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Research Article

Sofosbuvir Plus Ledipasvir Treatment in Patients with Hepatitis C Genotype 4d Infection who Previously Failed to Achieve Sustained Virological Response with Telaprevir or Boceprevir Combination Therapies

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Abstract

The optimal retreatment regimen for patients with Hepatitis C virus (HCV) infection who failed triple therapy with first generation protease inhibitors is undetermined. In this study, we aimed to investigate the efficacy and safety of combination therapy with Sofosbuvir (SOF) and Ledipasvir (LDV) for patients with chronic HCV GT-4d infections who previously failed to achieve SVR with peginterferon alfa-2a/ribavirin (peg IFN/RBV) and Telaprevir (TVR) or Boceprevir (BOC) therapies. This retrospective study enrolled 10 patients with genotype-4d (GT-4d) HCV infection who failed Peg IFN/RBV and TVR or BOC combination therapies. They were retreated with SOF/LDV therapy for 12 or 24 weeks and underwent physical examinations and blood tests at baseline, during treatment, and after therapy. The age range of the 10 patients (seven women, three men) was 27-64 years, and the average age was 51.90 ± 11.57. All patients were infected with HCV GT-4d. IL-28B genotype was found CT in seven patients and two patients had cirrhosis. The baseline viral load was high (HCV RNA > 800,000IU/mL) in all patients. At week 8, HCV RNA became negative in all cirrhotic and non-cirrhotic patients. The rates of Sustained Virological Response 12 (SVR12) were found 100% in all patients. No serious adverse events occurred that were related to study medications. This study revealed that SOF/LDV combination therapy was effective and safe for patients with HCV GT-4d infection who failed Peg IFN/RBV and TVR or BOC combination therapies.

Keywords: Hepatitis C virus; Genotype 4d; Sofosbuvir; Ledipasvir

Introduction

Hepatitis C virus (HCV) Genotype (GT) 4 accounts for 8-13% of all chronic HCV infections worldwide. HCV GT-4 is common in sub-Saharan Africa, northern Africa, the Middle East, and Southeast Asia [1-5]. HCV-G4 infection has recently spread to several European countries including Italy, France, Greece, and Spain due to changes in population structure, immigration, and transmission routes [2,4,6]. In Turkey, GT-1b virus causes approximately 90% of HCV infections, while types 2, 3, and 4 exist, albeit in low prevalences [7-10]. In recent years, there has been an increase in HCV GT-4 infections in Turkey. The frequency of GT-4 HCV infections is significantly higher in Kayseri, a relatively large city in Central Anatolia, compared to other provinces in Turkey [10-13]. However, two reports from Kayseri indicated unusually high for GT-4 infections in the province reaching a 35% among patients admitted to hospitals for treatment of chronic hepatitis C [12,13]. These are significantly higher than the average prevalence of 1.4% reported for type 4 HCV infections in Turkey [13]. It was shown recently that Kayseri GT-4 isolates are closely related with subtype 4d sequences [10,14].

HCV GT-4 has been considered "difficult to treat" with pegylated interferon (Peg IFN) and Ribavirin (RBV) treatment, with Sustained Virological Response (SVR) rates of approximately 50% [3,15]. Telaprevir (TVR)/Peg IFN/RBV combination therapy had limited antiviral activity in especially null responder patients who previously received Peg IFN/RBV treatment. SVR rate was found to be 25% [16]. On the other hand, a single tablet, fixed-dose combination of sofosbuvir, an RNA-directed RNA polymerase inhibitor, and Ledipasvir (LDV), a Nonstructural protein 5A (NS5A) inhibitor, has been approved for treatment of chronic HCV infection. Two studies using the fixed-dose combination in chronic HCV GT-4 for 12 weeks reported SVR rates at 12 weeks (SVR12) of 93-95% [2,4].

In this study, we aimed to investigate the efficacy and safety of 12 or 24 weeks of combination therapy with LDV and SOF for patients with chronic HCV GT-4d infections who previously failed to achieve SVR with Peg IFN/RBV and TVR or Boceprevir (BOC) therapies.

Materials and Methods

Patients

In this single-center, retrospective clinical study, closely monitored patients infected with HCV GT-4d who had previously received Peg IFN/RBV and TVR or BOC therapies but did not achieve SVR were evaluated. The age range of the 10 patients (seven women, three men) was 27-64 years, and the average age was 51.90 ±11.57. Patients with liver disease other than HCV infection, patients who were positive for anti-human immunodeficiency virus, and patients

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Table 1: The demographic characteristics and treatment outcomes of the patients.

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10*
Age (years)	57	46	39	52	27	64	56	61	55	62
Gender	F	M	M	F	F	F	M	F	F	F
Prior type of response			Null response							
PegIFN/RBV	Null response	Null response		Null response	Null response	Relapse	Partial response	Null response	Null response	Null response
TVR or BOC/ PegIFN/RBV	Null response	Null response	Null response	Null response	Null response	Null response	Relapse	Null response	Null response	Null response
Baseline ALT level (IU/L)	40	29	32	27	25	15	35	43	57	63
Baseline AST level (IU/L)	37	25	30	22	24	14	29	48	68	80
Viral load at baseline (IU/mL)	3,653,928	2,784,848	17,900,000	10,900,000	1,630,000	3,860,000	1,730,000	15,600,000	12,190,215	1,160,000
Liver biopsy**										
Necroinflammatin score	10	3	5	5	6	3	3	7	10	9
Fibrosis score	3	1	1	2	1	0	0	6	6	6
IL28B rs12979860 C/T gene polymorphism	CT	CT	TT	CT	CT	CT	CT	TT	TT	CT
On-treatment and post-treatment virologic responses (HCV RNA <15 IU/mL)										
At week 4	Negative	Negative	Negative	Negative	Positive	Positive	Negative	Positive	Positive	Positive
At week 8	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
At week 12	Negative (ETR)	Negative (ETR)	Negative (ETR)	Negative (ETR)	Negative (ETR)	Negative (ETR)	Negative (ETR)	Negative	Negative	Negative
At week 24	Negative (SVR)	Negative (SVR)	Negative (SVR)	Negative (SVR)	Negative (SVR)	Negative (SVR)	Negative (SVR)	Negative (ETR)	Negative (ETR)	Negative (ETR)
At week 36								Negative (SVR)	Negative (SVR)	Negative (SVR)

M: Male; F: Female; PegIFN; Pegylated interferon; RBV: Ribavirin, TVR: Telaprevir, BOC: Boceprevir, ALT: Alanin aminotransferase; AST: Aspartate aminotransferase SVR: Sustained virological response; ETR: End-of-treatment virological response; *Child-Pugh B; **Ishak scoring system

with active cancer were excluded from the study. Liver biopsies were performed percutaneously and assessed according to the Ishak scoring system [17]. All of the subjects provided written informed consent for both treatment and genetic analysis.

Study design

Patients were evaluated according to their baseline viral load (HCV RNA <800.000IU/mL or ≥800.000IU/mL), Interleukin (IL) 28B rs12979860 C/T polymorphism (CC, CT, or TT), stage of fibrosis, and type of prior response to Peg IFN/RBV and TVR or BOC therapies (null response, partial response, or relapse) [18,19]. The patients were given a fixed-dose combination tablet of 90mg LDV and 400mg SOF (Harvoni; Gilead Sciences, Foster City, CA 94404, USA) orally once-daily. The therapy was received for 12 weeks in non-cirrhotic patients and 24 weeks in cirrhotic patients [20,21].

Efficacy assessments

Quantitative HCV RNA was measured before the treatment and at weeks 4, 8, 12 (at weeks 16, 20, 24 in cirrhotic patients) and after treatment at weeks 12. End-of-Treatment Response (ETR), SVR and side effects of therapy were evaluated. ETR was defined as HCV RNA < Lower Limit of Quantification (LLOQ) (15IU/mL) at the end of therapy [18]. SVR12 was defined as HCV RNA < LLOQ 12 weeks after stopping study drug [2].

Safety assessments

The patients were assessed clinically and the essential biochemical, hematologic laboratory tests were performed monthly during treatment and follow-up. Side effects were recorded at each visit and the precautions were taken. Patients with serious side effects were controlled frequently; if necessary, they were hospitalized.

Blood samples and laboratory tests

Routine biochemical tests were performed on venous blood samples with an automated device and anti-HCV antibody examined using an enzyme immunoassay method (Architect System; Abbott Laboratories, Chicago, IL, USA). Quantitative HCV RNA measurement was performed with real-time polymerase chain reaction (COBAS Ampliprep/COBAS TaqMan 48, Roche Molecular Systems, and Mannheim, Germany). HCV genotyping was investigated by pyrosequencing method (Pyromark, Qiagen, Germany). A nested PCR approach was adopted to amplify the 472bp strech in the E1core gene between 843 and 1315 nucleotides using primers PR108, PR109, PR110, PR111 as described by Murphy et al [22]. A heminested PCR approach was adopted to amplify the 380 bp strech in the NS5B gene between positions 8256 and 8636 using primers PR3, PR4, and PR5 as described by Laperche et al [23]. The sequencing was done using Big dye sequencing chemistry with primers; PR3, PR5, PR108, PR109. 3130 ABI sequencer (ABI Prism, Applied Biosystems, USA) was used to generate the sequences. Phylogenetic analysis was performed using MEGA software 5.02 [24]. Genotyping for the IL-28B rs12979860 C/T polymorphism was performed by a polymerase chain reaction-based restriction fragment length polymorphism assay [25].

Table 2: Adverse Events during the Overall Treatment Period.

	12 or 24 weeks course of sofosbuvir plus ledipasvir therapy (n=10)
No. of patients with a serious adverse event	0
No. of patients with any adverse event	7 (70)
Fatigue	3 (30)
Asthenia	3 (30)
Appetite increase	3 (30)
Weight gain*	3 (30)
Headache	2 (20)
Nausea	1 (10)
Insomnia	1(10)
Pruritus	1(10)
Laboratory abnormality, n(%)	
Hyperglycemia**	1(10)

*More than 10% of body weight, **in patients with type 2 diabetes mellitus (glucose > 250mg/dL)

Results

Patients

The study included 10 patients: nine prior null responders and one relapse to TVR/Peg IFN/RBV combination treatment. Genotype analysis revealed that all patients were infected with HCV genotype 4 and all isolates were typed as 4d. IL-28B genotype was found CT in seven patients and two patients had cirrhosis. The baseline viral load was high (HCV RNA > 800,000IU/mL) in all patients.

Efficacy

The demographic characteristics and treatment outcomes of the patients included in this study are shown in (Table 1). At week 4, HCV RNA became negative (HCV RNA < LLOQ) in five non-cirrhotic patients but it was positive in all cirrhotic patients. At week 8, HCV RNA became negative in all cirrhotic and non-cirrhotic patients. The rates of EVR, and SVR12 were found 100% in all patients (Table 1).

Adverse events

Common side effects were fatigue, asthenia, appetite increase, weight gain and headache (Table 2). No patients discontinued treatment because of adverse events and no serious adverse events occurred that were related to study medications.

Discussion

Patients with HCV GT-4 have been noted to have poor treatment responses to Peg IFN and RBV. In one of our research, we showed that virological response rate at 24th week of treatment are high with TVR/Peg IFN/RBV combination therapy in patients infected with HCV GT-1 and G-4 but virologic eradication rate was found to be the highest in prior relapsers [9]. On the other hand, TVR/Peg IFN/RBV combination therapy had limited antiviral activity in especially for null responder patients with chronic HCV GT-4d infections who previously failed to achieve SVR with Peg IFN/RBV [17]. Only two studies, one phase II study with limited number of patients and one with a patient with mixed HCV GT-1 and GT-4 infection, are found in the literature pointing the success of TRV combination therapies in CHC patients infected with HCV GT-4 [26,27]. Current guidelines from the American Association for Study of Liver Diseases (AASLD) and European Association for the Study of Liver suggest fixed-dose combination of LDV/SOF for the treatment of HCV GT-4 infection [20,21].

In our study, the rate of SVR was found 100% in non-cirrhotic and cirrhotic patients. Nine patients were null responder, and one patient was relapser to TVR or BOC/Peg IFN/RBV combination treatment. IL-28B genotype was found CT in seven patients. The baseline viral load was high in all patients, and three patients had cirrhosis. LDV/SOF has demonstrated high SVR rates in clinical studies [1-4]. In a single-center, open-label phase IIa trial, Kohli and colleagues [4] assessed the safety and efficacy of SOF and LDV once daily for 12 weeks in HCV GT-4 patients. Sixty-two percent of the patients (13/21) were treatment naïve, and thirty-eight percent (8/21) had prior treatment experience. Advanced fibrosis or compansed cirrhosis was described in 9/21 (43%). Sixty-two percent of the patients had high baseline viral load (HCV RNA > 800,000IU/mL). SVR12 was achieved in 95% (CI: 76-100). In a open-label multicenter study evaluated LDV/SOF for 12 weeks in treatment-naïve and treatment-experienced patients with HCV GT-4 [2]. Of the 44 patients evaluated, 22 were treatment naïve, 10 had compansed cirrhosis, and 70% had baseline HCV RNA > 800,000IU/mL. SVR12 rates were found by 93% (CI: 81-99) of patients with rates being similar between treatment-naïve and -experienced groups. In our study, 5 (50%) of 10 patients treated with LDV/SOF had concentrations of HCV RNA that were less than the LLOQ by week 4 of treatment, but it was positive in all cirrhotic patients. At week 8, HCV RNA became negative in all cirrhotic and non-cirrhotic patients. The rates of End-of-Treatment Response (ETR) and SVR12 were found 100% in the all patients (Table 1).

In this study all of HCV isolates were subtyped as 4d. We know that subtype 4d is resistant to antivirals but virological response was obtained by treatment of SOF/LDV combination in the all patients. In a phase 2a study, 23% of patients had a subtype 4d [2]. This is the first study that evaluates the efficacy and safety of SOF/LDV combination therapy for patients with chronic HCV GT-4d infections who previously failed to achieve SVR with Peg IFN/RBV and TVR or BOC therapies.

Treatment with LDV/SOF generally well tolerated. All adverse

events were mild or moderate in severity. No serious adverse events occurred and no patients discontinued because of an adverse event. These findings were consistent with other studies [2,4].

Conclusions

LDV/SOF combination therapy was effective and well-tolerated for patients with HCV GT-4d infection. SVR rate was high with SOF/LDV combination therapy in both cirrhotic and non cirrhotic patients infected with HCV GT-4d who failed to achieve viral eradication with prior Peg IFN/RBV and TVR or BOC combination therapies.

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The study was approved by the Ethics Committee for Clinical Research at……..University, conforming to protocols in accordance with the Declaration of Helsinki (Decision number: 2016/615).

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