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RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

The efficacy of new treatment methods in HCV patients: a single center study

HCV hastalarında yeni tedavi yöntemlerinin etkinliği: tek merkezli bir çalışma

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ABSTRACT

Aim: Achieving sustained virologic response (SVR) is critical in patients with chronic hepatitis C virus (HCV) infection. Over the last few years, many developments have been made in HCV infection treatment with the evaluation of direct-actinga antivirals (DAAs). Treatment with DAAs resulted in high rates of SVR among patients with chronic HCV infection. The aim of our study aim to compare the treatment efficacy between different DAA regimens in patients with HCV.

Methods: In our study 290 patients were evaluated retrospectively with regard to the effects related to the use of DAAs and its effects on HCV-RNA. The primary end point was a SVR at 12 weeks after the end of the DAA therapy.

Results: In our study included 290 patients who were treated with DAA. The rate of SVR was 99% (98%; 95

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confidence interval [CI], 96 to 100) with 12 weeks of ledipasvir plus sofosbuvir (LDV+SOF), 96% (97.9%; 95% CI, 94 to 99) with 12 weeks of sofosbuvir plus ribavirin (SOF+RBV), and 90% (98.9%; 95% CI, 95 to 99) with 12 weeks of ombitasvir/paritaprevir/ritonavir plus dasabuvir (PrOD). In comparing LDV+SOF, SOF+RBV and PrOD, the chance of having SVR between these three DAA regimens was not significantly different.

Conclusion: DAA treatment regimens should be preferred in the first line drug for the treatment of chronic HCV infection because of the their significant clinical benefits.

Key words: Chronic Hepatitis C, direct-acting antiviral, sustained virologic response.

ÖZET

Amaç: Sürekli virolojik yanıtın (SVR) elde edilmesi, kronik hepatit C virüsü (HCV) enfeksiyonu olan hastalarda kritik öneme sahiptir. Geçtiğimiz birkaç yıl boyunca, HCV enfeksiyonu tedavisinde, direkt etkili antivirallerin (DAA) değerlendirilmesi ile birçok gelişme kaydedilmiştir. DAA' lar ile tedavi, kronik HCV enfeksiyonu olan hastalarda yüksek oranda SVR ile sonuçlandı. Çalışmamızın amacı, HCV' li hastalarda farklı DAA rejimleri arasındaki tedavi etkinliğini karşılaştırmaktır.

Yöntem: Çalışmamızda, 290 hasta DAA kullanımı ve HCV-RNA üzerindeki etkileri ile ilgili retrospektif olarak değerlendirildi. Birincil sonlanım noktası, DAA tedavisinin bitiminden 12 hafta sonraki SVR idi.

Bulgular: Çalışmamıza DAA ile tedavi edilen 290 hasta alındı. 12 hafta boyunca ledipasvir + sofosbuvir (LDV + SOF) ile SVR oranı %99 (%98; 95 güven aralığı [CI], 96-100), sofosbuvir + ribavirin (SOF + RBV) ile %96 (%97.9; %95 CI, 94-99), ve ombitasvir / paritaprevir / ritonavir + dasabuvir (PrOD) ile %90 (%98.9; %95 CI, 95-99) SVR oranı %99 idi. LDV + SOF, SOF + RBV ve PrOD' un karşılaştırılmasında, bu üç DAA rejimi arasında SVR elde etme şansı önemli ölçüde farklı değildi.

Sonuç: Kronik HCV enfeksiyonunun birinci basamak tedavisinde önemli klinik yararları nedeniyle DAA tedavi rejimleri tercih edilmelidir.

Anahtar kelimeler: Kronik Hepatit C, direkt etkili antiviral, sürekli virolojik yanıt.

INTRODUCTION:

The World Health Organization(WHO) have estimated the national and global rates of chronic hepatitis C virus (HCV) infection to be approximately 185 million people and also 360 000 people die each year from HCV related liver complications.[1, 2]. Chronic HCV is a major cause of cirrhosis, hepatocellular carcinoma and end-stage liver disease that require liver transplantation. Therefore, early diagnosis and initial treatment are very important to improve long-term health outcomes in patients with chronic HCV.[1] HCV shows high genetic heterogeneity, and it is classified into six major genotypes. Specifically, genotypes 1, 2, and 3 are found worldwide, with subtype 1a is predominant in the USA and subtype 1b is predominant in Europe, China and Japan. The response to treatment of each genotype varies, genotype 1 is most difficult to treat.[3, 4]

To reduce associated mortality and improve health-related quality of life for HCV patients, achievement of sustained virological response (SVR) is a surrogate endpoint for these goals.[5, 6] For the traditional treatment of chronic HCV, peginterferon alfa plus ribavirin (pegIFN/RBV) has been used. However, pegIFN/RBV achievement is limited and only has SVR rates of 40%-50% and is associated with lots of adverse events (Aes).[7, 8]

HCV infections treatment has significantly improved in the past few years with the development of direct-acting antiviral agents (DAAs). These new DAAs can be combined with or without pegIFN/RBV and could improve the SVR compared to pegIFN/RBV alone.[9] To the best our knowledge there were no evidence from randomized controlled trials that compare directly the different DAAs regimens and pegIFN/RBV. Therefore, our study was aimed to compare the clinical outcomes and efficacy of three new DAAs such as sofosbuvir plus ribavirin (SOF+RBV), ledipasvir plus sofosbuvir (LDV+SOF) and ombitasvir/paritaprevir/ritonavir plus dasabuvir (PrOD) in patients with HCV infection.

METHODS

Patients

In this study, 290 patients were evaluated retrospectively with regard to the effects related to the use of DAAs and its effects on HCV-RNA. The treatment results were collected and evaluated in our Internal Medicine and Gastroenterology Department between June 2018 and December 2018.

Patients eligible for our study were 18 years of age and above with different genotypes of HCV infection with or without cirrhosis, treatment-experienced or naive, were retrospectively followed and treated with LDV+SOF, SOF+RBV, and PrOD for 12 weeks. In patients with chronic HCV, cirrhosis was defined as a liver-biopsy specimen revealing evidence of cirrhosis (Metavir stage F4 [on a scale of F0 to F4, with higher stages indicating a greater degree of fibrosis] or Ishak score of 5 or 6 [on a scale of 0 to 6, with higher scores indicating a greater degree of fibrosis]).

Our exclusion criteria were: suspected or documented hepatocellular carcinoma and other solid organ or hematologic malignancies, decompensated liver cirrhosis (including a history of hepatic encephalopathy, ascites, or bleeding varices), human immunodeficiency virus coinfection, severe chronic kidney disease.

Study Design

This retrospectively study included 290 individuals with 3 different treatment regimens; LDV+SOF for 12 weeks, SOF+RBV for 12 weeks and PrOD for 12 weeks according to the therapeutic protocol. The patients were stratified according to genotype, naive or response to previous treatment and presence or absence of cirrhosis.

Subjects included in the study were grouped as:

Group 1: The patients who received LDV+SOF regimen. These patients were taken a combination tablet containing 90 mg of ledipasvir and 400 mg of sofosbuvir, administered orally once daily.

Group 2: The patients who received SOF+RBV regimen. These patients were taken 400 mg of sofosbuvir administered orally once daily along with ribavirin administered orally twice daily, with doses determined according to body weight (1000 mg daily in patients with a body weight of <75 kg, and 1200 mg daily in patients with a body weight of ≥75 kg). The dose of ribavirin could be decreased or discontinued according to the product label to manage hemoglobin reductions.

Group 3: The patients who received PrOD regimen. These regimen contains paritaprevir 75 mg boosted with ritonavir 50 mg and ombitasvir 12.5 mg 2 tablets in a single daily dose, and dasabuvir twice-daily administration.

Study Assessments

In the screening assessments, the serum HCV RNA level of all the patients was measured, in addition to other clinical tests and standard laboratory. The serum HCV RNA level of all patients was measured with the use of the COBAS TaqMan HCV Test, version 2.0, Roche Molecular Systems, which has a lower limit of quantification of 25 IU per milliliter. Versant HCV Genotype INNO-LiPA 2.0 assay (Siemens Healthcare Diagnostics) was used to determine the HCV genotype and subtype.

Standard laboratory testing, serum HCV RNA level measurement, vital signs, electrocardiography, and physical examinations were made during the treatment assessments

End Points

The primary efficacy end point was the rate of SVR, defined as the absence of HCV-RNA in serum (<25 IU per milliliter), at 12 weeks after the end of DAAs treatment among all the patients with chronic HCV who received treatment. The rate of SVR in each of the three DAAs treatment groups was compared in the primary efficacy analysis.

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Study Oversight

The study was conducted according to the recommendations of the Declaration of Helsinki, Good Clinical Practice guidelines, about biomedical research involving human subjects and the protocol was approved by the institutional ethics committee. Our study was firstly designed according to the protocol by the academic investigators and then conducted. These investigators collected the data and performed the statistical analyses. All the authors of our study had access to the data and assume responsibility for the integrity and completeness of the all reported data. All the authors affirm that the study was conducted with fidelity to the protocol. The manuscript was written by the first and second author with input from all coauthors.

Statistical Analysis

All analyses were performed with SPSS 20.0 (Chicago, IL, USA) statistical software package. The variables were divided into two groups as categorical and continuous variables. The normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. The continuous variables in the group were expressed as mean ± standard deviation while categorical variables are given in numbers and percentages. Continuous variables that showed normal distribution were compared using the Student t-test and ANOVA, whereas the Mann-Whitney U test and Kruskal-Wallis test were used for non normally distributed samples. The statistical details between the groups are indicated on the tables. Chi-square ($\chi 2$) test was used to compare categorical variables. The efficacy analysis examined data concerning the total patient population. A p value less than 0.05 was considered statistically significant.

RESULTS

Our study data were compared by dividing the patients in 3 different treatment groups as LDV+SOF, SOF+RBV, and PrOD.

Clinical, demographic and laboratory findings of the study groups

Of the 428 patients who were initially screened, 290 patients received treatment. There were 50 females and 61 males in the group 1 who received LDV+SOF regimen, 43 females and 45 males in the group 2 who received SOF+RBV regimen, whereas there were 41 females and 50 males in the group 3 who received PrOD regimen. Follow-up data at post-treatment week 4 and week 12 were available for 290 patient. Most of the patients were male. The baseline and demographic data and

clinical characteristics of the eligible patients were generally balanced among the three treatment groups except for treatment experienced patient, HCV genotypes and cirrhosis (Table 1a-b).

Treatment experienced patient was common in group 1. Genotype 1a and 1b were common in group 1 and 3 except for group 2 where genotype 2 and 3 were the most common instead (Table 1a-b). The prevalence of cirrhosis was found to be 31%, 5.1%, 6.5% in patients with group 1, 2 and 3, respectively. There is no statistically significant difference was detected in laboratory values. There were 32 patient with diabetes mellitus in group 1, whereas there were 10 and 12 patient with diabetes mellitus in group 2 and 3, respectively (Table 1a-b).

Efficacy

The criterion for the primary end point was met in all three treatment groups, with rates of SVR that were superior to the adjusted historical control rate of 60% (P<0.001 for all comparisons). The rates of SVR 12 weeks after the end of treatment were as follows: among 101 patients who was taken 12 weeks of LDV+SOF, 99 had a SVR (98%; 95% confidence interval [CI], 96 to 100); among 98 who was taken 12 weeks of SOF+RBV, 96 had a SVR (97.9%; 95% CI, 94 to 99); among 91 who was taken 12 weeks of PrOD, 90 had a SVR (98.9%; 95% CI, 95 to 99) (Table 2).

Overall at the end of treatment, 5 of the 290 patients (1%) had a no virologic response: 1 of 101 patients (1%) in the group 1, 2 of 98 (2%) in the group 2 and 1 of 91 patients (1%) in the group 3, whereas the patient with virologic breakthrough did not.

DISCUSSION

This study evaluated the effectiveness of second generation DAAs such as LDV+SOF, SOF+RBV and PrOD in HCV infected patients with or without cirrhosis, no significant alteration was observed in sustained virologic response. This trial showed that a 12-week regimen of second generation DAAs, constitutes effective treatment for patients who have HCV similar to COSMOS, OPTIMIS and ALLY clinical trials real-life studies.[10-12]

In the literature, there are previous systematic review articles that recommended DAA plus pegIFN/RBV regimens.[13, 14] However, the prior studies about the HCV treatment did not apply network meta-analysis in order to address the efficacy between the different DAA plus pegIFN/RBV regimens and pegIFN/RBV alone. Therefore, our study did not compare HCV treatment regimens with or without pegIFN/RBV. The response rates to interferon-based therapy, including protease-inhibitor–containing therapies, have been low in patients with cirrhosis.[15-20] The

low rates of response among patients with cirrhosis reflect both an unidentified effect of cirrhosis on responsiveness to treatment and an increased risk of interferon-related side effects.[21]

In the literature, previous studies suggested that the first generation of DAA (i.e. telaprevir, boceprevir) could improve the chance of having SVR in treatment-naive HCV. However, both boceprevir and telaprevir significantly increased the risk of adverse drug events (e.g. rash and anemia) and have an issue of pill burden.[22] The bocepravir and telaprevir treatments are no longer recommended as the first choice in the guidelines. For that reasons, the first generation DAA was not included in our study.

In the study of Welzel et al.[23] with 1017 patients, patients with genotype 1 and 4 were included. In this study ombitasvir/paritaprevir/ritonavir (OBV/PTV/r)±dasabuvir (DSV)±ribavirin (RBV) regimen was evaluated. In this study, it was found that SVR 12 was 96% in genotype 1 and 100% in genotype 4. We found in our study that SVR 12 was 98.9%. In the study conducted by Welzel et al., 1.5% of patients quited medications because of side effects but in our study, there were no patients that discontinued treatment.

In the study conducted by Deterding et al.[24] patients with genotype 1 were given 6 weeks LDV and SFV treatment. 22 patients were included in this study and SVR 12 was 100%. No side effects were seen in any of the patients. As a result of this study, 6 weeks of LDV+SFV treatment was found to be effective. Also, similar results were found in our study. In our study, SVR 12 was found to be 99% and no side effects were observed.

Feld et al.[25] evaluated ombitasvir / paritaprevir / ritonavir (OBV / PTV / r) ± dasabuvir (DSV) ± ribavirin (RBV) in patients with genotype 1 infection who had not received prior treatment and had no cirrhosis. 12 weeks of treatment was given and SVR was determined as 96.2%. Patients with no virologic response rate in patients infected with genotype 1a was 0.2% and genotype 1b was 1.5%. In our study, patients with no virologic response was 1%.

In our country, there is not enough study with DAAs. In a study conducted by Bayan K et al.[26] (OBV / PTV / r) ± dasabuvir (DSV) ± ribavirin (RBV) treatment was evaluated in 57 patients. 80.7% of the patients were genotype 1b. In our study, 72.5% of patients receiving (OBV/PTV/r)±dasabuvir (DSV)±ribavirin (RBV) treatment was genotype 1 b. In the study performed Bayan K et al., SVR 12 was 100% and the rate of discontinuation of medication was 1.7% but in our study, SVR 12 was found to be 99% and no patient discontinued treatment.

CONCLUSION

In our study, there was no discontinuation of treatment due to reasons such as side effects and we found that the rates of sustained virologic response in all three treatment groups were 94% or higher in the groups treated for 12 weeks. Our single center study showed that 12 weeks of the LDV+SOF, SOF+RBV, PrOD were a highly effective treatment for patients with chronic HCV infection with a different genotype. The duration of treatment was not seen the need to extend to 24 weeks.

Conflicts of Interest: There is no conflict of interest.

Table 1a. Comparison of general characteristics.

Characteristic	**LDV+SOF (n: 101)**	**SOF+RBV (n: 98)**	**PrOD (n:91)**	**p Value**
Age (mean±SD)	64.3±12.7	62.5± 12.3	60±15.3	**<0.01**
Female, n, (%)	50 (49.5)	43 (43.8)	41 (45)	.085
Treatment experienced, n, (%)	51 (50.5)	8 (8.2)	8 (8.8)	**0.01**
Comorbidities, n, (%)	34 (33.6)	14 (14.2)	13 (14.2)	**<0.01**
Diabetes mellitus	32(31.6)	10 (10.2)	12 (13)	**<0.01**
CAD	2 (2)	4 (4)	1 (1)	.12
Hb (g/dl±SD)	12.65±1.8	13.13± 1.31	11.33±1.53	0.260
AST (U/l±SD)	98.25±50.2	95.75±69.7	101.5±75.2	.95
ALT (U/l±SD)	95.0±46.0	86.5±69.1	98.6±69.2	.45
Platelets (1000/мl±SD)	145.24±8.2	142.75±4.5	148.62±2.6	.98
Albumin, g/dL (mean±SD)	4.02±0.8	4.01±0.6	4.05±0.4	.94
Total bilirubin, mg/dL (mean±SD)	1.08±0.42	1.05±0.6	1.2±0.4	.38

INR (mean±SD)	1.17±0.24	1.12±0.5	1.18±0.32	.15
HCV-RNA log10 IU/mL, mean±SD	6.21±0.62	6.23±0.54	6.25±0.70	.697

p <0.05, Statistically Significant

Table 1b. Comparison of general characteristics.

Characteristic	**LDV+SOF (n: 101)**	**SOF+RBV (n: 98)**	**PrOD (n:91)**	**p Value**
HCV Genotype:				
Genotype 1	1 (1)	0 (0)	2 (2.2)	.32
Genotype 1a	5 (5)	0 (0)	16 (17.6)	**<0.01**
Genotype 1b	86 (85.1)	0 (0)	66 (72.5)	**<0.01**
Genotype 2	0 (0)	25 (25.5)	0 (0)	**<0.01**
Genotype 2b	0 (0)	1 (1)	0 (0)	.37
Genotype 2c	0 (0)	1 (1)	0 (0)	.37
Genotype 3	0 (0)	65 (66.3)	0 (0)	**<0.01**
Genotype 3a	0 (0)	2 (2)	0 (0)	.13
Genotype 4	4 (4)	0 (0)	5 (5.5)	.07
Genotype 5a	1 (1)	0 (0)	0 (0)	.39
Genotype 2_3	0 (0)	4 (4.1)	0 (0)	.01
Genotype 2_4	1 (1)	0 (0)	0 (0)	.39
Genotype 3_4	2 (2)	0 (0)	0 (0)	.15
Genotype 1b_4	0 (0)	0 (0)	2 (2.2)	.11
Genotype 1a_2b	1 (1)	0 (0)	0 (0)	.39
Cirrhosis (%)	31 (31)	5 (5.1)	6 (6.5)	**<0.01**
HAI, mean±SD	8.93±2.97	7.02±2.30	7.39±2.61	**<0.01**
Fibrosis. mean±SD	3.29±1.41	1.97±0.89	2.25±0.97	**<0.01**

p <0.05, Statistically Significant

Table 1a-b. LDV+SOF: Ledipasvir Plus Sofosbuvir, SOF+RBV: Sofosbuvir Plus Ribavirin, PrOD: Ombitasvir/Paritaprevir/Ritonavir Plus Dasabuvir, CAD: Coronary Artery Disease, Hb: Hemoglobin, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, INR: International Normalized Ratio, HAI: Histological Activity Index.

Table 2. Response after 4- and 12-week treatment.

Response	**LDV+SOF (n: 101)**	**SOF+RBV (n: 98)**	**PrOD (n:91)**
HCV-RNA<25 IU/ml			
At 4 week At 12 week	95 (94) 99 (98)	94 (95.9) 96 (97.9)	88 (96.7) 90 (98.9)
Virologic breakthrough during treatment regimen	0	0	0
Patients with no virologic response	2(1)	2 (2)	1 (1)

LDV+SOF: Ledipasvir plus sofosbuvir, SOF+RBV: sofosbuvir plus ribavirin, PrOD: ombitasvir/paritaprevir/ritonavir plus dasabuvir.

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