Sustained Virological Response among Chronic Hepatitis C Patients Treated with Ledipasvir-Sofosbuvir in Yemen

Al-Amrani et al. Mansour A. Al-Amrani, Saleh S. Bahaj, and Enas A. Al-Ammari.

[1]Professor of Hepatology and Gastroenterology, Faculty of Medicine in Sana'a Yemen
[2]Professor of Medical Microbiology and Immunology, Faculty of Medicine in Sana'a Yemen
[3]Faculty of Medicine and Health Sciences Department of Medical Microbiology in Sana'a Yemen

Abstract— Hepatitis C virus (HCV) infection is a liver disease which spreads primarily through contact with the blood of an infected person. HCV infection can be either acute or chronic and affects mainly the liver. This non-randomized controlled trial study aimed to determine the success rate of SVR among chronic HCV patients treated with LDV/SOF in Yemen. This study was performed on 43 patients with chronic HCV infection who agreed to take the new treatment of HCV and attend hepatology clinics at HBGSRC. They were 21 (48.8%) males and 22 (51.2%) females, and the mean±SD of age was 54.0±9.7. All the information related to each individual was collected by using predesigned questionnaires that focused on socio-demographic data and risk factors. Blood specimens were collected from patients at four stages. The study showed a high success rate of SVR among chronic HCV patients treated with LDV/SOF as 39 (90.7 %) achieved positive SVR response while 4 (9.3%) patients failed to achieve the SVR. There were statistically significant differences in ALT, AST and AFP levels before treatment and at SVR P. value= (<0.001, <0.001 and 0.02) respectively. All patients completed the full course of LDV/SOF and there were not any reported severe side effects accompanied by the drug. We concluded that LDV/SOF is safe, highly effective with SVR success rate and provide high patient adherence. Therefore, our recommendation of hepatologists in Yemen to use this new LDV/SOF regimen for the treatment of HCV.

Keyword: Chronic Hepatitis C Patients, Ledipasvir, Sofosbuvir.

1 INTRODUCTION

Hepatitis C virus (HCV) infection is a major problem affecting about 184 million people worldwide, or roughly 3% of the world's population is currently infected (Hadigan, et al. 2011)[1]. While most countries have prevalence rates ranging from 1 to 2%, there are some countries with relatively high prevalence rates, including Egypt (15%), Pakistan (4.7%) and Taiwan (4.4%) (Sievert *et al*, 2011) [2]. In Yemen, The HCV infection prevalence rate is about 2% (Chaabna *et al*, 2016) [3]. HCV infection is one of the major causes of chronic liver-related diseases, including cirrhosis, liver failure and hepatocellular carcinoma (HCC) (Jazag *et al*, 2012) [4]. Since the identification of HCV, great strides have been made in the development of anti-HCV therapy (Feld and Hoofnagle, 2005) [5]. Initial studies used conventional interferon monotherapy (Hoofnagle *et al*, 1986) [6]. Subsequently, co-administration of ribavirin and polyethylene glycol with interferon (PegIFN-α) were used (Nieforth *et al*, 1996; Bruno *et al*, 2004) [7,8]. However, these interferon-based regimens were complex, toxic and required 6-12 months of therapy (Lam *et al*, 2015) [9]. Therefore, strategies of anti-HCV viral therapy have been improved for decades. Newer interferon-free regimens are now available and approved by the Food and Drug Administration (FDA). In 2014, ledipasvir/sofosbuvir (LDV/SOF) became the first HCV drug that does not require co-administration of interferon and/or ribavirin (Mullins *et al*, 2015) [10]. This new HCV antiviral therapy has short durations (8, 12 or 24 weeks), minimal side effects and efficacy approaching 90-100% (Lam *et al*, 2015) [9]. The goal of antiviral therapy is to cure HCV infection by viral clearance, achieving a sustained virological response (SVR). SVR is defined as an absence of detectable HCV RNA in the serum 12 weeks after LDV/SOF therapy is complete (Kowdley *et al*, 2014) [11]. Aims of the study were conducted to determine the success rate of sustained virological response among chronic hepatitis C patients treated with ledipasvir/sofosbuvir and evaluate the safety of treatment (side effects or complications).

2 MATERIALS AND METHODS

This was a non-randomized controlled trial (single group) study carried out during the period from January 2017 to December 2017 at HBGSRC in Sana'a city, Yemen. Forty- three patients with chronic hepatitis C infection were enrolled in this study and agreed to receive a fixed-dose combination tablet of 90 mg of ledipasvir and 400 mg of sofosbuvir orally once daily for 12 weeks. We evaluated the response by measuring the viral load before, during and 12 weeks after stopping treatment. Chronic hepatitis C patients ≥ 18 years old of both sex. Patients who decided to start LDV/SOF therapy. Patients with the following conditions will be excluded: HCV/HBV dual infection, HCV/HIV dual infection, severe co-morbidity (heart failure or renal failure), Hypersensitivity to LDV/SOF and under antiviral therapy other than LDV/SOF. The history was taken from each patient by using a standard questionnaire including name, age, sex, address etc. The blood specimens were collected by Vacuum Blood Collection System, 2 ml of whole blood was put in a tube containing Ethylene Diamine Tetra Acetic acid (EDTA) for Hemoglobin (Hb) and platelets tests while 7 ml was put in a plain tube, serum was separated from this tube by centrifugation following clotting of blood, then, serum

was used in the determination of HCV viral load and Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alpha-fetoprotein (AFP), Albumin, Creatinine, and Thyroid-stimulating hormone (TSH) levels. Blood specimens were taken from each patient 4 time (before treatment, after 4 weeks of treatment, at the end of treatment (12 weeks) and 12 weeks after stopping treatment). Quantitative assessment for HCV-RNA was done by Real-Time PCR using COBAS® TaqMan® Analyzer with High Pure System HCV test kit. Analysis of the data was performed by using SPSS (Version 21) and the quantitative data were expressed as the mean and standard deviation (SD) or median and range. Paired t-test was used to compare the quantitative data with normal distribution before and after stopping treatment of the same patient. Repeated measure ANOVA test was used to compare the quantitative data with normal distribution of three stages (before, during and at SVR of treatment) in the same patient. Friedman test was used to compare the quantitative data with non-normal distribution of three stages (before, during and after stopping treatment) in the same patient. The qualitative data were expressed as numbers and percentages. Chi-square ($\chi 2$) test was used for categorical variables to determine the P. value. P. value ≤0.05 was considered statistically significant.

3 RESULTS

This study was conducted to determine the success rate of sustained virological response of 43 chronic hepatitis C patients who were treated with LDV/SOF at HBGSRC in Sana'a city, Yemen. The results of this study are presented in the following tables and figures.

TABLE 1: BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTIC OF THE STUDY POPULATION

n = 43

Age-years	**mean±SD**	**54.0±9.7**
Sex		**n (%)**
Male		21 (48.8)
Female		22 (51.2)
Viral load		
> 800000 (IU/ml)		26 (60.5)
≤ 800000 (IU/ml)		17 (39.5)
Diabetes		**n (%)**
Yes		15 (34.9)
No		28 (65.1)
Baseline viral load (IU/ml) median (range)		**559243 (123-9280000)**
Biochemical markers	**mean±SD**	
ALT U/L		67.3±15.8
AST U/L		63.5±18.5
AFP ng/mL		3.5± 0.9

In the **(Table 1**). showed the baseline demographic and clinical characteristic of chronic hepatitis C patients enrolled in this study. A total of 43 chronic hepatitis C patients (48.8% male, 51.2% female) with age more than or equal to 18 years old with mean value 54.0±9.7 participated in this study. The patients were divided into low viral load patients, with viral load less than 800,000 IU/ml, n =26 (60.5%), and high viral load patients, with viral load, more than or equal to 800,000 IU/ml, n =17 (39.5%). When it comes to the clinical characteristic of the population, were a diabetic whereas 28 (65.1) were non-diabetic. The baseline laboratory tests were baseline viral load (IU/ml) with median (range) 559243 (123-9280000), ALT (U/L) with mean±SD = 67.3±15.8, AST (U/L) with mean±SD = 63.5±18.5, AFP (ng/mL) with mean±SD =3.5±0.9.

In **(Table 2).** showed that all the 4 (100%) negative SVR patients were female whereas the positive SVR patients, 21 (53.8%) was male and 18 (46.2%) were female. No statistically significant difference between sex and SVR (P. value > 0.05).

In the (**Table 3)** showed that out of the 39 (90.7%) positive SVR, 25 (64.1%) patients had low viral load (viral load less than 800,000 IU/ml) and 14 (35.9%) had high viral load (more than or equal to 800,000 IU/ml) whereas, in 4 (9.3%) negative SVR, 1 (25 %) patient had low viral load and 3 (75%) had high viral load. No statistically significant difference between pre-treatment viral load and SVR (P. value >0.05).

In the **(Table 4)** exposed that out of the 39 (90.7%) positive SVR, 13 (33.3%) patients were diabetic and 26 (66.7%) were non-diabetic while in 4 (9.3%) negative SVR, 2 (50%) were diabetic and 2 (50%) were non-diabetic. There was no statistically significant difference between diabetes and SVR (P.value > 0.05).

This study is shown in **(Table 5),** the mean±SD of ALT level before treatment was 67.3±15.8 while at SVR it was 22.5±5.5. There was a statistically significant difference in ALT level before treatment and at SVR (12 weeks after stopping treatment) (P.value < 0.001). The mean±SD of AST level before treatment was 63.5±18.5 while at SVR it was 23±7.5. There was a statistically significant difference in AST level before treatment and at SVR (12 weeks after stopping treatment) (P.value < 0.001). The mean±SD of AFP level before treatment was 3.5± 0.9 while at SVR it was 2.5±1.1. There was a statistically significant difference in AFP level before treatment and at SVR (12 weeks after stopping treatment) (P.value = 0.02).

TABLE 5. ALT, AST AND AFP LEVEL BEFORE TREATMENT AND AT SVR AMONG CHRONIC HCV PATIENTS TREATED WITH LEDIPASVIR/SOFOSBUVIR IN YEMEN, 2017.

		Effect of treatment		Paired t-test	PV
		Before (n=43)	SVR (n=43)		
ALT level (U/L)	Mean±SD	67.3±15.8	22.5±5.5	9.8	>0.001
AST level (U/L)	Mean±SD	63.5±18.5	23±7.5	5.9	>0.001
AFP level (ng/mL)	Mean±SD	3.5± 0.9	2.5± 1.1	2.7	0.02

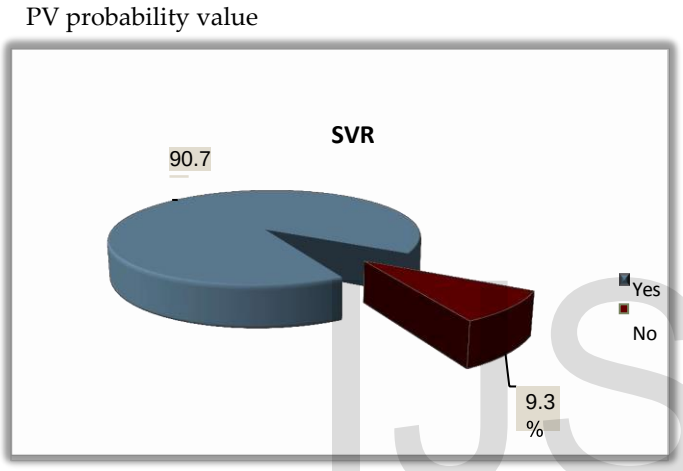

Fig. 1. The success rate of sustained virological response to chronic hepatitis C patients treated with ledipasvir/sofosbuvir in Yemen, 2017.

This study showed in the **(Figure 1**) a high percentage of 90.7% (95% CI [81.4-97.7]) of SVR among chronic HCV patients treat- ed with ledipasvir/sofosbuvir

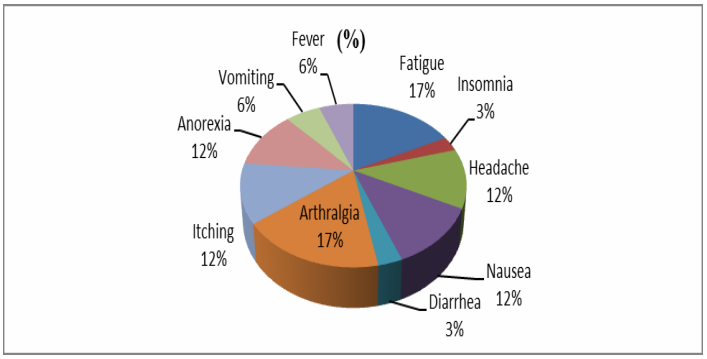

Fig. 2. shown side effects noted in patients treated with ledipasvir/sofosbuvir in Yemen, 2017.

This study shown in **(Fig. 2)** the side effects showed in the patients treated with LDV/SOF included fatigue (17%), insomnia (3%), headache (12%), nausea (12%), diarrhea (3%), arthralgia (17%), itching (12%), anorexia (12%), vomiting (6%) and fever (6%).

4 DISCUSSION

In recent years, the management of chronic hepatitis C virus (HCV) infection has been revolutionized by the introduction to interferon-free regimens consisting of oral DAA. These DAA regimens provide markedly better antiviral efficacy and tolerability than IFN regimens (Moon et al, 2017) [11]. One DAA regimen, the fixed-dose combination of the HCV N5A inhibitor ledipasvir and the NS5B inhibitor sofosbuvir (ledipasvir/sofosbuvir), was approved by the Food and Drug Administration (FDA) for the treatment of chronic HCV infection (Raedler, 2015) [12]. The main goal of the treatment of HCV is to achieve SVR. SVR has become the best indication of successful therapy for HCV infection (Lee and Friedman, 2014) [13]. In Yemen, the prevalence of HCV is documented. However, there are no studies concerning the SVR for LDV/ SOF. Our study was the first non-randomized controlled trial (single group) study conducted using DAA (LDV/ SOF) for HCV patients in Yemen to evaluate the efficacy and safety of using the 12-week treatment. The primary efficacy endpoint was the achievement of SVR. The SVR was evaluated by measuring HCV- RNA levels before, after 4 weeks and 12 weeks after stopping treatment. The results of our study were very encouraging as there was a statistically significant difference in viral load level before, during and after stopping treatment and the SVR rate was 90.7% (CI 81.4 -97.7). This result was in agreement with rates reported in clinical trials where the SVR rates were > 90% (Afdhal et al, 2014a; Afdhal et al, 2014b; Kowdley et al, 2014) [14,15,10]. In addition, the same result was reported by Abergel et al. (2016)[16] who showed that 44 patients with genotype 4 who initiated treatment with LDV/ SOF 41 (93%) reached the primary endpoint of SVR. However, in a study that was conducted in the Middle East and Africa by Kohli et al. (2015)[17], SVR was 100%. This small difference might be due to the difference in sample size. In the present study, there was no statistically significant difference between sex and SVR, (P. value=0.1). The same result was reported by Tsuji et al. (2018) [18] who showed that there was no statistically significant association with sex and SVR. The different finding was reported by O'brien et al. (2014) [19] who found a statistically significant difference between sex and SVR (PV=0.0008) and that women are more likely to clear HCV infection after treatment with LDV/ SOF. They justified their result stating that women are more likely to clear HCV spontaneously. In this present study, there was no statistically significant difference in SVR between those who had low baseline viral load < 800.000 IU/ml and who had a high baseline viral load ≥ 800.000 IU/ml (PV=0.3). This result was in confirming with a study reported by Backus et al. (2016)[20] who showed that there was no statistically significant association with baseline viral load and SVR in patients treated with

LDV/SOF. Furthermore, the same result was reported by Wong et al. (2017)[21] who showed that no significant differ-

ence in achieving SVR was observed when evaluating treatment outcomes by baseline HCV viral load (PV= 0.326). The present study showed that there was no statistically significant association with diabetes and SVR. This result was in confirming with a study reported by Backus et al. (2016) who found that diabetes did not predict SVR in patients treated with (LDV/ SOF). In our study, the number of patients with HCV suffering from diabetes was 15 (34.9)%. This confirmed the results of the previous studies by Kralj et al. (2016)[22]; Yoneda et al. (2007)[23] which proved the association with HCV and diabetes. These studies proved that HCV infection leads to insulin resistance, which, in turn, leads to type II dia- betes. Overall, the safety of LDV/SOF in HCV-infected pa- tients was consistent. In particular, this interferon- and ribavi- rinfree therapy was not associated with worsening of blood counts and renal function. Laboratory monitoring during and after treatment showed that LDV/SOF had no association with treatment-emergent anemia or decline in platelets. These results were in accordance with a study by Alqahtani et al. (2015)[24] who reported that treatment of LED/SOF alone was safer in patients with HCV infection. Our study was completely different from other studies that targeted patients treated with LED/SOF combination of ribavirin or interferon base treatment, as they reported anemia in many patients due to ribavirin and/or interferon (Lawitz et al, 2014; Sulkowski, 2005) [25,26]. This is likely a consequence of the fact that both Peg-IFN and RBV inhibit erythroid proliferation and differentiation, thereby contributing to anemia (Alqahtani et al, 2015). As a result, LDV/SOF has provided an opportunity to expand HCV treatment options of these patients for whom older regimens were relatively contraindicated. Another encouraging finding of our study was the impressive decrease in patients' liver enzymes and AFP. Albumin level stayed relatively stable from baseline throughout the 12- weeks posttreatment. These findings suggest that the drugs not only cleared the virus but also improved liver function in as short period of time. A similar study reported the decline in liver enzymes during treatment of LDV/SOF (Saab et al, 2017)[27]. All participants completed the full course of LDV/SOF and none discontinued treatment due to side effects. The most common side effects showed in the patients treated with LDV/SOF included fatigue (17%), insomnia (3%), headache (12%), nausea (12%), diarrhea (3%), arthralgia (17%), itching (12%), anorexia (12%), vomiting (6%) and fever (6%). which were not different from those reported in previously published studies on the use of LDV/SOF (Oderda, 2015; Mizokami *et al*, 2015; Wilder *et al*, 2016) [28,29,30]. The low incidence of adverse events coupled with the brief duration of this regimen contrast favorably with interferon-based treatment, which might mean that this combination treatment could improve treatment adherence and completion compared with interferon-based treatment (Lawitz *et al*, 2013) [31]. In the limitation of this study, genotype determination tests were not performed because many chemical reagents are not available due to the ongoing war although LED/SOF has pan-genotypic effect (Øvrehus *et al*, 2018) [32].

5 Conclusion and Recommendations

This study concluded the LDV/SOF therapy was a highly effective treatment for patients with chronic hepatitis C, moreover, was no statistically significant association between risk factors (age, sex, previous treatment, baseline viral load, EVR, and diabetes) and SVR. The laboratory monitoring showed an impressive decrease in liver enzymes over the course of treatment. Additionally, LDV/SOF therapy was safe. Furthermore, the treatment adherence was very high. Therefore, we suggest recommended hepatologists should replace the old drug (interferon-based treatment) with the new drug (LDV/SOF). Ministry of Public Health and Population should put greater emphasis on public health education, particularly creating awareness about the risk factors of hepatitis C virus infections (prevention is better than cure).

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Conflict of Interests Declaration

No

Funding

No

Abbreviation

AFP, Alpha Feto-Protein

ALT, Alanine Aminotransferase

AST, Aspartate Aminotransferase

SVR, Sustained virological response

WHO, World Health Organization

X2, Chi-Square

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TABLE 2
ASSOCIATION WITH SEX AND SVR AMONG CHRONIC HCV PATIENTS TREATED WITH LEDIPASVIR/SOFOSBUVIR IN THE REPUBLIC OF YEM- EN, 2017.

Sex	SVR						*χ^2	PV	RR	95% CI	
	+ve		-ve		Total						
	No	%	No	%	No	%				Lower limit	Upper limit
M	21	53.8	0	0	21	48.8					
F	18	46.2	4	100	22	51.2					
Total	39	90.7	4	9.3	43	100	2.3	0.1	1.2	1.0	1.5

*FISHER EXACT; X2 CHI-SQUARE; PV PROBABILITY VALUE; RR RELTIVE RISK; CL CONFIDENCE INTERVAL

TABLE 3. ASSOCIATION WITH PRE-TREATMENT VIRAL LOAD AND SVR AMONG CHRONIC HCV PATIENTS TREATED WITH LEDIPASVIR/SOFOSBUVIR IN YEMEN, 2017.

Pretreatment Viral load	SVR						*χ^2	PV	RR	95% CI	
	+ve		-ve		Total						
	No	%	No	%	No	%				Lower limit	Upper limit
Low	25	64.1	1	25	26	60.5					
High	14	35.9	3	75	17	39.5					
Total	**39**	**90.7**	**4**	**9.3**	**43**	**100**	2.3	0.3	1.2	0.9	1.5

*Fisher Exact χ^2 Chi-Square; PV probability Value; RR Relative Risk; Cl Confidence Interval

TABLE (4). ASSOCIATION WITH DIABETES AND SVR AMONG CHRONIC HCV PATIENTS TREATED WITH LEDIPAS-VIR/SOFOSBUVIR IN YEMEN, 2017.

Diabetes	SVR						*χ^2	PV	RR	95% CI	
	+ve		-ve		Total						
	No	%	No	%	No	%				Lower limit	Upper limit
Yes	13	33.3	2	50	15	34.9					
No	26	66.7	2	50	28	65.1					
Total	**39**	**90.7**	**4**	**9.3**	**43**	**100**	0.4	0.6	0.9	0.7	1.2

Fisher Exact x^2 Chi-Square; PV probability Value; RR Relative Risk; Cl confidence Interval