

The Efficacy of 12 Weeks of Sofosbuvir, Daclatasvir, and Ribavirin in Treating Hepatitis C Patients with Cirrhosis, Genotypes 1 and 3

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Abstract

Background: The combination of sofosbuvir and daclatasvir can be used to treat all genotypes of hepatitis C. Current guidelines for treating hepatitis C cirrhosis do not clarify whether 12 weeks or 24 weeks of treatment is appropriate.

Objectives: In the present study, we aimed at evaluating the efficacy of sofosbuvir, daclatasvir, and ribavirin given for 12 weeks in treating cirrhotic patients with hepatitis C genotypes 1 and 3 infections.

Methods: One hundred patients with hepatitis C and cirrhosis infected with Genotypes 1 and 3 were included in the present study. They were treated with 1 tablet of a combination pill of 400 mg sofosbuvir and 60 mg daclatasvir daily and weight-based ribavirin for 12 weeks. Response to treatment was assessed 12 weeks after the end of the treatment with a sensitive assay (SVR12). This study was registered with ClinicalTrials.gov, ID: NCT02596880.

Results: One patient developed increased creatinine level following severe diarrhea and gastroenteritis and was excluded, 1 patient died due to unrelated reasons and 4 others were lost to follow-up. Among the 94 patients who finished the study, 92 achieved SVR12 (98%, per-protocol, 92% intention-to-treat). None of the patients reported any side effects. Of the 100 original patients, 56 were Genotype 1 and 44 were Genotype 3. One of the two patients not achieving SVR12 was Genotype 1, and the other two were Genotype 3.

Conclusions: The fixed-dose combination drug of sofosbuvir and daclatasvir given together with weight-base ribavirin for 12 weeks is extremely effective and safe in treating HCV patients with Genotypes 1 and 3 and cirrhosis.

Keywords: Hepatitis C, Sofosbuvir, Daclatasvir, Sovodak

1. Background

Hepatitis C virus (HCV) infection is one of the most common causes of chronic hepatitis and liver transplant worldwide (1, 2). The prevalence of HCV infection in Iran is 0.3% - 0.5%, which is less than many neighboring countries (3). Nevertheless, HCV presents a major health problem in Iran and its prevalence is increasing (2, 4).

Treating HCV has recently been revolutionized by the introduction of effective direct acting antivirals (DAA) which have made possible interferon-free treatment with a very high success rate (5, 6). In fact, there is now a prospect for HCV elimination (7).

Many DAAs are currently available with sofosbuvir, an RNA polymerase inhibitor used as the base for most effective treatments. Sofosbuvir is not effective when given alone and should be combined with other DAAs such as ledipasvir, daclatasvir, or velpatasvir. Such combinations are highly effective with virtually no side effects (8-10). Daclatasvir and velpatasvir are pangenotypic agents and can be used for treating all HCV infections regardless of genotype. The addition of ribavirin to this treatment combination is frequently recommend for patients with cirrhosis,

especially if a three-month treatment duration is considered (11-13).

The main problem with the new treatments is its price, which makes it poorly suited for developing countries. The opportunity to scale up HCV elimination depends on efforts to guarantee that the new DAAs would be affordable in low-income settings. More recently, the generic versions of DAAs have become available at much lower prices.

The combination of sofosbuvir and daclatasvir (Sovodak, Abidi Pharmaceuticals, Tehran, Iran) shows promise as it is pangenotypic and easier to use than other combinations. Sovodak is a combination of 400 mg sofosbuvir and 60 mg daclatasvir in a single pill which has been formulated in Iran. The present study reports the results of treating 100 cirrhotic hepatitis C patients with Sovodak and ribavirin for 12 weeks. A preliminary report of the first 50 patients has been published elsewhere (14).

2. Methods

In the present study, 100 patients with chronic hepatitis C and cirrhosis were selected from referrals to Shariati hospital hepatitis C clinic in Tehran between September

and November 2015. Only Genotypes 1 and 3, the genotypes common in Iran, were included. The patients were confirmed as chronic HCV infection if they had at least 2 positive PCR tests for HCV at least 6 months apart with a sensitive test (lower limit of detection < 25 IU/mL). Cirrhosis was diagnosed by either liver biopsy or liver stiffness of 12 KPa or more. In cases where liver biopsy, or transient elastography were impossible (e.g., due to severe ascites), cirrhosis was diagnosed based on clinical characteristics such as ascites, splenomegaly, small echogenic liver, esophageal varices, etc.

Patients with significant renal failure defined as eGFR < 30 mL/min were excluded. Those with very advanced disease defined as MELD score > 20 or Child-Pugh score > 12 were also excluded. Other exclusion criteria were as follow: Heart rate < 50 beats/min, coinfection with HIV or hepatitis B virus, previous treatment failure with sofosbuvir-based regimen, taking amiodarone within the last 6 months, or not consenting to participate in the study. Previous failure with interferon-based regimens was not an exclusion criterion.

Treatment was started with 1 pill of Sovodak (Abidi Pharmaceuticals, Tehran, Iran) daily and 1000 mg ribavirin/day if the patients weighed less than 75 kg, or 1200 mg/day if they weighed 75 kg or more. Each Sovodak pill contains 400 mg sofosbuvir and 60 mg daclatasvir. Ribavirin was given in two divided daily doses. The treatment duration was 12 weeks (84 days) for all patients.

The participants were visited at weeks 1, 4, 8, 12 (end of treatment), and 24 (12 weeks after the end of treatment). During each visit, a complete examination was performed and the patients were asked about the side effects and compliance. Lab tests including viral count were also performed on each visit.

The success of treatment was defined as a negative HCV RNA PCR 12 weeks after the end of the treatment, which was measured using a sensitive assay with lower limit of detection less than 25 IU/mL (Sustained Viral Response 12 week, SVR12).

Data were analyzed using IBM SPSS Statistics Version 22.

Written consent was obtained from all patients. Moreover, the study protocol was approved by the institutional review board and ethics committee of the digestive disease research institute of Tehran University of Medical Sciences.

The present study was registered in ClinicalTrials.gov under the ID of NCT02596880.

3. Results

One hundred patients were enrolled in the present study. The baseline characteristics of the patients are displayed in [Table 1](#).

Table 1. Baseline Characteristics of the Participants

Variable	Value
Number	100
Sex, M/F	65/35
Mean age, years	54.9
Genotype	
1a	46
1b	10
3a	44
Mean liver stiffness, KPa	31.5
Mean viral count, IU/mL	3,220,000
Post-liver transplant	4
Decompensated cirrhosis	5
Concomitant autoimmune hepatitis	1

One patient with decompensated cirrhosis developed increased creatinine level following severe diarrhea and gastroenteritis at week 5 of the treatment. As increased creatinine is a contraindication to both sofosbuvir and ribavirin, treatment was halted and this patient was excluded from the study. The viral count at week 4 was undetectable in this patient.

One patient died before the end of the treatment. He developed perforated duodenal ulcer at week 3 of the treatment and passed away due to sepsis. Viral count at week 1 was undetectable. This patient had decompensated cirrhosis.

Four patients were lost to follow-up, three of which had finished full course of treatment without event. Ninety-four patients finished the study, of whom, 92 achieved SVR12 (97.9%) and only 2 had recurrence. The viral counts at weeks 1, 4, 8, and 12 for all the 100 cases were negative where available including patients lost to follow-up or those who dropped out for any other reason. There was only one patient with a viral count of 145 IU/mL at week 1 who subsequently did achieve SVR12. Treatment outcome is displayed in [Table 2](#).

None of the patients reported any side effects, and no significant anemia (> 10% decrease in hemoglobin) was observed during the study. All patients took the full 84 tablets.

4. Discussion

The combination of sofosbuvir and ledipasvir has gained special interest as the only single pill daily treatment for hepatitis C. Unfortunately, this combination is

Table 2. Treatment Outcome in 100 Patients with HCV and Cirrhosis^a

Variable	Value
Total number of patients	100
Treatment discontinued	1
Passed	1
Lost to follow-up	4
Completed study	94
SVR12	92
Genotype 1	52/53
Genotype 3	40/41
Per-protocol SVR	97.9%
Intention-to-treat SVR	92.0%

^aSVR12: sustained viral response 12 weeks after the end of the treatment.

only effective on Genotypes 1 and 4 which limits its usefulness in countries such as Iran where Genotype 3 comprises over 30% of the infections. Recently, the combination of sofosbuvir and velpatasvir (Epclusa), a single-pill solution, has been approved for all genotypes of hepatitis C, but it is too expensive for developing countries. The combination of sofosbuvir and daclatasvir, although approved for treating all genotypes, has not been presented as a single pill until now. In the current study, we demonstrated the efficacy of this combination as a single fixed-dose combination pill (Sovodak) in treating the most difficult cases of hepatitis C (i.e., those with cirrhosis and Genotype 3).

We observed an excellent response rate of 97.9% among patients who finished their treatment. Even the intention-to-treat response rate of 92% in this subgroup (cirrhosis) was very good compared to the literature. The literature indicates an SVR rate of above 95% for noncirrhotics (15) and around 80-90% for cirrhotic patients (11). It appears that our patients responded to DAA therapy better than expected, and this was not the first time that this phenomenon has been observed in Iranian patients. Previous reports of treatment with pegylated interferon and ribavirin from Iran also revealed better results than the general literature (16, 17). It appears that Iranian patients are somewhat easier to treat.

It is notable that none of our patients reported any side effects although we expected some degree of headache or fatigue. Furthermore, we had 100% compliance, which is unusual in clinical studies. Our explanation is that our patients who had failed or were not eligible for interferon-based treatment and were also rejected by transplant facilities assumed they had no hope for survival and were so delighted and thankful to be treated that they overlooked

any possible side effects they might have had even in direct questioning.

With the previous treatment of pegylated interferon and ribavirin, anemia was a frequent finding occasionally leading to dose adjustments and even treatment discontinuation. Anemia was usually attributed to ribavirin. Even erythropoietin was occasionally administered to counteract anemia (18). Therefore, the current recommendation for cirrhosis is to start ribavirin at 600 mg/day and then gradually increase the dose to 1000 or 1200 mg/day. In the present study, although ribavirin was given at a high dose right from the beginning, no significant anemia was observed. It appears that the anemia induced by ribavirin in the absence of interferon is not clinically important (12), and we believe it is not necessary to prescribe ribavirin in an ascending dose and the full dose can be given from the beginning.

Sex of our participants were immunocompromised or taking immunosuppression (liver transplant, autoimmune hepatitis). However, all achieved SVR. This confirms that the presence of immunosuppression does not affect treatment response when using interferon-free treatments.

Among our patients, 5 suffered from decompensated cirrhosis, 1 did not complete the treatment course, 1 died from reasons unrelated to the treatment, and 1 dropped out because of rise in creatinine. Although the other 2 patients with decompensated cirrhosis did achieve SVR, it was observed that treating HCV was not sufficient for this subgroup and they had to undergo liver transplantation as soon as possible. Recent literature suggests that treating hepatitis C before liver transplant might be more cost-effective than treating it after the transplant (19). Nonetheless, due to the high mortality rate of such cases, as observed in our patients, we advise against delaying liver transplant to treat hepatitis C in advanced cases.

In our study, it was found that on-treatment viral counts are usually negative. We conclude that there is no need to test for viral count during treatment. Although it might be argued that negative counts would encourage the patient and increase compliance.

Of special importance is that the rate of hepatocellular carcinoma (HCC) will probably decrease, but not disappear by successful treatment of hepatitis C in cirrhotics (20, 21). Thus, it is necessary to continue surveillance for HCC in these patients even if SVR is achieved.

Considering the results of this study, and the ease of use (a single pill a day) we believe Sovodak could be the first choice for treating all cases of hepatitis C. Considering the uniformity of treatment regimens across genotypes, it might not even be necessary to check the genotype in the future. Furthermore, this combination is also a good

choice for patients with HIV coinfection as it has the least interaction with HIV drugs (22, 23).

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Footnotes

Authors' Contribution: Shahin Merat, Hossein Poustchi, and Reza Malekzadeh contributed to the conception and design of the study; in addition, all authors contributed to acquisition, analysis, data interpretation, drafting, and critically revising the manuscript, and approval of the final version; moreover, all agreed to be accountable for all aspects of the work.

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