hemoglobin (9.8 mg/dL) was observed in cirrhotic patients receiving OMV/PTVr + RBV treatment.

The most common comorbidity was diabetes mellitus in 36.6 % of the patients (26/71), followed by hypertension in 11.3 % of patients (8/71). Ischemic cardiac disease was observed in 4.2 %, chronic obstructive pulmonary disease in 2.8 %, hypothyroidism in 2.8 %, and ankylosing spondylitis in 1.4 % of the patients. None of the comorbidities posed contra-indication for treatment (Table 3).

**Table 3:** Comorbidities and side effects of treatments

| Variable | Percent |
|---|---|
| ***Comorbid disease*** | |
| Diabetes mellitus | 26 |
| Hypertension | 11.3 |
| Ischemic heart disease | 4.2 |
| Chronic obstructive pulmonary disease | 2.8 |
| Hypotroid | 2.8 |
| Ankylosing spondylitis | 2.8 |
| | |
| ***Side effect*** | |
| Fatique | 19.7 |
| Headache | 5.6 |
| Weakness | 9.9 |
| Pirurutis | 2.8 |
| Poor appatite | 2.8 |

## DISCUSSION

In this retrospective study, the effectiveness and safeness of DAA therapy were investigated in hepatitis C genotype 4 subjects. While the recommended treatment regimen for HCV genotype 4 in clinical practice is OMV/PTVr + RBV for 12 weeks irrespective of cirrhotic status or therapy history of the patient [5,8], another recommended treatment regimen is the addition of RBV to LDV/SOF medications given to treatment-experienced or decompensated cirrhotic patients [14 ]. In this study, consistent with the literature, OMV/PTVr + RBV regimen was preferred in non-cirrhotic and compensated cirrhotic patients, irrespective of the treatment experience, while LDV/SOF + RBV regimen was

preferred in treatment-experienced patients, irrespective of cirrhosis state, and also in treatment-naive subjects with decompensated cirrhosis. When this study is considered in respect of the administered treatment regimens, the results might be important due to limited data regarding LDV/SOF + RBV treatment in hepatitis GT4 subjects.

In controlled clinical trials in OMV/PTVr + RBV-treated subjects [5], SVR12 values were between 94 and 100 %, and between 95 and 100 % in LDV/SOF ± RBV-treated patients [15]. Analysis of literature data showed that SVR12 values were between 99 and 100 % in non-cirrhotic patients given OMV/PTVr + RBV, and 97 – 100 % in patients who received LDV/SOF ± RBV [16]. From these studies, SVR12 in treatment-naive patients was 100 %, but it was reduced to 97 % in treatment-experienced patients. Our study detected 100 % SVR12 in all patients without cirrhosis, untreated or therapy-experienced subjects who received OMV/PTVr + RBV and LDV/SOF + RBV. In the present study, SVR12 value was 100 % in non-cirrhotic subjects, and in other patients, irrespective of treatment history. This is consistent with the best results obtained in the literature.

In this study, while SVR12 was 87.5 % in cirrhotic patients who received OMV/PTVr + RBV treatment, it was 93.3 % in cirrhotic patients given LDV/SOF + RBV treatment. In controlled clinical trials with small patient groups varying between 8 - 13 in number [15], and in a multi-center trial in Egypt [16], SVR12 using LDV/SOF + RBV was reported to be 100 % in cirrhotic patients. In a study with higher number of cirrhotic patients [17], it was reported that SVR12 was 93.2 % with LDV/SOF ± RBV. In controlled clinical trials performed using OMV/PTVr + RBV treatment [6,7], SVR12 values were in the range of 97 – 100 % in cirrhotic patients. Crespo *et al* reported a SVR12 level of 91.2 % in cirrhotic patients who received OMV/PTVr + RBV treatment [17]. Thus, the values of SVR12 in cirrhotic patients in the present study are lower than those obtained in controlled clinical trials.

In the literature, the effective factors for determination of SVR12 in logistic regression analysis have been identified to be age, albumin, treatment experience, bilirubin and BMI [18]. However, in this study, none of these factors was observed to have an effect on SVR12 except RVR. Although RVR is a predictor of SVR in peginterferon-based treatments is proven [9], there is no serious study regarding this effect in patients receiving DAA treatment. However, there are publications suggesting that RVR has no effect on SVR12 [10,16]. While RVR has been assessed in patients receiving DAA treatment in controlled clinical trials, it is not included among predictive factors for SVR12 [5]. In a study performed in genotype 3 patients, [11] RVR was reported to have an effect on SVR12. In this study, while SVR12 was 100 % in RVR subjects (55/71), it was markedly lower (87.5%; 16/71) in patients without RVR.

Therefore, RVR might be a parameter for SVR12 prediction during treatment monitorization. Based on these results and extant literature, each genotype should be examined separately, and more studies should be carried out in order to determine whether RVR is a predictor of SVR12.

A previous study has shown the incidence of serious adverse events (death, decompensation and need for treatment discontinuation) were 0 – 11 % in patients given LDV/SOF ± RBV, and 2.3 - 5.9 % in patients who received OMV/PTVr + RBV treatment [2]. In the present study, there were no dangerous adverse events. The only mild adverse effect was RBV-induced anemia seen in 25 % of the patients who received OMV/PTVr + RBV treatment and 35% of the patients given LDV/SOF + RBV treatment. This was controlled via dose adjustment. Since LDV/SOF + RBV treatment was preferred in cirrhotic and Child B patients, anemia was more frequent in this sub-group.

With respect to other adverse events, the most common ones were fatigue in 19.7 % of the patients, and headache in 9.9% of the patients, followed by diarrhea, pruritus and anorexia in 2.8% of the patients. It was observed that serious adverse events did not occur, in contrast to reports in the literature. This might be due to exclusion of patients with liver transplantation, chronic renal failure, decompensated liver cirrhosis, and subjects with high possibility of coinfection with HBV virus at the beginning of the investigation. The degree of serious adverse events due to these treatment regimens was low. This can be zeroed in on the selection of the patient groups.

## CONCLUSION

The treatment regimens OMV/PTVr + RBV and LDV/SOF + RBV HCV can safely and effectively used in genotype 4 patients. The RVR of the HCV genotype 4 patients who received this therapy might be a predictor of SVR12.

## DECLARATIONS

### *Conflict of Interest*

No conflict of interest associated with this work.

### *Contribution of Authors*

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

### *Open Access*



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