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Safety and Efficacy of Current DAA Regimens in Kidney and Liver Transplant Recipients with Hepatitis C: Results from the HCV-TARGET Study

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Abstract

Background—Data outside of clinical trials with direct acting antiviral (DAA) regimens with or without ribavirin as treatment of chronic HCV in solid organ transplant recipients is limited.

Methods—Liver transplant (LT), kidney transplant (KT) and dual liver kidney (DLK) transplant recipients from the HCV-TARGET database, a multicenter, longitudinal clinical care treatment cohort, treated with DAA regimens between January 1 2014 and February 15, 2016 were included to assess safety and efficacy.

Results—443 post-transplant patients were included (KT=60, LT =347, DLK=36); 42% had cirrhosis, 54% had failed prior antiviral therapy. Most had genotype (GT) 1 (87% with 52% G1a, 27% G1b, and 8% G1 no subtype) and were treated with sofosbuvir/ledipasvir (SOF/LDV) ± RBV (85%) followed by sofosbuvir + daclatasvir (SOF + DAC) ± ribavirin (9%) and ombitasvir/paritaprevir/ritonavir + dasabuvir (PrOD) ± RBV (6%). SVR12 rates were available on 415 patients and 397 patients (95.7%) achieved SVR12: 96.3%, 94.6% and 90.9% among LT, KT and DLK transplant recipients, respectively. Ribavirin did not influence SVR rates and was more often used in those with higher eGFR and lower creatinine. Female gender, baseline albumin 3.5 g/dL, baseline total bilirubin 1.2 mg/dL, the absence of cirrhosis and hepatic decompensation predicted SVR12. Six episodes of acute rejection (n=2 KT, 4 LT) occurred during HCV treatment in 4 and after cessation of treatment in 2.

Conclusion—In a large prospective observational cohort study, DAA therapy with SOF/LDV, PrOD and SOF plus DAC was efficacious and safe in, LT, KT, and DLK transplant recipients. Ribavirin did not influence SVR. Graft rejection was rare.

INTRODUCTION

Recurrent hepatitis C virus (HCV) is the foremost cause of liver graft loss and death in liver transplant (LT) patients infected with HCV. In patients who have detectable HCV RNA at the time of liver transplantation, HCV universally recurs and has an accelerated course with progression to advanced fibrosis in 20–54% of patients after 5 years post-LT.[1] Further, extrahepatic complications such as renal disease, and increase rate of diabetes mellitus attributable to hepatitis C infection can be encountered.[2] HCV infection is also more prevalent amongst kidney transplant (KT) recipients than in the US population.[3, 4] HCV in KT recipients accounts for decreased patient and kidney allograft survival accelerated hepatic fibrosis or cirrhosis, new-onset diabetes after transplantation, cardiovascular disease, sepsis, recurrent glomerulopathy, and *de novo* post-transplantation glomerular disease. Previously, interferon-based treatments in KT candidates and recipients with HCV were limited by both low response rates and high risk of graft rejection among recipients.[5–7] Thus, there is an unmet need for new HCV therapies for both liver and kidney transplant recipients.

Directly acting antiviral (DAA) therapies have revolutionized HCV treatment. However, limited data are available on their efficacy and safety in solid organ transplant recipients. Thus, analysis of real-world cohorts of liver and kidney transplant recipients may provide valuable insights into the safety and efficacy of these regimens in these cohorts.

PATIENTS AND METHODS

HCV-TARGET is a consortium of academic (n = 44) and community (n = 17) centers that provide medical care and antiviral treatment to HCV-infected patients. Since 2011, patients prescribed HCV treatment as part of routine clinical practice have been enrolled in a longitudinal prospective observational cohort study after offering consent. In the current study, data from sequential LT, KT and DLK transplant recipients treated for chronic HCV were collected prospectively from 37 sites (31 academic and 6 community centers) within a centralized database using standardized source data abstraction as previously described[8, 9] and managed using Research Electronic Data Capture electronic data capture tools hosted at the University of North Carolina Chapel Hill. Research Electronic Data Capture is a secure, web-based application designed to support data capture for research studies.[10] Patients were eligible if they were age 18 or older, LT, KT or DLK transplant recipients and were treated for HCV with an all-oral regimen with or without RBV. The cohort of patients included in this analysis started treatment no later than February 15, 2016 in order to allow for adequate follow-up time. This also reflects the time period when SOF/LDV, PrOD, and SOF/DAC with or without RBV were approved and available. We excluded patients treated with simeprevir plus sofosbuvir as they had been previously reported.[11] During the study period, 443 patients meeting these criteria were included (Figure 1). In light of the rapidly changing treatment options for HCV, the inclusion window for this cohort was defined *a priori* without reference to power/sample size calculations to provide a timely description of efficacy and safety of HCV treatment in LT, KT or DLK transplant recipients in clinical practice settings. The decision to initiate HCV treatment and the selection of the HCV treatment regimen (with or without ribavirin), the dose of ribavirin, and the duration of therapy was solely the responsibility of the treating clinician and his or her patient.

Measurements

Demographic, clinical, adverse event, and laboratory data were collected throughout the treatment period and the post-treatment follow-up period until the determination of SVR12. To account for variability in clinic visits in clinical practice, the window for HCV RNA assessment for SVR was 9 or more weeks following cessation of treatment.

Cirrhosis assessment—Liver disease stage (cirrhosis or no cirrhosis) was defined at the time of enrollment by biopsy and/or a combination of clinical, laboratory, histologic, and imaging criteria features.[8, 9] Patients with METAVIR stage 3 fibrosis by liver biopsy were defined as cirrhotic if they had any of the following: platelet count less than 140,000 per mL, presence of esophageal varices on esophagogastroduodenoscopy, nodular liver, portal hypertension, or ascites by radiologic imaging, noninvasive serum panels such as FibroSURE (Laboratory Corporation of America, Burlington, NC) consistent with stage 4 fibrosis, or liver stiffness measurement by elastography (FibroScan, Echosens North America, Cambridge, MA) consistent with stage 4 fibrosis (kPa ≥ 14). In the absence of liver biopsy, cirrhosis was defined as meeting any 2 of the earlier described non-histologic criteria.

Hepatic decompensation—History of hepatic decompensation was defined as evidence of prior or current diagnosis of ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, or variceal hemorrhage, or baseline concomitant medications with a specific indication for ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, or variceal hemorrhage.

Acute rejection—This was based on SAE reporting only. Additional details on the treatment and outcome of the rejection episode were obtained from the site investigator.

Outcomes

Efficacy—Treatment efficacy was measured as SVR12 defined as HCV-RNA level below the level of quantitation or undetected recorded at least 9 weeks after treatment was discontinued to account for variability of the follow up at each site. The evaluable population (EP) for SVR 12 was defined as the group of patients who ended treatment and had final treatment outcome available, including those who were lost to post treatment follow up (counted as treatment failures). The Per Protocol population (PP) for SVR 12 was patients who completed treatment or discontinued therapy early due to a virological failure and had virological data to assess for SVR12.

Safety—Adverse events (AEs) were captured as follows: any event that required a HCV medication dose reduction or discontinuation, or the addition of a concomitant medication for management; Anemia was defined as the presence of one of the following: (1) anemia reported as an AE by the investigator; (2) administration of red blood cell growth factors; or (3) blood transfusion. Serious AEs were any AEs that met the following criteria: (1) required hospitalization, or (2) met criteria for expedited reporting per FDA form MEDWATCH 35000. Events of special interest for this study were hepatic decompensation and acute rejection.

Analysis Strategy

Demographics and baseline laboratory values were collected and analyzed according to discrete sub-populations of interest (LT, KT and DLK), and frequencies of adverse events were presented by treatment regimen for all patients who started treatment (N=443). The unadjusted rates of SVR were calculated for LT, KT, and DLK groups in Evaluable Population (EP) included N=438 and per protocol (PP) population included N=412 (Figure 1). Confidence intervals of unadjusted rates were calculated using exact binomial methods.

Associations between each baseline covariate of interest and sustained virological response were estimated by multivariable logistic regression analyses with Firth penalized maximum likelihood estimation [12] (age and sex adjusted) for the LDV/SOF±RBV per protocol population [12]. The set of covariates was selected a priori based on a consensus of clinical expertise and included the most well-established baseline covariates associated with SVR: sex, age, albumin (<3.5g/dl, 3.5g/dl), platelet count (1000/uL), total bilirubin (<1.2mg/dl, >1.2mg/dl), cirrhosis status, history of hepatic decompensation, and history of liver or kidney transplant.

Additional Firth multivariable logistic regression analyses adjusted for cirrhosis status were performed on liver transplant population alone to ascertain relationship of RBV use to SVR taking into account that RBV is likely to be prescribed more often cirrhosis.

Analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC).

Informed Consent

The protocol was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The independent ethics committee at each participating study center or a Central Institutional Review Board approved the protocol if a local Institutional Review Board was not in place. All patients provided written informed consent for their participation. All authors had complete access to the study data, and reviewed and approved the final manuscript.

RESULTS

Patient Population

Between January 1, 2014 and February 15, 2016, there were 443 patients with chronic HCV who were post LT (n = 347; 78%), KT (n = 60; 14%) or DLK transplant (n = 36; 8%) treated for HCV (Figure 1). The majority of patients were men (n = 325; 73%), Caucasian (n = 310; 70%) and younger than 65 years (n = 310; 70%) (Table 1). HCV GT1a and 1b infections were present in 52% and 27%, respectively. A total of 54% (n=241) were treatment experienced, including 28 (6%) with prior exposure to first-generation protease inhibitors telaprevir or boceprevir. Forty-two percent (n=184) had cirrhosis, of whom 53% (n = 97) had a prior episode of hepatic decompensation and 52% (33/63 patients with available model for end-stage liver disease [MELD] score) had a pretreatment MELD score greater than or equal to 10 (Table 1).

The baseline clinical and laboratory characteristics were assessed for patients treated with and without RBV (Table 4). Among patients who received RBV (n = 228), 58% were treatment-experienced, 42% had a history of cirrhosis, and 22% had a history of hepatic decompensation. In comparison, among patients in the RBV-free group (n = 215), 50% had prior treatment experience, 41% had a history of cirrhosis, and 24% had a history of hepatic decompensation. Demographic data and baseline laboratory values were similar in both groups except for creatinine and estimated glomerular filtration rate (eGFR). Baseline creatinine levels were higher in the RBV-free group at 1.53 mg/dL (95% CI 1.3526, 1.7018) vs. 1.27 mg/dL (95% CI 1.1823, 1.3593) in the RBV-containing group (p = 0.0103). Similarly, eGFR was lower in the RBV-free group at 70.99 (95% CI 66.22, 75.76) vs. 82.40 (95% CI 78.02, 86.78) in the RBV-containing group (p = 0.0006). Although not statistically significant, more patients in the RBV-free group had genotype 1b (31% vs. 24%), while more patients in the RBV-containing group had genotype 3 (13% vs. 4%).

Of the 443 included patients, 378 (85%) were treated with SOF/LDV of whom 180 (48%) were treated with RBV, followed by sofosbuvir/daclatasvir (SOF + DAC) ± RBV containing regimens (9%); 31/39 received RBV, and ombitasvir/paritaprevir/ritonavir + dasabuvir

(PrOD) $\pm$ RBV (6%); 17/26 received RBV. SOF/LDV $\pm$ RBV was used in 86% of LT (n = 299), 82% of KT (n = 49) and 92% (n = 33) of DLK transplant recipients.

Efficacy

Per Protocol Population—Per protocol data was available for 412 patients (Figure 1). Of those with per protocol data, 395 patients (95.9%) achieved SVR12, with 96.6% (313/324) among LT recipients, 94.5% (52/55) among KT recipients and 90.9% (30/33) among DLK transplant recipients (Figure 2A, 2B, 2C). Of the patients who failed to achieve SVR12, the most frequent reason for not achieving SVR was post-treatment relapse. SVR12 rates were similar between LDV/SOF plus RBV vs. LDV/SOF alone among LT recipients 97% (95% CI 93–99) vs. 95% (95% CI 90–98), KT recipients (with and without RBV) 100% (95% CI 48–100) vs. 95% (95% CI 83–99) and DLK transplant recipients (with and without RBV) 100% (95% CI 74–100) vs. 89% (95% CI 65–99). Patients with cirrhosis vs. non-cirrhosis had similar SVR12 rates at 96% (95% CI 91–98) vs. 97% (95% CI 94–99) among LT recipients and 94% (95% CI 70–100) vs. 95% (95% CI 83–99) among KT recipients. Among DLK transplant recipients, patients with cirrhosis compared with non-cirrhosis had a numerically lower SVR; 85% (95% CI 55–98) vs. 95% (95% CI 75–100).

SVR12 rates were similar across genotype 1a vs. 1b at 96% (95% CI 92–98) vs. 99% (95% CI 94–100) among LT recipients, and 93% (95% CI 76–99) vs. 95% (95% CI 74–100) among KT recipients. Among DLK transplant recipients there was a numeric difference with SVR12 rates of 85% (95% CI 62–97) in genotype 1a patients vs. 100% (95% CI 63–100) in genotype 1b patients. Among LT recipients, 100% (27/27) GT3 infected patients, 100% (5/5) GT4 infected patients and 100% (2/2) GT6 infected patients achieved SVR12. Similarly, 100% of KT recipients with GT3 (2/2), GT4 (2/2) and GT6 (1/1) achieved SVR12.

In the Evaluable Population (N=438) 396 patients (90.4%) achieved SVR12, with 91.3% (314/344) among LT recipients, 89.7% (52/58) among KT recipients and 83.3% (30/36) among DLK transplant recipients (SVR rates in different subpopulations presented in Supplemental Figure 1A, 1B, 1C).

Predictors of SVR12

Associations between covariates of interest and SVR12 among patients with or without solid organ transplant who were treated with LDV/SOF $\pm$ RBV and had per protocol data are shown in Figure 3. Receipt of LT and/or KT did not predict SVR12 (OR 1.1, 95% CI 0.64–1.99, $p=0.74$) in logistic regression analysis minimally adjusted (to age and sex). Female gender, baseline albumin ≥ 3.5 g/dL, baseline total bilirubin ≤ 1.2 mg/dL, platelets and the absence of cirrhosis and hepatic decompensation predicted SVR12 in minimally adjusted regression analyses (Figure 3).

Among liver transplant recipients treated with LDV/SOF $\pm$ RBV, ribavirin use was not associated with SVR12 (OR=1.54, 95% CI 0.48–5.16, $p=0.46$) in logistic regression minimally adjusted to cirrhosis (Figure 4).

Safety and Tolerability

The overall rate of treatment discontinuation was 2.9%, with AEs being the most common reason (1.6%) (Table 2). Among patients receiving LDV/SOF $\pm$ RBV (n = 378), PrOD $\pm$ RBV (n = 26), DAC/SOF $\pm$ RBV (n = 39), the frequency of early discontinuation due to AEs was 1.3% (n=5), 0% (n=0) and 5.1% (n=2) respectively. The one patient that discontinued therapy early due to lack of efficacy was treated with LDV/SOF plus RBV. During the study, three deaths were observed, all of which were in LT recipients receiving LDV/SOF and all were deemed unrelated to HCV treatment. All three patients had compensated cirrhosis and the causes of death were, sepsis, subdural hematoma, and intraventricular hemorrhage.

The most common AEs and all SAEs are shown in Table 3. Serious adverse events were recorded in 45 patients (10%), and the incidence of such events was similar in patients taking or not taking ribavirin (8% and 13%, respectively). Notable serious adverse events included infections in 17 patients (4%), anemia in four patients (1%) and hepatic encephalopathy in five patients (1%). There were 6 patients who experienced rejection during treatment (n=4) or after treatment (n= 2). Two episodes occurred in KT recipients (on SOF+LDV and LDV+SOF+RBV) and 4 in LT recipients (two on SOF+LDV and LDV+SOF +RBV). Detailed data on the cases of rejection are presented in supplemental table 1. Among cirrhotic patients (n=184) serious adverse events were recorded in 26 patients (14%).

An analysis of eGFR was done over the DAA treatment period for 12 and 24 weeks in patients treated with and without RBV and there were no statistically significant changes observed between the two groups (Supplemental Figure 2a and 2b).

In the overall population the most common adverse events were fatigue, anemia, headache, nausea and diarrhea (Table 3). Fatigue was more common in patients taking ribavirin (35%) compared with patients taking a ribavirin free combinations (23%) (not shown). Patients taking ribavirin were more likely to develop anemia (36%) compared with patients not taking ribavirin (3%) (not shown).

DISCUSSION

This large cohort of DAA therapy in solid organ transplant recipients with recurrent hepatitis C from a wide array of transplant programs in the U.S. provides real-world data on the safety and efficacy of DAA therapy, especially SOF/LDV. In contrast to the clinical trials [13, 14], this population included patients with mild to severe liver and kidney dysfunction and reflects the challenges seen in clinical practice. Impressively, the SVR12 rates achieved appear to be quite comparable to those in the clinical trials [12,13]. Among patients with available virological outcomes, sustained viral clearance was achieved in 96% of SOF/LDV $\pm$ RBV treated patients, 92% of PrOD treated patients and SOF plus DAC $\pm$ RBV in 100% of patients. More importantly, treatment discontinuation was very infrequent highlighting the marked improvement in treatment tolerability in an IFN-free era. These results reinforce the success and ease of HCV therapy in the transplant setting in this current therapeutic environment.

We have previously published on the safety and efficacy of simeprevir and sofosbuvir with or without ribavirin [9]. The current study extends the DAA treatment experience to the drugs approved subsequently. The most frequently used DAA combination in our current cohort was SOF/LDV $\pm$ RBV. Impressively, the successful outcomes noted in our clinical practice experience is similar to what has been observed in clinical trials of carefully selected patients.[13, 14] The unique part of this data is that 122 LT PP recipients were treated with SOF/LDV without ribavirin and 116 (95 %) achieved SVR. The baseline characteristics of the study population were analyzed for patients treated with and without RBV and the only significant difference between the two groups was a higher baseline creatinine level and lower eGFR in the RBV-free group. These results present a major difference from the clinical trials in which a RBV-free regimen was not explored. Our large experience, along with a recent observational study with similar responses with a RBV-free regimen of SOF/LDV [15], should provide confidence in treating the LT recipients with a RBV-free regimen, particularly when there are adverse events or concerns of tolerability and perhaps by not risking efficacy. Nonetheless, we acknowledge limitations to our analysis; the present study was not randomized and our analysis was based on the per-protocol population. A smaller proportion of the transplant recipients were treated with PrOD. In, a multicenter phase 3 trial, 34 post LT patients with recurrent GT1 HCV and Metavir fibrosis stage F0–F2 were treated with PrOD and weight-based RBV for 24 weeks and achieved SVR24 rate of 96%.[16] Drug-drug interactions between ritonavir and calcineurin inhibitors are known to exist and prospective dose adjustments were made in the clinical trial for cyclosporine and tacrolimus. Thus this regimen is inherently challenging and is reflected in the limited use of it in clinical practice. The approval of daclatasvir was relatively more recent in the US and therefore it is likely that it was the reason for fewer patients to have been treated with DAC based regimen; the SVR rate was high in those treated with DAC/SOF $\pm$ RBV.

Among the LT patients receiving DAA therapy, we examined the factors associated with SVR12. Similar to findings in non-transplant patients, absence of advanced disease, as reflected by additional features of albumin ≥ 3.5 g/dl, total bilirubin of ≤ 1.2 mg/dl, and adequate platelet count, was consistently associated with better SVR rates. This argues for early treatment of recurrent HCV disease and certainly before the development of cirrhosis.

The safety profile observed in this large experience has been impressively good. Forty two percent of the SOF/LDV $\pm$ RBV cohort had cirrhosis and 23% had a history of hepatic decompensation; yet the SAE rate in the this group was 10 %. Most of the SAEs were of infection, a complication well recognized to occur in those with cirrhosis. The rate of discontinuation of therapy due to an adverse event was 1.3% which is a reflection of the excellent tolerability of these regimens.

Traditionally, rejection in the graft had been seen in the interferon era and it had been suggested that this was due to either the immunomodulatory effects of interferon or improved hepatic function, after successful eradication of the virus, and better pharmacokinetics of the CNIs leading to lower trough levels.[17] Acute cellular rejection historically, based on a recent SRTR data analysis, independent of HCV with or without therapy, occurred in approximately 10.9 % of LT recipients within the first six months of

transplant, and in 2.3 % beyond a year of LT, [18]; and in this experience rejection requiring treatment was reported in 6/443(1.4 %) patients. While it is difficult to attribute causality to HCV therapy, it is nevertheless important to be vigilant of such an occurrence particularly when there might be drug-drug interactions as with the PrOD regimen. One strategy to consider is of delaying treatment for about 3–6 after transplant as most rejection episodes after transplant occur early on in the post-transplant period.

The safety of DAAs in patients with renal impairment is a topic of considerable interest and clinical relevance as few patients in phase III clinical trials with severe kidney function impairment were enrolled. It is known that sofosbuvir and its circulating metabolite GS-331007 are cleared renally and there is a concern of sofosbuvir use in those with eGFR of < 30 ml/min.[19] As a consequence, international guidelines and product labeling state that no formal recommendation on dosing of sofosbuvir can be made in those with eGFR<30 ml/min. Only 6% of patients enrolled in the current analysis of post LT, post KT and post DLK populations had eGFR ≥ 30 ml/min and thus meaningful data on the impact of HCV therapy on renal function in those with severely impaired renal function could not be determined.

The real-world experience of treatment of kidney transplant patients is understandably more limited than in the post liver transplant population.[20–22] Beinhardt and colleagues recently demonstrated safety and efficacy of DAA regimens in 25 patients (24 on a sofosbuvir containing regimen), of which 10 were on hemodialysis, 8 were KT recipients and 7 were DLK recipients, with stable kidney function on treatment and 96% achieved SVR12.[20] Sawinski and colleagues demonstrated excellent efficacy and safety of DAAs in a group of 20 consecutive kidney transplant recipients, 88% were GT1, 50% had biopsy proven Metavir F3 of F4 fibrosis, and 60% had failed IFN based therapy. DAA therapy was initiated a median of 888 days after renal transplantation and there was a 100% rate of SVR12 and the most commonly used regimen was sofosbuvir plus simeprevir, less than half of patients required calcineurin inhibitor dose adjustment during treatment.[22] Kamar and colleagues similarly performed a pilot study to assess efficacy and safety of sofosbuvir based regimens in 25 kidney transplant recipients (76% GT1), with RVR achieved in 88% and SVR12 in 100% of patients. A decrease in calcineurin inhibitor levels was noted after HCV clearance. No adverse events were observed[21]. HCV-TARGET experience is the largest thus far with 347 liver transplant recipients, 60 kidney transplant recipients and 36 dual liver kidney transplant recipients where HCV therapy was highly efficacious and well tolerated independent of genotype 1 subtype, presence or absence of cirrhosis; a good number of patients were treated with a RBV free regimen.

In summary, in this large clinical practice, LT, KT and DLK patients across a spectrum of liver and kidney disease severity achieved high rates of SVR12 with DAA therapy. SOF/LDV was the most commonly used regimen and although ribavirin is recommended by guidelines for LT and DLK transplant recipients, nearly half of the patients were treated without ribavirin and achieve comparable SVR12 rates. This suggests that ribavirin may not be essential for all transplant recipients. While treatment is safe and extremely well tolerated, acute rejection can still occur, albeit infrequently, necessitating a thoughtful approach to the timing of treatment and careful monitoring during treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

AE	adverse event
DAC	daclatasvir
DAA	direct acting antiviral
DLK	dual liver kidney
FDA	Food and Drug Administration
GT	genotype
HCV	hepatitis C virus
HCV-TARGET	Hepatitis C Therapeutic Registry and Research Network
KT	kidney transplant
LDV	ledipasvir
LT	liver transplant
MELD	model for end-stage liver disease
PrOD	ombitasvir/paritaprevir/ritonavir + dasabuvir
RBV	ribavirin
SAE	serious adverse event
SOF	sofosbuvir
SVR	sustained virologic response
TAC	tacrolimus

References

1. Crespo G, Marino Z, Navasa M, Forns X. Viral hepatitis in liver transplantation. *Gastroenterology*. 2012; 142:1373–1383.e1. [PubMed: 22537446]

2. Perico N, Cattaneo D, Bikbov B, Remuzzi G. Hepatitis C infection and chronic renal diseases. *Clin J Am Soc Nephrol*. 2009; 4:207–20. [PubMed: 19129320]
3. Roth D, Gaynor JJ, Reddy KR, Ciancio G, Sageshima J, Kupin W, et al. Effect of kidney transplantation on outcomes among patients with hepatitis C. *J Am Soc Nephrol*. 2011; 22:1152–60. [PubMed: 21546575]
4. Lopez-Medrano F, Fernandez-Ruiz M, Morales JM, San-Juan R, Cervera C, Carratala J, et al. Impact of hepatitis C virus infection on the risk of infectious complications after kidney transplantation: data from the RESITRA/REIPI cohort. *Transplantation*. 2011; 92:543–9. [PubMed: 21869745]
5. Özgür O, Boyacıoğlu S, Telatar HH, Aberal M. Recombinant α -interferon in renal allograft recipients with chronic hepatitis C. *Nephrol Dial Transplantation*. 1995; 10:2104–2106.
6. Morales J, Aguado JM. Hepatitis C and renal transplantation. *Curr Opin Organ Transplant*. 2012; 17:609–615. [PubMed: 23111646]
7. Scott DR, Wong JK, Spicer TS, Dent H, Mensah FK, McDonald S, et al. Adverse impact of hepatitis C virus infection on renal replacement therapy and renal transplant patients in Australia and New Zealand. *Transplantation*. 2010; 90:1165–1171. [PubMed: 20861806]
8. Gordon SC, Muir AJ, Lim JK, Pearlman B, Argo CK, Ramani A, et al. Safety profile of boceprevir and telaprevir in chronic hepatitis C: real world experience from HCV-TARGET. *J Hepatol*. 2015; 62:286–93. [PubMed: 25218788]
9. Sulkowski MS, Vargas HE, Di Bisceglie AM, Kuo A, Reddy KR, Lim JK, et al. Effectiveness of Simeprevir Plus Sofosbuvir, With or Without Ribavirin, in Real-World Patients With HCV Genotype 1 Infection. *Gastroenterology*. 2016; 150:419–29. [PubMed: 26497081]
10. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009; 42:377–81. [PubMed: 18929686]
11. Brown RS Jr, O'Leary JG, Reddy KR, Kuo A, Morelli GJ, Burton JR Jr, et al. Interferon-free therapy for genotype 1 hepatitis C in liver transplant recipients: Real-world experience from the hepatitis C therapeutic registry and research network. *Liver Transpl*. 2016; 22:24–33. [PubMed: 26519873]
12. Firth D. Bias reduction of maximum likelihood estimates. *Biometrika*. 1993; 80:27–38.
13. Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. *Gastroenterology*. 2015; 149:649–659. [PubMed: 25985734]
14. Manns M, Samuel D, Gane EJ, Mutimer D, McCaughan G, Buti M, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. *The Lancet Infectious Diseases*. 2016; 16:685–697. [PubMed: 26907736]
15. Kwok RM, Ahn J, Schiano TD, Te HS, Potosky DR, Tierney A, et al. Sofosbuvir plus ledipasvir for recurrent hepatitis C in liver transplant recipients. *Liver Transpl*. 2016; 22:1536–1543. [PubMed: 27543748]
16. Kwo PY, Mantry PS, Coakley E, Te HS, Vargas HE, Brown R Jr, et al. An interferon-free antiviral regimen for HCV after liver transplantation. *N Engl J Med*. 2014; 371:2375–2382. [PubMed: 25386767]
17. Kugelmas M, Osgood MJ, Trotter JF, Bak T, Wachs M, Forman L, et al. Hepatitis C virus therapy, hepatocyte drug metabolism, and risk for acute cellular rejection. *Liver Transpl*. 2003; 9:1159–65. [PubMed: 14586876]
18. Levitsky J, Goldberg D, Smith AR, Mansfield SA, Gillespie BW, Merion RM, et al. Acute Rejection Increases Risk of Graft Failure and Death in Recent Liver Transplant Recipients. *Clin Gastroenterol Hepatol*. 2016
19. Noell BC, Besur SV, de Lemos AS. Changing the face of hepatitis C management - the design and development of sofosbuvir. *Drug Des Devel Ther*. 2015; 9:2367–74.
20. Beinhardt S, Al Zoairy R, Ferenci P, Kozbial K, Freissmuth C, Stern R, et al. DAA-based antiviral treatment of patients with chronic hepatitis C in the pre- and postkidney transplantation setting. *Transpl Int*. 2016; 29:999–1007. [PubMed: 27203857]

21. Kamar N, Marion O, Rostaing L, Cointault O, Ribes D, Lavayssiere L, et al. Efficacy and Safety of Sofosbuvir-Based Antiviral Therapy to Treat Hepatitis C Virus Infection After Kidney Transplantation. *Am J Transplant*. 2016; 16:1474–9. [PubMed: 26587971]
22. Sawinski D, Kaur N, Ajeti A, Trofe-Clark J, Lim M, Bleicher M, et al. Successful Treatment of Hepatitis C in Renal Transplant Recipients With Direct-Acting Antiviral Agents. *Am J Transplant*. 2016; 16:1588–95. [PubMed: 26604182]

Figure 1.

CONSORT of Patients.

AE, adverse event; DAC, daclatasvir; EOT, end of treatment; LDV, ledipasvir; MV, multivariable; PrOD, ombitasvir/paritaprevir/ritonavir/dasabuvir; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response

A.

B.

C.

Figure 2. Sustained Virologic Response (Per-Protocol population)

A. Liver Transplant Recipients

B. Kidney Transplant Recipients

C. Liver and Kidney Transplant Recipients

In Per Protocol population, SVR12 rates with 95% confidence intervals among all, cirrhotic, non-cirrhotic, LDV/SOF ± RBV treated, PrOD ± RBV treated and DAC/SOF ± RBV liver transplant recipients (panel A), kidney transplant recipients (panel B) and dual liver kidney transplant recipients (panel C).

DAC, daclatasvir; LDV, ledipasvir; LCL, lower confidence limit; PrOD, ombitasvir/
paritaprevir/ritonavir + dasabuvir; RBV, ribavirin; SOF, sofosbuvir; SVR12, sustained
virologic response at week 12; UCL, upper confidence limit

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Figure 3. Predictors of Sustained Virologic Response in the overall population

Multivariable analysis of SVR12 among patients with per protocol data treated with LDV/SOF $\pm$ RBV including patients with and without solid organ transplant. Associations between every baseline covariate and SVR12 were estimated with logistic regression using Firth penalized maximum likelihood estimation of the effect of a covariate of interest with adjustment for age and sex. Covariates treated in this manner are annotated with *.

Figure 4. Predictors of Sustained Virologic Response among LT patients

Multivariable analysis of SVR12 among LT patients with per protocol data treated with LDV/SOF $\pm$ RBV. KT patients were excluded from the analysis. Associations between every baseline covariate and SVR12 were estimated with logistic regression using Firth penalized maximum likelihood estimation of the effect of a covariate of interest with adjustment for age and sex. Covariates treated in this manner are annotated with *.

Table 1**Baseline Clinical and Laboratory Characteristics of All Participants**

	Liver Transplant (n = 347)	Kidney Transplant (n = 60)	Dual Liver Kidney Transplant (n = 36)	Totals (N = 443)
Male sex, n (%)	259 (75)	40 (67)	26 (72)	325 (73)
Age, yrs, median (range)	62 (21 – 85)	57 (32 – 75)	65 (48 – 79)	62 (21 – 85)
18–39, n (%)	5 (1.4)	4 (7)	0 (0)	9 (2)
48–64, n (%)	236 (68)	47 (78)	18 (50)	301 (68)
65, n (%)	106 (31)	9 (15)	18 (50)	133 (30)
Race, n (%)				310 (70)
White	263 (76)	23 (38)	24 (67)	64 (14)
Black or African American	28 (8)	30 (50)	6 (17)	69 (16)
Other / missing	56 (16)	7 (12)	6 (17)	
Hispanic ethnicity, n (%)	42 (15)	5 (8)	6 (17)	63 (14)
Prior HCV Treatment, n (%)	202 (58)	17 (28)	22 (61)	241 (54)
Prior DAA Failure, n (%)	25 (7)	1 (2)	2 (6)	28 (6)
ALT, IU/mL, median (range)	59 (9 – 956)	30 (10 – 190)	54 (19 – 342)	55 (9 – 956)
Total bilirubin, mg/dL, median (range)	0.8 (0.2 – 34.5)	0.6 (0.2 – 4.4)	0.6 (0.2 – 7.0)	0.7 (0.2 – 34.5)
Albumin, g/dL, median (range)	3.9 (2.1 – 5.2)	4.0 (2.7 – 4.7)	3.9 (2.2 – 4.5)	3.9 (2.1 – 5.2)
Platelets, (×10 ⁹ /μL), median (range)	144 (29 – 404)	182 (30 – 320)	143 (32 – 496)	150 (29 – 496)
Creatinine, mg/dL, median (range)	1.2 (0.5 – 9.5)	1.5 (0.8 – 9.0)	1.2 (0.6 – 6.4)	1.2 (0.5 – 9.5)
eGFR, mL/min, median (range) *	76.5 (9.1 – 262.2)	58.5 (7.4 – 156.4)	65 (20.1 – 128.9)	73 (7.4 – 262.2)
30, n (%)	12 (4)	8 (13)	2 (6)	22 (5)
> 30, n (%)	317 (91)	51 (85)	32 (89)	400 (90)
HCV RNA, IU/mL log10, median (range)	6.4 (1 – 8)	6.3 (0 – 8)	6.3 (1 – 8)	6.4 (0 – 8)
History of cirrhosis, n (%)	153 (44)	17 (28)	14 (39)	184 (42)
History of hepatic decompensation, n (%)	89 (26)	8 (13)	4 (11)	101 (23)
MELD score among cirrhotic patients with available score, n (%)				
<9	28 (52)	2 (29)	0 (0)	30 (48)
10–15	19 (35)	2 (29)	2 (100)	23 (37)
16–21	5 (9)	1 (14)	0 (0)	6 (10)

	Liver Transplant (n = 347)	Kidney Transplant (n = 60)	Dual Liver Kidney Transplant (n = 36)	Totals (N = 443)
21–39	2 (4)	2 (29)	0 (0)	4 (6)
HCV genotype, n (%)				
1a	181 (52)	29 (48)	22 (61)	232 (52)
1b	90 (26)	22 (37)	9 (25)	121 (27)
1 subtype not specified	28 (8)	3 (5)	3 (8)	34 (8)
2	3 (1)	1 (2)	1 (3)	5 (1)
3	34 (10)	2 (3)	1 (3)	37 (8)
4	6 (2)	2 (3)	0 (0)	8 (2)
5	1 (0.3)	0 (0)	0 (0)	1 (0.2)
6	2 (0.6)	1 (2)	0 (0)	3 (0.7)
Not reported	2 (0.6)	0 (0)	0 (0)	2 (0.5)
Immunosuppression regimen, n (%)				
Tacrolimus	255 (74)	43 (71)	30 (83)	328 (74)
Cyclosporine	58 (17)	7 (12)	6 (17)	71 (16)
Everolimus/sirolimus	45 (13)	4 (7)	1 (3)	50 (11)
Mycophenolate mofetil/mycophenolic acid	150 (43)	45 (75)	23 (64)	218 (49)

* available data in 59 of 60 KT recipients, 329 of 347 LT recipients and 34 of 36 DLK transplant recipients.

ALT, alanine aminotransferase; HCV, hepatitis C virus; eGFR, estimated glomerular filtration rate; MELD, model for end-stage liver disease

Table 2

Disposition of All Patients

	Liver Transplant (n = 347)	Kidney Transplant (n = 60)	Dual Liver Kidney Transplant (n = 36)	Totals (N = 443)
Started treatment, n (%)	347 (100)	60 (100)	36 (100)	443 (100)
Discontinued early, n (%)	9 (2.6)	4 (6.7)	0 (0)	13 (2.9)
Due to adverse event	6 (1.7)	1 (1.7)	0 (0)	7 (1.6)
Lack of efficacy	0 (0.0)	1 (1.7)	0 (0)	1 (0.2)
Admin reasons	3 (0.9)	2 (3.4)	0 (0)	5 (1.1)
Completed treatment, n (%)	338 (97.4)	56 (93.3)	36 (100)	430 (97)
Died, n (%)	3 (0.9)	0 (0.0)	0 (0)	3 (0.7)

Table 3

Most Common Adverse Events and All Serious Adverse Events

	LDV/SOF ± RBV (n = 378)	PrOD ± RBV (n = 26)	DAC + SOF ± RBV (n = 39)
Most common Adverse Event, n (%)	280 (74)	24 (92)	32 (82)
Fatigue	110 (29.1)	8 (30.8)	12 (30.8)
Anaemia	69 (18.3)	10 (38.5)	8 (20.5)
Headache	73 (19.3)	1 (3.8)	9 (23.1)
Nausea	41 (10.8)	4 (15.4)	7 (17.9)
Diarrhea	35 (9.3)	7 (26.9)	2 (5.1)
Vomiting	21 (5.6)	3 (11.5)	2 (5.1)
Dyspnea	21 (5.6)	4 (15.4)	1 (2.6)
Pruritus	17 (4.5)	6 (23.1)	3 (7.7)
Decreased appetite	19 (5.0)	4 (15.4)	1 (2.6)
Insomnia	17 (4.5)	3 (11.5)	2 (5.1)
Serious Adverse Events, n (%)	37 (10)	4 (15)	4 (10)
Infections and Infestations	14 (3.7)	2 (7.7)	1 (2.6)
Hepatic encephalopathy	3 (0.8)	0 (0.0)	1 (2.6)
Anemia	3 (0.8)	0 (0.0)	0 (0.0)
Vomiting	1 (0.3)	1 (3.8)	0 (0.0)
Pyrexia	1 (0.3)	1 (3.8)	0 (0.0)
Bile duct stenosis	1 (0.3)	0 (0.0)	1 (2.6)
Kidney transplant rejection	2 (0.5)	0 (0.0)	0 (0.0)

* SAE with more than 1 occurrence listed

Table 4a

Baseline demographics in patients treated with and without ribavirin

DEMOGRAPHICS			
	Treatment Group		
	No RBV	With RBV	<i>p</i> value
Variable	(N=215)	(N=228)	
SEX			0.2178
Female	63 (29.3%)	55 (24.1%)	
Male	152 (70.7%)	173 (75.9%)	
AGE			0.9108
18–39	5 (2.3%)	4 (1.8%)	
40–64	146 (67.9%)	155 (68.0%)	
65+	64 (29.8%)	69 (30.3%)	
Patient age at treatment initiation	215	228	0.2746
Median	61.0	62.0	
Min Max	21.0 79	32.0 85	
Mean	60.5	61.3	
Std	9	8	
RACE			0.5835
White	143 (66.5%)	167 (73.2%)	
Black or African American	42 (19.5%)	22 (9.6%)	
Other or Pending	30 (14.0%)	39 (17.1%)	
ETHNICITY			0.7212
Hispanic	32 (14.9%)	31 (13.6%)	
Non-Hispanic	177 (82.3%)	189 (82.9%)	
Other	1 (0.5%)	1 (0.4%)	
Not Reported	5 (2.3%)	7 (3.1%)	
Median	27.0	28.0	
Min Max	16.0 49	19.0 46	
Mean	27.7	28.8	
Std	6	5	
PRIOR HCV TREATMENT EXPERIENCE			0.0871
Naive	107 (49.8%)	95 (41.7%)	
Experienced	108 (50.2%)	133 (58.3%)	
TRIPLE THERAPY FAILURE			0.7118
Yes	11 (5.1%)	17 (7.5%)	
No	204 (94.9%)	211 (92.5%)	
HCV GENOTYPE			0.0675
1a	115 (54%)	117 (51%)	
1b	67 (31%)	54 (24%)	

DEMOGRAPHICS			
	Treatment Group		
	No RBV	With RBV	<i>p</i> value
1 unspecified	16 (7%)	18 (8%)	
3	8 (4%)	29 (13%)	

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Table 4b

Baseline laboratory data in patients treated with and without ribavirin

BASELINE LABORATORY VALUES			
	Treatment Group		
	No RBV	With RBV	<i>p</i> value
Variable	(N=215)	(N=228)	
ALT (IU/L)	203	219	0.5822
Median	54.0	55.0	
Min Max	9.0–956.0	9.0–875.0	
Mean	79.1	84.1	
Std	98.3	87.9	
AST (IU/L)	203	221	0.4852
Median	47.0	52.0	
Min Max	13.0–775.0	13.0–604.0	
Mean	72.2	77.7	
Std	88.1	75.0	
TOTAL BILIRUBIN (mg/dL)	196	214	0.4386
Median	0.7	0.8	
Min Max	0.2–19.6	0.3–34.5	
Mean	1.1	1.3	
Std	1.7	3.0	
TOTAL BILIRUBIN (mg/dL)			0.3256
1.2	161 (74.9%)	167 (73.2%)	
>1.2	35 (16.3%)	47 (20.6%)	
Pending	19 (8.8%)	14 (6.1%)	
PLATELETS (×10E3/uL)	206	218	0.9020
Median	148.0	150.0	
Min Max	29.0–496.0	38.0–427.0	
Mean	160.1	161.0	
Std	68.5	73.9	
PLATELETS (×10E3/uL)			0.7718
100,000+	170 (79.1%)	174 (76.3%)	
<100,000	36 (16.7%)	44 (19.3%)	
Pending	9 (4.2%)	10 (4.4%)	

BASELINE LABORATORY VALUES			
	Treatment Group		
	No RBV	With RBV	<i>p</i> value
ALBUMIN (g/dL)	187	192	0.1869
Median	3.9	3.9	
Min Max	2.1–4.9	2.6–5.2	
Mean	3.8	3.9	
Std	0.6	0.5	
ALBUMIN (g/dL)			0.5250
3.5+	148 (68.8%)	158 (69.3%)	
<3.5	39 (18.1%)	34 (14.9%)	
Pending	28 (13.0%)	36 (15.8%)	
CREATININE (mg/dL)	204	218	0.0103
Median	1.2	1.2	
Min Max	0.5–9.5	0.5–6.7	
Mean	1.5	1.3	
Std	1.3	0.7	
CREATININE (mg/dL)			
1.5	147 (68.4%)	180 (78.9%)	0.0697
>1.5–2.0	36 (16.7%)	26 (11.4%)	
>2.0	21 (9.8%)	12 (5.3%)	
Pending	11 (5.1%)	10 (4.4%)	
eGFR	204	218	0.0006
Median	65.8	77.2	
Min Max	7.4–262.2	11.2–197.7	
Mean	71.0	82.4	
Std	34.5	32.8	
eGFR			0.1504
30	15 (7.0%)	7 (3.1%)	
>30	189 (87.9%)	211 (92.5%)	
Pending	11 (5.1%)	10 (4.4%)	