Original Article

Effectiveness of Ledipasvir/Sofosbuvir with/without Ribavarin in Liver Transplant Recipients with Hepatitis C

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Abstract

Background and Aims: Recurrent infection of hepatitis C virus (HCV) in liver transplant (LT) recipients is universal and associated with significant morbidity and mortality. **Methods:** We retrospectively evaluated the safety and efficacy of ledipasvir/sofosbuvir with and without ribavirin in LT recipients with recurrent genotype 1 hepatitis C. **Results:** Eighty-five LT recipients were treated for recurrent HCV with ledipasvir/sofosbuvirwith and without ribavirin for 12 or 24 weeks. The mean (± standard deviation [SD]) time from LT to treatment initiation was 68 (±71) months. The mean (± SD) age of the cohort was 63 (±8.6) years old. Most recipients were male (70%). Baseline alanine transaminase, total bilirubin, and HCV ribonucleic acid (RNA) values (± SD) were 76.8 (±126) mg/dL, 0.8 (±1.3) U/L, and 8,010,421.9 (±12,420,985) IU/mL, respectively. Five of 43 recipients who were treated with ribavirin required drug cessation due to side effects, with 4 of those being anemia complications. No recipient discontinued the ledipasvir/sofosbuvir. Eighty-one percent of recipients had undetectable viral levels at 4 weeks after starting therapy, and all recipients had complete viral suppression at the end of therapy. The sustained viral response at 12 weeks after completion of therapy was 94%. **Conclusion**: Ledipasvir and sofosbuvir with and without ribavirin therapy is an effective and well-tolerated interferon-free treatment for recurrent HCV infection after LT. Anemia is not uncommon in LT recipients receiving ribavirin.

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Introduction

Hepatitis C virus (HCV) is the leading indication for liver transplantation (LT) in the United States.[1] Post-LT recipients universally develop recurrent HCV infection. Recipients with HCV have 30% higher mortality at 5 years and can develop aggressive recurrent disease.[2–4] Whereas 20% of infected patients in the general population develop cirrhosis after 2 decades, a similar percentage of transplant recipients develop cirrhosis after just 5 years.[4–6]

HCV treatment of LT recipients has substantially evolved over the past several decades. Due to the significant side effects associated with treatment, HCV therapy was initially limited to patients at risk of progressive liver disease. However, recent advances in treatment have lowered the treatment threshold, particularly among LT recipients.[7–10] Given that the sustained viral response (SVR) in the general population is similar to that in the transplant community, transplant recipients are no longer considered to be a difficult to treat population.[11–13]

A number of all-oral antiviral therapies have been used to treat recurrent HCV in LT recipients. These regimens differ by their treatment duration, need for ribavirin, and potential drug interaction.[14–35] Furthermore, antiviral treatment in LT recipients has been found to be cost effective.[36] The purpose of this study was to determine the efficacy of ledipasvir and sofosbuvir with or without ribavirin (LDV/SOF ± RBV) in a non-clinical trial setting. The hypothesis of our study was that LDV/SOF ± RBV is safe and effective in LT recipients.

Methods

We performed a retrospective chart review of all adult LT recipients who had been treated with LDV/SOF at the University of California Los Angeles Medical Center (UCLA) between September 2014 and June 2016.

Inclusion criteria included age of at least 18 years at the beginning of treatment, diagnosis of genotype 1 HCV infection, and detectable HCV ribonucleic acid (RNA) after LT.

Quantitative PCR was used to detect the HCV RNA viral load. A polymerase chain reaction was used to amplify the viral target RNA followed by hybridization for HCV genotyping. Exclusion criteria included evidence of allograft rejection on biopsy within 6 months of starting the antiviral therapy and critical illness (i.e. patients with circulatory shock, respiratory failure, and acute renal failure requiring urgent dialysis) at start of therapy.

Data were obtained by review of medical records and review of the UCLA LT database after Institutional Review Board approval. Demographic data (age, sex), HCV genotype, history of LT, history of previous HCV therapy, non-liver related medical history (active cardiopulmonary disease, hemodialysis, stroke, non-liver malignancy, diabetes), co-existent liver disease (non-alcoholic fatty liver disease [NAFLD], hepatitis B infection, autoimmune hepatitis, hepatocellular carcinoma [HCC]), and immunosuppressant regimen were recorded. The presence and severity of liver fibrosis was assessed using imaging, blood work and histology. Fibrosis-4 (FIB-4) scores were used to determine cirrhosis in patients without imaging and biopsy.

Transplant recipients were treated with LDV 90 mg and SOF 400 mg in a fixed-dosed combination tablet once daily with or without ribavirin (600 mg per day) for 12 weeks or 24 weeks. Recipients were preferably treated for 24 weeks if they had baseline or treatment-related anemia. Anemia was defined as hemoglobin < 12 g/dL. SVR was defined as an undetectable HCV value at 12 weeks after treatment completion (SVR12). The SVR was calculated on an intent-to-treat basis. The goal therapeutic range for tacrolimus was 6–10 ng/mL and for cyclosporine was 100–200 ng/mL.

A set of hematologic data, biochemical data, and HCV RNA levels were collected at initiation of treatment, 4 weeks after initiation of treatment (4W), end of therapy (EOT), and 12 weeks after treatment completion. Continuous variables were presented as mean [±standard deviation (SD)], and categorical variables were expressed as percentage. A mixed effects model using random intercepts by recipient was used in STATA 13 (College Station, TX, USA) to evaluate the changes in hematologic and biochemical data at the above defined time periods. A *p*-value of 0.05 or less in regression coefficients or in pairwise comparisons between time points was considered statistically significant.

Results

Baseline characteristics

We identified 85 consecutive LT recipients who were treated for HCV genotype 1 using LDV/SOF ± RBV (Table 1). Eighty-two of the recipients (96.5%) had undergone only one LT, and three were treated after their second or third LT. Seven recipients had undergone simultaneous liver-kidney transplantation. Most recipients were men, and the overall mean (± SD) age was 63.1 (± 8.6) years. Forty-six patients (54.1%) were treatment-naïve. Eighteen patients were treatment-experienced before orthotopic (O)LT, and 21 after OLT. Most had been treated prior with an interferon-based antiviral regimen (69.2%). Most patients were on tacrolimus based immunosuppressant regimen (88.2%).

The mean (±SD) time from transplantation to treatment initiation with LDV/SOF based therapy was 68.3 (±70.6) months. Forty-eight (57%), including a recipient with fibrosing cholestatic hepatitis, had a liver biopsy before starting

Table 1. Patient demographics

Parameter	Result
Number of Patients	85
Age in years, mean ± SD	63.1 ± 8.6
Male, *n* (mean ± SD %)	57 (70.0 ± 47.3 %)
Medical history, *n* (%)	
Active cardiopulmonary disease[†]	9 (10.6%)
Hemodialysis	10 (11.8%)
Stroke	7 (8.2%)
Recent non-HCC malignancy within 5 years	9 (10.6%)
Diabetes	27 (31.8%)
Lymphoma	1 (1.2%)
Co-existent liver disease(s), *n* (%)	
Non-alcoholic fatty liver disease (NAFLD)	1 (1.2%)
Hepatitis B	3 (3.9%)
Autoimmune hepatitis	1 (1.2%)
Hepatocellular carcinoma	40 (47.1%)
Mean time from LT to Treatment Initiation in months (±SD)	68.3 (±70.6)
Received more than one LT	3 (3.5%)
Treatment-naïve, *n* (%)	46 (54.1%)
Treatment-experienced, *n* (%)	39 (45.9%)
Treatment prior to LT	18 (46.2%)
Interferon/ribavirin	15 (83.3%)
Sofosbuvir/ribavirin	1 (5.6%)
Sofosbuvir/simeprevir	2 (11.1%)
Treatment post-LT	21 (53.8%)
Interferon/ribavirin	10 (47.6%)
Sofosbuvir/interferon/ribavirin	2 (9.5%)
Sofosbuvir/ribavirin	4 (19.0%)
Sofosbuvir/simeprevir ± ribavirin	4 (19.0%)
Ribavirin monotherapy	1 (4.8%)
Stage of fibrosis at start of treatment, *n* (%)	
0-1	33 (38.8%)
2-3	18 (21.2%)
4	34 (40%)
Presence of fibrosing cholestatic hepatitis	1 (1.2%)
Immunosuppression therapy, *n* (%)	
Tacrolimus only	30 (35.3%)
Tacrolimus + mycophenolate ± prednisone	39 (45.9%)
Tacrolimus + sirolimus ± prednisone	6 (7.1%)

(continued)

Table 1. (continued)

Parameter	Result
Cyclosporine only	3 (3.5%)
Cyclosporine + mycophenolate	4 (4.7%)
Sirolimus + mycophenolate	2 (2.4%)
Sirolimus + prednisone	1 (1.2%)
Treatment regimen, *n* (%)	
Sofosbuvir/ledipasvir for 12 weeks	18 (21.2%)
Sofosbuvir/ledipasvir + ribavirin for 12 weeks	33 (38.8%)
Sofosbuvir/ledipasvir for 24 weeks	29 (34.1%)
Sofosbuvir/ledipasvir + ribavirin for 24 weeks	5 (5.9%)

Abbreviations: COPD, chronic obstructive pulmonary disease; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; SD, standard deviation; LT, liver transplantation.
[†]Examples of active cardiopulmonary diseases include coronary artery disease, heart failure, chronic obstructive pulmonary disease, and idiopathic pulmonary fibrosis.

antiviral therapy. Almost half the LT recipients had a diagnosis of cirrhosis (*n* = 34, 40%) prior to treatment initiation. The diagnosis of HCC was the indication for LT in 37 (37/40) of the recipients. A diagnosis of HCC was made incidentally at the time of surgery in 3 (3/40) of the recipients. Out of the 10 (11.8%) recipients on dialysis, 6 (60%) were treated with LDV/SOF without ribavirin. Twenty (74.1%) of the recipients with baseline anemia were treated with LDV/SOF without ribavirin. Baseline laboratory values are shown in Table 2.

Fifty-one recipients were started on LDV/SOF ± RBV with a goal duration of 12 weeks, and treatment was extended in

4 recipients due to detectable HCV viral levels at week 4 of treatment (Fig. 1). All 4 of these recipients were also being treated with ribavirin. Thirty-four patients of the entire cohort of 85 recipients received LDV/SOF ± RBV with a goal duration of 24 weeks. No interruptions in antiviral therapy occurred in any of the recipients.

Biochemical and HCV RNA viral response

From baseline to 12 weeks post-treatment, there was a statistically significant decrease in the alanine transaminase (ALT) and total bilirubin levels. The mean (±SD) ALT value decreased from 76.8 (± 126) IU/L to 27.6 (± 24.5) IU/L (*p* = 0.001). The mean (±SD) baseline serum HCV RNA was 8,010,421.9 IU/mL (±12,420,985) (Table 2). Eighty-one of the 85 recipients had their viral load measured at 4 weeks of treatment. HCV RNA was undetectable in 65 recipients, detectable but unquantifiable in 5 recipients, and quantifiable in 11 recipients. The viral load was undetectable in all patients at the end of treatment. Eighty (94.1%) recipients achieved SVR 12 (Table 4, Fig. 2). Thirty-one of the 34 (91.2%) patients with cirrhosis achieved SVR12 with antiviral therapy. Forty-nine of 51 (96.1%) patients without cirrhosis achieved SVR12. Thirty-eight of the HCC recipients achieved SVR12 (95%). The two patients that did not achieve SVR had HCC as an indication for LT. The SVR12 in recipients without a diagnosis of HCC was 93%. There was no statistically significant difference in SVR12 between cirrhotic and non-cirrhotic patients (*p* = 0.385) and between HCC and non-HCC recipients (*p* = 1).

Five recipients experienced viral relapse. Viral relapse occurred in all recipients within 4 weeks of completing antiviral therapy. Four recipients were retreated and achieved SVR12 with alternative treatment regimens (Table 3). The fifth recipient expired due to primary lung cancer. Resistance associated mutations were assessed after viral relapse with

Table 2. Mean (and standard deviation) of laboratory values

| Laboratory test	Baseline	4 Weeks	EOT	SVR12	Pt Diff	*p*-Value[*]
Platelet count (x1000 cells/μL)	143.4 ± 59.1	160.1 ± 65.6	159.9 ± 76.1	152.6 ± 67.5	9.2 (9.2)	0.054
Albumin (g/dL)	4.1 ± 1.2	4.1 ± 0.4	4.1 ± 0.4	4.1 ± 0.5	0 (0)	0.822
AST (U/L)	62.4 ± 79.5	25.0 ± 13.9	25.6 ± 20.3	28.2 ± 22.3	−34.3 (−34.3)	<0.001
ALT (U/L)	76.8 ± 126	25.2 ± 19.2	24.6 ± 21.7	27.6 ± 24.5	−49.3 (−49.3)	0.001
Total bilirubin (mg/dL)	0.8 ± 1.3	0.9 ± 0.7	0.9 ± 1.2	0.7 ± 0.9	−0.1 (−0.1)	0.453
Serum creatinine (mg/dL)[†]	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	0 (0)	0.514
Alkaline phosphatase (U/L)	129.5 ± 175.3	111.4 ± 176.7	99.6 ± 53.6	124.2 ± 134.7	−5.3 (−5.3)	0.694
Hemoglobin (g/dL)	12.8 ± 1.7	11.9 ± 2.3	12.0 ± 2.1	13.2 ± 1.8	0.3 (0.3)	0.033
In patients *with* RBV therapy	13.2 ± 1.3	11.5 ± 2.1	12.0 ± 1.7	13.4 ± 1.6	0.2 (0.2)	0.477
In patients *without* RBV therapy	12.5 ± 2.0	12.3 ± 2.5	12.1 ± 2.5	13.0 ± 2.0	0.5 (0.5)	0.017

Abbreviations: EOT, end of treatment; SVR12, sustained viral response at 12 weeks; AST, aspartate transaminase; ALT, alanine transaminase; Pt Diff, point difference.
[*]Baseline vs. SVR12 paired *t*-test.
[†]Patients on dialysis were not included in the calculation of mean and standard deviation for serum creatinine.
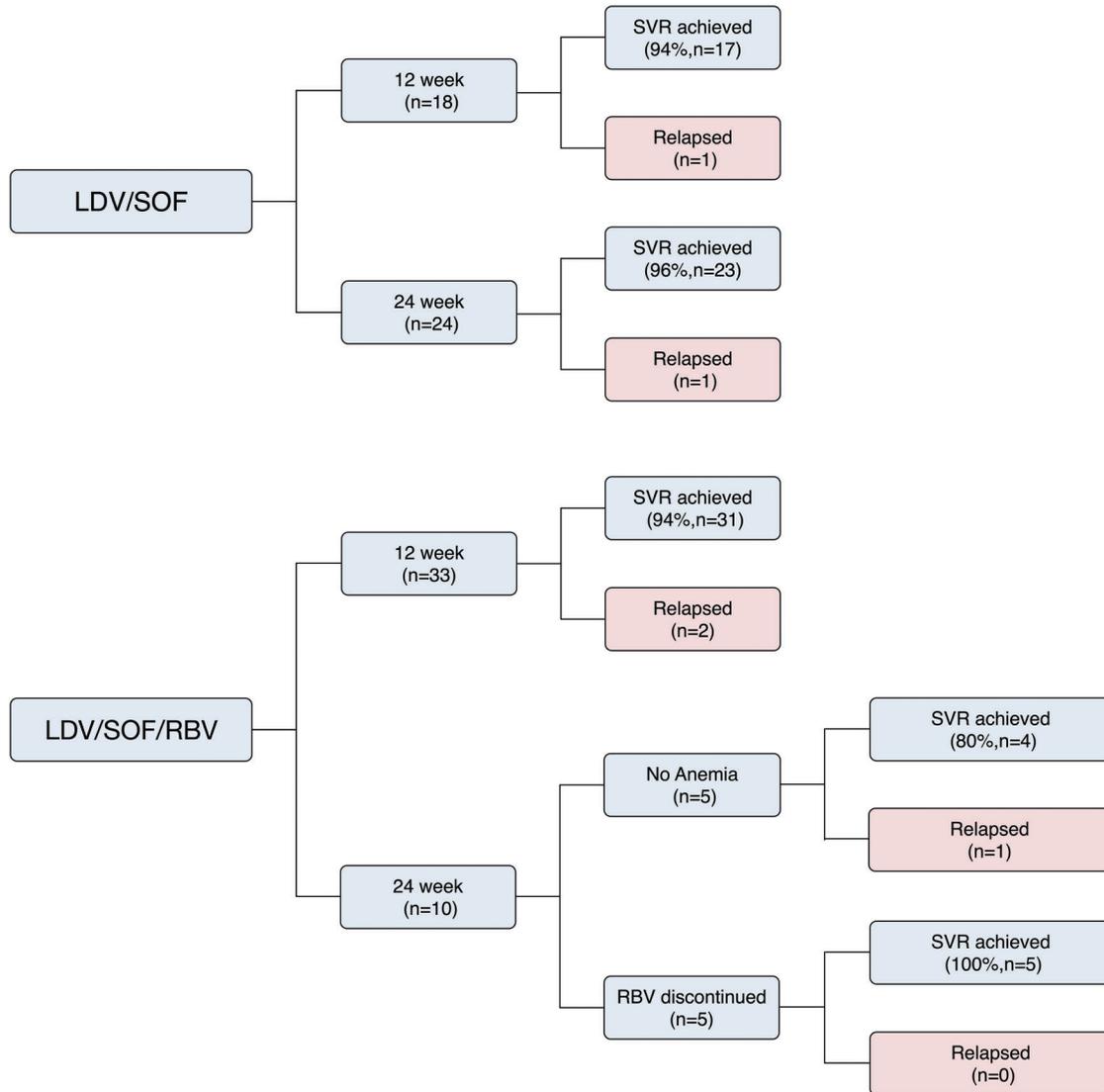
Fig. 1. Patient disposition.
Abbreviations: LDV, ledipasvir; SOF, sofosbuvir; RBV, ribavirin; SVR, sustained viral response.
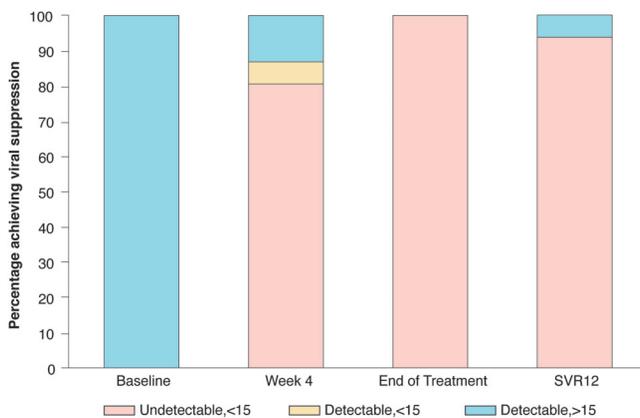
Fig. 2. Overall viral kinetics.
Abbreviation: SVR, sustained viral response.

LDV/SOF. Their characteristics and outcomes are shown in Table 3.

There was a statistically significant change in the distribution of fibrosis stage as determined by FIB-4 scores, between the start of treatment and SVR12 ($p < 0.001$) (Fig. 3). The number of recipients with stage 0-1 at baseline and SVR12 was 7 (8%) and 21 (25%), respectively. The number of recipients with cirrhosis at baseline and SVR12 was 32 (38%) and 20 (24%), respectively.

Safety

Anemia was the most common safety issue in our cohort treated with LDV/SOF with ribavirin. Five of the 43 recipients required ribavirin cessation and their treatment with LDV/SOF monotherapy was extended for a total treatment duration of 24 weeks. Anemia occurred within 4 weeks of starting therapy in 4 of the recipients. One patient discontinued

Table 3. Characteristics and outcomes of recipients who relapsed

ID	Age/Sex	GT	Prior treatment	RAM	Fibrosis stage	Treatment regimen	LT to treatment Time	Immuno-suppressant	Outcome
6	57/M	1a/1b	SOF/SIM × 12 w	NS5A ~ Q30Q/H/K/N NS3/4A ~ Q80K	3	LDV/SOF/RBV × 12 w	24 Months	Tacrolimus, Sirolimus	Deceased (Lung Cancer)
9	59/M	1a	Naïve	NS5A ~ None NS3/4A ~ V55A	2	LDV/SOF × 12 w	60 Months	Tacrolimus	SVR12 with LDV/SOF/RBV × 24 w
59	63/M	1b	SOF/RBV × 24 w	NS5A ~ Y93H NS3/4A ~ None	2	LDV/SOF/RBV × 24 w	108 Months	Tacrolimus	Retreated and relapsed on SOF/SIM/RBV. SVR12 with SOF/RBV/EBR/GZR
82	53/M	1a	SOF/RBV × 24 w	NS5A ~ None NS3/4A ~ None	4	LDV/SOF × 24 w	8 Months	Tacrolimus, Mycophenolate	SVR12 with SOF/RBV/EBR/GZR
88	65/M	1a	SOF/RBV × 24 w	NS5A ~ L31, H58P NS3/4A ~ Q80K	2	LDV/SOF/RBV × 12 w	114 Months	Tacrolimus	SVR12 with SOF/SIM/RBV × 24 w

Abbreviations: ID, identification; M, male; GT, genotype; SOF, sofosbuvir; SIM, simeprevir; LDV, ledipasvir; RBV, ribavirin; IFN, interferon; EBR, elbasvir; GZR, grazoprevir; LT, liver transplantation; W, weeks; SVR, sustained viral response; RAM, resistance-associated mutations.
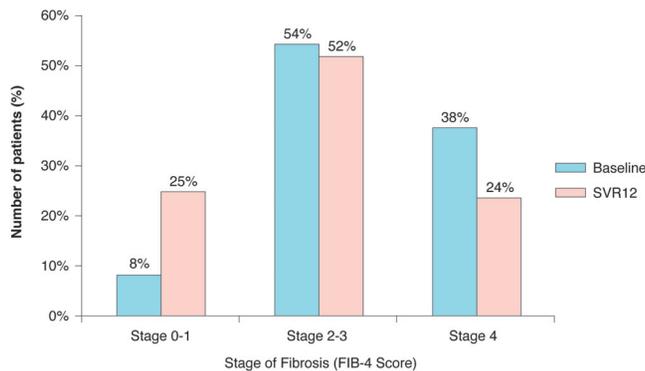
Fig. 3. Fibrosis-4 score at baseline and SVR12.
Abbreviations: FIB-4, fibrosis-4 score; SVR, sustained viral response.

ribavirin because of potential anemia given underling chronic kidney disease (stage II) and his advanced age. However, the patient did not develop anemia during ribavirin therapy. All the recipients who developed anemia were 64 years of age or older. No transplant recipient required erythropoietin-stimulating agents or a blood transfusion. No transplant recipients discontinued LDV/SOF for adverse effects.

Discussion

The results of our study highlight the efficacy, safety and tolerability of LDV/SOF in LT recipients. The SVR12 in our cohort was 94%, and no patient developed adverse side-effects related to LDV/SOF. In contrast, the use of ribavirin, even at non-weight based dosing, was associated with significant anemia in 4 of 43 ribavirin recipients. None of the patients in our cohort required admission, erythropoietin-stimulating agents, or a blood transfusion.

The results of our study add to the increasing body of literature supporting the role of direct-acting agents (DAAs) in LT recipients. Potentially, LT recipients may represent a cohort of patients in which HCV may be completely eliminated. Indeed, the combined guidance position paper by the American Association for the Study of Liver Diseases (commonly known as AASLD) and Infectious Diseases Society of America (commonly known as IDSA) places LT recipients at the highest priority for antiviral therapy.[10] Until recently, liver biopsies were routinely performed in LT recipients since interferon–based therapy was associated with substantial adverse effects. Today, multiple antiviral regimens are available with comparable SVR12 (Table 4). There are important differences among the strategies, such as need for ribavirin, duration of treatment, and potential drug interactions. Furthermore, some DAAs are contraindicated in decompensated liver disease and in patients with compromised renal function.[37–40]

Treatment of HCV in LT recipients is an evolving field. When we started utilizing DAAs in transplant recipients, there were no DAA regimens approved for patients with advanced kidney disease. Recently, two regiments were approved by the Federal Drug Administration in patients undergoing hemodialysis: a) dasabuvir plus ombitasvir, paritaprevir, and ritonavir; and b) elbasvir and grazoprevir. However, there is a paucity of experience using elbasvir and grazoprevir in LT recipients and there are substantial drug interactions with dasabuvir plus ombitasvir, paritaprevir, and ritonavir which limit current

Table 4. Summary of major trials evaluating direct-acting agents for recurrent HCV infection in post-liver transplants

Author[Ref]	Genotype	Therapy	Duration in weeks	*n*	SVR
Charlton *et al.*[14]	1, 3, 4	SOF/RBV	24	40	70% (55–73%)[*]
Forns *et al.*[15]	1-4	SOF/RBV	24–48	92	59% (43–73%)[‡]
Charlton *et al.*[16]	1, 4	LDV/SOF/RBV	12	116	92%[†] (60–100%)[††]
			24	113	95%[†] (75–100%)[††]
Manns *et al.*[17]	1	LDV/SOF/RBV	12	100	95%[†] (50–100%)[††]
			24	99	98%[†] (80–100%)[††]
Elfeki *et al.*[18]	1	LDV/SOF	12	32	100%
			24	14	100%
Kwok *et al.*[19]	1	LDV/SOF	8	7	86%
			12	69	94%
			24	41	95%
	1-4	LDV/SOF/RBV	12	39	97%
			24	6	100%
Omichi *et al.*[20]	1	LDV/SOF	18	18	100%
	1	ASV/DCV	24	9	100%
Saab *et al.*[21]	1	SOF/SIM	12	30	93%
Khemichian *et al.*[22]	1	SOF/SIM	12	32	94%
Pungpapong *et al.*[23]	1	SOF/SIM/RBV	12	105	90%
Gutierrez *et al.*[24]	1	SOF/SIM/RBV	12	61	93%
Punzalan *et al.*[25]	1	SOF/SIM	12	42	95%
Crittenden *et al.*[26]	1	SOF/SIM/RBV	12	56	88%
Brown *et al.*[27]	1	SOF/SIM/RBV	12	151	88%
Jackson *et al.*[28]	1	SOF/SIM	12	67	88%
Kwo *et al.*[29]	1	OBV/DSV/PTV/r	24	34	97%
Flisiak *et al.*[30]	1, 4	OBV/DSV/PTV/r	24	21	100%
Poordad *et al.*[31]	1	SOF/DCV/RBV	12	41	95%
Leroy *et al.*[32]	1, 4	SOF/RBV	12	8	88%
	1, 3, 4	SOF/DCV	12	15	100%
Coilly *et al.*[33]	1-5	SOF/DCV±RBV	12, 24	137	96% (75–100%)[**]
Dumortier *et al.*[34]	1-5	SOF/DCV/RBV	12–24	125	93% (92–94%)[††]
Welzel *et al.*[35]	1-5	SOF/DCV/RBV	24	85	94% (92–100%)[*]

Abbreviations: HCV, hepatitis C virus; SVR, sustained viral response; SOF, sofosbuvir; SIM, simeprevir; LDV, ledipasvir; RBV, ribavirin; ASV, asunaprevir; DCV, daclatasvir; DSV, dasabuvir; OBV, ombitasvir; PTV/r, paritaprevir with ritonavir; n/N, sample size/population size.
[*]Ranges in parenthesis represent SVR12 in patients with different genotypes.
[‡]Ranges in parenthesis represent SVR12 in patients treated <12 months or >12 months after liver transplantation.
[†]SVR12 was calculated by adding all responders in different Child-Turcotte-Pugh groups, divided by the study population.
[††]Ranges in parenthesis represent different SVR12 in various groups of cirrhosis.
[**]Ranges in parenthesis represent SVR12 in patients with or without ribavirin, treated for either 12 weeks or 24 weeks.

use.[41] In our early experience, we decided to proceed with sofosbuvir-based regimens, even in patients on hemodialysis if we felt the benefits outweighed the risks. Indeed, 10 recipients on our study were on dialysis. The decision to proceed with treating patients on hemodialysis was based on earlier experience.[42]

An important area of discussion is the timing of antiviral therapy.[43] The efficacy of antiviral therapy is well established in LT recipients. An important caveat is that relatively early treatment is preferable since some strategies appear to have a drop off in SVR12 with increasing amount of liver damage.[16]

In particular, outcomes are significantly better when initiated early in the course of fibrosing cholestatic hepatitis.[32,44] Another option is to treat patients before LT. Many providers have based their views on the experience of hepatitis B virus therapy in patients with advanced disease who had remarkable improvement in liver function with viral suppression.[45–47] In fact, data from a recent publication suggests that liver function may stabilize provided that the model of end-Stage liver disease (commonly known as MELD) is less than 15 and select patients may indeed be removed from the transplant list.[48] On the other hand, renal insufficiency,

inability to use HCV-positive grafts, lower SVR in patients with advanced liver disease, and possible viral resistance with relapse are several factors that may temper widespread enthusiasm for treating patients before LT.[49]

Our study has a number of limitations. First, the cohort is from a single center and may not be generalizable to other institutions. Nevertheless, we treated consecutive patients who represent the spectrum of LT recipients with cirrhosis and are treatment experienced. Another limitation is the lack of a control group. We do not feel the absence of a control group is a serious detriment to our study particularly given the lack of noticeable adverse effects that impact drop out from the study. Larger studies may uncover unfavorable side effects not identified in this study. Another limitation of our study is the heterogeneity of our drug regimens. Most of the time, the final drug regimen was determined after discussion with health care providers since recipients were often treated before the official guidance on LT recipients was published. On the other hand, the results of the study represent an early real-life experience with LDV/SOF.

The results of our single center, non-clinical trial, real world experience demonstrate the safety, efficacy, and tolerability of LDV/SOF with and without ribavirin in post-LT patients. This combination of DAAs should be considered in LT recipients with recurrent HCV who are candidates for antiviral therapy. Further studies are needed to compare the utility of LDV/SOF with other non-interferon based therapies.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study design (SS, JR, MAJ), performance of experiments/ acquisition of data (TMF, MHM, CAK, NLE), analysis and interpretation of data (SS, JR, MAJ, SNB, SK), manuscript writing (SS, JR, MAJ), critical revision (SS, GC, FAD, MME, SBH, RWB), statistical analysis (JG).

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