Chung Shan Medical Journal 2022; 33:9-16

Original Article

Treatment of hepatitis C with direct-acting antiviral agents in renal transplant recipients: a long-term and real-world experience

Sheng-Wen Wu[1,2], Chi-Chih Wang[2,3], Ming-Chang Tsai[2,3], Jong-Da Lian[1*]

[1] *Division of Nephrology, Chung Shan Medical University Hospital, Taichung, Taiwan*
[2] *The School of Medicine, Chung Shan Medical University, Taichung, Taiwan*
[3] *Division of Gastroenterology and Hepatology, Chung Shan Medical University Hospital, Taichung, Taiwan*

Purpose: Direct- acting antivirals (DAAs) are showing encouraging results in hepatitis C virus (HCV) eradication and drug safety, but limited data exist for renal transplant recipients (RTRs). In addition, data are lacking regarding the outcomes of RTRs who failed a previous DAA regimen.
Method: We collected data from 17 consecutive HCV-infected RTRs treated with DDAs to evaluate DAA efficacy, relevant side effects, and long-term patient outcomes. Initial DAA regimens included sofosbuvir (SOF)-based regimens in 16 patients (94%) and daclatasvir plus asunaprevir in 1 patient.
Results: All patients exhibited a rapid virologic response to therapy and 14 patients (82.3%) achieved a sustained virologic response at 12 weeks after the end of therapy. The anti-HCV regimens were well tolerated, but the tacrolimus level decreased significantly at 2 weeks after treatment. Two RTRs with prior DAA failure were successfully retreated with SOF plus velpatasvir (VEL).
Conclusions: IFN-free DAAs were efficacious and well-tolerated in our Asian RTRs. Patients should be carefully monitored to avoid sub-therapeutic immunosuppression in routine practice, regardless of DAA regimens. This is a first report that the combination of SOF and VEL is apparently effective and well-tolerated in RTRs with prior DAAs failure. Further studies are needed to verify our findings.

Keywords: Direct- acting antiviral; hepatitis C; sustained virologic response; calcineurin inhibitor; renal transplantation

1. Introduction:

Chronic hepatitis C virus (HCV) infection causes devastating complications, including liver cirrhosis, hepatocellular carcinoma, and even mortality.1,2 Patients with chronic HCV infection also have a higher prevalence of chronic kidney disease (CKD) and end stage renal disease (ESRD) and show increased mortality when compared with the general population.[3,4] The combination of pegylated interferon (IFN) and low-dose ribavirin (RBV) is only moderately effective for the treatment of HCV in ESRD patients.[5] Therefore, the occurrence of chronic HCV infection in renal transplant recipients (RTRs) is frequent and associated with worsening survival when compared with RTRs without HCV infection.[6,7] However, IFN therapy is generally contraindicated for RTRs due to the risk of renal allograft rejection.[8] In recent years, many direct- acting antivirals (DAAs) have shown encouraging results in HCV eradication and drug safety in the general population and in liver transplant recipients.[9,10] However, only a few observational studies and small clinical trials have evaluated the efficacy and safety of DAA therapy in

* Corresponding Author: Jong-Da Lian
Address: No. 110, Sec. 1, Jianguo N. Rd., Taichung City, 40201, Taiwan
Tel: +886-4-24739595 ext. 32629
E-mail: s41111.tw@yahoo.com.tw

RTRs, and especially in Asian patients. In addition, data are lacking regarding the outcomes of RTRs who failed a previous DAA regimen. The aim of the present study was therefore to investigate the long-term outcomes of RTRs treated with DAAs in a real-world Asian clinical practice.

2. Materials and methods:

2.1. Patients and anti-HCV therapy

From May 2015 to May 2017 at Chung-Shan Medical University Hospital (Taichung, Taiwan), 17 RTRs infected with hepatitis C underwent IFN-free DAAs anti-HCV therapy. All patients were human immunodeficiency virus-negative and none was co-infected with hepatitis B. Antiviral combinations have changed during this period while different types of DAAs have become available in Taiwan. In summary, the chosen therapeutic regimens were consistent with recommendations in the general guideline. The length of therapy was determined by following the manufacturer's label guidelines. The dosage of RBV was 1200mg per day, given in 2 divided doses, and adjusted based on the renal function of the patients.

2.2. Data collection and study assessments

After obtaining approval from the local Institutional Research Board at Chung-Shan Medical University Hospital (CS19111), we collected clinical characteristics (body weight, blood pressure, clinical events, and self-reported adverse effects of drugs) and laboratory parameters (HCV viral load, serum creatinine, liver function tests, blood sugar level, lipid profiles, urinalysis, and hemoglobin) every month to every three months. Plasma HCV RNA was analyzed using the Roche Cobas AmpliPep/Cobas Taqman HCV Quantitative Test, V2.0. The HCV genotype was determined using a Linear Array HCV Genotyping Test (Roche). We used the fibrosis-4 (FIB4) index to evaluate the severity of liver fibrosis. Recognizing that the investigators could adjust the calcineurin inhibitor (CNI) dosage at each study time point, we used the CNI concentration-to-dose ratios (the CNI level divided by CNI dosage) rather than the CNI levels alone to determine the actual impact of the DAA treatment on the CNI level. We followed up all patients until June 2019, loss of follow-up, or death.

2.3. Statistical analyses:

All data were expressed as mean ± standard deviation (SD), unless stated otherwise. All analyses were performed using SPSS software for Windows (Version 19.0; SPSS, Chicago, IL, USA). Analyses were performed with χ^2 testing for categorical variables (Fisher's exact test used for violations of Cochran's assumptions) and *t* tests for continuous variables (Mann-Whitney test for non-normally distributed variables). A two-sided P-value of less than 0.05 was considered statistically significant.

3. Results:

3.1. Baseline characteristics of study population:

The patients' clinical characteristics and parameters are presented in Table 1. The age of the 17 patients (10 men, 7women) ranged from 54 to 80 years old (mean 62 years). All patients received a CNI (tacrolimus in 14 patients and cyclosporine in 3 patients) and mycophenolate mofetil or enteric-coated mycophenolate sodium. A total of 14 of the 17 patients received low-dose prednisolone (5 mg per day or every other day). The mean time from transplant to treatment was 10.0± 5.6 years (range, 0.5 to 19 years). Overall, 9 patients (52.9%) had genotype 2, 6 (35.2%) had genotype 1, and 2 (11.7%) had genotype 6. The mean serum creatinine level at the start of the DAA treatment was 1.8 ± 0.7 mg/dl. Three patients starting anti-HCV treatment had hepatic HCV flare-ups (defined as an abrupt rise in alanine aminotransferase (ALT) and/or a rise in bilirubin level).

3.2 The clinical efficacy and adverse effects:

All patients completed 12 (n= 16) or 24 (n= 1) weeks of DAA treatment, which included Sofosbuvir (SOF) plus RBV (n= 7), SOF plus ledipasvir (LDV) (n= 8), SOF plus LDV plus RBV (n= 1), and daclatasvir (DCV) plus asuaprevir (ASV) (n= 1). At week 4 after treatment and at the end of treatment, HCV RNA was undetectable in all patients. A total of 14 (82.4 %) patients achieved a sustained virologic response at 12 weeks after the end of therapy (SVR12). DAAs were well-tolerated in all

Table 1: The clinical characteristics and parameters of kidney transplant patients before and after direct antiviral agent treatment

Patient	Age	Immunosuppressant	FIB-4 index	Time from transplant to treatment (years)	Genotype	Viral load (log IU/ml)	DAAs	ALT (mg/dl)		Creatinine (mg/dl)		SVR12
								Before	After	Before	After	
1	64	TAC/MMF/steroid	2.0	8.7	2	19.1	SOF/RBV	18	13	2.2	2.4	Yes
2	80	CsA/MMF	2.4	5.6	1b	12.1	SOF/LDV	57	27	0.9	0.9	Yes
3	40	TAC/MMF/steroid	7.5	12.2	1b	69	SOF/LDV/ RBV	19	20	1.6	1	No
4	73	TAC/MMF/steroid	6.3	17.6	6	2.5	SOF/LDV	75	36	1.9	1.6	Yes
5	63	TAC/MMF	2.7	0.5	2	5.7	SOF/RBV	80	14	1.9	1	Yes
6	61	TAC/EVE/steroid	5.3	0.9	1a	21.4	SOF/LDV	292	8	2.7	1.5	Yes
7	61	TAC/MMF/steroid	1.2	4.8	1b	31	DCV/ASV	16	9	2.2	2.5	Yes
8	67	TAC/MMF/steroid	1.9	3.1	2	8.5	SOF/RBV	43	18	2	1.9	Yes
9	66	TAC/MMF/steroid	2.3	12.3	1b	47.6	SOF/LDV	61	16	1.5	1.6	Yes
10	60	TAC/MMF/steroid	2.6	10.0	2	43.1	SOF/RBV	49	16	3	3.1	Yes
11	67	CsA/MMF/steroid	2.7	14.4	2	398	SOF/RBV	69	23	0.8	0.9	No
12	56	TAC/MMF/steroid	0.9	19.0	1b	40.1	SOF/LDV	24	12	1.1	1	Yes
13	54	TAC/MMF/steroid	3.0	11.2	2	7.6	SOF/RBV	273	11	2.1	2.5	Yes
14	57	CsA/MMF	1.0	16.2	2	43.7	SOF/RBV	18	18	0.6	0.7	No
15	65	TAC/MMF/steroid	1.8	12.5	2	0.6	SOF/LDV	30	16	2.2	2.6	Yes
16	67	TAC/MMF/steroid	3.7	13.5	6	1.7	SOF/LDV	31	11	2	2	Yes
17	54	TAC/MMF/steroid	2.8	8.0	2	0.4	SOF/LDV	90	30	1.5	1.4	Yes

DAA, direct anti-viral agents; TAC, tacrolimus; MMF,mycophenolate mofetil; CsA, cyclosporine; EVE, everolimus; FIB-4 index, Fibrosis-4 Index; SOF, sofosbuvir; RBV, ribavirin; LDV, ledipasvir; DCV, daclatasvir; ASV,asunaprevir; SVR12, sustained virologic response at 12 weeks after therapy

patients. The liver function tests (including ALT and bilirubin level) in all patients returned to within the normal range at the end of therapy and none developed hepatic failure. The difference in mean serum creatinine level before and after treatment did not reach statistical significance. It is important to note that a total of 6 (75%) of the 8 patients with RBV supplements needed erythropoietin treatment or blood transfusion.

3.3. The impact of DAA treatment on CNI levels:

The tacrolimus trough (TAC) level per mg tacrolimus decreased significantly from 2.6± 2.2 ng/ml/mg at the initiation of treatment (IOT), 2.0± 1.8 at week 2 of treatment (W2) (P =0.01), 1.9± 1.7 at week 4 of treatment (W4) (P =0.004), to 1.6± 1.4 at the end of treatment (EOT) (P =0.003) (Figure 1A). The cyclosporine trough (CsA) level per mg cyclosporine did not significantly decrease over the study period. (Figure 1B)

3.4. Long-term follow-up:

After a mean follow-up of 34.8 months, all 14 patients with SVR12 had persistent undetectable HCV PCR results. The further management and clinical results in the other 3 patients who did not

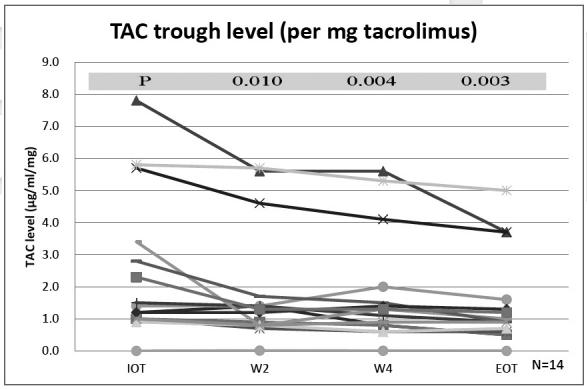


Figure 1A. The tacrolimus (TAC) concentration-to-dose ratios at various time points after initiation of therapy. P values were compared to the TAC level of IOT. TAC level: tacrolimus trough level; IOT: initiation of therapy; W2: 2 weeks after therapy; W4: 4 weeks after therapy; EOT: end of therapy

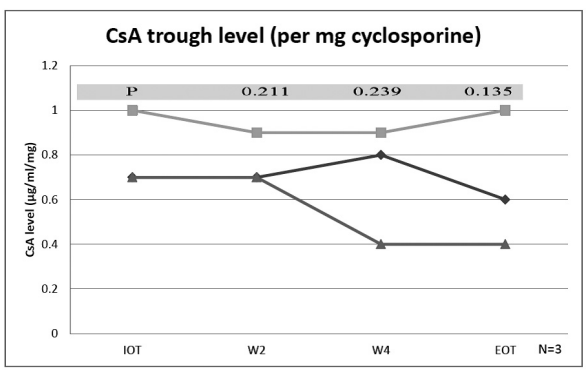


Figure 1B. The cyclosporine (CsA) concentration-to-dose ratios at various time points after initiation of therapy. P values were compared to the CsA level of IOT. CsA level: cyclosporine trough level; IOT: initiation of therapy; W2: 2 weeks after therapy; W4: 4 weeks after therapy; EOT: end of therapy

achieve SVR12 with the initial DAAs are shown in Table 2. Patient 3 received 24 weeks of SOF/LDV/RBV and had rapid virologic response at 1 month after treatment. However, she had a hepatitis C relapse one month after the end of treatment and died due to septic shock 1 year later. Patient 11 failed to achieve SVR12 with 12 weeks of SOF/velpatasvir (VEL)/RBV, but achieved SVR12 after retreatment with 24 weeks of SOF/VEL/RBV. Patient 14 had a rapid virologic response at 1 month after treatment with SOF/VEL and SVR12 until the last follow-up. SOF/VEL with or without RBV were well-tolerated in the latter two patients.

4. Discussion:

Our cohort study found IFN-free DAAs were efficacious and well-tolerated in our Asian RTRs. Regardless of DAA regimens, patients with receiving DAAs should be carefully monitored to avoid sub-therapeutic immunosuppression in routine practice. The combination of SOF and VEL is apparently effective and well-tolerated in RTRs with prior DAAs failure.

Chronic HCV infection has a well-known association with worse patient survival in ESRD patients and RTRs.[11,12] Furthermore, HCV infection is significantly linked to higher graft loss in RTRs, due to the increased risk of post-transplantation diabetes mellitus,[13] glomerulonephritis,[14] and transplant glomerulopathy[15] in those patients. IFN based therapy is poorly tolerated, relatively ineffective, and therefore contraindicated in RTRs.[16] Over the past

Table 2: Clinical management and outcome of patients with prior direct antiviral agent failure

	Genotype	Viral load (log IU/ml)	FIB-4 index	First DAAs (duration of therapy)	2nd DAAs (duration of therapy)	3rd DAAs (duration of therapy)	Cure of HCV infection	Patient Outcome
Patient 3	1b	69	7.5	SOF / LDV / RBV (12 weeks)	SOF / LDV / RBV (24 weeks)	NA	No	Dead
Patient 11	2	398	2.7	SOF / RBV (12 weeks)	SOF / VEL / RBV (12 weeks)	SOF / VEL / RBV (24 weeks)	Yes	Alive
Patient 14	2	43.7	1.0	SOF / RBV (12 weeks)	SOF + VEL (12 weeks)	NA	Yes	Alive

DAA, direct antiviral agent; FIB-4, Fibrosis-4 Index; SOF, sofosbuvir; LDV, ledipasvir; RBV, ribavirin; NA, not applicable VEL, velpatasvir

decade, the development of new DAAs has brought encouraging results in the general population and in liver transplant patients.[17] At present, only a few observational and two prospective clinical trials have evaluated the efficacy and safety of DAAs in RTRs. Furthermore, few Asian patients were enrolled in these studies. Colombo et al. randomly treated 114 RTRs (94% were white and 91% had genotype 1) with 12 or 24 weeks of SOF/LDV combined therapy.[18] All 114 patients achieved SVR12. In another clinical trial (MAGELLAN-2 trial), 18 (98%) out of 20 RTRs with HCV genotypes 1 to 6 (78% were white) treated with non-SOF based DAAs (glecaprevir/pibrentasvir) achieved SVR12.[19] Several retrospective or prospective cohort studies have revealed a cure rate (SVR12) of 91% - 100% in a total of more than 300 RTRs. [20-28] The overall SVR12 rate in our study was only 82.4 %. Although the previous studies revealed a similar response rate to DAAs for hepatitis C in all races (except for the black race), [29,30] we still could not exclude a lower response rate in our Chinese patients was due to an effect of race or even genetic makeup. Furthermore, we noted that 2 out of 3 patients who had a relapse had favorable profiles of treatment responses (including genotype 2 and no evidence of liver cirrhosis). Therefore, we speculated that the treatment failure in these 2 patients was probably a consequence of a higher pre-therapy viral load and/or the DAA regimen with SOF/ RBV. Although some previous studies revealed a cure rate of 100% in patients treated with SOF/RBV, [20,21,27] our result may imply that the effectiveness of SOF/RBV is probably insufficient for the elimination of HCV infection in RTRs, irrespective of their cirrhosis status or genotype.

One important point to note is the clinical impact of DAA therapy on the blood level of CNI in clinical practice. Previous studies have revealed contradictory results. For example, Kamar et al. [20] and Musialik et al.[28] mentioned a significant decrease in CNI levels at week 4 during therapy and the end of therapy, whereas Lubetzky et al. [23] reported stable CNI levels in 94% of their patients during therapy. Furthermore, Fernandez et al.[22] found that 17 % of tacrolimus users and 50% of cyclosporine users needed to decrease their doses of CNI. The one explanation for this discrepancy is that the investigators could adjust the CNI dose arbitrarily at various time points during the DAA treatment. We avoided the influence of dosage adjustment on CNI level by our use of CNI concentration-to-dose ratio (CNI levels per mg CNI) to clarify the clinical impact of DAAs on the CNI level. Our study revealed that the TAC level per mg tacrolimus, but not the CsA level per mg cyclosporine, decreased significantly at any time point of study period. CNIs (tacrolimus or cyclosporine) are well known substrates of the cytochrome p450 isoenzymes 3A 4/5 and P-glycoprotein (P-gp); therefore, potential drug-drug interactions can occur with DAAs. While SOF or SOF/LDV (the regimens used in most of our patients) do not interact with CYP3A4/5 or P-gp, [31] we think that the decreased CNI level after DAA therapy may reflect an augmented CNI metabolism after elimination of HCV-associated liver injury, rather than drug-drug interactions. This was consistent with many previous studies, either in RTRs or liver transplant patients, [28,32,33] and should serve as a reminder that patients treated with tacrolimus should be carefully monitored after DAA treatment (ideally as early as 2 weeks after starting therapy) to avoid sub-therapeutic immunosuppression in routine practice. Conversely, the lack of statistical significance in the change of CsA level was, at least in part, attributed to the very small patient numbers (only 3 patients).

To the best of our knowledge, only one study has reported the outcome of HCV-infected RTRs with prior DAA failure. In the study by Lin et al., [34] 2 patients who had genotype 1a infection and relapsed after 12 weeks of SOF and simeprevir (SIM) were re-treated with SOF/DCV/RBV for 24 weeks. SVR12 was achieved in both, but no data were provided regarding long-term outcomes. The combination of SOF and VEL is an FDA-approved DAA regimen in the general population with pan-genotypic HCV infection. [35,36] The SOF/VEL has been confirmed as highly effective and well tolerated and has no expected drug-drug interaction with immunosuppressants in liver transplant patients; [37] however, no similar reports has been published for its use in RTRs. In the present study, we reported that two patients with prior DAA failure were successfully cured with SOF/VEL and SOF/VEL/RBV, respectively, and neither showed any obvious

adverse effects. Notably, however, patient 11 had an HCV relapse after 12 weeks of SOF/VEL/RBV. The choice of DAA regimen for retreatment of persons who failed to respond to an initial therapy depends on the agent the individual has been exposed to, and the current suggestion for SOF/VEL failure is SOF/VEL/voxilaprevir (VOX) in the general population. [38,39] However, no guideline suggestions have been made for RTRs. We endeavored to prolong the SOF/VEL/RBV treatment course to enhance the effect of the second treatment course and our patient was finally cured after a retreatment with a total of 24 weeks of SOF/VEL/RBV. Therefore, the combination of SOF and VEL with or without RBV seems to be effective in RTRs with prior DAA failure. A longer course of therapy should be considered in patients with prior DAA failure and high HCV viral load, but this needs to be clarified with further studies.

Our study has several limitations. The main limitations are that it was an observational study and the patient number was small. Furthermore, the FIB-4 index we used in study has a potenital limitation in predicting the presence or severity of liver fibrosis. [40] Lastly, the patients' characteristics and the DAA regimens (94% were SOF based) were quite heterogeneous and complex; however, our study mostly closely reflects the results from real-world clinical practice.

In conclusion, anti-HCV therapy with IFN-free DAAs was efficacious and well-tolerated in our Asian RTRs. Enhanced metabolism of CNI rather than dug-drug interactions between DAAs and immunosuppressants decreases CNI level while treating HCV. Therefore, patients should be carefully monitored to avoid sub-therapeutic immunosuppression in routine practice. Finally, this is the first reported use of the combination of SOF and VEL, with or without RBV, in RTRs, and this combination seems to be effective and well-tolerated in RTRs with prior DAA failure. Further studies are needed to verify our findings.

Conflicts of Interest: None declared

Reference

1. Hu KQ, Tong MJ. The long-term outcomes of patients with compensated hepatitis C virus-related cirrhosis and history of parenteral exposure in the United States. Hepatology. 1999;29(4):1311-6.
2. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis. 2005;5(9):558-67.
3. Molnar MZ, Alhourani HM, Wall BM, Lu JL, Streja E, Kalantar-Zadeh K, et al. Association of hepatitis C viral infection with incidence and progression of chronic kidney disease in a large cohort of US veterans. Hepatology. 2015;61(5):1495-502.
4. Kalantar-Zadeh K, Kilpatrick RD, McAllister CJ, Miller LG, Daar ES, Gjertson DW, et al. Hepatitis C virus and death risk in hemodialysis patients. J Am Soc Nephrol. 2007;18(5):1584-93.
5. Liu CH, Kao JH. Treatment of hepatitis C virus infection in patients with end-stage renal disease. J Gastroenterol Hepatol. 2011;26(2):228-39.
6. Ladino M, Pedraza F, Roth D. Hepatitis C Virus Infection in Chronic Kidney Disease. J Am Soc Nephrol. 2016;27(8):2238-46.
7. Baid-Agrawal S, Pascual M, Moradpour D, Somasundaram R, Muche M. Hepatitis C virus infection and kidney transplantation in 2014: what's new? Am J Transplant. 2014;14(10):2206-20.
8. Terrault NA, Adey DB. The kidney transplant recipient with hepatitis C infection: pre- and posttransplantation treatment. Clin J Am Soc Nephrol. 2007;2(3):563-75.
9. Gitto S, Gamal N, Andreone P. NS5A inhibitors for the treatment of hepatitis C infection. J Viral Hepat. 2017;24(3):180-6.
10. Gadiparthi C, Cholankeril G, Perumpail BJ, Yoo ER, Satapathy SK, Nair S, et al. Use of direct-acting antiviral agents in hepatitis C virus-infected liver transplant candidates. World J Gastroenterol. 2018;24(3):315-22.
11. Fabrizi F, Takkouche B, Lunghi G, Dixit V, Messa P, Martin P. The impact of hepatitis C virus infection on survival in dialysis patients: meta-analysis of observational studies. J Viral Hepat. 2007;14(10):697-703.
12. Fabrizi F, Martin P, Dixit V, Messa P. Meta-analysis of observational studies: hepatitis C and survival after renal transplant. J Viral Hepat. 2014;21(5):314-24.

13. Fabrizi F, Martin P, Dixit V, Bunnapradist S, Kanwal F, Dulai G. Post-transplant diabetes mellitus and HCV seropositive status after renal transplantation: meta-analysis of clinical studies. Am J Transplant. 2005;5(10):2433-40.
14. Morales JM. Hepatitis C virus infection and renal disease after renal transplantation. Transplant Proc. 2004;36(3):760-2.
15. Baid-Agrawal S, Farris AB, 3rd, Pascual M, Mauiyyedi S, Farrell ML, Tolkoff-Rubin N, et al. Overlapping pathways to transplant glomerulopathy: chronic humoral rejection, hepatitis C infection, and thrombotic microangiopathy. Kidney Int. 2011;80(8):879-85.
16. Awan AA, Jadoul M, Martin P. Hepatitis C in Chronic Kidney Disease - An Overview of the KDIGO Guideline. Clin Gastroenterol Hepatol. 2019.
17. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol. 2018;69(2):461-511.
18. Colombo M, Aghemo A, Liu H, Zhang J, Dvory-Sobol H, Hyland R, et al. 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. Ann Intern Med. 2017;166(2):109-17.
19. Reau N, Kwo PY, Rhee S, Brown RS, Jr., Agarwal K, Angus P, et al. Glecaprevir/Pibrentasvir Treatment in Liver or Kidney Transplant Patients With Hepatitis C Virus Infection. Hepatology. 2018;68(4):1298-307.
20. 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(5):1474-9.
21. 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(5):1588-95.
22. Fernandez I, Munoz-Gomez R, Pascasio JM, Baliellas C, Polanco N, Esforzado N, et al. Efficacy and tolerability of interferon-free antiviral therapy in kidney transplant recipients with chronic hepatitis C. J Hepatol. 2017;66(4):718-23.
23. Lubetzky M, Chun S, Joelson A, Coco M, Kamal L, Ajaimy M, et al. Safety and Efficacy of Treatment of Hepatitis C in Kidney Transplant Recipients With Directly Acting Antiviral Agents. Transplantation. 2017;101(7):1704-10.
24. Morales AL, Liriano-Ward L, Tierney A, Sang M, Lalos A, Hassan M, et al. Ledipasvir/sofosbuvir is effective and well tolerated in postkidney transplant patients with chronic hepatitis C virus. Clin Transplant. 2017;31(5).
25. Bhamidimarri KR, Ladino M, Pedraza F, Guerra G, Mattiazzi A, Chen L, et al. Transplantation of kidneys from hepatitis C-positive donors into hepatitis C virus-infected recipients followed by early initiation of direct acting antiviral therapy: a single-center retrospective study. Transpl Int. 2017;30(9):865-73.
26. Eisenberger U, Guberina H, Willuweit K, Bienholz A, Kribben A, Gerken G, et al. Successful Treatment of Chronic Hepatitis C Virus Infection With Sofosbuvir and Ledipasvir in Renal Transplant Recipients. Transplantation. 2017;101(5):980-6.
27. Goel A, Bhadauria DS, Kaul A, Prasad N, Gupta A, Sharma RK, et al. Experience with direct acting antiviral agents for treating hepatitis C virus infection in renal transplant recipients. Indian J Gastroenterol. 2017;36(2):137-40.
28. Musialik J, Kolonko A, Kwiecien K, Owczarek AJ, Wiecek A. Effectiveness and safety of sofosbuvir-based therapy against chronic hepatitis C infection after successful kidney transplantation. Transpl Infect Dis. 2019;21(3):e13090.
29. Su F, Green PK, Berry K, Ioannou GN. The association between race/ethnicity and the effectiveness of direct antiviral agents for hepatitis C virus infection. Hepatology. 2017;65(2):426-38.
30. O'Brien TR, Kottilil S, Feld JJ, Morgan TR, Pfeiffer RM. Race or genetic makeup for hepatitis C virus treatment decisions? Hepatology. 2017;65(6):2124-5.
31. Morcos PN, Moreira SA, Brennan BJ, Blotner S, Shulman NS, Smith PF. Influence of chronic hepatitis C infection on cytochrome P450 3A4 activity using midazolam as an in vivo probe substrate. Eur J Clin Pharmacol. 2013;69(10):1777-84.
32. Fernandez-Ruiz M, Polanco N, Garcia-Santiago A, Munoz R, Hernandez AM, Gonzalez E, et al. Impact of anti-HCV direct antiviral agents on graft

function and immunosuppressive drug levels in kidney transplant recipients: a call to attention in the mid-term follow-up in a single-center cohort study. Transpl Int. 2018;31(8):887-99.
33. Smolders EJ, Pape S, de Kanter CT, van den Berg AP, Drenth JP, Burger DM. Decreased tacrolimus plasma concentrations during HCV therapy: a drug-drug interaction or is there an alternative explanation? Int J Antimicrob Agents. 2017;49(3):379-82.
34. Lin MV, Sise ME, Pavlakis M, Amundsen BM, Chute D, Rutherford AE, et al. Efficacy and Safety of Direct Acting Antivirals in Kidney Transplant Recipients with Chronic Hepatitis C Virus Infection. PLoS One. 2016;11(7):e0158431.
35. Feld JJ, Jacobson IM, Hezode C, Asselah T, Ruane PJ, Gruener N, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. N Engl J Med. 2015;373(27):2599-607.
36. Foster GR, Afdhal N, Roberts SK, Brau N, Gane EJ, Pianko S, et al. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. N Engl J Med. 2015;373(27):2608-17.
37. Agarwal K, Castells L, Mullhaupt B, Rosenberg WMC, McNabb B, Arterburn S, et al. Sofosbuvir/velpatasvir for 12weeks in genotype 1-4 HCV-infected liver transplant recipients. J Hepatol. 2018;69(3):603-7.
38. Bourliere M, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M, et al. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. N Engl J Med. 2017;376(22):2134-46.
39. Panel A-IHG. Hepatitis C Guidance 2018 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clin Infect Dis. 2018;67(10):1477-92.
40. Gonzalez Guilabert MI, Hinojosa Mena-Bernal C, del Pozo Gonzalez J, del Pozo Perez MA. [Retrospective study of FibroScan, APRI, FIB-4 and FORNS indexes compared with liver biopsy in the evaluation of liver fibrosis in patients with chronic hepatitis C monoinfection and HIV coinfection]. Gastroenterol Hepatol. 2010;33(6):425-32.