Efficacy And Safety of Sofosbuvir Based Regimens For Treatment of Hepatitis C Recurrence After Living Donor Liver Transplantation: An Experience From India

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Introduction: **Results of Sofosbuvir based regimens for hepatitis C (HCV) recurrence after liver transplantation are available from well-designed clinical trials. Most of the data is from deceased donor liver transplant (DDLT) setting, and data on "real world" experience for HCV recurrence after living donor liver transplantation (LDLT) is limited.** ***Material and methods:*** **Consecutive 78 patients who completed Sofosbuvir based HCV treatment after liver transplantation were included. Following Sofosbuvir based regimens were used; Sofosbuvir + Ribavirin (n = 58), Sofosbuvir + Ledipasvir ± Ribavirin (n = 5), Sofosbuvir + Daclatasvir ± Ribavirin (n = 15). Treatment was given for 12 weeks (triple therapy) or 24 weeks (dual therapy).** ***Results:*** **A total of 74/78 (94.8%) patients achieved end of treatment response (ETR) while 4 did not achieve ETR. A total of 68/76 (89.4%) patients achieved sustained virological response at 12 weeks (SVR12). while 2 are waiting for 12 weeks follow up after ETR. Twelve patients had history of failed previous treatment with Peginterferon and Ribavirin after LDLT, all these patients achieved ETR and 11/12 had SVR12. There was no statistical difference in response rates between genotype 1 or 3. Eighteen patients (16 on Ribavirin) had hemoglobin < 8 g/dl; two patients complained fatigue in absence of anemia.** ***Conclusion:*** **Sofosbuvir based regimens are safe and highly effective in treatment of HCV recurrence after LDLT. (J Clin Exp Hepatol 2018;8:121–124)**

Hepatitis C

Hepatitis C virus (HCV) related liver disease is a common indication of liver transplantation in India and western world. Post-transplantation HCV recurrence occurs in all of untreated patients. HCV recurrence after liver transplantation was associated with graft fibrosis, cirrhosis and decompensated liver disease.[1–4] Successful treatment of HCV after liver transplantation improves outcomes considerably.[5] HCV treatment after liver transplantation was effective only in a minority of patients and with significant side effects in the Peginterferon era. The results were even worse for genotype 1 than genotype 3.[6–8] Outcomes of HCV treatment improved markedly in terms of sustained virological response and adverse events after introduction of direct acting antivirals (DAAs).[9] Most of data is available from well conducted trials in the deceased donor liver transplantation (DDLT) setting. We describe our experience of Sofosbuvir based treatment regimens for HCV recurrence in living donor liver transplant (LDLT) recipients.

MATERIAL AND METHODS

The study was conducted at a tertiary care center in North India. It included patients who underwent DAA treatment for HCV recurrence after LDLT from April 2015 to December 2016; the data was collected prospectively. The study was approved by the Institutional ethics committee. A total of 78 patients who completed 12 week treatment, or had no response on treatment were included in this analysis. Post liver transplantation immunosuppression protocol consisted of a triple drug regimen in the first 3 months including Tacrolimus, Mycophenolate and Steroids (tapered in 3 months). The work up before HCV treatment consisted of complete blood counts, liver function tests, renal functions tests, HCV RNA quantitative (before treatment) and HCV genotype. Complete blood counts and liver function tests were done every 2 weeks during treatment. HCV RNA was repeated at 4 weeks, 12 weeks or 24 weeks (at the end of treatment) and 12 weeks after end of treatment. The following definitions were

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Abbreviations: DAA: direct acting antivirals; DDLT: deceased donor liver transplant; ETR: end of treatment response; HCV: hepatitis C; LDLT: living donor liver transplantation; RVR: rapid virological response; SVR12: sustained virological response at 12 weeks
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used; rapid virological response (RVR) was defined as negative HCV at 4 weeks of treatment, end of treatment response (ETR) was defined as negative RNA at the end of treatment, sustained virological response was defined as negative HCV RNA at 12 weeks after end of treatment (SVR12). Selection of patients for DAA treatment for HCV recurrence after LDT was based on clinical indications or in presence of biochemical (abnormal liver function tests) and liver biopsy findings when available. Liver biopsy was done as per the clinical indication. HCV treatment was started 12 weeks after LDLT or earlier (<3 months) if patient received pulse steroids for acute cellular rejection (DAA started to prevent flare up of HCV) or a liver biopsy (done for abnormal liver function tests) showed HCV recurrence. Sofosbuvir (400 mg) once a day and weight based Ribavirin was used for total treatment duration of 24 weeks before availability of Ledipasvir or Daclatasvir at our center in India. This regimen was not used after availability of Ledipasvir and Daclatasvir. The patients received 2 DAAs (Sofosbuvir plus either Ledipasvir or Daclatasvir with or without Ribavirin after availability of Ledipasvir and Daclatasvir at our center. The treatment duration was planned for 12 weeks (triple therapy) or 24 weeks (dual therapy with DAAs or Sofosbuvir + Ribavirin). The data is shown as number, percentage and median (25–75 IQR). Two groups were compared with Fisher's exact test or Chi-square test (categorical variables), Student's *t* test (continuous parametric data) or Mann–Whitney test (non parametric data).

Table 1 Baseline Characteristics of Study Cohort (*n* = 78).

Parameter	Result
Age, mean (SD)	50 ± 7 years
Sex	57 males, 21 females
HCV RNA IU/ml	1.3×10^7 (2.1×10^5–4.9×10^6)
Genotype 1/3/4/6	17/55/5/1
Follow up before HCV treatment months, median (IQR)	12 (2–27)
Prior treatment exposure to pegIFN	13
AST at treatment IU/L	56 (34–102)
ALT at treatment IU/L	72 (44–133)
Transplant to HCV treatment with DAAs interval months	12 (2–27)

Table 2 Selection of Patients for HCV Treatment (*n* = 78).

Initiation of treatment	Number of patients
Treatment started at the time of pulse steroids for biopsy proven acute cellular rejection	12
Treatment started due to abnormal liver function tests	41
Treatment started at 3 months without raised liver function tests	5
Old transplants, treatment initiated at availability of direct acting antivirals	20

RESULTS

The study cohort included 78 patients (57 males and 21 females) who completed treatment for HCV treatment or had no response (not able to achieve HCV RNA negative status till end of treatment). The mean age of cohort was 50 ± 7 years. HCV treatment was started after a median of 21.8 months post LDLT, 57 were males and 21 were females. The baseline characteristics of study cohort and selection of patients for treatment are shown in Tables 1 and 2. The mean HCV RNA before treatment was 6×10^6 IU/ml. HCV treatment was started at 12 (IQR 2–27, range 1–90) months. Forty-nine patients underwent liver biopsy at some point before HCV treatment for raised liver function tests. Twelve patients had acute cellular rejection [biopsy done at 3 (1–5) months], 25 patients had histological HCV recurrence [biopsy at 7 (1–18) months] and rest of 12 had other diagnosis (mainly ischemia reperfusion injury. Ten of 25 patients with biopsy proven histological HCV recurrence had stage 1 or 2 Ishak's fibrosis. HCV treatment was started along with pulse steroids for histological proven acute cellular rejection in 12 patients. The following Sofosbuvir based regimens were used: Sofosbuvir + Ribavirin (*n* = 58), Sofosbuvir + Ledipasvir (*n* = 4), Sofosbuvir + Ledipasvir + Ribavirin (*n* = 1), Sofosbuvir + Daclatasvir (*n* = 11), Sofosbuvir + Daclatasvir + Ribavirin (*n* = 4). The SVR rates according to treatment regimen and genotype are shown in Tables 3 and 4. Twelve patients had history of failed previous treatment with Peginterferon and Ribavirin after LDLT, all these patients achieved ETR and 11/12 had SVR12. Treatment was started <3 months after LDLT in 21 patients due to pulse steroids (for acute cellular rejection) or histological recurrence or abnormal liver function tests; SVR12 was achieved in 16/19 (84.2%, SVR awaited in 2), which was not statistically different from patients with treatment initiation after >3 months, 52/56 (92.9%), $P = 0.395$. Three patients had marked steatosis (>60%) at liver biopsy along with other features of HCV recurrence; 2 of these had SVR12 with Sofosbuvir + Ribavirin regimen and SVR is awaited in 1 patient with Sofosbuvir + Daclatasvir + Ribavirin. SVR12 was achieved in 20/22 (90%) patients with a histological recurrence of HCV recurrence and in all patients with fibrosis.

Comparison of SVR Versus Non-SVR Groups

A total of 8 patients had no SVR; either treatment failure (*n* = 4) or relapse (*n* = 4). All these patients were compliant

Table 3 HCV Genotype and Treatment Response (n = 78).

	Genotype 1 *N* = 17	Genotype 3 *N* = 55	Genotype 4 *N* = 5	Genotype 6 *N* = 1
Treatment response	ETR 16/17 SVR 15/17 (88.2%) no response in 1, relapse in 1	ETR 53/55 SVR12 in 49/54 (90.7%) Relapse in 3, no response in 2 SVR awaited in 1	ETR 5/5 SVR12 in 4/4 (100%) SVR12 awaited in 1	No response to treatment

Table 4 Treatment Regimens and Response in Whole Cohort (*n* = 78).

	Sofosbuvir + Ribavirin *n* = 58	Sofosbuvir + Ledipasvir ± Ribavirin *n* = 5	Sofosbuvir + Daclatasvir ± Ribavirin *n* = 15
RVR	54 (93.1%)	5 (100%)	15 (100%)
ETR	54 (93.1%)	5 (100%)	15 (100%)
SVR12	51/58 (87.9%)	4/4 (100%) Awaited in 1	13/14 (92.8%) Awaited in 1
No ETR	4	0	0
Relapse after ETR	3	0	1

to therapy. When these patients were compared to patients with SVR12, there was no significant difference regarding age (50 ± 6 years in SVR group versus 52 ± 14 years in non SVR group, $P = 0.705$), pre treatment transaminases [AST 55 (34–95) versus 73 (31–152), $P = 0.664$ and ALT 72 (44–116) versus 88 (38–246), $P = 0.368$ in SVR versus no SVR groups), HCV RNA levels [1.3×10^6 (1.9×10^5–3.6×10^6) versus 6.1×10^5 (2.8×10^5–3×10^7) in SVR versus no SVR group, $P = 0.501$). Liver transplantation to treatment interval was 13(2–30) versus 5 (2–12) in SVR and non SVR group, $P = 0.426$. All the patients with fibrosis ($n = 10$) and history of ACR ($n = 12$) achieved SVR12. Diabetes was present in 2/8 (25%) of non-SVR patients as compared to 16/68 (23.5%) patients with SVR, $P = 0.732$; we do not have BMI data at the time of start of DAA treatment. There was no difference in immunosuppression regimens in these groups. All non-SVR were males, although it was not statistically significant, $P = 0.157$. SVR rates were not different for genotype 3 (49/54, awaited in 1) as compared to other genotypes (19/22, $P = 0.683$. Although SVR rates were lower in Sofosbuvir + Ribavirin (51/58, 87.9%) as compared to other regimens (17/18, 94.4%), it was not statistically different, $P = 0.671$. The 8 patients in non SVR group were retreated with Sofosbuvir + Ribavirin + Daclatasvir or Ledipasvir; 2 has achieved SVR, 5 achieved ETR (and waiting for 12 weeks period to test for HCV RNA) while 1 is on treatment.

The adverse event profile of HCV treatment is shown in Table 5. Eighteen patients (16 on Ribavirin) had hemoglobin <8 g/dl, 3 of these patients were in early treatment initiation group (<3 months post transplantation). Two patients complained fatigue in absence of anemia. None of patients had acute cellular rejection or renal dysfunction during DAAs treatment.

DISCUSSION

Recurrence of untreated HCV after liver transplant is universal. In absence of effective therapy, HCV recurrence was associated with significant morbidity and mortality in interferon era.[8] Peginterferon and Ribavirin treatment for post transplant HCV recurrence was associated significant side effects and poor SVR rates and SVR rates were worse for genotype 1 as compared to genotype 3.[6,8] With evolution of DAA based therapies, these patients could be treated with more efficacy and less side effects.[9–12] The Solar 1 and 2 trials included post transplant cohorts treated with Sofosbuvir, Ledipasvir and Ribavirin and showed good SVR rates. The SOLAR 1 study achieved >95% SVR12 in patients without cirrhosis or with compensated cirrhosis, the SVR rates were 60–75% in patients with severe hepatic impairment.[9] The SOLAR 2 cohort of post-transplantation patients also reports similar results; >90% SVR in patients with or without compensated cirrhosis while 5/7 for Child's C patients.[12] The DAA based treatment is also shown to be highly effective in HIV infected post transplant patients also. In the study by

Table 5 Treatment Related Adverse Events in 78 Patients.

Adverse event	Hemoglobin <8 g/dl	Fatigue	Acute cellular rejection or renal dysfunction
Number of patients (%)	18 (16 of these patients were on Ribavirin)	9 (7 of these had hemoglobin <8, 2 complained fatigue without having anemia)	None

Castells et al.; SVR could be achieved in all 22 patients[13]; multiple studies have shown safety and good efficacy of DAA based regimens. Several findings are common among these studies; advanced fibrosis is associated with poor SVR and side effects occur mainly in Ribavirin arm.[14–22] A systemic review including 1730 patients treated with Sofosbuvir based interferon free treatment showed 90% SVR in post transplantation patients. SVR rates were lower for patients with advanced fibrosis.[23] All the patients in current study had early stages of fibrosis and thus it was not a significant factor between SVR and non-SVR groups. It is difficult to differentiate acute cellular rejection with HCV recurrence sometimes and certain histopathological features favor one over other. Most of the studies on use of DAA post-transplantation are in DDLT setup, and data on its use in LDLT patients is scarce.[20] The current study shows that Sofosbuvir based regimens are safe and effective in LDLT also. The SVR rates are slightly lower in current study despite absence of cirrhosis in treatment cohort possibly because we used Sofosbuvir and Ribavirin initially due to unavailability of other DAAs. The Sofosbuvir based regimens were also effective in prior Peginterferon treatment failure group as 11/12 could achieve SVR12. We noted adverse events mainly in Ribavirin group. The current treatment regimens are quite safe in terms of side effects. The incidence of adverse events was 8.3% and only 3.3% discontinued treatment due to side effects in the reported systemic review.[23] The optimal timing of HCV treatment after liver transplantation is not clear. We found early treatment (<3 months after transplantation) quite safe and effective. The SVR rates should improve further with recent availability of other DAAs (Ledipasvir, Daclatasvir and Velpatasvir) in our setup. To conclude, we present our experience of DAAs for treatment of HCV after LDLT and found a good SVR rate. Sofosbuvir based regimens were well tolerated following liver transplantation with minimal side effects. Anemia was usually seen in the Ribavirin group. Early institution of DAA post liver transplant was also safe and effective.

CONFLICTS OF INTEREST

The authors have none to declare.

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