Original Article

Daclatasvir/Sofosbuvir versus Ledipasvir/Sofosbuvir in Patients with Hepatitis C Virus Infection Genotypes 1 and 3

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Abstract

Background: The new direct-acting antiviral agents (DAAs) with high efficacy, low resistance, and low rate of adverse events (AEs) have shown promising outcomes for hepatitis C virus (HCV) treatment. This study assessed the efficacy and safety of Daclatasvir/Sofosbuvir (DCV/SOF) compared to Ledipasvir/Sofosbuvir (LDV/SOF) in patients with HCV infection in the real-world setting in Iran.

Materials and Methods: A total of 42 patients with HCV infection were treated with either LDV/SOF (genotype 1) or DCV/SOF (genotypes 1, 3 or unknown) with or without ribavirin (RBV). Assessment of risk factors, laboratory tests, sustained virologic response at post-treatment week 12 (SVR12), and AEs were performed.

Results: The highest risk factor for HCV transmission was major surgery (50.0%), followed by tattooing (40.5%), phlebotomy (40.5%), and dental surgery (40.5%). No statistically significant relationships between genotypes and risk factors were observed. In both treatment groups (LDV/SOF and DCV/SOF), all of the patients (100%) with or without cirrhosis and treatment-experience achieved SVR12. One patient with a history of failed LDV/SOF therapy achieved SVR12 following retreatment with DCV/SOF. Both treatment regimens were well-tolerated. No serious AEs or discontinuation due to AEs was observed. The most common AE across both treatment groups were fatigue (42.9%), followed by anxiety (28.6%). Numerically, more adverse events were found with the LDV/SOF regimen than with the DCV/SOF regimen.

Conclusion: Our study showed an excellent safety and efficacy of DCV/SOF and LDV/SOF in Iranian patients infected with HCV. The incidence of AEs among patients treated with LDV/SOF was higher than those receiving SOF/DCV.

Keywords: Hepatitis C, Real-world data, Direct-acting antiviral agents, Risk factors

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Introduction

Hepatitis C virus (HCV) infection is a major cause of liver diseases, hepatic cirrhosis and hepatocellular carcinoma (HCC). Worldwide, over 170 million individuals are infected with HCV, and approximately 71 million people had viraemic infections in 2015[1]. In Iran, HCV prevalence is less than 0.5%, equating 186500 people[2]. Before 2014, pegylated- interferon (PEG- IFN) in combination with ribavirin (RBV) was the only drug approved by the United States Food and Drug Administration (FDA) for HCV treatment[3]. However, limitations such as low sustained virologic response (SVR) rate and significant side effects have

restricted interferon-based therapy[4]. Since 2011, the new direct-acting antiviral agents (DAAs) with high efficacy, low resistance, and low rate of adverse events have shown promising outcomes for HCV treatment[5], of which Sofosbuvir (SOF), Ledipasvir (LDV) and Daclatasvir (DCV) are currently available in Iran[2]. HCV genotypes (GTs) are diverse across the world with each one having a unique response to antiviral treatment[6, 7]. Globally, the most common genotype is HCV GT-1 (46%), and in Iran, GT-1 and 3 are the major genotypes[2, 5]. Since 2014, LDV/SOF combination has been approved by the FDA to treat HCV infection genotypes 1, 4, 5, and 6 for patients with or without cirrhosis, HCC, and prior treatment[5, 8]. DCV/SOF has been proven to be active against all common genotypes, and also can be safely effective for patients with HIV-HCV co-infection and advanced liver diseases[9]. Most real-world studies on DAAs are related to the West, and data from Asia or developing countries are limited. In this study, we assessed the efficacy and safety of SOF/DCV compared to SOF/LDV in patients with HCV infection, with or without cirrhosis and treatment experience in the real-world setting in Iran.

Methods

Study design and participants:

This was an open-label trial study of patients with chronic HCV infection, who visited Labbafinezhad Hospital between October 2017 and November 2018. Patients were treated with either LDV 60 mg plus SOF 400 mg, once-daily for 12 weeks (genotype1), or DCV 60 mg/SOF 400 mg once daily for 12 weeks (GT1, 3, or unknown genotype). Adding RBV or increase in the treatment duration may occur at the physician's discretion. Adding RBV to the patient's treatment regimen might occur if the patient had either cirrhosis or HCV treatment experience. Patients were excluded from our study if they became pregnant during their treatment or did not complete their assigned treatment. Patient demographics, risk factors, serum viral load, HCV genotype, cirrhosis status, HCV treatment experience, HBV co-infection, laboratory tests and liver enzymes before treatment, end of treatment and 12 weeks after end of treatment were reviewed from the patient's clinical records. Liver cirrhosis was diagnosed based on clinical findings, laboratory results, biopsy or Fibroscan (liver stiffness value>13 kPa).

Assessment:

The primary endpoint was defined by sustained virologic response at 12 weeks after end of treatment (SVR12). Adverse events (AEs) and abnormality in laboratory tests and liver enzymes were also assessed.

Statistical analysis:

Statistical analyses were performed using Chi-square test for categorical variables, and the Student's t-test or the Mann-Whitney U test for continuous variables via the SPSS version 24.0. P values of < 0.05 were considered statistically significant.

Ethics:

This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences and the Infectious Diseases and Tropical Medicine Research Center (approval number: Ir.sbmu.msp.rec.1397.131) which was in accordance with the Helsinki Declaration.

Results

Baseline characteristics:

Of the 45 patients who were screened across our study, one patient became pregnant at week 5 of treatment, and was removed from our cohort, and 2 were lost to follow-up. Of the 42 remaining patients, 35 were treatment-naïve, and 7 were treatment-experienced. Among the treatment-experienced patients, 3 received LDV/SOF for 12 weeks, 2 received DCV/SOF for 12 weeks, one patient with cirrhosis received LDV/SOF/RBV for 12 weeks, and one received DCV/SOF/RBV for 24 weeks. Treatment-naïve patients were as follows: 18 received LDV/SOF for 12 weeks, one received DCV/SOF for 24 weeks, 4 with cirrhosis received LDV/SOF/RBV for 12 weeks, one received DCV/SOF/RBV for 12 weeks, and one with cirrhosis received DCV/SOF/RBV for 24 weeks, 10 received DCV/SOF for 12 weeks (figure 1). One patient in the LDV/SOF group had co-infection with HBV-HCV.

Overall, HCV genotypes were as follows: 1a (15/42; 35.7%), 1a/1b (14/42; 33.3%), 3a (8/42; 19.0%) and 11.9% (5/42) were unknown. In the LDV/SOF group, 50.0% (13/26) of patients were GT 1a, and the rest (13/26) were GT 1a/1b. In the DCV/SOF group, the most common GT was 3a (8/16; 50.0%), followed by

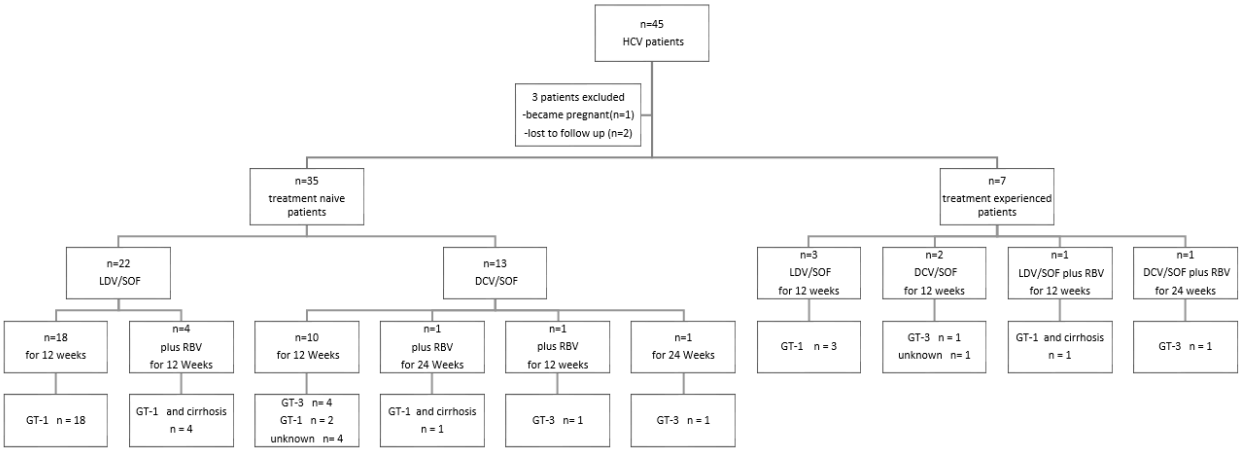

Figure 1. Flow chart of patients throughout the study. HCV, hepatitis C virus; SOF, sofosbuvir; LDV, ledipasvir; DCV, daclatasvir, RBV, ribavirin.

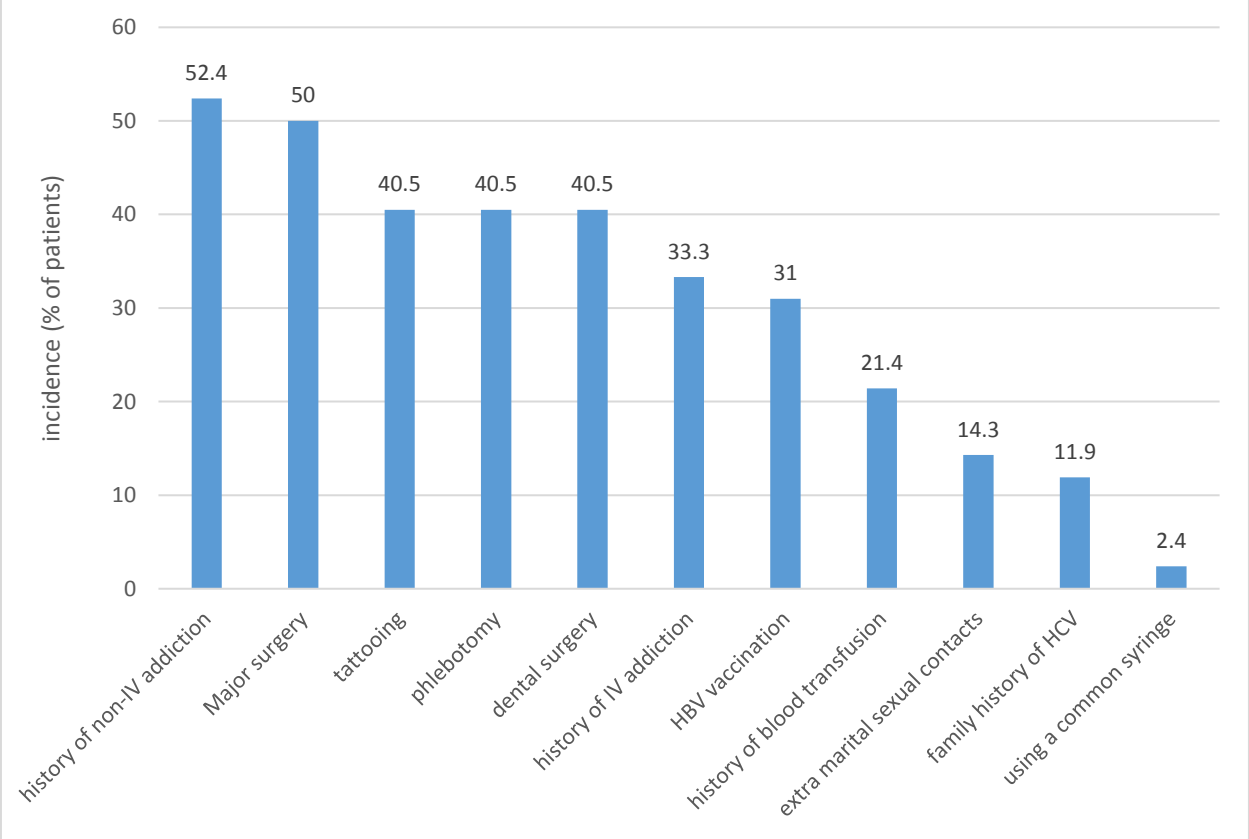

Figure 2. Distribution of risk factors.

unknown (5/16; 31.3%), 1a (2/16; 12.5%), 1a/1b (1/16; 6.3%). 9.5% of patients had a platelet count of less than 90,000 per mm^3. 2.4% had an albumin level ≤ 3.5 g/dL. No patients had both a platelet count of less than 90,000 per mm^3 and an albumin level of less than 3.5 g/dL. 35.7% and 16.7% had an ALT and AST level of more than 1.5 x ULN, respectively. 14.3% had both an ALT and AST level of more than 1.5 x ULN. There were no significant differences in baseline characteristics of patients between two treatment groups (table 1).

Overall, the highest risk factor for HCV transmission

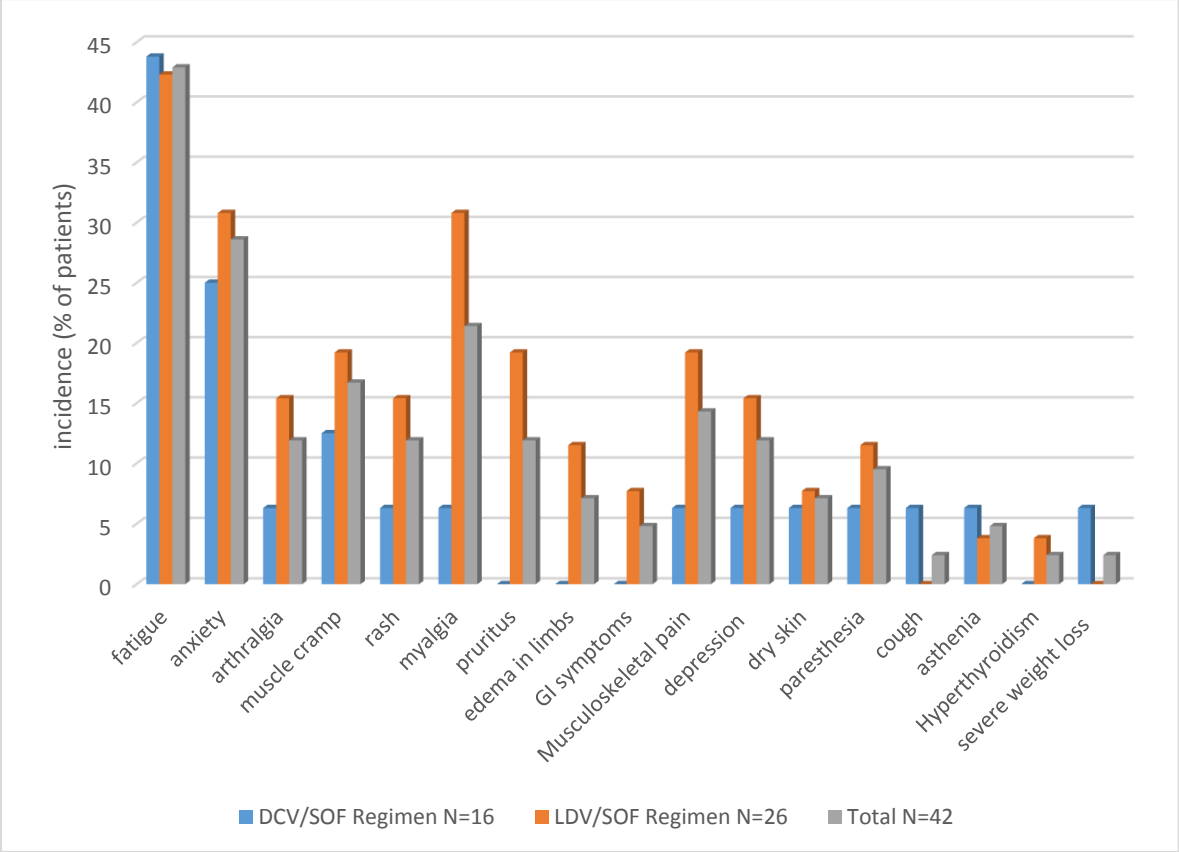

Figure 3. Adverse events during treatment.

was major surgery (50.0%; 21/42), followed by tattooing (40.5%; 17/42), phlebotomy (40.5%; 17/42), dental surgery (40.5%; 17/42), and history of IV-drug use (33.3%; 14/42) (Figure 2). No statistically significant relationships between genotypes and risk factors were observed (Table 2).

Efficacy:

In the LDV/SOF group with or without RBV, all 26 patients (13 patients with subtype 1a, 13 with subtype 1a/1b) (100%) achieved SVR12. Among the 16 patients (8 individuals with GT-3, 3 with GT-1, 5 with unknown genotype) who received DCV/SOF with and without RBV, the rate of SVR12 was 100%. One patient with an unknown genotype and a history of failed LDV/SOF therapy achieved SVR12 following retreatment with DCV/SOF. No SVR12-related P value was computed since SVR12 was a constant.

Safety:

Overall, of the 42 patients, 25 (59.5%) had at least one adverse event (AEs), of whom 9 (56.2%) and 16 (61.5%) were in the DCV/SOF and LDV/SOF groups, respectively. The most common AEs across both treatment groups were as follows: fatigue (42.9%), anxiety (28.6%), myalgia (21.4%), muscle cramp (16.7%), musculoskeletal pain (14.3%). No patients discontinued treatment due to AEs. Similar proportion of patients with at least one AE was observed in two treatment groups (9 (56.2%) versus 16 (61.5%)). Numerically, more adverse events were found with the LDV/SOF regimen than with the DCV/SOF regimen (arthralgia (15.4% versus 6.3%), muscle cramp (19.2% versus 12.5%), rash (15.4% versus 6.3%), myalgia (30.8% versus 6.3%), pruritus (19.2% versus 0%), edema in limbs (11.5% versus 0%), musculoskeletal pain (19.2% versus 6.3%), GI symptoms (7.7% versus 0%), depression (15.4% versus 6.3%), paresthesia (11.5% versus 6.3%). Numerically, no higher rate of AEs was observed in patients with RBV-containing regimen or 24 weeks of treatment than those not receiving RBV or treated for 12 weeks. Totally, there were no hemoglobin levels <10 g/dL, no platelet count of less than 50,000, no AST/ALT elevations > 5.0 x

Table 1: Baseline characteristics of patients treated with SOF/DCV or SOF/LDV.

Baseline patient characteristics	**LDV/SOF Group**	**DCV/SOF Group**	**P value**
Sex (male), no %	19 (73.1)	14 (78.5)	0.224
Age – yr	49.08±2.929	44.79±2.993	0.353
Baseline viral load, no %			0.504
≤2,000,000 IU/mL	10 (38.5)	7 (43.7)	
>2,000,000 IU/mL	15 (57.7)	9 (56.3)	
Cirrhosis, no %	5 (19.2)	1 (6.3)	0.380
Fibrosis, no %	3 (11.5)	0	0.275
Fatty liver, no %			0.376
Grade I	2 (7.7)	5 (31.3)	
Grade II	2 (7.7)	1 (6.3)	
Prior treatment, no %			1.00
PEG-INF/RBV	4(15.3)	1 (6.3)	
SOF/RBV	0	1 (6.3)	
LDV/RBV	0	1 (6.3)	
Treatment duration, no %			
24 W	0	3 (18.8)	
12 W	26 (100)	13 (81.3)	
Adding RBV, no %	5 (19.2)	3 (18.8)	1.00
Albumin g/dL , median (range)	4.6(3.5-5.2)	4.6(4.2-6.7)	0.084
Albumin ≤3.5 g/dL, no %	1(3.8)	0	
Hemoglobin g/dL , median (range)	14.1(9.5-17.7)	14.2(12.8-17.4)	0.277
INR ,median (range)	1.1(.9-2.1)	1.1(1-1.6)	0.485
PT second, median (range)	12.5(9.6-15.6)	12(9-17)	0.313
Bilirubin mg/dL , median (range)	1(.3-2.1)	1(.5-5.1)	0.647
Platelets x 10^3 per mm^3, Median (range)	206.5(45-350)	242(78-320)	0.398

Platelet count≤90,000 per mm³, no %	2 (7.7)	2 (12.5)	
ALT IU/L, median (range)	40.5(17-123)	41(15-149)	0.826
ALT > 1.5 x ULN, no %	9 (34.6)	6 (37.5)	
AST IU/L, median (range)	34(16-245)	38.5(20-119)	0.826
AST > 1.5 x ULN, no %	5 (19.2)	2 (12.5)	

Table 2: Risk factor distribution according to HCV genotypes.

	HCV genotypes, NO (%)				
Risk factors	1a,15 (100)	1a/1b, 14 (100)	3a, 8 (100)	Total, N=37	P value
Major surgery	8 (53.3)	9 (64.3)	4 (50.0)	21 (56.8)	0.834
tattooing	4 (26.7)	5 (35.7)	5 (62.5)	14 (37.8)	0.382
phlebotomy	6 (40.0)	6 (42.9)	6 (75.0)	18 (48.6)	0.356
dental surgery	6 (40.0)	7 (50.0)	3 (37.5)	16 (43.2)	0.860
history of IV addiction	4 (26.7)	3 (21.4)	2 (25.0)	9 (24.3)	0.921
HBV vaccination	3 (20.0)	6 (42.9)	6 (75.0)	15 (40.5)	0.358
history of blood transfusion	3 (20.0)	3 (21.4)	3 (37.5)	9 (24.3)	0.476
extra marital sexual contacts	2 (13.3)	3 (21.4)	3 (37.5)	8 (21.6)	0.828
family history of HCV	1 (6.7)	3 (21.4)	3 (37.5)	7 (18.9)	0.261
using a common syringe	0	1 (7.1)	0	1 (2.7)	0.446

ULN, no bilirubin levels > 2.5 x ULN, and no INR > 2.0 x ULN at 12 weeks after end of treatment (table 3, figure 3)

Discussion

In the present study, distribution of HCV subtypes was as follows: 1a (35.7%), 1a/1b (33.3%), 3a (19.0%) and 11.9% were unknown. This result was consistent with a study by Jahanbakhsh Sefdi et al., performed on 11,561 chronically HCV infected patients in Iran, reporting that subtype 1a (44.9%) was the most common subtype[6]. Nonetheless, it is in contrast to observations in other studies in Iran by Ranjbar Kermani et al.[10], Sofian et al.[11], and Ansari et al.[12], which showed the prevalence of subtype 3a was 61.3%, 52.9%, 52.0%, respectively.

Some studies revealed that HCV mixed-genotype infection may lead to severe disease, unresponsiveness to antiviral treatment or relapse after antiviral therapy[6, 13]. Our data showed a high rate of mixed HCV infection subtype 1a/1b (33.3%), which is comparable with the finding by Sofian et al.[11] and Rafiei et al.[14], that found the presence of subtype 1a/1b was 17.8% and 8.2% in Iranian patient populations, respectively. Moreover, a study by Ansari et al.[12] in Iran demonstrated a high rate of mixed-genotype infections (20.0%). Nevertheless, our result is in contrast to other Iranian studies[6, 10], stating that no or a few mixed infections were observed. It seems that the prevalence of mixed HCV infections are due to different studied populations, genotyping

Table 3: Adverse events during treatment.

EVENTs, n%	**DCV/SOF Regimen N=16**	**LDV/SOF Regimen N=26**	**Total N=42**
patients with at least 1 AE	9 (56.2)	16(61.5)	25(59.5)
serious AE	0	0	0
death	0	0	0
AE leading to discontinuation	0	0	0
fatigue	7 (43.8)	11 (42.3)	18 (42.9)
anxiety	4 (25.0)	8 (30.8)	12 (28.6)
arthralgia	1 (6.3)	4 (15.4)	5 (11.9)
muscle cramp	2 (12.5)	5 (19.2)	7 16.7)
rash	1 (6.3)	4 (15.4)	5 (11.9)
myalgia	1 (6.3)	8 (30.8)	9 (21.4)
pruritus	0	5 (19.2)	5 (11.9)
edema in limbs	0	3 (11.5)	3 (7.1)
GI symptoms	0	2 (7.7)	2 (4.8)
Musculoskeletal pain	1 (6.3)	5 (19.2)	6 (14.3)
depression	1 (6.3)	4 (15.4)	5 (11.9)
dry skin	1 (6.3)	2 (7.7)	3 (7.1)
paresthesia	1 (6.3)	3 (11.5)	4 (9.5)
cough	1 (6.3)	0	1 (2.4)
asthenia	1 (6.3)	1 (3.8)	2 (4.8)
Hyperthyroidism	0	1 (3.8)	1 (2.4)
severe weight loss	1 (6.3)	0	1 (2.4)
Laboratory abnormalities			
Platelet count≤ 50,000 per mm^3, n %	0	0	0
Hemoglobin level, n %			
< 10 g/dL	0	0	0
< 8.5 g/dL	0	0	0
INR > 2.0 x ULN, n %	0	0	0

Bilirubin > 2.5 x ULN, n %	0	0	0
ALT			
> 2.5 x ULN, n %	0	1 (3.8)	1 (2.4)
> 5.0 x ULN, n %	0	0	0
AST			
> 2.5 x ULN, n %	1 (6.3)	0	1 (2.4)
> 5.0 x ULN, n %	0	0	0

methods, and rout of transmission[12, 13].

The results of this study indicated that the highest risk factor for HCV transmission was major surgery (50.0%), followed by tattooing (40.5%), phlebotomy (40.5%), dental surgery (40.5%), and history of IV-drug use (33.3%). Nevertheless, our finding is in contrast to observations by other Iranian studies [2, 15-17], showing intravenous drug users (IVDUs) were the main population at risk of HCV infection. This difference may be due to our small size of studied population (Figure 2).

Numerous investigators demonstrated that the route of HCV transmission may affect the HCV genotype distribution [18, 19]. In our data, the most common risk factor for subtype 1a was major surgery (8/15, 53.3%), followed by dental surgery (6/15, 40.0%), and phlebotomy (6/15, 40.0%). In our patients with HCV subtype 1a/1b, the risk factors were as follows: major surgery (64.3%, 9/14), dental surgery (50%, 7/14), phlebotomy (42.9%, 6/14), tattooing (35.7%, 5/14). The authors presumed that there may be an association between surgery and HCV infection GT 1 although there was no statistically significant difference (Table 2). This finding is similar to some recent studies [20-22], which reported an association between surgery and GT 1. In patients with subtype 3a, the highest risk factor was phlebotomy (6/8, 75.0%), followed by tattooing (5/8, 62.5%), although no statistically significant relationships were observed (Table 2). Our result is in consistent with a study in Iran [10], and France [23] , showing an association between tattooing and subtype 3a. However, our finding is in contrast to some studies [18, 19, 21] demonstrating that IV-drug users may be associated with GT 1 and 3.

In the management of HCV-GT 1 infection, the LDV/SOF regimen with or without ribavirin (RBV) can be applied for non-cirrhotic patients or those with compensated cirrhosis [24]. Our real-world data of patients with HCV GT-1 (13 patients with subtype 1a, 13 with subtype 1a/1b), who received SOF/LDV with or without RBV, showed that the SVR12 rate was 100%. Our result showed a higher rate of SVR12 than those reported from clinical trials and other real life studies around the world [5, 24-28], which demonstrated the SVR12 rates were generally 91% to 98%. However, our data was similar to a study in India, which showed SVR12 was 100% in 145 HCV GT-1 patients treated with LDV/SOF with or without RBV [26].

Some investigators reported that in HCV GT-1 patients treated with LDV/SOF, cirrhosis may lead to lower SVR12 rate due to lower drug delivery, altered drug metabolism, and impaired immune response [5, 27]. Increase in treatment duration to 24 weeks or addition of RBV may help to improve the SVR12 rate in these patients [5]. In our study, 4 cirrhotic, HCV GT-1 patients treated with 12 weeks of LDV/SOF plus RBV, and one patient with cirrhosis, HCV-treatment experience, and GT-1 who received a 12-week treatment with LDV/SOF plus RBV, achieved SVR12. It seems that the addition of RBV may be a benefit to improve the SVR12 rate in cirrhotic patients especially in situations in which next generation DDAs are not available.

In the current study, among the 16 patients (8 individuals with GT-3, 3 with GT-1, and 5 with unknown genotype) who received DCV/SOF with and without RBV, the rate of SVR12 was 100%. Our data was comparable to the findings from clinical trials and other real-life studies across the world [9, 26, 29-33], which showed a high efficacy of DCV/SOF with or without RBV.

In the present study, one patient with an unknown genotype and a history of failed LDV/SOF therapy achieved SVR12 following retreatment with DCV/SOF. A possible reason for failure with LDV/SOF may be due to viral genotype. Studies showed that the SVR rate for HCV GT-3 patients receiving LDV/SOF is low (approximately 62.0%) [2]. Moreover, resistance-associated substitutions may lead to different resistance fold changes in different DAA-based regimens [1]. No common AEs were observed during retreatment with DCV/SOF.

The authors presume that the high rate of SVR12 (100%) in both treatment groups (LDV/SOF and DCV/SOF) in our study may be due to the small number of patients, having no HCV GT-3 patients with cirrhosis (difficult to treat patients), and no or few patients are co-infected with HBV or HIV.

In our study, both treatment regimens (LDV/SOF and DCV/SOF) were well-tolerated. No serious AEs or discontinuation due to AEs were observed. At least one adverse event occurred in 61.5% (16/26) and 56.2% (9/16) of patients in the LDV/SOF and DCV/SOF groups, respectively. Our result showed a lower risk of AEs than report from the ION phase 3 study [24], which observed treatment –related AEs in 74% of non-cirrhotic patients treated with LDV/SOF and 88% of cirrhotic patients who received LDV/SOF plus RBV. In our data, no higher rate of AEs were observed in patients with RBV-containing regimen or 24 weeks of treatment than those not receiving RBV or treated for 12 weeks. However, our result is in contrast to the phase 3 studies which reported a higher incidence of AEs among the patients treated with LDV/SOF plus RBV than those treated with LDV/SOF alone [24]. In the LDV/SOF group, the most common adverse event was fatigue (42.3%), followed by anxiety (30.8%), myalgia (30.8%), muscle cramp (19.2%), pruritus (19.2%), and musculoskeletal pain (19.2%). Among the patients treated with SOF/DCV, the major adverse event was fatigue (43.8%), followed by anxiety (25.0%). Numerically, more adverse events were found with the LDV/SOF regimen than with the DCV/SOF regimen.

In our study, there were several limitations. First, the small number of patients in two treatment groups, and subgroups with cirrhosis and prior treatment-experience which limits the comparison between them. Second, lack of RAS testing which limits the analysis of the impact of resistance-associated substitutions on the efficacy of treatment.

Conclusion

Our study showed an excellent safety and efficacy of DCV/SOF and LDV/SOF in Iranian patients infected with HCV. Although, the incidence of AEs among the patients treated with LDV/SOF was higher than those receiving SOF/DCV. The highest risk factor for HCV transmission was major surgery (50.0%), followed by tattooing (40.5%), phlebotomy (40.5%), dental surgery (40.5%), and history of IV-drug use (33.3%). Further research in a real-world setting is needed to investigate the effect of baseline patient characteristics, viral mixed-genotypes and resistance-associated substitutions on sustained virologic response.

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