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Original Article

# The comparison of two different direct acting antiviral regimens in treatment of chronic hepatitis C virus

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**Abstract**

**Aim:** Chronic hepatitis C virus (HCV) is considered a critical threat to the public health in the world. We compared treatment outcomes of Ombitasvir, Paritaprevir and Ritonavir with Dasabuvir (PrOD) and Ledipasvir (LDV) and Sofosbuvir (SOF) in real world patients with chronic HCV in treatment-naïve and pre-treated patients with chronic HCV.

**MaterialS and Methods:** 91 adult patients enrolled in our study and were divided in two groups. The first group; consisted of 53 patients, who orally received a fixed-dose combination tablet comprised of LDV and SOF once daily for 24 weeks. The second group; consisted of 38 patients, who orally received a fixed-dose combination tablet comprised of PrOD twice daily for 12 weeks without regard to fat or calorie content.

**Results:** The results showed that sustained virologic response (SVR) rates were 100% in the both groups analyzed. 76 adverse events were occurred in total. 46 of overall adverse events were found on patients in the first group and 30 of those events were found on patients in the second group. Weakness (13.1%), pruritus (5.5%), myalgia (1.1%) nausea (5.5%), dry mouth (1.1%) and insomnia (1.1%) were observed among the patients. Twelve weeks after initiating treatment, virologic suppression was accomplished for all patients in the both groups. Additionally, laboratory analysis concluded that HCV-RNA levels of the overall patients were negative after 48 weeks of the onset of the treatment.

**Conclusion:** The real world comparative analysis of two distinct treatment regimens concluded that administration of PrOD and LDV/SOF on the patients with chronic HCV has an extremely effective outcome. SVR12 rates of 100% were obtained in both treatment regimens for all treatment naïve and treatment-experienced patients regardless of cirrhosis occurrence and of HCV genotype.

**Keywords:** Chronic hepatitis C virus; direct acting antivirals; treatment

## INTRODUCTION

HCV infection is a global public health threat and it is estimated that 71 million people were living with HCV in 2015 and approximately 1.75 million new cases of HCV infection occur every year (1). Severe complications, such as hepatocellular carcinoma and cirrhosis, can be triggered by the chronic HCV infection, and those complications are considered as primary causes of mortality from HCV infection (2).

The clinical guidelines for HCV treatment are being updated frequently, as the therapy regimens advanced over time (2). The interferon (INF) based therapy, introduced in 1991, had been the fundamental treatment alternative for HCV with low SVRs, below 50%, until recent medications designated as the direct acting antivirals (DAA), which were introduced in 2011 with revolutionary SVRs over 90% (3). Complicated treatment regimens with insufficient results on chronic HCV infection was transformed to simply treated therapies with few side-effects and contra indications through groundbreaking progress of DAAs (4,5). The development of DAAs has boosted the SVR rates and adverse effect profiles in the treatment of patients chronically infected by HCV (3).

NS2-3 and NS3-4A proteases, NS5B RdRp and NS3 helicase are HCV enzymes and are crucial for HCV replication (5). DAA regimens are molecules aiming particular nonstructural proteins in the HCV RNA, preventing infection and viral replication (6). DAAs, HCV enzyme inhibitors, have different mechanisms of action against HCV RNA. There are three fundamental types of DAAs, which target the inhibition of the different enzymes in HCV (3). The first type of DAAs includes NS3/4A inhibitor that covers paritaprevir, grazoprevir, boceprevir, simeprevir, telaprevir, asunaprevir and vaniprevir (7). The NS5A protease inhibitor constitutes the second type of DAAs that includes ombitasvir, daclatasvir, elbasvir,

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ledipasvir and velpatasvir (8). The third type of DAAs comprises NS5B nucleotide inhibitor and non-nucleoside polymerase inhibitors that include sofosbuvir and dasabuvir respectively (9,10).

The aim of our study was to compare and evaluate administration of PrOD and SOF/LDV to evaluate the effectiveness and safety in treatment of patients chronically infected with HCV in the real-world.

## MATERIALS and METHODS

91 adult patients with chronic HCV infection were enrolled in this study. Diagnosis, treatment and follow-up of all patients were administered at the Faculty of Medicine at Düzce University and Bolu State Hospital in Turkey. The time period of this study covers from 2015 to 2018. The inclusion criteria adopted were patients over 18 years-old, infected with chronic HCV with or without cirrhosis, with treatment-experienced or treatment-naïve. No exclusion criteria were adopted regarding age and limits for body-mass index and age. Liver-biopsy was administered for 50 patients to determine cirrhosis cases in line with Ishak score of 5 or 6 (this scale consists scores between 0 and 6, and higher scores indicate a greater degree of fibrosis). Combinations of Pegile-Interferon + RBV ± TVR / BOC were previously administered to treatment-experienced patients; however all of these patients had a relapse of HCV infection.

### Study Design

We conducted a multi-center, real-world and an open-label study at Duzce University Hospital and Bolu State Hospital. The enrolled patients in this study were separated and analyzed into two groups. 53 patients were categorized in the first group and those patients were orally administrated a tablet of fixed-dose combination containing of 90 mg of LDV and 400 mg of SOF once daily. 38 patients were categorized in the second group and those patients were orally administrated a tablet of fixed-dose combination comprising of 12.5 mg of OBV, 75 mg of PTV and 50 mg of R and another fixed-dose table comprising of 250 mg of DSV twice daily, one in the morning and one in the evening after meals without regard to fat or calorie content. Patients in the first group were received SOF/LDV regularly during 24 weeks and the patients in the second group were received PrOD regularly during 12 weeks.

All of the patients in the both group were thoroughly examined and assessed about the likelihood of adverse events in both treatment regimens. Adverse events and laboratory parameters were measured, assessed and recorded before treatment and 2, 4, 12, 24, 36 and 48 weeks after the start of the treatment. Clinical conditions of the patients with cirrhosis were controlled by adopting the Child-Pugh score system. HCV infection was diagnosed by a positive test for anti-HCV antibodies endorsed by a positive HCV viral load.

None of the samples for laboratory parameters was acquired during renal crisis, acute liver or under any acute illness. The real-time polymerase chain reaction was used in line with standard methods to measure HCV-RNA levels.

### Study Oversight

The present study was approved by Ethics Committee of Duzce University and was carried out within the framework of the Declaration of Helsinki, the Principles of Good Clinical Practice guidelines, and the local regulatory requirements. Each of the patients gave written informed consent. The authors documented the clinical and demographic characteristics of all patients, compiled and edited the raw data for the analysis, performed the statistical analysis and followed up the all phases of the study. The authors discreetly maintained the data and confidentiality accomplished concomitant treatments, clinical and other medical assessments according to the standard clinical practice.

### Study Assessments

Serum biomarkers covering albumin (ALB), bilirubin (BIL), creatinine (CRE), hemoglobin (HB), international normalised ratio (INR), platelets count (PLT), total leukocyte (white blood cell-WBC) and urea (URE), and laboratory data on alanine aminotransferase (ALT), aspartate aminotransferase (AST) and HCV ribonucleic acid (RNA) level were measured and assessed during the follow up.

### Study Endpoints

The rate of the patients accomplishing SVR at 12 weeks (SVR12) was determined as the primary efficacy endpoint of this study. Definition of SVR 12 was adopted as the proportion of patients with HCV RNA concentration in serum less than 25 IU/mL 12 weeks after the accomplishment of treatment. Any adverse event causing discontinuation of the treatment was determined as the primary safety endpoint of our study.

### Statistical Analyses

The descriptive statistics on clinical and demographic characteristics of patients including range, mean, standard deviation, frequency (count) and relative frequency (percentage) are briefly presented. Due to the non-normally distribution of the data, the non-parametric Mann-Whitney test for continuous variables and the Chi-square test for categorical variables were conducted for the comparison of the quantitative variables of two groups. The Wilcoxon signed-rank test was conducted for the serial measurements of pretreatment and end of treatment. The results of p values less than 0.05 were assessed as statistically significant and confidence intervals were adopted at 95% level. All the analysis in this study were tested by The Statistical Package for the Social Sciences (SPSS) 25.

## RESULTS

Descriptive statistics of the analysis is given in Table 1. For the purpose of comparing the treatment regimens administered, the patients were categorized into two different groups. 53 patients in the first group orally received LDV and SOF and 38 patients in the second group orally received PrOD. The mean ages were 65 in the first group, 60 in the second group and 63 for overall.

**Table 1. Demographic and Clinical Characteristics (%)**

| Characteristic | 1st Group LDV+SOF (n=53) | 2nd Group PrOD (n=38) | Total |
|---|---|---|---|
| **Age** | | | |
| Mean | 65 | 60 | 63 |
| Range | 25-86 | 20-86 | 20-86 |
| **Gender** | | | |
| Female | 28 (21.71) | 27 (41.86) | 55 (63.57) |
| Male | 25 (19.38) | 11 (17.05) | 36 (36.43) |
| **Genotype** | | | |
| 1a | 3 (2.33) | - | 3 (2.33) |
| 1b | 51 (38.76) | 37 (58.91) | 88 (97.67) |
| **Fibrosis** | | | |
| 0 | 3 (3.30) | 1 (1.10) | 4 (4.40) |
| 1 | 1 (1.10) | 4 (4.40) | 5 (5.49) |
| 2 | 3 (3.30) | 10 (10.99) | 13 (14.29) |
| 3 | 6 (6.59) | 7 (7.69) | 13 (14.29) |
| 4 | 3 (3.30) | 3 (3.30) | 6 (6.59) |
| 5 | 6 (6.59) | - | 6 (6.59) |
| 6 | 1 (1.10) | 2 (2.20) | 3 (3.30) |
| **Cirrhosis** | 10 (10.99) | 9 (9.89) | 16 (17.58) |
| **Previous Treatment(s)** | | | |
| Naive | 14 (15.38) | 29 (31.87) | 43 (47.25) |
| IFN+RBV | 35 (38.46) | 9 (9.89) | 44 (48.35) |
| TVR+BOC | 4 (4.40) | - | 4 (4.40) |
| **HCV-RNA** | | | |
| Mean, log10 IU/mL | 5.69 | 5.68 | |
| ≥5 log10 IU/ml (%) | 44 (83%) | 27 (71%) | 71(78%) |
| Viral load (IU/ml) | 1797026 ± 3725150 | 1767124 ± 2957085 | 1784540 ± 3425458 |

PrOD: Paritaprevir, Ritonavir, Ombitasvir, Dasabuvir; LDV: Ledipasvir; SOF: Sofosbuvir; HCV: Hepatitis C Virus; RNA: Ribonucleic Acid; IFN: Pegile-Interferon; RBV: Ribavirin, TVR: Telaprevir; BOC: Boceprevir; ml: Milliliter; IU: International Unit; L: Liter; n: Number of Patients

**Table 2. Demographic and Clinical Characteristics (%)**

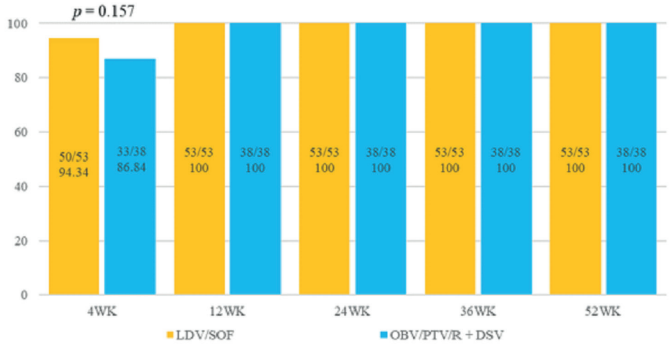
| | 1st Group (LDV+SOF) | | | 2nd Group (OBV/PTV/R + DSV) | | |
|---|---|---|---|---|---|---|
| | d0 | 24WK | p value | d0 | 12WK | p value |
| **ALT** | 54 | 20 | **0.000** | 49 | 14 | **0.000** |
| **AST** | 57 | 25 | **0.000** | 43 | 17 | **0.000** |
| **WBC** | 6103 | 6967 | **0.040** | 6455 | 6749 | 0.459 |
| **HB** | 13 | 13 | 0.245 | 13.1 | 12.9 | **0.044** |
| **PLT** | 186 | 210 | **0.027** | 206 | 213 | 0.281 |
| **URE** | 35 | 39 | **0.037** | 36 | 37 | 0.217 |
| **CRE** | 0.88 | 0.78 | 0.906 | 1 | 1 | 0.866 |
| **BIL** | 0.72 | 0.63 | 0.170 | 0.61 | 0.54 | 0.091 |
| **ALB** | 4 | 4 | 0.882 | 4 | 4 | 0.312 |
| **PT** | 12 | 12 | 0.210 | 12 | 11 | **0.049** |
| **INR** | 1 | 1 | 0.134 | 1 | 1 | 0.122 |

Statistically significantp values (<0,005) are in bold.
PrOD: Paritaprevir, Ritonavir, Ombitasvir, Dasabuvir; SOF: Sofosbuvir, LDV: Ledipasvir, d0: The beginning of treatment (baseline), ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, WBC: White Blood Cell (total leukocyte), HB: Hemoglobin, PLT: Platelets Count, URE: Urea, CRE: Creatinine, BIL: Bilirubin, ALB: Albumin, PT: Prothrombin Time, INR: International Normalized Ratio, n: number of patients, WK: Week

The overall age of the patients ranged between 20 and 86. The number of the females patients were 28 and 27, and the number of the male patients were 25 and 11, in both groups respectively. 3 patients were infected by HCV genotype 1a and 88 of them were infected by HCV genotype 1b. 43 patients were treatment naïve and 48 patients were previously treated with Pegile-Interferon+Ribavirin (IFN+RBV) or Telaprevir+Boceprevir (TVR+BOC). Liver biopsises revealed that 22 patients had none or minimal fibrosis (Ishak F0, 1, 2), portal fibrosis was found (Ishak F3) on 13 patients, bridging fibrosis (Ishak F4) was found on 6 patients and 10 patients had cirrhosis (Ishak F5,6). Mean baseline HCV RNA values of the groups were 5.69 log IU/mL and 5,68 log IU/m, respectively.

Data on the laboratory parameters measured at the start and the end of the treatment are summarized in Table 2. ALT and AST values were significantly decreased in the both group (p = 0.000 for both). Increase in PLT (p= 0.027), URE (p = 0.037) and WBC (p = 0.040) in the first group and decrease in HB ( p=0.044) and PT ( p=0.049 ) in the second group were found to be statistically significant.

The rates of SVR for the both groups are presented in Figure 1. Following the four treatment weeks, HCV RNA levels were not detectable for 50 (94.34%) of 53 patients in the first group (LDV/SOF) and for 33 (86.84%) of 38 patients in the second group (PrOD). Virological suppression was accomplished for all patients in all groups at the end of 12 weeks of treatment including patients with cirrhosis.




PrOD: Paritaprevir, Ritonavir, Ombitasvir, Dasabuvir; LDV: Ledipasvir; RBV: Ribavirin; n: number of patients, WK; week

**Figure 1.** Rates of SVR

Cases on the adverse events are presented in Table 3. The adverse events were moderate or mild in severity. None of the patients experienced any serious adverse event leading to discontinuation of the treatment. 76 patients did not experience any adverse events, while 25 patients experienced at least one adverse event during the study. The patients experienced pruritus (5.5%), weakness (13.2%), myalgia (1.1%), dry mouth (1.1%), nausea (5.5%) and insomnia (1.1%).

**Table 3. Adverse Events (%)**

| Characteristic | 1st Group (LDV/SOF) | 2nd Group (PrOD) | Total | p value |
|---|---|---|---|---|
| None | 46 (1.09) | 30 (32.96) | 76 (83.52) | 0.497 |
| Weakness | 6 (6.59) | 6 (6.59) | 12 (13.19) | 0.534 |
| Pruritus | 3 (3.29) | 2 (2.19) | 5 (5.49) | 0.935 |
| Myalgia | 1 (1.09) | - | 1 (1.09) | 0.395 |
| Nausea | 1 (1.09) | 4 (4.39) | 5 (5.49 | 0.074 |
| Dry Mouth | 1 (1.09) | - | 1 (1.09) | 0.395 |
| Insomnia | - | 1 (1.09) | 1 (1.09) | 0.235 |

**Statistically significantp values (<0,005) are in bold.**
**PrOD: Paritaprevir, Ritonavir, Ombitasvir, Dasabuvir;SOF: Sofosbuvir; LDV: Ledipasvir; RBV: Ribavirin; n: number of patients**

## DISCUSSION

The global prevalence of HCV ranges between 0.5% (South-East Asia Region) and 2.3% (Eastern Mediterranean Region) with an overall prevalence rate of 1% (1). The World Health Assembly's goal is to eliminate viral hepatitis through reduction 90% in incidence and 65% in mortality (11). Substantial breakthroughs have significantly increased the effectiveness of treatment for patients chronically infected with HCV after the introduction of DAAs in 2011. The treatment of patients chronically infected with HCV through DAAs has been proved to be superior to interferon-free treatments in both efficacy and safety.

The aim of our study was to assess and compare the efficacy and safety of the treatment with a fixed dose of LDV/SOF during 24 weeks of treatment period and the treatment with a fixed dose of PrOD during 12 weeks of treatment period. The SVR rates and the adverse events of the patients in the two groups received two distinct therapies. The results of our analysis indicated that HCV-RNA was negative after 12 weeks of the onset of the treatment among all patients in the both groups. SVR12 rates of 100% were achieved for the both regimens. The results concluded that treatment with a fixed-dose combination of LDV/SOF during 24 weeks and the treatment with a fixed-dose combination of PrOD during

12 weeks are highly effective and well-tolerated in the treatment of the patients chronically infected with HCV.

Significantly high SVR rates up to 99% were achieved in different phase studies with different protocols and patient groups treated with DAAs (6,12-18). The results of our study are consistent with, and complement, the recent real-world and clinical studies confirming that LDV/SOF (19-21) and PrOD (22-25) are well tolerated and effective in patients chronically infected with HCV. A review study on the treatment of chronic HCV infection with OBV/PTV/R+DSV covering the time period between 1996 and 2015 showed that SVR12 rates for non-cirrhotic patients with genotype 1b changed between 96-100%, regardless of inclusion of ribavirin (26). Another review study of Phase 1, 2, and 3 studies on the treatment of chronic HCV infection with LDV/SOF covering the time period between 1966 and 2014 demonstrated that SVR rates changed between 94-99% (27). Ormeci N et al. found the SVR rate of 97.93% in their retrospective study (28). The SVR ratio in our study is similar to the results from other studies.

The success of the treatment with interferon-based regimens can be influenced by the different factors, including cirrhosis, body mass index, sex, age, response to previous treatments and HCV-RNA levels. Both treatment regiments in our study were successful for all patients with cirrhosis and with high viral load (≥5 log IU/mL).

Treatment experienced patients are generally excluded from registration studies or assessed in distinct studies. 53% of patients in our study were treatment experienced. Of overall treatment experienced patients, 92% of them were previously treated with IFN+RBV and 8% of them were previously treated with TVR+BOC. The overall SVR rates of our study were not influenced by the inclusion of the previously treated patients. It was also concluded that there was no difference between the treatment-naïve and treatment experienced patients, in terms of response to the treatment.

Introduction of DAAs has led to discontinuation of interferon-based treatments due to the highly effective results and the negligible adverse effects. No serious adverse effect leading to the discontinuation of the treatment was reported in any of the patients in our study. Both of the treatment regimens compared in our study were found to be well tolerated and safe. Adverse effects experienced by the patients in our study were pruritus, weakness, myalgia, dry mouth, nausea and insomnia. Similar side effects have been reported in other studies as well.

While the introductory outcomes of DAA combinations indicate enhanced efficacy, diminished resistance and improved safety, the progress of new types of DAA and second generation protease inhibitors, currently in the clinical experimental phase promise far reaching success to eradicate HCV globally. Despite this entire high SVR rate, there is a small group of patients who are unresponsive to the treatment. The most important reason for non-responsiveness to treatment with DAAs is resistance-associated variant of HCV against drugs. Drug-specific resistance-associated variants are seen in approximately 15% of viruses and they reduce the SVR rate (29). Thus, the drug resistance of DAA is a complex and unavoidable problem, which may result in bad response to antiviral therapy and relapse in HCV infected patients. Cabalak M et al. in their study demonstrated that the overall treatment failure rate was 2.9% (5/172), all of whom relapsed (30). For the purpose of decreasing frequency of resistance-associated variants, it is useful and common to select different classes of DAAs for combined treatment. And it is still important to correctly determine the HCV genotype and subtype, as well to detect pre-existing resistance-associated variants in a sequence, in order to guide selection of most appropriate antiviral regimen (31). The limitations of our study are the small sample size and non-equally randomized groups in a single-center. Further studies can be conducted with greater sample size with equally randomized groups from multi-centers.

## CONCLUSION

In conclusion, the both oral DAA treatments including a fixed-dose combination of LDV/SOF during 24 weeks and a fixed-dose combination of PrOD during 12 weeks were associated with 100% SVRs at post-treatment period in patients chronically infected with HCV with or without cirrhosis.

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