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Research Article

Efficacy of Ledipasvir and Sofosbuvir in Patients with Hepatitis C Virus

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A B S T R A C T

Background: Hepatitis C infection is a communicable liver disease that, if not treated properly, can be life-threatening. Treatment of hepatitis C virus (HCV) infection has witnessed a dramatic improvement during the last several years after the introduction of direct-acting antiviral drugs (DAAs). One of the initial DAAs is the combination of ledipasvir and sofosbuvir (Led/Sof).

Objective: To evaluate the efficacy of Led/Sof in treating patients with HCV infections and identify common HCV genotypes.

Patients and Methods: This retrospective study was conducted over a 15-month period and included 122 patients with HCV infection. All patients underwent HCV polymerase chain reaction (PCR) and genotyping at the time of diagnosis. Only patients with genotypes (GT) 1 and 4 were included, and those with other genotypes were excluded. All patients received a fixed-dose combination tablet of Led/Sof (Harvoni brand, 90 mg ledipasvir and 400 mg sofosbuvir) once daily for 12 weeks. HCV PCR was repeated 12 weeks after finishing treatment with Led/Sof to assess the sustained virological response (SVR).

Results: The overall SVR was 95.08%; the best SVR was associated with GT 4 (96.67%), followed by GT1a (93.88%) and GT1b (92.31%). Those with treatment naïve (TN) patients had SVR of 94.85%, and those with treatment experienced (TE) patients had SVR of 96%. Non-cirrhotic patients had much better SVR (98.02%) than cirrhotic patients, including both compensated (76.92%) and decompensated (87.5%) liver cirrhosis. HCV GT 4 was the most common genotype in Baghdad (60 patients, 49.2%), followed by GT 1a (49 patients, 40.2%) and GT 1b (13 patients, 10.6%).

Conclusions: Led/Sof (Harvoni) achieved high SVR rates in different HCV genotypes, particularly GT4. Led/Sof is equally effective in both treatment-naïve and treatment-experienced patients. Cirrhotic patients had lower SVR than non-cirrhotic patients. GT 4 is the most prevalent HCV genotype.

Keywords: Hepatitis C Virus, Hcv Genotypes, Liver Cirrhosis

Introduction

Background

Hepatitis C virus (HCV) is an RNA virus of the family Flaviviridae. it can cause acute infection, chronic infection, liver fibrosis, cirrhosis, hepatocellular carcinoma (HCC), and death.[1] Around 50–80% of patients with acute HCV infection developed chronic hepatitis. It is the leading indication for liver transplantation in many parts of the world.[2,3] In 2022, the World Health Organization (WHO) estimated that around 58 million people had chronic HCV infection.[4]

The direct-acting antiviral (DAA) regimens are considered targeted drugs that have been developed to cure HCV infection, even in patients who were difficult to treat in the past, like patients with HIV co-infection, patients with decompensated liver disease, and patients with renal impairment.[5] Cure from HCV is defined as undetectable HCV RNA levels in the blood by polymerase chain reaction (PCR) 12 weeks after the end of therapy, which is referred to as a sustained virological response (SVR).[6] The goal of treatment is clearance of infection, thus reducing the progression of liver disease to cirrhosis and cirrhosis-related complications such as portal hypertension and hepatocellular carcinoma, as well as a reduction in liver-related morbidity and mortality. Treatment is recommended for all patients with HCV except those with short life expectancy (less than 12 months)[8] HCV genotypes are distributed differently across various regions, which affects how the disease progresses and how treatment works. There are eight genotypes of HCV, and they differ in where they are found, how quickly liver disease gets worse, and how they respond to treatment. Most new treatments can work for all genotypes. Approximately 75% of HCV patients in the United States have genotype 1 (subtypes 1a or 1b), while 20–25% have genotypes 2 or 3, with small numbers of patients infected with genotypes 4, 5, or 6. Most new pangenotypic treatment regimens[10] can overcome genotypic differences. HCV genotype 4 had the highest prevalence in the Middle East, including Arab countries, with a rate of 74.7%, followed by genotype 1 (15.1%), genotype 3 (4.2%), and genotype 2 (1.7%).[11]

Drugs regimens comprise direct-acting antiviral drugs (DAAs) used in combination to inhibit different steps in the HCV life cycle. The genotype of the virus has played a crucial role in determining appropriate treatment regimens for patients[12] (Tables 1 and 2).

Ledipasvir and sofosbuvir are both direct-acting antiviral agents. Sofosbuvir is a liver-targeted nucleotide prodrug of the active triphosphate GS-461203, which has been approved for use in HCV genotypes 1,4,5, and 6. It works as an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which acts as a chain terminator. Ledipasvir is an NS5A inhibitor that is active against genotypes 1a, 1b, 4a, and 5a and (with lower activity) against genotypes 2a and 3a. Its exact mechanism of action is unknown; it is thought to inhibit hyperphosphorylation of NS5A, which seems to be required for viral production. The NS5A and NS5B inhibitors exhibit a synergistic effect when used in combination.[13,14] The high efficiency of Harvoni is attributed to the two direct antiviral agents with different mechanisms of action, which can be more effective than single-agent regimens. Furthermore, ledipasvir is effective against S282T (the single variant that can increase viral resistance to sofosbuvir) and can reduce the probability of viral escape and development of resistance strain.[15]

Table 1.Treatment-naïve without cirrhosis or with compensated cirrhosis

Regimen	Genotype	Classification	Duration
Glecaprevir/pibrentasvir	1–6	Recommended	8 wk
Ledipasvir/sofosbuvir	1, 4, 5, 6	Recommended	12 wk
Sofosbuvir/velpatasvir	1–6	Recommended	12 wk
Elbasvir/grazoprevir	1b, 4	Recommended	12 wk

Table 2.Treatment-naive with decompensated cirrhosis

Regimen	Genotype	Classification	Duration
Ledipasvir/sofosbuvir + weight-based ribavirin	1, 4, 5, 6	Recommended	12 wk
Ledipasvir/sofosbuvir	1, 4, 5, 6	Recommended	24 wk
Sofosbuvir/velpatasvir	1–6	Recommended	24 wk
Sofosbuvir/velpatasvir +weight-based ribavirin	1–6	Recommended	12 wk

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The present study was conducted to evaluate the efficacy of Led/Sof (Harvoni) in HCV treatment, including patients who were treatment-naïve, treatment experienced, cirrhotic, and non-cirrhotic patients, and to assess the prevalence of HCV genotypes.

Patients And Methods

This is a cross-sectionalthat included 122 patients with chronic HCV who were evaluated and treated as outpatients at the Gastroenterology and Hepatology Teaching Hospital in Baghdad, Iraq, during the period from October 2022 to January 2024. HCV infection is confirmed by PCR-based viral load and genotype testing. The inclusion criteria include patients with HCV genotype 1b, and 4, whether the patients are treatment-naive (defined as patients who have never been treated for their HCV infection) or treatment experienced (defined as patients who were previously treated with pegylated IFN and ribavirin), and non-cirrhotic or cirrhotic patients, whether compensated or decompensated. All patients received Led/Sof (Harvoni brand) with a fixed-dose combination tablet containing 90 mg of ledipasvir and 400 mg of sofosbuvir, one tablet daily for three months. Twelve weeks after the end of treatment (EOT), patients were tested for HCV PCR. Harvoni is a brand of the Gilead company that was provided by the Iraqi Ministry of Health (MOH). Patients with hepatocellular carcinoma (HCC), HCV genotypes other than GT 1 and 4, and patients with renal failure (RF) were excluded from the study. A consent form was signed by each participant prior to the commencement of data collection.

Anti-HCV antibody was assayed using a HISCL 5000 analyzer (Sysmex Corp., Kobe, Japan), and serum HCV RNA was quantified using a Roche COBAS® TagMan HCV Test (V3.0, cutoff value, 15 IU/mL; Roche Molecular Systems, Branchburg, NJ, USA). HCV genotyping was performed using a gene sequencing assay. Laboratory tests, including CBC, ALT, AST, prothrombin time, and serum HCV RNA quantitation, were repeated 12 weeks after EOT.

Patients' demographics (age, gender, smoking status, family history of HCV, and alcohol drinking) and clinical characteristics (comorbidities, treatment naïve or experienced, and patients' Child-Pugh score) were reported for all patients in a preformed questionnaire.

Comparison between continuous variables before and after treatment was performed by the paired Student t-test. Comparisons between categorical variables were performed by the chi-square test. All data were analyzed. Statistical processing of the data was performed using SPSS for Windows, v. 25.0 (IBM Corp., Armonk, New York, USA).

Results

The mean age of 122 patients was 37.34±15.31 years, with a range of 16 to 73 years. Males were more common than females (77 patients, 63.11%), with a male-to-female ratio of 1.7:1. One hundred thirteen patients (92.62%) had no family history of hepatitis C History of smoking and alcohol drinking in 31 (25.41%) and 3 (2.46%) patients, respectively. Comorbidities were reported in 43 patients (35.25%), with the most common comorbidities being diabetes (28 patients, 22.95%) and hypertension (12 patients, 9.88%) (Table 3).

Most patients (97 out of 122, 79.51%) were treatment naïve, while the remaining 25 patients (20.49%) were treatment experienced; 21 patients had cirrhosis (17.21%), 13 patients (61.9%) had compensated cirrhosis with Child Pugh A, and 8 patients (38.1%) had decompensated cirrhosis (5 patients were Child Pugh B and 3 patients with Child Pugh C). Genotype 4 was the most common genotype, reported in 60 patients (49.18%), followed by genotype 1a in 49 patients (40.16%), and finally genotype 1b in 13 patients (10.66%).

116 patients out of 122 (95.1%) achieved SVR, while 6 patients (4.9%) failed to achieve SVR. Regarding the changes in the liver function tests, there was a statistically significant reduction in the AST, ALT, ALP, and viral load after treatment with Led/Sof (Table 4).

AST = aspartate transferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase

In the treatment of naive patients, the SVR rates for GT1a and 1b were 34 (97.14%) and 9 (90%), respectively, and for genotype 4, it was 49 (94.23%) patients. While the SVR in treatment experienced patients with GT 1a, 1b, and 4 was 13(92.86%),3(100%) and 8(100%) patients, respectively. For 101 non-cirrhotic patients, the SVR rates were 38 (97.44%), 10 (100%), and 51 (98.08%) for GT 1a, 1b, and 4, respectively. For 21 cirrhotic patients, 8 (80%) with GT 1a achieved SVR, compared to 2 (66.67%) with GT 1b and 7 (87.5%) with GT 4 (Table 5).

The overall SVR rate for all HCV genotypes was 95.08%; genotype 4 was associated with the best SVR rate (96.67%). Both treatment naïve and treatment experienced patients had high SVR of 94.84% and 96%, respectively. Non-cirrhotic patients had better SVR (98.02%) than cirrhotic patients, whether compensated (76.92%) or decompensated (87.5%), as shown in Figure 1.

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Table 3.Demographic data of the study patients

(n=122)

Variables	Values
Age, years Mean±SD Range	37.34±15.31 16-73
Gender Male Female	77(63.11%) 45(36.89%)
Family History of hepatitis C and other diseases Yes No	9(7.38%) 113(92.62%)
Smoking Yes No	31(25.41%) 91(74.59%)
Alcoholism Yes No	3(2.46%) 119(97.54%)
Co-morbidities None Diabetes Hypertension Others	79(64.75%) 28(22.95%) 12(9.84%) 3(2.46%)

Table 4.Comparison of liver function tests before- and after treatment

(n=122)

Variable (Mean±SD)	Before treatment	After treatment	P-value
AST(IU/L)	41.66±30.69	23.02±11.21	<0.001
ALT(IU/L)	56.69±47.21	27.71±17.58	<0.001
ALP(IU/L)	108.52±58.56	86.72±43.42	<0.001
Viral load (IU/mL)	5777758.54±36767249.62	11.79±125.88	<0.001

AST = aspartate transferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase

Table 5.SVR of compensation and decompensation cirrhotic patients according to viral genotype

Viral Genotypes	Compensated (n=13)		Decompensated (n=8)	
	SVR (%)	Non-response (%)	SVR (%)	Non-response (%)
1a	3(75%)	1(25%)	5(83.33%)	1(16.67%)
1b	1(50%)	1(50%)	1(100%)	0(0%)
4	6(85.71%)	1(14.29%)	1(100%)	0(0%)

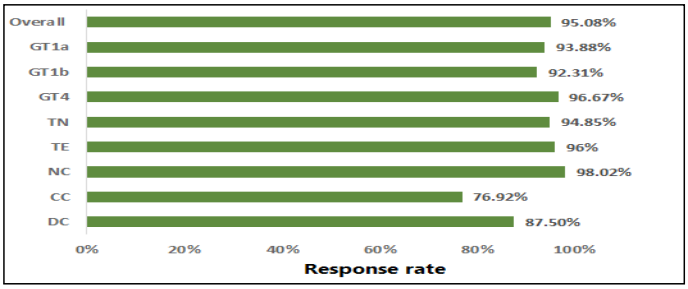

Figure 1.SVR according to HCV genotypes, previous HCV treatment (TN= treatment naïve, TE= treatment experience), and liver condition (NC=Non cirrhotic, CC=Compensated, DC= Decompensated

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Discussion

HCV GT 4 was found to be the most common GT among patients in this study, followed by GT 1a and 1b (49.18%, 40.16%, and 10.66%, respectively). This was consistent with other epidemiological studies conducted in Iraq (16, 17). Thus, there is a consensus that GT 4 and, to a lesser extent, GT 1 are responsible for the vast majority of HCV infection in Baghdad patients, although patients with other genotypes were excluded from this study.

The overall SRV rate was 95.08% and for GT 1a was 93.88%, for GT 1b was 92.31%, and for GT 4 was 96.67%. These results were in line with most previous studies worldwide, which reported a very high response rate for Led/Sof treatment in HCV GT 1 and 4.[18,19] The SVR was 94.85% among treatment naïve patients, while it was 96% in the treatment-experienced patients. These findings are similar to the results of other papers.[20,21,22]

According to the present study, non-cirrhotic patients had a remarkably higher SVR than cirrhotic patients (90.08% versus 80.95%). Other papers.[23,24,25] were in keeping with our study. The exact mechanism by which liver cirrhosis influences the response rate is not clear. However, the changes in homeostasis and liver circulation may be explained by this.

In this study, patients with decompensated cirrhosis had a higher SVR than those with compensated cirrhosis (87.5% versus 76.92%). Most previous studies indicated no significant difference in SVR between compensated and decompensated cirrhosis.[18,22] This incongruence may be due to the small sample size in the present study.

Led/Sof treatment was significantly associated with improved liver enzymes; these results are consistent with other recent studies.[26,27]

Conclusions

Led/Sof (Harvoni) is an effective drug used to treat HCV, in particular GT 4 and GT 1, as it has a high SVR in treatment-naïve, treatment-experienced, cirrhotic, or non-cirrhotic patients. Patients with liver cirrhosis had lower SVR12 than those without cirrhosis; treatment with Led/Sof was associated with significant improvement in liver function tests. HCV GT4 was the most prevalent genotype.

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