Annals of Internal Medicine ORIGINAL RESEARCH

Treatment With Ledipasvir–Sofosbuvir for 12 or 24 Weeks in Kidney Transplant Recipients With Chronic Hepatitis C Virus Genotype 1 or 4 Infection

A Randomized Trial

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Background: Use of interferon and ribavirin to treat chronic hepatitis C virus (HCV) infection in kidney transplant recipients is limited because of the risk for allograft rejection and poor tolerability.

Objective: To evaluate the safety and efficacy of the interferon- and ribavirin-free regimen ledipasvir–sofosbuvir in kidney transplant recipients with chronic genotype 1 or 4 HCV infection.

Design: Randomized, phase 2, open-label study. (ClinicalTrials.gov: NCT02251717)

Setting: 5 sites in Europe.

Patients: Treatment-naive or -experienced kidney transplant recipients with chronic genotype 1 or 4 HCV infection, with or without compensated cirrhosis, and with an estimated glomerular filtration rate (eGFR) of 40 mL/min or greater were randomly assigned 1:1 to receive ledipasvir (90 mg) and sofosbuvir (400 mg) for 12 or 24 weeks.

Measurements: The primary end point was sustained virologic response at 12 weeks after therapy ended (SVR12).

Results: Among 114 patients, the median age was 53 years, 58% were male, 91% had genotype 1 infection, 69% were treatment naive, and 15% had compensated cirrhosis. The median eGFR was 56 mL/min (range, 35 to 135 mL/min). One hundred percent of patients (57 of 57) treated for 12 weeks (95% CI, 94% to 100%) and 100% of those (57 of 57) treated for 24 weeks (CI, 94% to 100%) achieved SVR12. Serious adverse events were reported in 13 patients (11%). Of these, 3 events—syncope, pulmonary embolism, and serum creatinine increase—in 3 patients were determined to be treatment related. One patient permanently discontinued treatment because of an adverse event (syncope). The most frequent adverse events overall were headache (n = 22 [19%]), asthenia (n = 16 [14%]), and fatigue (n = 11 [10%]).

Limitations: The study was open label, no inferential statistics were planned, and only patients with genotype 1 or 4 infection were included. Few patients with HCV genotype 1a and cirrhosis were enrolled.

Conclusion: Treatment with ledipasvir–sofosbuvir for 12 or 24 weeks was well-tolerated and seemed to have an acceptable safety profile among kidney transplant recipients with HCV genotype 1 or 4 infection, all of whom achieved SVR12.

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Nearly 10% of kidney transplant recipients in Western countries have chronic hepatitis C virus (HCV) infection (1). The higher HCV prevalence in kidney transplant recipients than in the general population is a direct consequence of the association between HCV infection and kidney impairment as well as an increased risk for HCV infection acquired during hemodialysis or from blood transfused before routine HCV screening (2, 3). Chronic HCV infection increases the risk for end-stage renal disease (4–7) and, in kidney transplant patients, is associated with higher graft loss and mortality rates (8–10). Treatment with interferon regimens has been limited because of the increased risk for interferon-mediated graft rejection and relatively low efficacy, resulting in an unacceptable risk–benefit ratio (8, 11). Direct-acting antiviral agents (DAAs) were developed that are highly effective against all HCV genotypes and seemed to be safe and effective in clinical trials as well as in studies of immunocompromised patients, such as orthotopic liver transplant recipients with HCV infection. Interest in using DAAs to treat HCV infection in kidney transplant patients has increased; however, data regarding their use in this population are very limited (3, 12, 13). In 2 small studies, treatment with a combination of DAAs for 12 weeks led to high rates of sustained virologic response (SVR) in kidney transplant recipients, with no significant adverse events or graft rejection noted (14, 15).

In clinical trials, the fixed-dose combination of ledipasvir and sofosbuvir given for 12 or 24 weeks provided SVR rates ranging from 93% to 99% in treatment-naive and -experienced patients with HCV genotype 1, 4, 5, or 6 infection (16–20). European and North American guidelines recommend as first-line options treatment with ledipasvir–sofosbuvir for 12 weeks, along with ribavirin for patients without cirrhosis or with riba-

See also:

Web-Only
Supplement

virin for those with cirrhosis, or for 24 weeks without ribavirin in patients with cirrhosis who are intolerant or have a contraindication to ribavirin (21, 22). The high efficacy observed with fixed-dose ledipasvir–sofosbuvir, even when not administered with ribavirin, represents a critical advantage for treating patients with impaired kidney function, avoiding the need for complicated ribavirin dosing strategies and assessment of ribavirin blood concentration. In addition, the lack of significant drug–drug interactions between ledipasvir–sofosbuvir and immunosuppressant drugs and the absence of a clinically relevant effect of hepatic dysfunction on drug pharmacokinetics support its use in treating HCV recurrence after liver transplantation (23, 24). On the basis of these encouraging data, we conducted the first multinational, randomized, controlled study to make an exploratory comparison of the efficacy and safety of 12 and 24 weeks of ledipasvir–sofosbuvir without ribavirin in kidney transplant patients with chronic HCV genotype 1 or 4 infection.

METHODS

Setting and Participants

Patients were enrolled at 5 clinical sites in 4 European countries: Italy, France, Austria, and Germany. Eligible patients were aged 18 years or older; had chronic HCV genotype 1 or 4 infection, with plasma HCV RNA levels of 15 IU/mL or greater; and had received a kidney transplant at least 6 months before the baseline study visit. Patients with compensated cirrhosis were eligible, with cirrhosis defined as a METAVIR score of 4 or an Ishak score of 5 or greater by biopsy, a FibroScan (Echosens) value greater than 12.5 kPa, or a FibroTest (BioPredictive) score greater than 0.75 plus an aspartate aminotransferase–platelet ratio index greater than 2. Patients were excluded from participation if they had a body mass index less than 18 kg/m^2; decompensated liver disease (that is, presence of ascites, encephalopathy, or variceal hemorrhage); an electrocardiogram with clinically significant abnormalities; HIV infection; hepatitis B virus infection; creatinine clearance less than 40 mL/min, as calculated by the Cockcroft–Gault equation; an albumin level lower than 30 g/L; an international normalized ratio greater than 1.5 times the upper limit of normal (unless the patient had hemophilia or was stable while receiving an anticoagulant regimen affecting international normalized ratio); a hemoglobin level lower than 100 g/L; a platelet level of 50 × 10^9 cells/L or less; a direct bilirubin level greater than 1.5 times the upper limit of normal, except for patients with Gilbert syndrome; and an alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase level greater than 10 times the upper limit of normal. All patients provided written informed consent before undertaking any study-related procedures.

Study Design

Patients were randomly assigned 1:1 to receive either 12 or 24 weeks of treatment with a fixed-dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg) once daily by means of an integrated Web response system (Bracket). A statistician employed by the sponsor generated the randomization code by using SAS version 9.2 (SAS Institute). Randomization was stratified by genotype, treatment history (treatment naive or experienced), and the presence or absence of cirrhosis. Investigators, patients, and trial personnel were not blinded to treatment assignment.

The study protocol was approved by each institution's review board or ethics committee before study initiation. The study was conducted in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice Guidelines and the Declaration of Helsinki. All authors had access to the study data and reviewed and approved the final manuscript before journal submission.

Study Assessments

Plasma HCV RNA was analyzed by using the COBAS AmpliPrep/COBAS TaqMan HCV Test, v2.0 (Roche Molecular Systems), with a lower limit of quantification (LLOQ) of 15 IU/mL. Hepatitis C virus genotype and subtype were determined by using the Versant HCV Genotype INNO-LiPA 2.0 assay (Siemens). An interleukin-28B genotype test was done through polymerase chain reaction amplification and sequencing of the rs12979860 single-nucleotide polymorphism.

Plasma samples for viral sequencing were collected at the same time points as those for HCV RNA levels. Deep sequencing of the NS5A and NS5B regions of the HCV RNA with MiSeq technology (DDL Diagnostic Laboratory) was performed on samples collected from all patients at baseline and on posttreatment samples from all patients with virologic failure. The resulting sequences were compared with reference sequences to determine the prevalence of resistance-associated substitutions (RASs) and the association of RASs with virologic outcomes. Resistance-associated substitutions present at more than 15% of sequence reads are reported.

Adverse events were recorded from day 1 of treatment until 30 days after the last dose; serious adverse events and adverse events related to protocol-mandated procedures were collected from screening through the last day of follow-up (posttreatment week 24) or 30 days after the last dose. The data included reported adverse events as well as the results of physical examinations and clinical laboratory tests, vital signs, and electrocardiogram recordings. Treatment-emergent clinical and laboratory adverse events were summarized by using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0 (the MedDRA trademark is owned by the International Federation of Pharmaceutical Manufacturers and Associations on behalf of the ICH). Virologic relapse was defined as HCV RNA at the LLOQ or higher during the posttreatment period in a patient who had HCV RNA less than the LLOQ at the end of treatment.

End Points and Statistical Analysis

The primary efficacy end point was the percentage of patients with HCV RNA less than the LLOQ 12 weeks

after stopping the study drug (SVR12). In the primary efficacy analysis, the SVR12 rate was calculated with a 2-sided 95% exact CI by using the Clopper–Pearson method (25). Patients with missing HCV RNA values at posttreatment week 12 who had posttreatment HCV RNA values less than the LLOQ before and after the missing posttreatment week 12 value were assumed to have achieved SVR12. This study was exploratory in nature; no inferential statistics or statistical comparisons were planned. The primary safety end point was any adverse event leading to permanent discontinuation of the study drug. We used SAS, version 9.2, for all statistical analyses.

Role of the Funding Source

The sponsor designed and conducted the study in collaboration with the principal investigators, collected the data, and monitored the study conduct.

RESULTS

Study Population

Of 130 patients screened, 16 (12.3%) were excluded: 11 did not meet eligibility criteria, 2 withdrew consent, and 3 were excluded because of existing clinically significant medical conditions (atrial fibrillation, planned heart surgery, and hyponatremia with a urinary tract infection). A total of 114 patients were enrolled and treated at 5 sites in 4 European countries between 7 November 2014 and 16 June 2015 (**Appendix Figure**, available at www.annals.org). Overall, 94% of the patients were white and 58% were male (**Table 1**). Most were treatment naive (69%), did not have cirrhosis (85%), and had genotype 1 infection (91%). Of the patients with genotype 1 infection, 75% had genotype 1b infection.

Efficacy

Ledipasvir–sofosbuvir treatment resulted in rapid HCV RNA suppression (**Table 2**). By week 4, 102 of 114 patients (89%) had HCV RNA less than the LLOQ (with target not detectable in 68%). By week 8, all 113 evaluable patients (100% [excluding 1 patient in the 12-week group who discontinued study treatment at week 4 because of a serious adverse event]) had HCV RNA less than the LLOQ (with target not detectable in 112 of 113 [99%]). At the end of treatment, all 113 evaluable patients (100%) had HCV RNA less than the LLOQ (target not detectable). All 57 patients (100% [95% CI, 94% to 100%]) in the 12-week treatment group achieved SVR12, including the patient who had discontinued treatment at week 4. All 57 patients (100% [CI, 94% to 100%]) in the 24-week group also achieved SVR12. Of 114 patients, 113 achieved SVR24; 1 patient from the 24-week group had achieved SVR12 but discontinued the study before the posttreatment week-24 visit because of hospitalization due to osteoarthritis, which was not considered treatment related.

Viral Resistance Testing

At baseline, NS5A RASs (15% cutoff) were detected in 22 of 113 patients (19%). All 22 patients achieved SVR12, including 9 who had variants that confer greater than 100-fold reduced susceptibility to ledipasvir in vitro.

Safety and Tolerability

In general, the adverse events reported in this study were consistent with those reported in previous studies of ledipasvir–sofosbuvir (**Table 3**). The most common adverse event among all treatment groups was headache, followed by asthenia. Serious adverse events occurred in 13 patients; 3 of these events—increased serum creatinine, syncope, and pulmonary embolism—were considered treatment related.

The first patient was a 42-year-old woman with cirrhosis who had received a kidney transplant in October 2005 for chronic kidney failure. While receiving 24 weeks of ledipasvir–sofosbuvir, she had 2 urinary tract infections: the first beginning on day 13 of treatment, for which she received ciprofloxacin, and the second beginning on day 83 (study week 12), for which she received amoxicillin–clavulanic acid, which has been associated with interstitial nephritis. Because her serum creatinine levels increased from study week 8 onward, study treatment was interrupted temporarily between weeks 12 and 16. At posttreatment week 24, the patient still had elevated serum creatinine (360 μmol/L [4.3 mg/dL]) and low eGFR (14.4 mL/min) levels. Further follow-up with this patient after study completion was not possible.

The second patient was a 58-year-old woman who was treatment naive, did not have cirrhosis, and had HCV genotype 1. During week 2 of 12-week ledipasvir–sofosbuvir treatment, she had atrial fibrillation, for which an external cardiologist prescribed amiodarone, a medication prohibited by the protocol. Despite the study site's indication to stop amiodarone and prescribe a new drug (unspecified) to treat the atrial fibrillation, the patient continued with amiodarone treatment. She had bradycardia and syncope at week 4, after which she discontinued study treatment.

The third patient was a 49-year-old woman with obesity who had received a kidney transplant in July 2003. While receiving 24 weeks of ledipasvir–sofosbuvir, she had a pulmonary embolism that was treated successfully with anticoagulants without interruption of antiviral therapy.

Twenty-five patients (22%) had grade 3 to 4 laboratory abnormalities (**Appendix Table 1**, available at www.annals.org). Hyperuricemia, which occurred in 10 patients (9%), was most common; 6 (5%) of these cases were considered treatment related. There were no reports of gout among the patients with hyperuricemia during the study. Two patients (2%) had a grade 3 creatinine increase. One case, which the investigating physician considered to be treatment related, occurred in the previously described 42-year-old woman with hypertension, compensated cirrhosis, and stage 3 chronic kidney disease, whose creatinine clearance (by Cockcroft–Gault equation) was 55 to 61 mL/min, with a creatinine level of 88.4 to 106.1 μmol/L (1 to 1.2 mg/dL) at baseline. The patient had a recurrent urinary tract

Table 1. Demographic and Baseline Characteristics*

Characteristic	Ledipasvir-Sofosbuvir		Total (n = 114)
	12 wk (n = 57)	24 wk (n = 57)	
Median age (range), *y*	53 (31–72)	53 (25–75)	53 (25–75)
Male, *n (%)*	33 (58)	33 (58)	66 (58)
Race, *n (%)*			
White	54 (95)	53 (93)	107 (94)
Black	2 (4)	2 (4)	4 (4)
Asian	1 (2)	1 (2)	2 (2)
Other	0 (0)	1 (2)	1 (1)
Median body mass index (range), *kg/m²*	23 (18–43)	24 (20–39)	24 (18–43)
Interleukin-28B genotype, *n (%)*			
CC	14 (25)	18 (32)	32 (28)
CT	34 (60)	34 (60)	68 (60)
TT	9 (16)	5 (9)	14 (12)
HCV genotype, *n (%)*			
1 (no confirmed subtype)	2 (4)	0 (0)	2 (2)
1a	7 (12)	10 (18)	17 (15)
1b	42 (74)	43 (75)	85 (75)
4	6 (11)	4 (7)	10 (9)
Median HCV RNA level (range), *$\log_{10}$ IU/mL*	6.4 (4.5–7.6)	6.2 (4.7–7.0)	6.3 (4.5–7.6)
Prior HCV treatment, *n/N (%)*			
No	40/57 (70)	39/57 (68)	79/114 (69)
Yes	17/57 (30)	18/57 (32)	35/114 (31)
Peginterferon and ribavirin	7/17 (41)	5/18 (28)	12/35 (34)
Peginterferon	4/17 (24)	4/18 (22)	8/35 (23)
Interferon	6/17 (35)	7/18 (39)	13/35 (37)
Interferon and ribavirin	0/0 (0)	1/18 (6)	1/35 (3)
Missing data	0/0 (0)	1/18 (6)	1/35 (3)
Compensated cirrhosis, *n (%)*	8 (14)	9 (16)	17 (15)
Fibrosis stage of noncirrhotic participants, *n/N (%)*			
No or minimal (F0, F0–F1, or F1)	19/49 (39)	16/48 (33)	35/97 (36)
Moderate (F1–F2 or F2)	19/49 (39)	15/48 (31)	34/97 (35)
Severe (F3, F3–F4, or F4)	11/49 (22)	17/48 (35)	28/97 (29)
Median time since kidney transplantation (range), *y*	10.0 (0.5–40.0)	12.0 (0.8–42.0)	12.0 (0.5–42.0)
Median creatinine clearance by Cockcroft-Gault method (range), *mL/min/1.73 m²*	50 (37–135)	60 (35–130)	56 (35–135)
Receiving immunosuppressants, *n (%)*			
Systemic corticosteroids	39 (68)	42 (74)	81 (71)
Other immunosuppressants	56 (98)	55 (97)	111 (97)
Type of immunosuppressant used, *n (%)*			
Corticosteroids	39 (68)	42 (74)	81 (71)
Tacrolimus	24 (42)	30 (53)	54 (47)
Mycophenolate	38 (67)	31 (54)	69 (61)
Cyclosporine	23 (40)	21 (37)	44 (39)
Azathioprine	6 (11)	8 (14)	14 (12)
Immunosuppressants, *n (%)*†			
1	6 (11)	5 (9)	11 (10)
2	23 (40)	22 (39)	45 (39)
≥3	28 (49)	28 (49)	56 (49)

HCV = hepatitis C virus.
* Percentages may not sum to 100 due to rounding.
† Information on immunosuppressant medications was unavailable for 2 patients in the 24-wk treatment group.

infection between treatment weeks 12 and 16, when her renal function became further impaired, with a decrease in creatinine clearance from 33 mL/min (creatinine, 172.4 μmol/L [1.95 mg/dL]) at week 12 to 16.8 mL/min (creatinine, 335.9 μmol/L [3.8 mg/dL]) at week 16. Ledipasvir–sofosbuvir treatment was interrupted during this period and resumed at week 16 to complete the 24-week course. The patient's creatinine clearance was 14 mL/min (creatinine, 387.0 μmol/L [4.4 mg/dL]) at the end of treatment and 14.4 mL/min (creatinine, 382.0 μmol/L [4.3mg/dL]) 24 weeks later.

Renal function remained stable in most patients, both during study treatment and up to posttreatment week 4 (median change in creatinine clearance [eGFR by Cockcroft–Gault equation], −0.6 to −3 mL/min) (**Figures 1** and **2** and **Appendix Table 2**, available at www.annals.org). Overall, 25 patients (22%), including 8 who had an eGFR less than 40 mL/min at baseline, had decreases to below 40 mL/min. None of the 8 patients who had creatinine clearance less than 40 mL/min at baseline had a reduction in creatinine clearance to less than 30 mL/min during therapy. Four patients with clearance greater than 40 mL/min at baseline had decreases to less than 30 mL/min during therapy, including the patient who temporarily stopped receiving the study drug because of a urinary tract infection and had an increased creatinine level (described earlier). In 3 patients, creatinine clearance increased to greater than 30 mL/min at the last visit recorded; the patient who had interrupted study treatment had a final value of 14.4 mL/min. All but 1 of the 6 patients with cirrhosis whose creatinine clearance level decreased to below 40 mL/min continued study treatment without interruption; none permanently discontinued study treatment.

Twenty-one patients (18%) required adjustment in their immunosuppressant regimen: 7 patients had dosage reductions, 10 had dosage increases, and 4 required both reductions and increases. Thirteen of the 21 required dosage adjustment to manage immunosuppressant levels, 4 to align the dosage with the site's policy for managing immunosuppressants, 3 to address suspected drug–drug interactions, and 1 because of a skin eruption. **Appendix Table 3** (available at www.annals.org) provides details on all changes in immunosuppressive regimens during the study. No documented episodes of graft rejection were reported during the study.

DISCUSSION

Chronic HCV infection is a significant cause of diminished graft survival in kidney transplant patients, and only limited data are available to guide clinical decision making regarding HCV therapy in this patient population. In the past, management of HCV infection was complicated by generally poor tolerance of interferon- and ribavirin-based regimens in graft recipients (because of hematologic side effects) and the potential for rejection due to interferon's immunemodulating effects (8).

Such treatment constraints, however, were lessened recently by the advent of oral DAA regimens that seem to be safe and effective in liver transplant recipients (26, 27). In the SOLAR-1 (Study Assessing the Efficacy and Safety of Alpelisib Plus Fulvestrant in Men and Postmenopausal Women With Advanced Breast Cancer Which Progressed on or After Aromatase Inhibitor Treatment) and SOLAR-2 studies, a 12-week course of ledipasvir–sofosbuvir plus ribavirin resulted in SVR rates as high as 96% in liver transplant patients with well-compensated Child–Pugh class A cirrhosis due to recurrent HCV genotype 1 or 4. However, in patients with Child–Pugh class C decompensated cirrhosis, the success rate was reduced to 60%, which improved

Table 2. Response During and After Treatment

Variable	Ledipasvir–Sofosbuvir		Total (*n* = 114)
	12 wk (*n* = 57)	24 wk (*n* = 57)	
HCV RNA level less than the LLOQ during treatment, *n/N (%)*			
Baseline	0/57 (0)	0/57 (0)	0/114 (0)
Week 1	9/57 (16)	7/57 (12)	16/114 (14)
Week 2	31/57 (54)	33/57 (58)	64/114 (56)
Week 4	50/57 (88)	52/57 (91)	102/114 (89)
Week 8	56/56 (100)*	57/57 (100)	113/113 (100)
Week 12	56/56 (100)*	57/57 (100)	113/113 (100)
Week 16	NA	57/57 (100)	57/57 (100)
Week 20	NA	57/57 (100)	57/57 (100)
Week 24	NA	57/57 (100)	57/57 (100)
HCV RNA level less than the LLOQ after end of treatment, *n/N (% [95% CI])*			
SVR4	57/57 (100 [94–100])	57/57 (100 [94–100])	114/114 (100 [97–100])
SVR12	57/57 (100 [94–100])	57/57 (100 [94–100])	114/114 (100 [97–100])
Overall virologic failure (relapse), *n/N (%)*	0/0 (0)	0/0 (0)	0/0 (0)

HCV = hepatitis C virus; LLOQ = lower limit of quantification; NA = not available; SVR4 = sustained virologic response at 4 wk; SVR12 = sustained virologic response at 12 wk.
* Excluding 1 patient in the 12-wk group who discontinued study treatment early at week 4 because of a serious adverse event. This patient achieved SVR12.

Table 3. Overall Adverse Events, Discontinuations, and Laboratory Abnormalities*

Variable	Ledipasvir-Sofosbuvir, *n* (%)	
	12 wk (*n* = 57)	24 wk (*n* = 57)
Any adverse event	34 (60)	44 (77)
Permanent treatment discontinuation due to adverse event	1 (2)	0
Temporary treatment discontinuation due to adverse event	1 (1)	1 (1)
Deaths	0 (0)	0 (0)
Treatment-related serious adverse events	1 (2)	2 (4)
All serious adverse events	5 (9)	8 (14)
Hemorrhagic diarrhea	0 (0)	1 (2)
Erysipelas	1 (2)	0 (0)
Gastroenteritis	1 (2)	0 (0)
Urinary tract infection	0 (0)	1 (2)
Incisional hernia	0 (0)	1 (2)
Shunt thrombosis	0 (0)	1 (2)
Serum creatinine level increased	0 (0)	1 (2)†
Invertebral disc protrusion	0 (0)	1 (2)
Papillary thyroid cancer	0 (0)	1 (2)
Syncope	1 (2)†	0 (0)
Suicide attempt	1 (2)	0 (0)
Acute kidney injury	1 (2)	0 (0)
Pulmonary embolism	0 (0)	1 (2)†
Arteriovenous shunt operation	0 (0)	1 (2)
Grade 3 or 4 laboratory abnormalities	12 (21)	13 (23)
Hemoglobin deficiency	1 (2)	1 (2)
Lymphocytopenia	1 (2)	1 (2)
Neutropenia	0 (0)	1 (2)
Thrombocytopenia	1 (2)	0 (0)
Leukopenia	0 (0)	1 (2)
International normalized ratio	0 (0)	1 (2)
Creatinine level	1 (2)	1 (2)
Lipase level	2 (4)	1 (2)
Hyperglycemia	0 (0)	1 (2)
Hyponatremia	0 (0)	1 (2)
Hyperuricemia	6 (11)	4 (7)
Urine blood level	1 (2)	2 (4)
Glycosuria	0 (0)	2 (4)
Adverse event occurring in ≥10% of patients		
Headache	9 (16)	13 (23)
Asthenia	8 (14)	8 (14)
Fatigue	4 (7)	7 (12)

* Values are numbers of patients (percentages).
† Event attributed by the investigator to treatment.

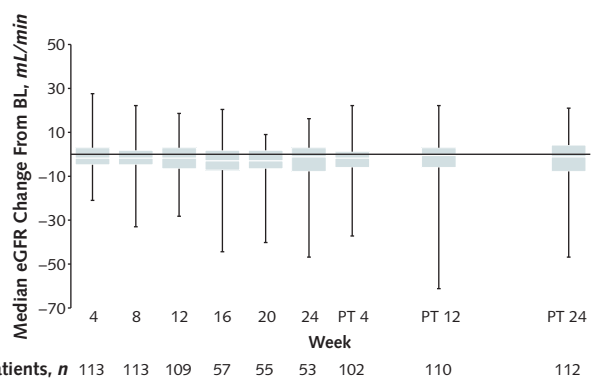
only marginally by extending the length of ledipasvir–sofosbuvir treatment to 24 weeks (75% SVR) (28, 29). High SVR rates (97%) also were achieved by using the protease inhibitor–based regimen paritaprevir–dasabuvir–ombitasvir and ribavirin in liver transplant recipients without advanced fibrosis who had HCV genotype 1 infection. However, this strategy requires substantial adjustment of calcineurin inhibitor dosing in most patients (30). These studies were instrumental in understanding the safety and efficacy of diverse classes of oral DAAs in liver transplant patients receiving immunosuppressive regimens, which helped set the stage for testing the feasibility of oral DAA therapy in kidney transplant recipients with HCV infection.

In this multicenter European study, 114 kidney graft recipients with predominantly genotype 1 infection (in addition to 10 patients with genotype 4 infection) were randomly assigned to receive ledipasvir–sofosbuvir for 12 or 24 weeks to assess the potential clinical benefits of a ribavirin-free DAA regimen in this patient population. By protocol, all patients had compensated liver disease and stable eGFR values above 40 mL/min at screening, although by the day 1 visit, 8 patients had eGFR values between 35 mL/min and 40 mL/min. Overall, treatment for either 12 or 24 weeks resulted in 100% SVR12, with the 2 therapeutic regimens proving to be similar in terms of adverse events and efficacy in the patients with HCV genotype 1 and the small group with HCV genotype 4 infection.

Consistent with the results of studies of sofosbuvir-based regimens for HCV treatment in liver transplant patients, viral suppression in our population did not seem to be affected by posttransplant immunosuppressive treatment. In the SOLAR-1 and -2 studies, which included liver transplant patients with compensated or decompensated cirrhosis, ledipasvir–sofosbuvir was administered only in combination with ribavirin, precluding an assessment of benefit from ribavirin (28, 29). In our study, none of the patients had clinically decompensated cirrhosis, only 15% had cirrhosis, and 29% had severe liver fibrosis. Despite patients being treated with immunosuppressive regimens for an average of 10 years, median pretreatment HCV RNA levels, which ranged from 4.45 to 7.62 log IU/mL (median, 6.40 log IU/mL in the 12-week and 6.24 log IU/mL in the 24-week group), were not significantly higher than those reported in immunocompetent patients. These HCV RNA levels, as well as the generally mild stage of hepatitis in the participants, may have resulted in the high absolute SVR rates achieved in this study. The exclusion of ribavirin also may have contributed to increased safety and adherence without compromising treatment efficacy, even in patients in whom previous interferon-based treatment failed.

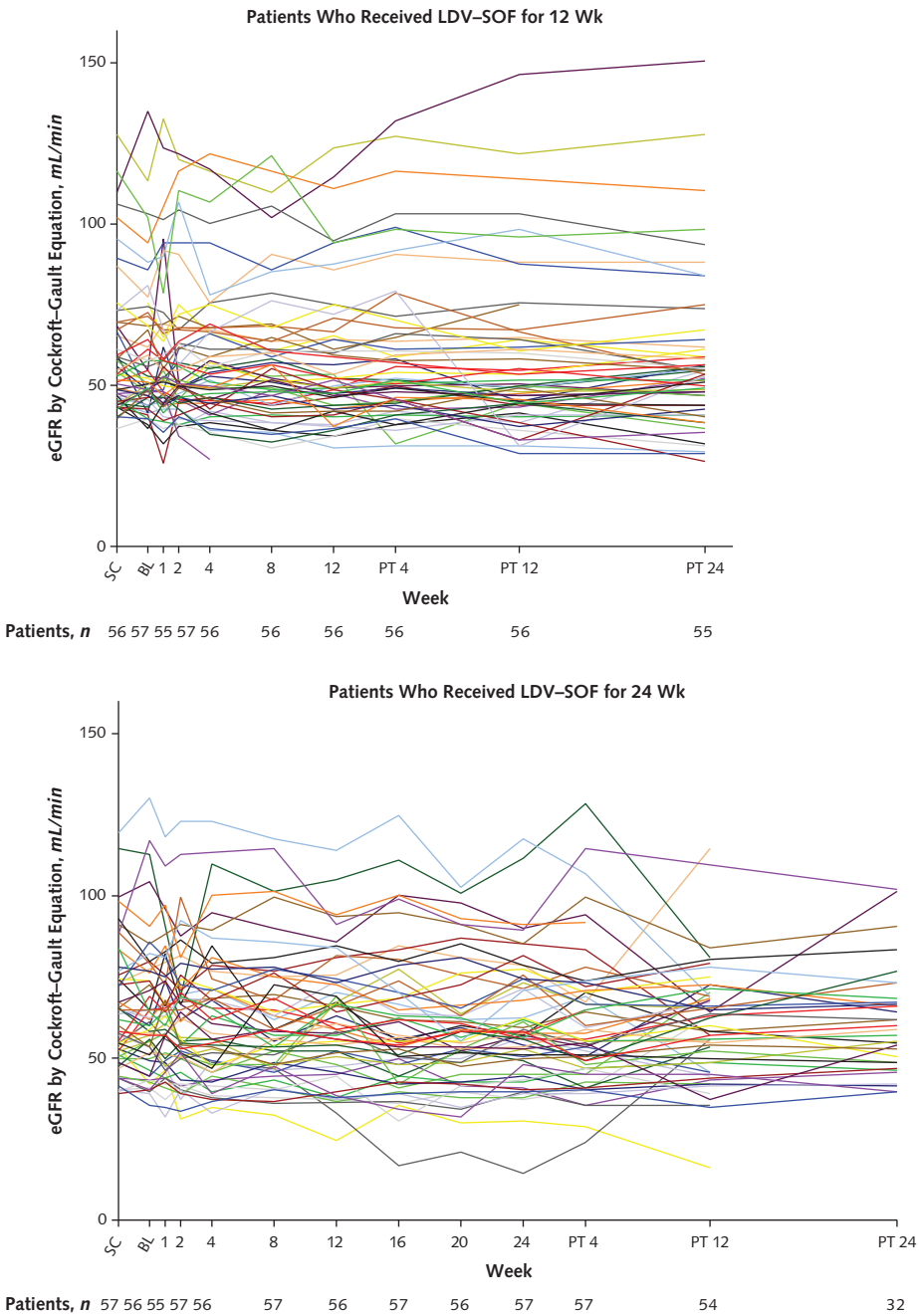
Twenty-one patients (18%) required adjustment in their calcineurin inhibitor–based immunosuppressant

Figure 1. Median change in eGFR by Cockcroft–Gault equation.



The horizontal line is the median value, the box is interquartile range, and the whiskers show overall range. BL = baseline; eGFR = estimated glomerular filtration rate; PT = posttreatment.

Figure 2. Individual-patient eGFRs over time.



Results for treatment weeks 16, 20, and 24 are available only for patients who received LDV-SOF for 24 wk. BL = baseline; eGFR = estimated glomerular filtration rate; LDV-SOF = ledipasvir-sofosbuvir; PT = posttreatment; SC = screening.

regimen. In most patients, modifications in the dosage or type of calcineurin inhibitor were determined by the attending nephrologist, independent of antiviral therapy. Antiviral therapy was well-tolerated by all but 1 patient, who prematurely discontinued treatment at week 4 because of bradycardia leading to syncope, which was temporally associated with the coadministration of amiodarone, a drug prohibited by the study protocol and now considered contraindicated in patients receiving sofosbuvir-containing regimens (31).

Our results are consistent with those of 2 small studies in the United States and France. In the U.S. study, 20 patients, most of whom had genotype 1 HCV infection and half of whom had advanced liver fibrosis or received an HCV-infected donor graft, achieved SVR after treatment with a sofosbuvir-based regimen. Seven of the patients received ledipasvir in addition to sofosbuvir. The time to serum HCV RNA clearance ranged from 29 to 59 (mean, 34) days (14). Nearly half of the patients (45%) required adjustments in their calcineurin

inhibitor dosage during antiviral therapy. In 4 patients (20%), serum creatinine transiently increased by more than 22.1 μmol/L (0.25 mg/dL), which was attributed to tacrolimus toxicity. No episodes of rejection occurred among these patients. Similar outcomes were observed in the study from France, in which 25 kidney transplant recipients, all with an eGFR greater than 30 mL/min, received treatment with sofosbuvir-based regimens and achieved SVR12 with no serious adverse events (15).

Interpretation of our study's results is limited by its open-label design and the exclusion of patients with HCV genotypes other than 1 or 4. Other limitations include the underrepresentation of patients with HCV genotype 1a and those with cirrhosis, as well as the small percentage of nonwhite patients enrolled. Because our study excluded patients with creatinine clearance less than 40 mL/min, our results cannot be generalized to patients with more severe renal impairment. Postmarketing data suggest that patients with creatinine clearance less than 30 mL/min should be monitored closely during treatment with DAA regimens (32).

A safe and highly effective interferon-free regimen to treat HCV infection in kidney transplant recipients might provide patients with end-stage renal disease access to HCV-infected donor kidneys. This possibility has implications for public health policy in an era when the ever-increasing success of kidney transplantation as a life-saving procedure has led to a demand for donor organs far exceeding the supply. This is particularly the case in the United States, where the wait time for a donated kidney may be years, whereas the average wait time for an HCV-infected organ is in the range of months (33).

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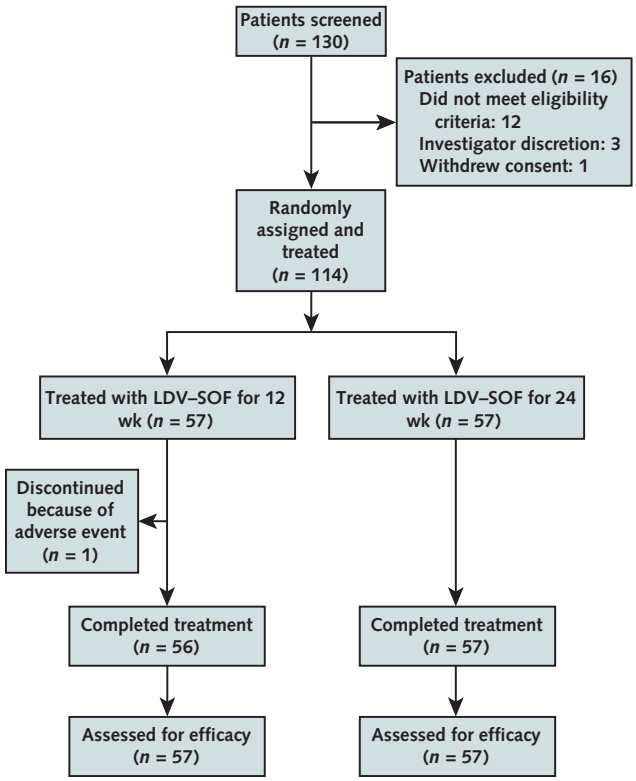
Appendix Figure. Patient disposition.



LDV–SOF = ledipasvir–sofosbuvir.

Appendix Table 1. Grade 3 and 4 Adverse Events*

Events	Ledipasvir–Sofosbuvir	
	12 wk (*n* = 57)	24 wk (*n* = 57)
Grade 3 (severe)		
Anemia	1 (2)	0 (0)
Aortic stenosis	0 (0)	1 (2)
Diarrhea hemmorhagic	0 (0)	1 (2)
Erysipelas	1 (2)	0 (0)
Gastroenteritis	1 (2)	0 (0)
Hypoparathyroidium	0 (0)	1 (2)
Intervertebral disc protusion	0 (0)	1 (2)
Papillary thyroid cancer	0 (0)	1 (2)
Pulmonary embolism	0 (0)	1 (2)
Total grade 3 events	3 (5)	5 (9)
Grade 4 (life-threatening)		
Suicide attempt	1 (2)	0 (0)
Total grade 4 events	1 (2)	0 (0)

* Values are numbers of patients (percentages).

Appendix Table 2. Estimated Glomerular Filtration Rate and Change From Baseline, by Visit*

Variable	Ledipasvir-Sofosbuvir for 12 wk (n = 57)†								Ledipasvir-Sofosbuvir for 24 wk (n = 57)							
	Patients, *n*	Mean	SD	Minimum	Quartile 1	Median	Quartile 3	Maximum	Patients, *n*	Mean	SD	Minimum	Quartile 1	Median	Quartile 3	Maximum
Baseline	57	59.1	20.51	36.6	46.2	50.4	68.4	135.0	57	63.5	20.26	35.4	49.8	60.0	73.8	130.2
At week 1	55	58.4	21.16	25.8	44.4	52.2	66.0	132.6	54	62.9	18.25	31.8	48.6	61.8	73.8	118.2
At week 2	57	59.5	22.34	34.2	45.6	50.4	67.2	121.8	56	62.9	20.62	31.2	50.1	58.8	72.0	123.0
At week 4	57	58.4	21.35	27.0	44.4	52.8	66.6	121.8	56	62.7	20.63	33.0	47.1	59.1	72.9	123.0
At week 8	56	58.7	21.34	30.6	44.1	52.5	64.2	121.2	57	61.3	19.62	32.4	47.4	57.0	72.6	117.6
At week 12	53	57.0	21.23	30.6	42.6	49.8	64.2	123.6	56	61.9	18.66	24.6	49.2	59.7	72.9	114.0
At week 16	NA	–	–	–	–	–	–	–	57	60.2	21.25	16.8	44.4	55.2	70.2	124.8
At week 20	NA	–	–	–	–	–	–	–	55	59.1	18.98	21.0	45.0	56.4	65.4	102.6
At week 24	NA	–	–	–	–	–	–	–	53	60.6	19.76	14.4	48.0	57.0	73.2	117.6
At follow-up week 4	50	58.6	21.84	31.2	44.4	50.4	66.0	127.2	52	59.6	20.98	24.0	45.9	55.2	69.6	128.4
Change at week 1	55	–0.4	9.49	–23.4	–4.8	–1.8	1.8	40.8	54	0.3	6.30	–12.0	–4.8	0.0	4.2	17.4
Change at week 2	57	0.4	7.56	–24.6	–3.0	–0.6	4.2	22.2	56	–0.6	7.00	–16.8	–4.2	–0.9	2.1	20.4
Change at week 4	57	–0.7	7.96	–21.0	–4.8	–1.8	4.2	27.6	56	–1.2	6.19	–15.0	–4.5	–1.8	1.5	19.8
Change at week 8	56	–0.6	8.38	–33.0	–4.5	–0.6	3.0	22.2	57	–2.2	7.00	–14.4	–6.0	–2.4	1.2	21.6
Change at week 12	53	–1.6	7.62	–20.4	–7.2	–1.8	3.0	16.8	56	–2.0	8.97	–28.2	–6.0	–1.8	2.4	18.6
Change at week 16	NA	–	–	–	–	–	–	–	57	–3.3	9.03	–44.4	–7.2	–3.0	1.8	20.4
Change at week 20	NA	–	–	–	–	–	–	–	55	–4.4	9.51	–40.2	–6.6	–3.0	1.8	9.0
Change at week 24	NA	–	–	–	–	–	–	–	53	–2.7	10.00	–46.8	–7.8	–1.2	3.0	16.2
Change at follow-up week 4	50	–0.4	7.60	–16.8	–4.8	–0.9	1.8	22.2	52	–3.3	9.11	–37.2	–8.1	–3.0	0.6	15.6

NA = not available.
* Values are mL/min/1.73 m^2 unless otherwise indicated.
† Results for weeks 16, 20, and 24 are not available for patients who received treatment for 12 wk.

Appendix Table 3. Patients With Change in Immunosuppressant Medications

Generic Name	Reported Drug Name	Dose	Dose Frequency	Route	Start Date (Study/Follow-up* Day)	Stop Date (Study/Follow-up* Day)	Reason for Regimen Change
Patient 1							
Treatment = LDV–SOF 12 weeks; age/sex/race/ethnic = 65/F/WH/NH; first dose = 2014-11-25; last dose = 2015-02-17 (85)							
Cyclosporine	Neoral	50 mg	QD	Oral	1987-07	2015-01-28 (65 D)	Suspected drug-drug interaction: related to treatment regimen
Prednisone	Neoral cortancyl	75 mg	QD	Oral	2015-01-29 (66 D)	(Cont.)	
	Cortancyl	5 mg	QD	Oral	1987-07	(Cont.)	
Patient 2							
Treatment = LDV–SOF 12 weeks; age/sex/race/ethnic = 63/M/WH/NH; first dose = 2014-12-10; last dose = 2015-03-04 (85)							
Mycophenolate mofetil	Cellcept	500 mg	TID	Oral	2004	(Cont.)	
Tacrolimus	Advagraf	2 mg	QD	Oral	2004	2015-07-09 (127* D)	Management of rejection
	Advagraf	3 mg	QD	Oral	2015-07-10 (128* D)	(Cont.)	
Patient 3							
Treatment = LDV–SOF 12 weeks; age/sex/race/ethnic = 44/F/WH/H; first dose = 2014-12-10; last dose = 2015-03-06 (87)							
Mycophenolate sodium	Myfortic	360 mg	BID	Oral	2004	(Cont.)	
Prednisone	Cortancyl	5 mg	QD	Oral	2004	(Cont.)	
Tacrolimus	Advagraf	2 mg	QD	Oral	2004	2014-12-18 (9 D)	Management of rejection
	Advagraf	1.5 mg	QD	Oral	2014-12-19 (10 D)	2015-02-14 (67 D)	Management of rejection
	Advagraf	2 mg	QD	Oral	2015-02-15 (68 D)	2015-04-12 (37* D)	Management of rejection
	Advagraf	2.5 mg	QD	Oral	2015-04-13 (38* D)	(Cont.)	
Patient 4							
Treatment = LDV–SOF 12 weeks; age/sex/race/ethnic = 57/F/WH/NH; first dose = 2014-11-17; last dose = 2015-02-09 (85)							
Azathioprine	Imurel	50 mg	BID	Oral	1974	(Cont.)	
Hydrocortisone	Hydrocortisone (Roussel)	10 mg	QD	Oral	2014-10-27 (-21 D)	(Cont.)	Renal insufficiency status
Prednisone	Cortancyl	10 mg	QD	Oral	1974	(Cont.)	
Patient 5							
Treatment = LDV–SOF 12 weeks; age/sex/race/ethnic = 56/F/WH/NH; first dose = 2015-01-09; last dose = 2015-04-01 (83)							
Mycophenolate mofetil	Cellcept	1750 mg	QD	Oral	2009-12-29 (-5 Y)	2015-01-27 (19 D)	Other: Cellcept is out of the trade
	Myfenax	1750 mg	QD	Oral	2015-01-27 (19 D)	(Cont.)	
Prednisone	Deltacortene	7.5 mg	QD	Oral	2009-12-29 (-5 Y)	2015-08-29 (150* D)	Other: Optimize minimum dosage of immunosuppressant
	Deltacortene	6.25 mg	QD	Oral	2015-08-30 (151* D)	(Cont.)	
Patient 6							
Treatment = LDV–SOF 12 weeks; age/sex/race/ethnic = 53/M/WH/NH; first dose = 2015-03-12; last dose = 2015-06-03 (84)							
Prednisone	Deltacortene	5 mg	QD	Oral	2005-07-13 (-10 Y)	(Cont.)	
Tacrolimus	Prograf	1.5 mg	QD	Oral	2005-07-13 (-10 Y)	2015-07-14 (41* D)	Other: PK
	Prograf	2 mg	QD	Oral	2015-07-15 (42* D)	(Cont.)	

Continued on following page

Appendix Table 3.–Continued

Generic Name	Reported Drug Name	Dose	Dose Frequency	Route	Start Date (Study/Follow-up* Day)	Stop Date (Study/Follow-up* Day)	Reason for Regimen Change
Patient 7							
Treatment = LDV–SOF 12 weeks; age/sex/race/ethnic = 66/M/WH/NH; first dose = 2015-04-15; last dose = 2015-07-07 (84)							
Mycophenolate sodium	Myfortic	540 mg	QD	Oral	2002-01	(Cont.)	
Tacrolimus	Tacrolimus	0.5 mg	QD	Oral	2001-03-26 (-14 Y)	2015-06-25 (72 D)	Other: PK
	Tacrolimus	0.75 mg	QD	Oral	2015-06-26 (73 D)	(Cont.)	
Patient 8							
Treatment = LDV–SOF 12 weeks; age/sex/race/ethnic = 69/F/WH/NH; first dose = 2015-05-06; last dose = 2015-07-29 (85)							
Sirolimus	Sirolimus	1 mg	QD	Oral	2006	2015-06-07 (33 D)	Suspected drug-drug interaction: not related to treatment regimen
	Sirolimus	0.75 mg	QD	Oral	2015-06-08 (34 D)	(Cont.)	
Patient 9							
Treatment = LDV–SOF 12 weeks; age/sex/race/ethnic = 54/M/WH/NH; first dose = 2015-05-13; last dose = 2015-08-04 (84)							
Cyclosporine	Neoral	25 mg	BID	Oral	1995-09-05 (-20 Y)	(Cont.)	
Prednisone	Deltacortene	5 mg	QD	Oral	2014-09	2015-03-18 (-56 D)	Other: Switch to sirolimus
	Deltacortene	5 mg	QD	Oral	2015-05-13 (1 D)	2015-08-08 (4* D)	Other: Optimize minimal level of immunosuppressant
Sirolimus	Sirolimus	0.5 mg	QD	Oral	2015-03-19 (-55 D)	(Cont.)	
Patient 10							
Treatment = LDV–SOF 24 weeks; age/sex/race/ethnic = 45/F/WH/NH; first dose = 2014-12-16; last dose = 2015-06-02 (169)							
Azathioprine	Imurel	75 mg	QD	Oral	1989	(Cont.)	
Cyclosporine	Neoral	90 mg	QD	Oral	1989	2015-01-08 (24 D)	Management of rejection
	Neoral	100 mg	QD	Oral	2015-01-09 (25 D)	2015-02-05 (52 D)	Management of rejection
	Neoral	110 mg	QD	Oral	2015-02-06 (53 D)	(Cont.)	
Prednisone	Cortancyl	5 mg	QD	Oral	1989	(Cont.)	
Patient 11							
Treatment = LDV–SOF 24 weeks; age/sex/race/ethnic = 54/M/WH/NH; first dose = 2014-12-17; last dose = 2015-06-04 (170)							
Cyclosporine	Neoral	190 mg	QD	Oral	2014-02	2015-01-22 (37 D)	Management of rejection, suspected drug-drug interaction: related to treatment regimen
	Neoral	225 mg	QD	Oral	2014-01-23 (38 D)	(Cont.)	
Mycophenolate mofetil	Cellcept	2 g	QD	Oral	2014-02	(Cont.)	
Prednisone	Cortancyl	10 mg	QD	Oral	2014-02	2015-01-22 (37 D)	Other: Normal gradual stop
	Cortancyl	7.5 mg	QD	Oral	2015-01-23 (38 D)	(Cont.)	

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Appendix Table 3–Continued

Generic Name	Reported Drug Name	Dose	Dose Frequency	Route	Start Date (Study/Follow-up* Day)	Stop Date (Study/Follow-up* Day)	Reason for Regimen Change
Patient 12							
Treatment = LDV–SOF 24 weeks; age/sex/race/ethnic = 55/F/BL/NH; first dose = 2014-11-12; last dose = 2015-04-29 (169)							
Azathioprine	Imurel	150 mg	QD	Oral	2014-11-27 (16 D)	(Cont.)	
Cyclosporine	Neoral	75 mg	BID	Oral	2015-04-20 (160 D)	(Cont.)	
Mycophenolate mofetil	Cellcept	500 mg	BID	Oral	2012-09	2014-11-26 (15 D)	Management of rejection
Prednisone	Cortancyl	7.5 mg	QD	Oral	2012-09	(Cont.)	
Tacrolimus	Advagraf	5 mg	QD	Oral	2012-09	2015-04-19 (159 D)	Management of rejection
Patient 13							
Treatment = LDV–SOF 24 weeks; age/sex/race/ethnic = 67/F/WH/NH; first dose = 2014-11-20; last dose = 2015-05-06 (168)							
Everolimus	Certican	500 µg	BID	Oral	2014-08-07 (-105 D)	(Cont.)	
Mycophenolate mofetil	Cellcept	500 mg	BID	Oral	2006	2015-02-08 (81 D)	Other: skin problem
	Cellcept	250 mg	BID	Oral	2015-02-09 (82 D)	(Cont.)	
Prednisone	Cortancyl	10 mg	QD	Oral	2006	(Cont.)	
Patient 14							
Treatment = LDV–SOF 24 weeks; age/sex/race/ethnic = 51/F/BL/NH; first dose = 2015-01-05; last dose = 2015-06-22 (169)							
Cyclosporine	Neoral	175 mg	QD	Oral	2007	2015-05	Management of rejection
	Neoral	75 mg	BID	Oral	2015-05	(Cont.)	
Mycophenolate mofetil	Cellcept	1000 mg	BID	Oral	2007	(Cont.)	
Prednisone	Cortancyl	10 mg	QD	Oral	1987	(Cont.)	
Patient 15							
Treatment = LDV–SOF 24 weeks; age/sex/race/ethnic = 41/M/WH/NH; first dose = 2015-02-11; last dose = 2015-07-29 (169)							
Mycophenolate mofetil	Cellcept	1000 mg	BID	Oral	2014-01-30 (-1 Y)	(Cont.)	
Prednisone	Decortin	7.5 mg	QD	Oral	2014-01-30 (-1 Y)	(Cont.)	
Tacrolimus	Prograf	1 mg	BID	Oral	2014-01-30 (-1 Y)	2015-05-20 (99 D)	Other: immunosuppressive Adjustment
	Prograf	1 mg	TID	Oral	2015-05-21 (100 D)	(Cont.)	
Patient 16							
Treatment = LDV–SOF 24 weeks; age/sex/race/ethnic = 43/F/WH/NH; first dose = 2015-06-24; last dose = 2015-12-08 (168)							
Tacrolimus	Prograf	1 mg	BID	Oral	1994	2015-08-03 (41 D)	Other: PK
Tacrolimus	Prograf	1.5 mg	BID	Oral	2015-08-04 (42 D)	2005-10-13 (112 D)	Other: PK
Tacrolimus	Prograf	3.5 mg	QD	Oral	2015-10-14 (113 D)	(Cont.)	

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Appendix Table 3–Continued

Generic Name	Reported Drug Name	Dose	Dose Frequency	Route	Start Date (Study/Follow-up* Day)	Stop Date (Study/Follow-up* Day)	Reason for Regimen Change
Patient 17							
Treatment = LDV–SOF 24 weeks; age/sex/race/ethnic = 69/F/WH/NH; first dose = 2015-07-06; last dose = 2015-12-20 (168)							
Methylprednisolone	Medrol	2 mg	QD	Oral	2013-07	2015-10-14 (101 D)	Other: Improved immunosuppression
	Medrol	1 mg	QD	Oral	2015-10-15 (102 D)	(Cont.)	
Mycophenolate mofetil	Mycophenolate	500 mg	BID	Oral	2013-07	2015-10-14 (101 D)	Other: PK
	Mycophenolate	250 mg	TID	Oral	2015-10-15 (102 D)	(Cont.)	
Tacrolimus	Tacrolimus	0.5 mg	BID	Oral	2013-07	(Cont.)	
Patient 18							
Treatment = LDV–SOF 12 weeks; age/sex/race/ethnic = 52/M/WH/NH; first dose = 2015-07-09; last dose = 2015-09-30 (84)							
Methylprednisolone	Medrol	4 mg	QD	Oral	2013-06-29 (-2 Y)	(Cont.)	
Mycophenolate sodium	Myfortic	720 mg	BID	Oral	2013-06-29 (-2 Y)	(Cont.)	
Tacrolimus	Advagraf	2.5 mg	QD	Oral	2013-06-29 (-2 Y)	2015-07-13 (5 D)	Other: PK
	Advagraf	2 mg	QD	Oral	2015-07-14 (6 D)	(Cont.)	
Patient 19							
Treatment = LDV–SOF 24 weeks; age/sex/race/ethnic = 64/M/WH/NH; first dose = 2015-03-12; last dose = 2015-08-29 (171)							
Mycophenolate mofetil	Cellcept	500 mg	BID	Oral	2007	(Cont.)	
Tacrolimus	Prograf	0.5 mg	BID	Oral	2007	2015-09-21 (23* D)	Institutional protocol defined change
	Prograf	1 mg	BID	Oral	2015-09-22 (24* D)	(Cont.)	
Patient 20							
Treatment = LDV–SOF 24 weeks; age/sex/race/ethnic = 49/M/WH/NH; first dose = 2015-03-12; last dose = 2015-08-30 (172)							
Mycophenolate mofetil	Myfenax	2 g	QD	Oral	2012	2015-09-21 (22* D)	Institutional protocol defined change
	Myfenax	2 g	QD	Oral	2015-09-22 (23* D)	(Cont.)	
Tacrolimus	Advagraf	1 mg	QD	Oral	2007	2015-05-13 (63 D)	Institutional protocol defined change
	Advagraf	1.5 mg	QD	Oral	2015-05-14 (64 D)	2015-09-21 (22* D)	Institutional protocol defined change
	Advagraf	3 mg	QD	Oral	2015-09-22 (23* D)	(Cont.)	
Patient 21							
Treatment = LDV–SOF 24 weeks; age/sex/race/ethnic = 42/F/WH/NH; first dose = 2015-05-28; last dose = 2015-11-12 (169)							
Mycophenolate mofetil	Mycofenolat	250 mg	TID	Oral	2005-10	2015-10-08 (134 D)	Institutional protocol defined change
	Mycofenolat	250 mg	BID	Oral	2015-10-09 (135 D)	(Cont.)	
Prednisone	Prednisone	20 mg	QD	Oral	2015-09-23 (119 D)	2015-09-30 (126 D)	Renal insufficiency status
	Prednisone	15 mg	QD	Oral	2015-10-01 (127 D)	2015-10-08 (134 D)	Renal insufficiency status
	Prednisone	10 mg	QD	Oral	2015-10-09 (135 D)	2015-10-16 (142 D)	Renal insufficiency status
	Prednisone	5 mg	QD	Oral	2015-10-17 (143 D)	(Cont.)	
Tacrolimus	Advagraf	0.5 mg	QD	Oral	2005-10	2015-09-22 (118 D)	Institutional protocol define change
	Advagraf	3.5 mg	QD	Oral	2015-09-23 (119 D)	2015-10-08 (134 D)	Renal insufficiency status
	Advagraf	4 mg	QD	Oral	2015-10-09 (135 D)	(Cont.)	

BID = twice daily; BL = black; F = female; H = Hispanic; LDV–SOF = ledipasvir–sofosbuvir; M = male; NH = non-Hispanic; PK = pharmacokinetics; QD = once daily; TID = 3 times daily; WH = white.
* Follow-up days as calculated from date of last dose.