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OPEN ACCESS

Journal of Surgery

Sun L, et al. J Surg 6: 1402.

DOI: 10.29011/2575-9760.001402

Research Article

Sofosbuvir-Based Ribavirin-Free Direct Antivirus Agent for Hepatitis C Recurrence after Liver Transplantation: A Single-Centre Study

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Citation: Sun L, Li G, Wu J, Zhao X, Zhang H, et al. (2021) Sofosbuvir-Based Ribavirin-Free Direct Antivirus Agent for Hepatitis C Recurrence after Liver Transplantation: A Single-Centre Study. J Surg 6: 1402. DOI: 10.29011/2575-9760.001402

Received Date: 03 June, 2021; **Accepted Date:** 09 June, 2021; **Published Date:** 11 June, 2021

Abstract

Background: Recurrence of Hepatitis C Virus (HCV) infection after liver transplantation is common among recipients, which is the most common cause of graft loss and death. Eradication of HCV can significantly improve the survival rate of both grafts and recipients. The emergence of novel Direct Antivirus Agent (DAA) has made revolutionary progress in the treatment of chronic HCV infection, with virological response rate exceeds 90%. However, real-world data on DAA treatment for HCV recurrence after Liver Transplant (LT) among Chinese population is limited.

Methods: This retrospective cohort study included all patients who received DAA treatment for recurrent post-transplantation HCV infections in the Beijing You'an Hospital between January 2011 and February 2018. Patient baseline information was collected within 2 weeks prior to DAA treatment. Laboratory data and non-invasive liver fibrosis were obtained at the end of DAA treatment and 12 weeks thereafter. Virological response at the end of treatment and the Sustained Virologic Response (SVR12) were determined as undetectable HCV-RNA level. Adverse Events (AE) due to DAA treatment were also identified. Descriptive analysis was performed to describe the patients' baseline characteristics and laboratory test results. Overall survival following post-transplantation DAA treatment was assessed using the Kaplan-Meier curves.

Results: In total, 13 patients were identified in the study, including 6 (46.2%) male and 7 (53.8%) female patients with an average age of 54 (±5.5) years. All 13 patients received sofosbuvir-based (without ribavirin) DAA regiment, of which 3, 6 and 4 patients respectively received sofosbuvir alone, sofosbuvir and ledipasvir, and sofosbuvir and daclatasvir. The SVR of the 12th and the 24th week were both 100%. During treatment with DAA, 3 cases of mild AE occurred, including two patients with fatigue and one patient with muscle soreness. The 1-, 3- and 5-year overall survival rates after transplantation were 100%, 91.7% and 71.3%, respectively.

Conclusions: This study suggested that DAA is highly effective and safe in the treatment of hepatitis C recurrence after LT in a single-center cohort of patients with HCV-related ESLD from a Chinese perspective.

Keywords: Direct antivirus agent; Hepatitis C recurrence; Liver transplantation; Real-world data

Introduction

According to WHO report [1], about 3% world's population are suffering from hepatitis C virus (HCV) infection worldwide, and more than 170 million chronic HCV patients have potential risk of cirrhosis and/or liver cancer. HCV-associated End-Stage Liver Disease (ESLD) is a major indication for liver transplantation, however, post-transplantation hepatitis C recurrence is fairly common with up to 50% of recipients presenting histological evidence of recurrence within first year of transplantation,

and 20-54% developing advanced fibrosis within 5 years of transplantation [2-4]. Severe histological recurrence is the most common cause of graft loss and death and eradication of HCV can significantly improve both survival rates of grafts and recipients. The traditional treatment for hepatitis C infection relapse with Interferon (IFN-α) and Ribavirin (RBV) was suboptimal, which is mainly due to frequent side effects, high drug withdrawal rate (up to 40%) and low Sustained Virus Response (SVR) rate [5]. The emergence of novel Direct Antivirus Agents (DAAs) has made a revolutionary progress in the treatment of hepatitis C all over the world, including Sofosbuvir (SOF), Daclatasvir (DCV), Ledipasvir (LDP), with or without ribavirin [6-12]. The reported SVR rate after novel DAA treatment among HCV patients has been steadily high (over 90%) based on data from different regions across the world [13-16].

However, there is limited number of studies on DAAs treatment for hepatitis C recurrence after liver transplantation in Chinese population. In a timespan of seven years concerned in present study, 13 patients with HCV-associated ESLD underwent liver transplantation and received sofosbuvir-based DAA (without ribavirin) for hepatitis C recurrence in our surgical center. This study aims to evaluate the effectiveness and safety of the DAA treatment using real-world evidence and to provide us guided experience in the treatment of post-transplantation hepatitis C recurrence.

Methods

Study Cohort and Data

The study included all adult (>=18 years) patients who underwent liver transplantation, experienced hepatitis C recurrence and received DAA treatment (pre-treatment HCV-RNA > 20IU/ mL) in Beijing You'an Hospital (BYAH), Capital Medical University, between January 2011 and February 2018. Patients who experienced rejection reactions, cytomegalovirus or other hepatoviruses, biliary or vascular complications, or serious organ dysfunction, were excluded. The data used in the study was derived from the Electronic Medical Records (EMRs) of BYAH, which is a high-volume tertiary teaching hospital with over 300,000 patients (outpatient and inpatient) annually [17]. The hospital implemented a comprehensive EMR system in 2008, which records entire clinical information of patients during hospitalization and outpatient follow-up, including surgery/ procedure records, death records, laboratory test results, diagnostic imaging results, pathology reports, physician notes, and electronic drug prescriptions [17]. All patients provided informed consents, and this study was approved by the Ethics Committee of Beijing You'an Hospital, Capital Medical University.

Study Variables

Patient baseline (within 2 weeks prior to DAA treatment) information including age, gender, indications for LT, comorbidities, pre-LT Model of End-stage Liver Disease (MELD) scores, pre-LT Child-Turcotte-Pugh (CTP) scores, anti-HCV failure history, non-invasive fibrosis scores, pretreatment Log10 HCV-RNA, HCV genotype, LT-DAA intervals, DAAs regimens, immunosuppressant regimens, were obtained from the EMR. The subsequent laboratory data were collected at the end of DAA treatment as well as 12 weeks thereafter, including liver and renal function, Complete Blood Count (CBC), coagulation panel, HCV-RNA quantitative, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Total Bilirubin (TBil) and Alkaline Phosphatase (ALP), Albumin (ALB), International Standardization Ratio (INR), Creatinine (Cr), Estimated Glomerular Filtration Rate (eGFR), White Blood Cell Count (WBC), Platelet (PLT), Hemoglobin (HGB), and blood glucose (BG). The non-invasive liver fibrosis tests including fibrosis score on Four Factors (FIB-4) and aspartate aminotransferase-platelet ratio index (APRI) were obtained both at the baseline and the end of DAA treatment. Virological response was determined as undetectable HCV RNA level at the end of treatment, and the Sustained Virologic Response (SVR12) was determined as undetectable HCV RNA level 12 weeks or more after the end of DAA treatment. The adverse reactions (fatigue, headache, muscle soreness, nausea, etc.) during treatment were collected through EMR system and telephone follow-up up to the end of the study period.

Data Analysis

Descriptive analysis was performed to describe the patient baseline characteristics and laboratory test results. The frequency and percentage for categorical variables, as well as means and standard deviation for continuous variables were reported. Paired student's t-test was employed to assess the changes in continuous variables (such as Cr, CBC and BG) between baseline and the end of treatment. Overall survival following post-transplantation DAA treatment was assessed using the Kaplan-Meier curves. The differences were considered statistically significant when P value was less than 0.05. All statistical analysis was performed using SPSS 22.0 (IBM, Armonk, NY, USA).

Results

Patient Characteristics

In total, 13 patients were included in the study, including 6 (46.2%) male and 7 (53.8%) female patients. The average age was 54 (±5.5) years, and the median age was 53 (interquartile range: 59-50.5) years. All patients had HCC related cirrhosis and two of them had concurrent liver cancer. Before transplantation, the average Child-Pugh score was 8.8 (SD±2.1), and the average MELD index was 13.9±11.1. Five patients had comorbid diabetes and four patients had comorbid hypertension. Prior to transplantation, HCV-RNA ranged from 2.78×103 to 5.13×107 IU/ml with average Log10 HCV-RNA of 6.4(±1.3). The majority of patients were 1b

HCV genotype (10 patients, 76.9%), whereas 2 patients were 2a genotype, and 1 patient was 3b genotype. Four (30.8%) patients had a history of IFN+EBV anti-HCV treatment either before or after transplantation but before DAA (due to unavailability of DAA at the time of treatment) (Table 1).

Treatment Received

Variable	Category	Frequency (%) or median (IQR)
Sex	Male	6 (46.15%)
	Female	7 (53.85%)
Age (year)		53.85±5.51
Indication for LT	Cirrhosis	11
	Liver cancer	2
Comorbidity	Diabetes Mellitus	5
	Hypertension	4
Preoperative MELD score		
Preoperative Child-Pugh score		
Previous anti-HCV treatment	Yes	5 (38.46%)
	No	8 (61.54%)
Liver fibrosis		
	FIB-4	8.09±7.56
	APRI	4.01±4.32
Log10 HCV-RNA before treatment		6.36±1.26
HCV genotype	1b	10 (76.92%)
	2a	2 (15.39)
	3b	1 (7.69%)
Duration between LT and DAA (month)		31.08 ± 23.47
DAA regimen	Sofosbuvir	3 (23.08%)
	Sofosbuvir + Ledipasvir	6 (46.15%)
	Sofosbuvir + Daclatasvir	4 (30.77%)
Antirejection regimen	Tacrolimus	7 (53.84%)
	Sirolimus	3 (23.08%)
	Tacrolimus + Sirolimus	2 (15.39%)
	Cyclosporine	1 (7.69%)

Table 1: Patient characteristics and clinical variables.

Note: IQR: Interquartile Range; LT: Liver Transplantation; MELD: Model For End Stage Liver Disease; HCV: Hepatitis C Virus; RNA: Ribonucleic Acid; Log10 HCV-RNA: Ten Logarithm Of HCV-RNA Copies; DAA: Direct Antivirus Agent; FIB-4: Fibrosis Score On Four Factors; APRI: Aspartate Aminotransferase-Platelet Ratio Index. Five patients received the classic Orthotopic Liver Transplantation (OLT), and 8 patients underwent piggyback liver transplantation. The average interval between transplantation and initial DAA treatment was 31.1±23.5 months ranging from 1 to 64 months. All 13 patients received sofosbuvir-based (without ribavirin) DAA regiment, of which 3, 6 and 4 patients received sofosbuvir alone, sofosbuvir and ledipasvir, and sofosbuvir and daclatasvir, respectively. Eight patients completed 12 weeks, and 5 patients completed 24 weeks of DAA. Regarding the anti-rejection treatment, the number of patients received the regiment of tacrolimus alone, sirolimus alone, tacrolimus+sirolimus, or cyclosporine, was 7, 3, 2 and 1, respectively (Table 1).

Virological Response

Virological clearance was observed in all cases at the end of treatment (i.e. HCV-RNA < 20 IU/ml), and SVR was 100% at both 12th and 24th week. No virological recurrence was observed during the follow-up period (Table 2).

Changes in Liver-Related Laboratory Tests and Fibrosis Scores

Variable	Baseline	End of DAA treatment	P -value
ALT (U/L)	125.01±148.77	24.01±14.19	0.023
AST (U/L）	135.19±131.90	35.22±30.84	0.005
Total bilirubin (μmol/L)	19.32±7.43	15.69±7.18	0.058
Prealbumin (mg/L)	186.02±78.86	218.00±84.00	0.177
Albumin (g/L)	39.32±4.30	40.74±4.31	0.234
Serum cholinesterase activity (U/L)	7262.85±3440.10	7988.69±2970.57	0.400
γ-GT (U/L）	162.55±126.80	38.72±26.23	0.004
ALP (U/L）	124.52±57.81	113.00±77.65	0.634
PT(s)	10.95±1.26	10.97±1.25	0.856
INR	0.97±0.11	1.00±0.12	0.859
WBC (×109/L)	4.42±2.03	5.15±2.75	0.143
Hemoglobin (g/L)	129.92±23.32	129.52±28.26	0.940
Platelet (×109/L)	116.54±68.65	140.69±96.02	0.056
Lymphocyte (×109/L)	1.30±0.81	1.53±1.15	0.247
Blood sugar	6.90±3.11	6.77±1.71	0.831
Creatinine	74.92±16.56	83.23±21.64	0.083
eGFR	87.04±16.63	82.25±17.50	0.101
FIB-4	8.09±7.56	4.09±4.60	0.100
APRI	4.01±4.32	1.02±1.43	0.014

Table 2: The description of serum laboratory variables for the study cohort.

Note: DAA: Direct Antivirus Agent; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; γ-GT: Gamma-Glutamyl Transferase; ALP: Alkaline Phosphatase; PT: Prothrombin Time; INR: International Normalized Ratio; WBC: White Blood Cells; eGFR: Estimated Glomerular Filtration Rate; FIB-4: Fibrosis Score On Four Factors; APRI: Aspartate Aminotransferase-Platelet Ratio Index.

Compared with baseline values, the indicators of liver inflammation and cholestasis were significantly declined at EOT (ALT 125.0±148.8 vs 24.0±14.2 U/L, P<0.05; AST 135.2±131.9 vs 35.2±30.8 U/L, P<0.05; and γ-GT 162.6±126.8 vs 38.7±26.2 U/L, P<0.01) (Figure 1). The APRI also significantly decreased at EOT compared to the corresponding baseline values (4.0±4.3 vs 1.0±1.4, P<0.05), while the TBil, serum albumin, ALP, PT, INR and FIB-4 showed no significant difference (Figures 1 and 2).

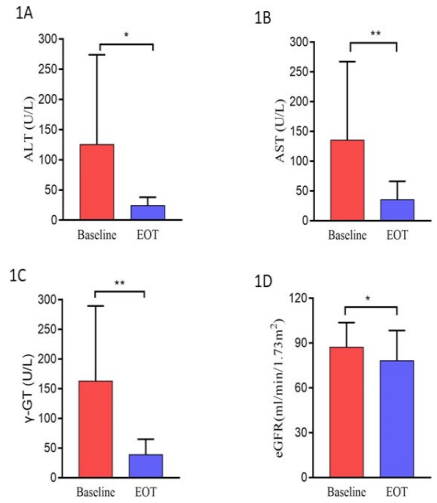

Figure 1: The ALT, AST, rGT and eGFR values at the baseline and at the end of direct antivirus agent treatment. EOT: End Of Treatment; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; γ-GT: Gamma-Glutamyl Transferase; eGFR: Estimated Glomerular Filtration Rate.

Safety and tolerability

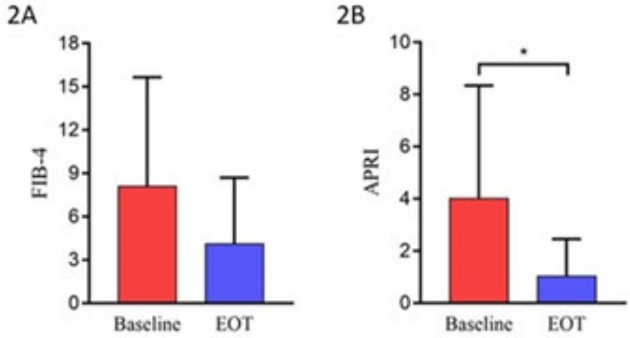

Figure 2: The liver fibrosis scores at the baseline and at the end of direct antivirus agent treatment. FIB-4: fibrosis score on four factors; APRI: Aspartate Aminotransferase-Platelet Ratio Index.

Compared with baseline, WBC, HGB, PLT, Cr and blood glucose showed no significant changes at EOT, whereas the eGFR was significantly improved (78.1±20.3 vs 87.0±16.6, P<0.05) (Figure 2). During the treatment with DAA, 3 adverse events occurred, with an AE incidence of 23.1% (3/13). Two patients developed fatigue and one patient complained about muscle soreness, which was mild and alleviated spontaneously. No severe AE or associated drug withdrawal or death occurred during the treatment.

Survival after liver transplantation and DAA treatment

The patients were followed up for 11-107 months, with a median follow-up period of 62 (interquartile range: 30 - 89.5) months. Ten patients had long-term survival, while one patient died of cerebral hemorrhage at 63 months after LT (32 months after DAA treatment), one patient died of pulmonary infection at 62 months after LT (18 months after DAA treatment), one patient performed re-transplantation due to graft dysfunction and died at 28 months post-LT (25 months after DAA treatment). The overall survival rates were 100%, 91.7% and 71.3% at 1-, 3- and 5-year after transplantation, respectively (Figure 3).

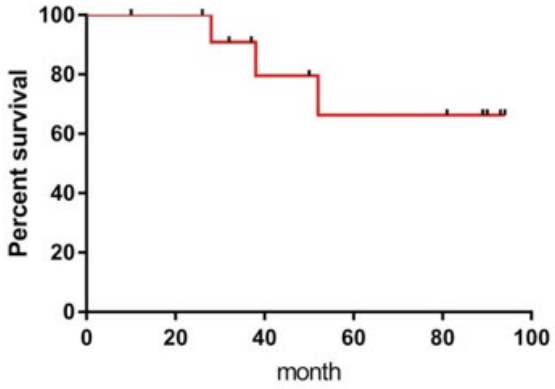

Figure 3: The Kapplan-Miere curve for the study cohort.

Discussion

Prior to the DAA era, the treatment of HCV recurrence after liver transplantation mainly relied on the interferon or pegylated interferon regimen with RBV. This traditional antiviral regimen can result in frequent adverse reactions and high discontinuation rates (up to 40%), with only 15-35% sustained viral response rate [5]. In addition, interferon with immunoregulation will increase the incidence of acute cellular rejection after transplantation [18-20], and its interaction with immunosuppressant further complicates antiviral therapy [21,22]. Therefore, the graft and patient survival rates were significantly lower in HCV recipients compared to non-HCV recipients [23]. With the advent of the new generation of DAA drugs, the clinical outcomes of HCV relapsed patients after liver transplantation have been considerably improved worldwide. In our institute, DAA therapy based on sofosbuvir without ribavirin was used, and SVR12 and SVR24 reached 100% in these 13 patients. Sofosbuvir is an effective HCV NS5B polymerase inhibitor with pan-genotypic activity and a high resistance barrier, which was approved for the treatment of hepatitis C virus in 2013

[24]. Both daclatasvir and ledipasvir are effective pan-genotype NS5A inhibitors, both of which can interfere with HCV replication. Although the previous American Association for the Study of Liver Diseases guideline recommended the use of ribavirin, its antiviral mechanism remains unclear. Moreover, ribavirin can cause a series of side effects such as severe anemia, hemopenia, and renal function injury [8], which further complicates the management of LT recipients. Therefore, ribavirin was not used in the regiment in our center.

After ribavirin-free DAA treatment for post-transplant recurrent hepatitis C, liver function was significantly improved. Compared with values before treatment, liver enzymes (ALT, AST) and cholestatic injury indexes (GGT) were notably refined, and noninvasive liver fibrosis indexes were remarkably reduced. Shoreibah M and coworkers also reported the application of a number of ribavirin-free DAA treatment regiments for hepatitis C recurrence after LT, and found similar results as ours [6,8]. In our study, a few cases (3/13) had mild adverse reactions such as fatigue and muscle soreness, without severe adverse events, graft dysfunction, or drug withdrawal during treatment. During follow-up, 2 patients died and 1 graft dysfunction occurred, which however were not related to the adverse effects of the transplant operation itself or DAA medication. In our study, none of the patients needed adjustment of immunosupressants during DAA treatment, and no rejection reactions or drug toxicity were observed, which may be partially due to the effect of sofosbuvir on calcineurin inhibitors.

Previous studies have shown that DAA therapy has a lower SVR12 rate in hepatitis C recurrence LT recipients with advanced fibrosis, cirrhosis, prior antiviral therapy, and some specific genotypes. In this study, 4 patients had a history of IFN antiviral failure, and 1 case was type-3a HCV. These patients received a 24-week course of DAA, while the other 8 patients received a 12-week course. All patients obtained a sustained virological response. The high virologic clearance rate in our cohort was probably owing to the mild degree of fibrosis before DAA treatment. The optimal timing for perioperative DAA therapy in liver transplantation is also worth discussing. Theoretically, the earlier DAA treatment is initiated, the better clinical outcome and cost-effectiveness benefit patients will have. To date, however, there is no clinical consensus on scheme and standard of DAA treatment for hepatitis C recurrence after liver transplantation. Our experience is that DAA therapy should be initiated as soon as possible conditional on stable function of liver and other major organs. The reason is that HCV recurrence after liver transplantation can induce tissue inflammation and liver fibrosis to varying degrees over time. HCV recurrence can also lead to metabolic and extrahepatic complications such as diabetes mellitus (DM), depression, kidney disease, non-Hodgkin's lymphoma, osteoporosis, and non-hepatic malignancies [25-28]. Ten cases in this study suffered from LT prior to the availability of the new generation of DAA drugs, thus the transplantation-DAA treatment interval was long (11-64 months). With the widespread use of new generation of DAA and the accumulation of experience, recent 3 patients in our study experienced a much shorter interval (1-3 months) between LT and initiation of DAA antiviral treatment. However, this study has some limitations. First, this is a single-center retrospective study with a small sample size. Second, the data sources were limited to general demographic information and laboratory tests, without graft biopsy information before and after DAA treatment to reveal the graft pathologic changes. Therefore, well-designed multi-center prospective studies are warranted in future to further evaluate the efficacy and significance of DAA treatment in the Chinese population.

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