



Effects of 12-week treatment with Sovodak in patients infected by genotype 1 hepatitis C virus

Hosein Mehdipour¹ , Yaghoob Moaddab¹, Khalil Azizian², Morteza Ghojzadeh³, Mohammad Hossein Somi^{*1} 

¹ Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

² Department of Medical Microbiology, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

³ Research Development and Coordination Center, Tabriz University of Medical Sciences, Tabriz, Iran

Article info

Article History:

Received: 30 Dec. 2018

Accepted: 19 Jan. 2019

ePublished: 10 Mar. 2019

Keywords:

Sofosbuvir,
Daclatasvir,
Hepatitis C Virus,
Safety

Abstract

Introduction: It has been shown that the combination therapy of Sofosbuvir-Daclatasvir (Sof/Dac) has a high rate of success in the treatment of patients. For the first time, a single pill of Sof/Dac has been formulated in Iran (Sovodak). In this regard, the present study was carried out aiming to investigate the safety and efficacy of Sovodak for 12 weeks during treatment of patients infected by genotype 1 hepatitis C virus (HCV).

Methods: In this study, 50 patients (25 and 25 treatment-naïve and treatment-experienced patients, respectively) infected by HCV genotype 1 received Sovodak (1pill per day) for 12 weeks. Ribavirin was added for patients who had definitive evidence of liver cirrhosis. The sustained virological response (SVR12) was investigated 12 weeks after the end of the therapy.

Results: All 50 patients completed the treatment period. The mean age of patients was 54.40 ± 11.69 years, in addition, 60% and 90% of the patients were male and infected by HCV genotype 1b, respectively. After 4 and 12 weeks of treatment with Sovodak, the HCV ribonucleic acid (RNA) titer was undetectable in 82% and 100% of the patients, respectively and 100% of them achieved SVR12. None of the subjects reported treatment discontinuation because of adverse events, however, 3 patients reported transient side effects including foot swelling, headache, and vomiting.

Conclusion: The results of this study showed that once-daily Sovodak single-pill for 12 weeks is an effective and safe medicine for treating patients infected by HCV genotype 1.

Citation: Mehdipour H, Moaddab Y, Azizian K, Ghojzadeh M, Somi MH. **Effects of 12-week treatment with Sovodak in patients infected by genotype 1 hepatitis C virus.** J Anal Res Clin Med 2019; 7(1): 1-6. Doi: 10.15171/jarcm.2019.001

Introduction

Hepatitis C virus (HCV) infection is one of the crucial hepatic infections worldwide, especially in developing countries. The last estimates indicated that around 185 million people are infected by HCV, and it is the cause of 54000 deaths per years.¹ If left untreated, it can lead to serious health complications including liver cirrhosis and hepatocellular carcinoma (HCC).²

The HCV has seven genotypes^{3,4} among which the genotype 1 (G1) is the most common (around 46%) and the most difficult

genotype to treat.^{5,6} Previously, interferon (IFN)-based HCV therapies were used for the treatment of patients with HCV, however, this regimen offered only 40% cure for HCV-G1 and was accompanied by several side effects such as depression, cytopenia, fatigue, hemolytic anemia, and rash.⁷

Nowadays, the direct-acting antiviral (DAA) drugs are used for HCV treatment. Sofosbuvir is one of the most popular DAAs which is administrated for 12 or 24 weeks depending on a patient's condition.⁶ In the Sofosbuvir-based regimens, Sofosbuvir is

* Corresponding Author: Mohammad Hossein Somi, Email: mhosseinsina@yahoo.com



used along with other DAA drugs such as Ribavirin, Ledipasvir, or Daclatasvir. Daclatasvir has a high broad activity against HCV genotypes. The combination therapy of Sofosbuvir-Daclatasvir (Sof/Dac) has been shown to have a high rate of success in the treatment of patients with HCV genotype 1.⁸⁻¹⁰ Recently, for the first time, a single pill of Sof/Dac has been formulated in Iran and its efficacy has been examined in a study among patients with HCV G1 and G3 and cirrhosis. In the present study, the aim was to investigate the safety and efficacy of Sovodak regimen in patients who were diagnosed with HCV genotype 1 infection.

Methods

Patients: In the present multicenter, prospective, open-label study, 58 patients with positive HCV ribonucleic acid (RNA) titer were recruited from the gastroenterology and liver clinics affiliated to Tabriz University of Medical Sciences, Tabriz, Iran. Patients who were co-infected with human immunodeficiency viruses (HIV) or hepatitis B virus (HBV), had recent liver transplantation, pregnant women, and those who had no interest to use of Sovodak pill were excluded from the study. Finally, 50 patients were included and among whom, 25 patients were treatment-naïve (group A) and 25 were treatment-experienced undergoing previous failed treatment by IFN and ribavirin (group B). The informed consent was obtained from the participants. The study protocol was approved by the ethical committee of Tabriz University of Medical Sciences (IR.TBZMED.AC.IR.1395.871).

Medication: The Sovodak (Abidi Pharmaceuticals, Tehran, Iran), including Sofosbuvir 400 mg and Daclatasvir 60 mg, was administered orally for 12 weeks. Moreover, ribavirin was prescribed for 12 weeks for patients who had definitive evidence of liver cirrhosis such as increased international normalized ratio (INR), thrombocytopenia, esophageal varices, or other symptoms of portal hypertension (1000 and 1200 mg for patients with a body weight of < 75 and > 75 kg, respectively).

Efficacy assessment and safety monitoring:

HCV RNA levels were measured 4 weeks and 12 weeks after initiation of the intervention and also 12 weeks after cessation of the treatment. HCV RNA levels were investigated by real-time HCV assay (Roche Molecular Systems) with a lower limit of quantitation of 25 IU/ml and a lower limit of detection of 20 IU/ml. HCV RNA levels for the sustained virological response (SVR) were collected and analyzed 12 weeks after the end of the treatment. All side effects after Sovodak administration were followed and recorded. Laboratory tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, prothrombin time (PT), INR, platelet, hemoglobin (Hb), white blood cells (WBCs), creatinine, albumin (ALB), and blood urea nitrogen (BUN) were performed by the standard methods before treatment, 4 and 12 weeks after initiation of the treatment, and 12 weeks after cessation of the treatment.

Data were analyzed using SPSS software (version 19.0, SPSS Inc., Chicago, IL, USA). In addition, the normal distribution of data was checked using the Kolmogorov-Smirnov (K-S) test. The quantitative and qualitative data were presented as mean \pm standard deviation (SD) and rate (%), respectively. The differences between treatment-naïve and previously treated patients were analyzed using the chi-square test and Fisher's exact test (for qualitative data) and independent samples t-test and paired samples t-test (for quantitative data). The P value < 0.05 was considered as statistically significant.

Results

Demographic and baseline characteristics of patients are presented in table 1. The mean age of patients was 54.40 ± 11.69 years, and 60% of patients were male. Moreover, 90% and 10% of the subjects were infected with HCV G1b and HCV G1a, respectively. There were no statistically significant differences in baseline characteristics between the two groups (P < 0.05).

Table 1. Demographic and baseline characteristics of patients

Variable		Group A (n = 25)	Group B (n = 25)	Total	P
Age (years) (mean ± SD)		53.08 ± 13.30	55.72 ± 9.94	54.40 ± 11.69	0.430
Male [n (%)]		17 (56.7)	13 (43.3)	30 (60.0)	0.240
Female [n (%)]		8 (40.0)	12 (60.0)	20 (40.0)	
Genotype [n (%)]					
1a		3 (60.0)	2 (40.0)	5 (10.0)	-
1b		22 (48.9)	23 (51.1)	45 (90.0)	
Background diseases [n (%)]	Yes	15 (53.6)	13 (46.4)	28 (56.0)	0.560
	No	10 (45.5)	12 (54.5)	22 (44.0)	
Cirrhosis [n (%)]	Yes	13 (52.0)	12 (48.0)	25 (50.0)	0.610
	No	12 (48.0)	13 (52.0)	25 (50.0)	

Totally, 56% of patients had background diseases including leprosy (n = 10), diabetes mellitus (DM) (n = 9), end-stage renal disease (ESRD) (n = 4), ischemic heart disease (IHD) (n = 1), chronic obstructive pulmonary disease (COPD) (n = 1), systemic lupus erythematosus (SLE) (n = 1), and hyperlipidemia (n = 1). Of 50 patients, 2 patients had renal transplantation. Moreover, 12 and 13 patients respectively in treatment-naïve group and treatment-experienced group had definitive evidence of liver cirrhosis and received ribavirin in addition to Sovodak. There were no statistically significant differences between the two groups regarding background diseases and cirrhosis.

Treatment Efficacy: Significant reduction in HCV RNA level was observed in all patients treated by Sovodak. At week 4, HCV RNA titer rapid virological response (RVR) in 41 (82%) patients was undetectable or less than 25 IU/ml. After 12 weeks of treatment using Sovodak regimen, HCV RNA titer was undetectable in all patients. Furthermore, 12 weeks after the end of the treatment, 100% of patients achieved SVR12.

No severe side effects were reported by patients and only foot swelling, headache, and nausea and vomiting were observed in 3 patients (n = 1 for each side effect).

The effect of Sovodak on laboratory parameters outcomes in treatment-naïve and previously treated patients are presented in table 2.

Table 2. Laboratory parameters outcomes in treatment-naïve and treatment experience groups

Parameters	Treatment-experienced				P	Treatment-naïve				P
	Before treatment (n = 25)		After treatment (n = 25)			Before treatment (n = 25)		After treatment (n = 25)		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
ALT (IU/ml)	61.46	26.52	19.08	3.74	<0.001	71.68	35.94	20.96	6.21	<0.001
AST (IU/ml)	62.79	32.07	20.75	6.27	<0.001	67.20	33.50	22.88	10.21	<0.001
ALP (IU/ml)	232.37	114.15	203.22	69.19	0.246	257.36	94.64	223.00	71.69	0.005
Total bilirubin (mg/dl)	1.51	0.68	1.30	0.53	<0.001	1.49	0.78	1.33	0.65	0.069
Direct bilirubin (mg/dl)	0.40 [#]	(0.10-0.80) [¥]	0.30 [#]	(0.1-0.60) [¥]	>0.999 [*]	0.40 [#]	(0.11-1.50) [¥]	0.30 [#]	(0.10-1.83) [¥]	0.156 [*]
PT (mg/dl)	13.49	1.01	13.30	1.19	0.025	14.21	2.47	13.49	1.95	>0.999
INR (mg/dl)	1.24	0.19	1.17	0.21	0.001	1.25	0.39	1.16	0.37	<0.001
Alb (mg/dl)	4.16	0.45	4.27	0.45	<0.001	4.14	0.44	4.30	0.46	0.002
Log PLT (mg/dl)	11.60	0.59	11.86	0.50	0.007	11.71	0.77	12.00	0.70	0.007
Hb (mg/dl)	13.28	1.40	14.00	1.55	0.008	14.00	1.11	14.32	0.90	0.002
Log WBC (mg/dl)	8.40	0.47	8.81	0.59	0.003	8.63	0.41	8.81	0.32	0.008
Creatinine (mg/dl)	1.05 ^{**}	(0.70-7.06) ^{***}	0.90 ^{**}	(0.60-6.80) ^{***}	<0.001 [*]	1.00 ^{**}	(0.60-8.60) ^{***}	0.90 ^{**}	(0.70-7.50) ^{***}	0.027 [*]
Log BUN (mg/dl)	2.84	0.39	2.69	0.35	<0.001	2.81	0.54	2.75	0.54	0.172

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; PT: Prothrombin time; INR: International normalized ratio; Alb: Albumin; Hb: Hemoglobin; WBC: White blood cell; BUN: Blood urea nitrogen; PLT: Platelet

*Wilcoxon test, [#]Median, [¥](Min-Max)

In all patients, compared with baseline values, the significant decreases were observed in laboratory parameters except for total and direct bilirubin and PT in previously treated patients and total and direct bilirubin and log BUN in treatment-naïve patients.

Discussion

Considering the superiority of IFN-free regimens for chronic hepatitis C, the different combinations of DAA have been studied in the treatment of HCV and high SVR12 and patient-related outcomes were reported. For ease of use, a single tablet containing different DAAs was formulated previously. The tablet comprising of sofosbuvir and ledipasvir was not effective in the treatment of genotypes 1 and 3 viruses, the most prevalent genotypes in Iran. Another single pill containing Sofosbuvir and Velpatasvir has limited use in Iran because of its high price. Recently, Sovodak, a single pill containing sofosbuvir and daclatasvir has been formulated in Iran. In the present study, the effect of Sovodak in the treatment of naïve and previously treated patients with HCV G1 infection was studied and high SVR (100%) was achieved in both groups. To the best of our knowledge, the efficacy of Sovodak was only studied in one study. Merat et al. investigated the effect of Sovodak among treatment-naïve patients with HCV G1 or G3 and cirrhosis and reported the SVR12 rate as 98%.¹¹ In the present study, higher SVR12 (100%) level was obtained in patients with HCV G1, which may be due to the differences in the genotypes of patients and the presence of background diseases.

Although the effect of Sovodak as a single pill has been evaluated in only one previous study, several studies have assessed the efficacy of Sof/Dac combination in the treatment of HCV (with different genotypes) and provided varying results. In three studies which only included the patients with HCV G1, the SVR12 ranged between 84.9%-100%.^{9,12,13} The differences in SVR12 between studies may be due to the

differences in inclusion criteria (patients with cirrhosis or not) and using other antiviral drugs such as ribavirin along with Sof/Dac.

In the present study, there were no differences between treatment-naïve and treatment-experienced patients regarding SVR12. The results of previous studies in this regard are contradictory. Nelson et al. reported that in cirrhotic and non-cirrhotic patients with HCV genotype 3 (HCV G3), 12-week treatment with Sof/Dac resulted in SVR12 rates as 90% and 86% in the treatment-naïve and treatment-experienced patients, respectively.¹⁴ In another study, Pol et al. reported SVR12 rate of 96% and 88% respectively in treatment-naïve and treatment-experienced patients with HCV G1 treated by Sof/Dac.⁹ The differences among the results of studies may be due to differences in HCV genotypes of patients, inclusion criteria, history of care or compliance between treatment-experienced and treatment-naïve groups.

Recently, it has been indicated that cirrhosis was associated with treatment failure in patients with HCV treated with Sof/Dac. However, adding ribavirin to Sof/Dac regimen had been shown to increase the response rate. In the present study, SVR12 was obtained among all patients (cirrhotic and non-cirrhotic patients). This rate in cirrhotic patients was higher than previous reports. Recently, Pol et al. showed that the SVR12 rate in cirrhotic patients with HCV G1 who were treated with So/Dac plus ribavirin was 100% and 91.3% in treatment-naïve and treatment-experienced patients, respectively.⁹ In another study on cirrhotic patients with HCV G1, the SVR12 in treatment-experienced group was 88%.¹⁵ In another study among patients with HCV G3 and cirrhosis, SVR rates of 50.0% and 87.5% were obtained in treatment-naïve and treatment-experienced groups, respectively.¹⁰ The differences between the results of different studies may be related to the differences in viral load and HCV genotypes, underlying disease, and the genetics of patients.

In line with the results of previous studies,^{11,16} none of the patients in the current

study experienced treatment discontinuation because of adverse events. However, Merat et al. reported that 30% of patients treated by Sovodak regimen had experienced fatigue.¹¹ Moreover, improvement in liver-related laboratory parameters was observed in the current study. However, due to the short follow-up period, a definitive conclusion could not be made regarding treatment-related changes in liver disease. Longer follow-up period is needed to assess long-term improvements in liver disease parameters following viral clearance.

The present study was accompanied by some limitations including limited sample size, exclusion of patients with other HCV genotypes except HCV G1, and no follow-up period after viral clearance.

Conclusion

In conclusion, the present study showed that the oral Sovodak regimen including sofosbuvir and daclatasvir resulted in a high SVR rate in both treatment-naïve and treatment-experienced patients. Moreover, this regimen provides a highly effective, safe, and easy of use (single-tablet per day) option

for the cure of patients infected by HCV genotype 1.

Acknowledgments

The authors gratefully acknowledge liver and gastrointestinal diseases research center, for financial support, Tahmineh Azemi and staff of Gastroenterology and Liver clinics, Tabriz University of Medical Sciences for their kind cooperation. Besides, the authors appreciate the patients and their families.

Authors' Contribution

All of the authors contributed equally.

Funding

Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical sciences, Tabriz, Iran.

Conflict of Interest

Authors have no conflict of interest.

Ethical Approval

The study protocol was approved by the ethical committee of Tabriz University of Medical Sciences (IR.TBZMED.AC.IR.1395.871).

References

1. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: New estimates of age-specific antibody to HCV seroprevalence. *Hepatology* 2013; 57(4): 1333-42. DOI: 10.1002/hep.26141
2. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol* 2014; 61(1 Suppl): S45-S57. DOI: 10.1016/j.jhep.2014.07.027
3. Abdullah Sinjari H Y, Bakr K A. Prevalence and risk factors of hepatitis B and C virus infections among patients undergoing hemodialysis in Kurdistan, Iraq. *Hepat Mon* 2018; 18(5): e11776. DOI: 10.5812/hepatmon.11776
4. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med* 2014; 370(21): 1993-2001. DOI: 10.1056/NEJMoa1316145
5. Mizokami M, Yokosuka O, Takehara T, Sakamoto N, Korenaga M, Mochizuki H, et al. Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naïve and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial. *Lancet Infect Dis* 2015; 15(6): 645-53. DOI: 10.1016/S1473-3099(15)70099-X
6. Summers BB, Beavers JW, Klibanov OM. Sofosbuvir, a novel nucleotide analogue inhibitor used for the treatment of hepatitis C virus. *J Pharm Pharmacol* 2014; 66(12): 1653-66. DOI: 10.1111/jphp.12294
7. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014; 370(20): 1889-98. DOI: 10.1056/NEJMoa1402454
8. Butt AA, Yan P, Shaikh OS, Chung RT, Sherman KE. Sofosbuvir-based regimens in clinical practice achieve SVR rates closer to clinical trials: Results from ERCHIVES. *Liver Int* 2016; 36(5): 651-8. DOI: 10.1111/liv.13036
9. Pol S, Corouge M, Vallet-Pichard A. Daclatasvir-sofosbuvir combination therapy with or without ribavirin for hepatitis C virus infection: from the

- clinical trials to real life. *Hepat Med* 2016; 8: 21-6. DOI: 10.2147/HMER.S62014
10. Leroy V, Angus P, Bronowicki JP, Dore GJ, Hezode C, Pianko S, et al. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: A randomized phase III study (ALLY-3+). *Hepatology* 2016; 63(5): 1430-41. DOI: 10.1002/hep.28473
 11. Merat S, Sharifi A H, Haj-Sheykholeslami A, Poustchi H, Fattahi B, et al. The efficacy of 12 weeks of sofosbuvir, daclatasvir, and ribavirin in treating hepatitis C patients with cirrhosis, genotypes 1 and 3. *Hepat Mon* 2017; 17(1): e44564. DOI: 10.5812/hepatmon.44564
 12. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med* 2014; 370(3): 211-21. DOI: 10.1056/NEJMoal306218
 13. Ji D, Chen GF, Wang C, Wang YD, Shao Q, Li B, et al. Twelve-week ribavirin-free direct-acting antivirals for treatment-experienced Chinese with HCV genotype 1b infection including cirrhotic patients. *Hepatol Int* 2016; 10(5): 789-98. DOI: 10.1007/s12072-016-9755-0
 14. Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology* 2015; 61(4): 1127-35. DOI: 10.1002/hep.27726
 15. Cheung MCM, Walker AJ, Hudson BE, Verma S, McLauchlan J, Mutimer DJ, et al. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol* 2016; 65(4): 741-7. DOI: 10.1016/j.jhep.2016.06.019
 16. Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. *Hepatology* 2016; 63(5): 1493-505. DOI: 10.1002/hep.28446