

Research Article

The Effectiveness of Sovodak in the Treatment of Patients with Chronic Hepatitis C

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Abstract

Background: Recently, interferon-free treatment has been considered for the treatment of chronic hepatitis C due to their high therapeutic success and lack of serious side effects. The combination of Sofosbuvir and Daclatasvir is effective in the treatment of the disease because of its pan-genotype. In the present study, the effectiveness of Sovodak, which is a combination of the aforementioned two drugs in one tablet, in the treatment of patients with chronic hepatitis C and cirrhosis was investigated.

Methods: Patients with chronic hepatitis C whose diagnosis was confirmed by HCV RNA-PCR test were included in the study. These patients received one Sovodak tablet daily (for 12 weeks for non-cirrhotic patients and 24 weeks for cirrhotic patients). Sustained virologic response (SVR) was assessed by PCR test 12 weeks after the end of the treatment and one year later. Also, serum levels of liver enzymes, platelet count, and liver stiffness (using elastography method) were measured and their levels were compared before and after treatment in patients.

Results: Findings related to the PCR test in patients showed that the level of SVR was 100% in patients 12 weeks after treatment (SVR-12). In three cirrhotic patients who received only 12 weeks of drug treatment, the disease recurred a year later. According to the results, ALT and AST serum levels were significantly decreased ($P < 0.001$), and platelet count level was increased ($P < 0.001$) one year after the end of

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the treatment period. Also, the liver stiffness index measured using FibroScan was significantly decreased in patients 12 weeks after the end of the treatment ($P < 0.001$). **Conclusion:** The results of this study, in line with other studies, showed the effective role of Sovodak in completely eliminating the HCV virus in patients with chronic hepatitis C. Cirrhotic patients need to receive treatment for at least six months.

Keywords: Sovodak, hepatitis C, sustained virologic response, effectiveness, liver cirrhosis

1. Introduction

Chronic hepatitis is one of the most important health challenges in the world due to the difficulty of its treatment. Chronic hepatitis C can lead to liver cirrhosis, hepatocellular carcinoma, liver failure, and finally, death [1]. It is estimated that about 60–113 million people worldwide are affected by this disease and the prevalence is increasing [2]. Its prevalence in Iran is reported to be about 0.3–0.5% [3] and is expected to increase further if the current conditions persist [4].

Hepatitis C virus (HCV) is a single-stranded RNA and enveloped virus belonging to the *Flaviviridae* family and has six genotypes and a large number of subtypes [5–8]. Treatment for chronic hepatitis C, before the development of direct-acting antiviral (DAA) drugs, mainly involved the administration of pegylated interferon (IFN) Alfa with Ribavirin. Treatment is successful when HCV RNA is undetected at the end of treatment [9]. The side effects of interferon are sometimes so severe that the drug cannot be used completely. Particularly in patients with cirrhosis, thrombocytopenia, and anemia, it is often impossible to use this substance. Sometimes interferon aggravates the liver disease and even death. The treatment period with interferon can last up to one and a half years and includes weekly injections of the drug along with five to six tablets of Ribavirin daily. With all of the above, even if the drug is fully used, the response to treatment is about 60% or up to 70%, and many patients, such as those with cirrhosis or HIV, respond less to the treatment [10].

With the introduction of DAA drugs, chronic hepatitis C can now be treated without interferon and there is a lot of hope for effective treatment of this disease to the point that some studies have even suggested the possibility of eradicating the disease as the eradication of the first chronic viral disease in the world [11]. The approach of most

therapies based on DAAs is Sofosbuvir, which alone is not effective and should be used in combination with other medicines such as Daclatasvir or Ledipasvir. The most familiar drug is Harvoni, a combination of Sofosbuvir and Ledipasvir in one tablet. This drug is effective only on genotypes 1 and 4, which includes a maximum of 50–60% of Iranian patients [12]. The combination of Daclatasvir and Sofosbuvir is effective on all genotypes (pan-genotype) and can be used even without checking the genotype. The combination of these two drugs in one tablet is only available in Iran, which is known as Sovodak [13]. The present study investigated the effectiveness of Sovodak in the treatment of patients with chronic hepatitis C and cirrhosis.

2. Materials and Methods

2.1. Study design

In this non-experimental study (before and after), all patients with chronic hepatitis C referred to the outpatient clinic of the liver and gastrointestinal unit of *Tohid* Hospital, *Sanandaj, Iran* in 2018, were selected by census method.

2.2. Patients

The inclusion criteria of the study comprised of patients aged between 20 and 80 years and a confirmed diagnosis of the disease by HCV RNA–PCR test. Patients with renal failure (eGFR < 30 ml/min), heart rate < 50, co-infection with HBV and HIV, and patients taking *amiodarone* were excluded from the study.

2.3. Treatment and intervention methods

One Sovodak tablet (Sofosbuvir [400 mg] + Daclatasvir [60 mg] made in Rojan Pharma, Tehran, Iran) was prescribed daily for all patients. Non-cirrhotic patients were treated for 12 weeks and patients with liver cirrhosis were treated for 24 weeks. The drugs were given to patients monthly and were evaluated for side effects and proper use of the drug.

2.4. Paraclinical investigation

Serum levels of liver enzymes including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured by kinetic method (Pars Azmoon Co., Tehran, Iran). Platelet count was also measured at the beginning and 12 weeks after the end of the treatment in all patients. All experiments were conducted in a laboratory. The rate of hepatic fibrosis in the patients was assessed by the Transient Elastography method using a FibroScan (EchoSens, Paris, France) at the beginning and one year after the end of the treatment period. Fibrosis results were reported in kilopascal (Kpa). Diagnosis of cirrhosis in patients was based on the results of FibroScan ($F > 14$ Kpa) and the incidence of clinical manifestations including a set of clinical symptoms, physical findings, laboratory, and radiological findings such as ascites, cytopenia, splenomegaly, esophageal varices.

To evaluate the response to treatment, 12 weeks after the end of treatment and to evaluate the recurrence, one year after the end of treatment, HCV RNA-PCR test was performed with a diagnostic accuracy of 25 viral units per ml (copies/ml) of all patients.

2.5. Statistical analysis

Statistical analysis was performed using SPSS software version 20. The Kolmogorov-Smirnov test was used to analyze the hypotheses for the normality of quantitative data. Qualitative variables were calculated as frequency (percentage), quantitative variables with normal mean distribution (SE), and qualitative variables with abnormal distribution with mean (IQR). Due to the abnormality of data distribution, the Wilcoxon signed-rank test was used to compare changes before and after the treatment of variables. P -value < 0.05 was considered as a significant level.

3. Results

A total of 50 patients were enrolled in the study, and excluding 3, all 47 of them completed the treatment period. The demographic and clinical characteristics of the studied patients are summarized in Table 1. The mean age of patients was $49.30 \pm (10.71)$ years (with a minimum of 25 years and a maximum of 71 years). Overall, 42 patients (84%) were men and 8 (16%) were women. Most patients (32, 64%) were aged between 40 and 60 years, 10 (20%) were under 40 years old, and only 8 people were

over 60 years old. Pretreatment viral load in 25 patients (71.4%) was <600,000 IU/MI and in 10 patients (28.6%) \geq 600,000 IU/MI.

Seven patients (14%) were genotype 1, seven (14%) were genotype 3, and the genotype of the remaining thirty-six patients (72%) was not determined. Based on the results of FibroScan, 13 patients (26%) had cirrhosis of the liver. Findings related to the PCR test in patients revealed that the level of sustained virologic response (SVR) 12 weeks after the end of treatment in patients was 100%. Moreover, at one-year follow-up, recurrence was not observed in 47 patients (94%). In three cirrhotic patients who were treated for only three months due to non-referral to complete the second trimester of the treatment, although the response to treatment was complete, the disease recurred after one year. The patients were re-treated for 24 weeks, the response to treatment was complete and a year later, no recurrence of the disease was observed in them.

Table 2 shows the level of liver enzymes and the platelet count before and 12 weeks after the end of the treatment period in the studied patients. Based on the results, serum ALT and AST levels in patients after treatment were decreased ($P < 0.001$), and platelet count increased ($P < 0.001$) significantly. Also, the liver stiffness index measured using FibroScan was decreased ($P < 0.001$) significantly in patients after the end of the treatment period. One year after the end of treatment, patients had a median of 18% reduction in liver stiffness index measured by FibroScan, from 6.95 (IQR; 5.15–15.00) KPa to 5.70 (IQR; 3.57–14.40) Kpa ($p < 0.001$) compared to the data before Sovodak administration.

TABLE 1: Baseline characteristics of the study patients ($n = 50$).

Variables		
Age (yr), Mean \pm (SD)		49.30 \pm (10.71)
Sex, n (%)	Male	42 (84.0%)
	Female	8(16.0%)
Viral load, n (%)	<600,000 IU/MI	25 (71.4%)
	\geq 600,000 IU/MI	10 (28.6%)
Genotypes, n (%)	1	7 (50.0%)
	2	0 (0%)
	3	7 (50.0%)
Degree of fibrosis; n (%)	Normal	25 (50.0%)
	F1	3 (6.0%)
	F2	3 (6.0%)
	F3	6 (12.0%)
	F4	13 (26.0%)

TABLE 2: Comparison of ALT, AST, platelet count, and liver stiffness index before and after treatment in patients with chronic hepatitis C.

Variables	Before treatment	12 weeks after completing therapy	P-value
	Med (IQR)	Med (IQR)	
ALT, U/L	42.00 (27.50–72.50)	27.50 (24.00–32.25)	<0.001
AST, U/L	50.00 (30.75–70.50)	25.00 (22.00–28.00)	<0.001
Platelet count, μ l	179000.00 (102500.00–215250.00)	200500.00 (109250.00–225250.00)	<0.001

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase

4. Discussion

The main findings of this study indicate that the administration of Sovodak for 12 and 24 weeks in non-cirrhotic and cirrhotic patients with chronic hepatitis C, respectively, is completely effective in treatment, and that if the treatment is given to cirrhotic patients for only 12 weeks, there is a possibility of recurrence of the disease despite the success of SVR-12. In recent years, studies have been conducted on the effectiveness of Sovodak or its family in the treatment of chronic hepatitis C. In the study of Mehdipour *et al.* (2019), as in our study, the level of SVR12 in patients with HCV infection and genotype 1 treated with Sovodak was reported to be 100%. Although in this study, the duration of treatment for cirrhotic patients was the same as for non-cirrhotic patients, that is, 12 weeks, Ribavirin was included in their treatment diet [14]. In another study on the effectiveness of Sovodak on the treatment of 1,361 patients with hepatitis C and different genotypes, the level of SVR-12 was reported to be 98%. In this study, the duration of treatment in cirrhotic patients was 24 weeks and if Ribavirin was administered with Sovodak, it was 12 weeks. There was no significant difference between the SVR12 levels in cirrhotic patients treated with Sovodak for 12 weeks with Ribavirin and 24 weeks without Ribavirin [15]. In other studies, the level of SVR-12 in the treatment of patients with hepatitis C with Sofosbuvir and Daclatasvir has been reported to be 84.9–100% [16–21]. Differences in SVR12 between several studies may be due to differences in inclusion criteria (patients with cirrhosis or not), specific genotype, previous treatment history, treatment failure, recurrence, multidrug usage, and use of other antiviral drugs such as Ribavirin with Sofosbuvir/Daclatasvir.

Nelson *et al.* reported that in patients with HCV genotype 3, 12 weeks of treatment with Sofosbuvir and Daclatasvir resulted in SVR-12 levels of up to 90% in patients without cirrhosis and 86% in patients with cirrhosis [22]. In another study, Pol *et al.* reported 96% and 88% of SVR12 in patients without cirrhosis and cirrhosis with HCV

and genotype 1 treated with Sofosbuvir and Daclatasvir, respectively [16]. Merat *et al.* (2017) in a study evaluated the effectiveness of treatment with Sovodak and Ribavirin for 12 weeks in cirrhotic patients with hepatitis C and genotypes 1 and 3, in which the SVR12 level was 98%. In two patients in which the recurrence occurred, one patient had genotype 1 and other one had genotype 3 [23]. In the study of Leroy *et al.* (2016), SVR12 in cirrhotic patients with HCV genotype 3 infection with 12 and 16 weeks of treatment with Sofosbuvir/Daclatasvir with Ribavirin were 83% and 89%, respectively [24]. In the present research, it was shown that if cirrhotic patients were treated for 24 weeks, their SVR12 was 100% and there was no recurrence of the disease at the one-year follow-up. However, in three patients who continued treatment for only 12 weeks, although they achieved SVR12, recurrence occurred a year later, with re-treatment for 24 weeks, complete response to treatment, and no recurrence for up to a year.

In the present study, unlike the other aforementioned studies, the treatment period in cirrhotic patients was 24 weeks and Ribavirin was not used. The results of the present study showed that the rate of liver stiffness, measured by FibroScan, after taking Sovodak in these patients decreased significantly. Sustained viral response (SVR) is associated with cessation of disease progression and reduction of its complications, including reduced incidence of hepatocellular carcinoma [25–27]. In previous studies, liver tissue healing after an SVR has been reported [28–31]. The results of a study revealed that treatment of chronic hepatitis C with DAA drugs in patients with cirrhosis of the liver or advanced liver fibrosis is associated with cessation of cirrhosis and regression of liver fibrosis in about 50% of patients [32].

Other findings of this study showed that taking Sovodak in patients with chronic hepatitis C would significantly decrease the liver enzyme levels. This finding was in agreement with the results of other studies that have been conducted in this field [14, 19, 20] which indicates the effect of Sovodak on reducing liver enzymes levels to normal, which could be due to the preventive effect of Sovodak on further destruction of liver tissue by HCV and possibly liver tissue healing. Also in our study, platelet count, in line with the effect of Sovodak in removing the virus, showed changes in recovery so that cirrhotic patients had an increase in platelet count to normal range. The main limitations of this study were the small number of sample and the lack of genotype of all patients.

5. Conclusion

The results of our study in line with other research, the effective role of Sovodak in removing the HCV virus in patients with chronic hepatitis C was 100%. Therefore, this drug is recommended due to the pan-genotype of the drug and its cheapness compared to similar cases, without the need to determine the genotype and high cost of testing and also the lack of significant drug side effects, for the treatment of all patients with chronic hepatitis C in both cirrhotic and non-cirrhotic patients regardless of the type of HCV genotype.

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Ethical considerations

The study protocol was approved by the ethics committee of Kurdistan University of Medical Sciences, Sanandaj, Iran (No. IR.MUK.REC.1398.254) and before the study, informed consent was obtained from all participants.

Competing interests

The authors declare that they have no competing interests.

Availability of data and material

All data are available upon reasonable request.

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References

- [1] Lauer, G. M. and Walker, B. D. (2001). Hepatitis C virus infection. *New England Journal of Medicine*, vol. 345, no. 1, pp. 41–52.
- [2] Manns, M. P., Buti, M., Gane, E., et al. (2017). Hepatitis C virus infection. *Nature Reviews Disease Primers*, vol. 3, pp. 1–19.
- [3] Merat, S., Rezvan, H., Nourai, M., et al. (2010). Seroprevalence of hepatitis C virus: the first population-based study from Iran. *International Journal of Infectious Diseases*, vol. 14, no. 3, pp. e113–e116.
- [4] Hatzakis, A., Chulanov, V., Gadano, A., et al. (2015). The present and future disease burden of hepatitis C virus (HCV) infections with today's treatment paradigm—volume 2. *Journal of Viral Hepatitis*, vol. 22, no. 1, pp. 26–45.
- [5] Penin, F., Dubuisson, J., Rey, F. A., et al. (2004). Structural biology of hepatitis C virus. *Hepatology*, vol. 39, no. 1, pp. 5–19.
- [6] Pawlotsky, J. M. (2002). Use and interpretation of virological tests for hepatitis C. *Hepatology*, vol. 36, no. 1, pp. s65–s73.
- [7] Pawlotsky, J. M., Lonjon, I., Hezode, C., et al. (1998). What strategy should be used for diagnosis of hepatitis C virus infection in clinical laboratories? *Hepatology*, vol. 27, no. 6, pp. 1700–1702.
- [8] Simmonds, P., Bukh, J., Combet, C., et al. (2005). Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes. *Hepatology*, vol. 42, no. 4, pp. 962–973.
- [9] Hadziyannis, S. J., Sette, Jr., H., Morgan, T. R., et al. (2004). Peginterferon- α 2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Annals of Internal Medicine*, vol. 140, no. 5, pp. 346–355.
- [10] Jabari, H., Bayatian, A., Sharifi, A. H., et al. (2010). Safety and efficacy of locally manufactured pegylated interferon in hepatitis C patients. *Archives of Iranian Medicine*, vol. 13, no. 4, pp. 306–312.
- [11] Hagan, L. M., Wolpe, P. R., and Schinazi, R. F. (2013). Treatment as prevention and cure towards global eradication of hepatitis C virus. *Trends in Microbiology*, vol. 21, no. 12, pp. 625–633.
- [12] Samimi-Rad, K., Nategh, R., Malekzadeh, R., et al. (2004). Molecular epidemiology of hepatitis C virus in Iran as reflected by phylogenetic analysis of the NS5B region. *Journal of Medical Virology*, vol. 74, no. 2, pp. 246–252.
- [13] Sharifi, A. H., Haj-Sheykholeslami, A., Poustchi, H., et al. (2016). Efficacy of locally manufactured sofosbuvir and daclatasvir (Sovodak) in combination with ribavirin in

- treating patients with chronic hepatitis c and cirrhosis in Iran – preliminary report. *Govaresh*, vol. 21, pp. 93–97.
- [14] Mehdipour, H., Moaddab, Y., Azizian, K., et al. (2019). Effects of 12-week treatment with Sovodak in patients infected by genotype 1 hepatitis C virus. *Journal of Research in Clinical Medicine*, vol. 7, no. 1, pp. 1–6.
- [15] Merat, S. (2020). SD1000: high sustained viral response rate in 1361 patients with hepatitis C genotypes 1, 2, 3, and 4 using a low-cost, fixed-dose combination tablet of generic sofosbuvir and daclatasvir: a multicenter, phase III clinical trial. *Clinical Infectious Diseases*, vol. 70, no. 10, pp. 2206–2212.
- [16] Pol, S., Corouge, M., and Vallet-Pichard, A. (2016). Daclatasvir–sofosbuvir combination therapy with or without ribavirin for hepatitis C virus infection: from the clinical trials to real life. *Hepatic Medicine: Evidence and Research*, vol. 8, p. 21.
- [17] Ji, D., Chen, G.-F., Wang, C., et al. (2016). Twelve-week ribavirin-free direct-acting antivirals for treatment-experienced Chinese with HCV genotype 1b infection including cirrhotic patients. *Hepatology International*, vol. 10, no. 5, pp. 789–798.
- [18] Welzel, T. M., Petersen, J., Herzer, K., et al. (2016). Daclatasvir plus sofosbuvir, with or without ribavirin, achieved high sustained virological response rates in patients with HCV infection and advanced liver disease in a real-world cohort. *Gut*, vol. 65, no. 11, pp. 1861–1870.
- [19] Ahmed, O. A., Safwat, E., Khalifa, M. O., et al. (2018). Sofosbuvir plus daclatasvir in treatment of chronic hepatitis C genotype 4 infection in a cohort of Egyptian patients: an experiment the size of Egyptian village. *International Journal of Hepatology*, vol. 2018, article id. 9616234.
- [20] Abdel-Moneim, A., Aboud, A., Abdel-Gabaar, M., et al. (2018). Efficacy and safety of sofosbuvir plus daclatasvir with or without ribavirin: large real-life results of patients with chronic hepatitis C genotype 4. *Hepatology International*, vol. 12, no. 4, pp. 348–355.
- [21] Omar, H., El Akel, W., Elbaz, T., et al. (2018). Generic daclatasvir plus sofosbuvir, with or without ribavirin, in treatment of chronic hepatitis C: real-world results from 18,378 patients in Egypt. *Alimentary Pharmacology & Therapeutics*, vol. 47, no. 3, pp. 421–431.
- [22] Nelson, D. R., Cooper, J. N., Lalezari, J. P., et al. (2015). All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology*, vol. 61, no. 4, pp. 1127–1135.
- [23] Merat, S., Sharifi, A. H., Haj-Sheykholeslami, A., et al. (2017). The efficacy of 12 weeks of sofosbuvir, daclatasvir, and ribavirin in treating hepatitis C patients with cirrhosis,

- genotypes 1 and 3. *Hepatitis Monthly*, vol. 17, no. 1, p. e44564.
- [24] Leroy, V., Angus, P., Bronowicki, J. P., et al. (2016). Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: a randomized phase III study (ALLY-3+). *Hepatology*, vol. 63, no. 5, pp. 1430–1441.
- [25] Hung, C. H., Lee, C. M., Lu, S. N., et al. (2006). Long-term effect of interferon alpha-2b plus ribavirin therapy on incidence of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. *Journal of Viral Hepatitis*, vol. 13, no. 6, pp. 409–414.
- [26] Kasahara, A., Tanaka, H., Okanou, T., et al. (2004). Interferon treatment improves survival in chronic hepatitis C patients showing biochemical as well as virological responses by preventing liver-related death. *Journal of Viral Hepatitis*, vol. 11, no. 2, pp. 148–156.
- [27] Veldt, B., Saracco, G., Boyer, N., et al. (2004). Long term clinical outcome of chronic hepatitis C patients with sustained virological response to interferon monotherapy. *Gut*, vol. 53, no. 10, pp. 1504–1508.
- [28] Maylin, S., Martinot–Peignoux, M., Moucari, R., et al. (2008). Eradication of hepatitis C virus in patients successfully treated for chronic hepatitis C. *Gastroenterology*, vol. 135, no. 3, pp. 821–829.
- [29] Mallet, V., Gilgenkrantz, H., Serpaggi, J., et al. (2008). Brief communication: the relationship of regression of cirrhosis to outcome in chronic hepatitis C. *Annals of Internal Medicine*, vol. 149, no. 6, pp. 399–403.
- [30] D'Ambrosio, R., Aghemo, A., Rumi, M. G., et al. (2012). A morphometric and immunohistochemical study to assess the benefit of a sustained virological response in hepatitis C virus patients with cirrhosis. *Hepatology*, vol. 56, no. 2, pp. 532–543.
- [31] George, S. L., Bacon, B. R., Brunt, E. M., et al. (2009). Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: a 5-year follow-up of 150 patients. *Hepatology*, vol. 49, no. 3, pp. 729–738.
- [32] Shiha, G., Soliman, R., Mikhail, N., et al. (2020). Changes in hepatic fibrosis stages after achieving SVR following direct-acting anti-viral treatment: a prospective study. *GastroHep*, vol. 2, no. 1, pp. 39–48.