Journal of Renal and Hepatic Disorders

CODON PUBLICATIONS

REVIEW ARTICLE

Interactions between Immunosuppressive Therapy and Direct-Acting Antivirals in Kidney Transplant Recipient with Hepatitis C Infection

Paolo Carta, Federica Curci, Leonardo Caroti, Larti Aida, Lorenzo Di Maria, Lino Cirami

Nephrology and Dialysis Unit, Careggi University Hospital, Florence, Italy

Abstract

Hepatitis C virus (HCV) causes increased mortality and morbidity in kidney transplant patients. Interferon-based therapies are poorly tolerated and involve the risk of rejection. The new direct-acting antiviral drugs (DAAs) have revolutionized the treatment of HCV infection in transplant patients. This observational study evaluates changes in immunosuppressive therapy during treatment with DAA in renal transplant recipients.

In our transplant center, we selected seven HCV-positive patients at the time of transplantation , four men and three women, with an average age of 61 ± 7 years, in therapy with DAA. The dose and the blood levels of the immunosuppressive drugs were evaluated at the beginning and end of antiviral therapy, together with creatinine and proteinuria.

Viremia was negativized in all patients within the initial 8 weeks of therapy. Currently, the number of patients is too limited to perform a statistical analysis and obtain significant results. In one patient, the dose of Cyclosporine was lowered to 10 mg, while for the remaining patients it was not necessary to change the dose of immunosuppressive drugs.

DAAs give encouraging results in the eradication of HCV in renal transplant recipients, although they are associated with potential adverse drug interactions. The preliminary data of our study suggest that it is not necessary to change the dose of immunosuppressive drugs during therapy and that creatinine and proteinuria remain stationary. We will achieve more significant results in the future, adding more patients to our study. However, further randomized trials are necessary to confirm the safety of DAAs.

Monocentric experience of the use of DAAS in kidney transplant patients with HCV infection.

Keywords: direct-acting antivirals; HCV infection; kidney transplantation; immunosuppression

Received: 04 May 2020; *Accepted after Revision*: 07 May 2020; *Published*: 20 May 2020

Author for correspondence: Dr Paolo Carta, Nephrology and Dialysis Unit, Careggi University Hospital, Florence, Italy. Email: cartapa@aou-careggi.toscana.it

How to cite: Paolo C, et al. Interactions between Immunosuppressive Therapy and Direct-Acting Antivirals in Kidney Transplant Recipient with Hepatitis C Infection. J Ren Hepat Disord. 2020;4(1):31–34.

Doi: http://dx.doi.org/10.15586/jrenhep.2020.67

Introduction

Before the introduction of new direct-acting antiviral drugs (DAAs), anti-hepatitis C virus (HCV) therapy was based on Interferon and Ribavirin, but these drugs were poorly used in kidney transplantation because of an increased risk of rejection and direct nephrotoxicity, respectively.

The use of DAAs has revolutionized the treatment of HCV infection, leading to a very effective clearance of viral load and expanding the population of potentially treatable patients.

There have been debates regarding the use of DAAs in kidney transplantation because of potential interactions with the immunosuppressive drugs.

Evidence from literature has demonstrated that an adjustment in immunosuppressive medications was necessary in 18% of kidney transplant patients treated with DAAs (1).

In this study, we evaluated retrospectively the safety and efficacy of DAAs in kidney transplant patients.

Methods

In this single-center, observational retrospective study, we selected all the patients that were treated with DAAS for HCV chronic infection from the cohort of kidney transplant patients on follow-up in our transplant center at the time of the analysis.

Treatment included the use of Daclatasvir 60 mg + Sofosbuvir 400 mg in three patients, Sofosbuvir 600 mg + Velpatasvir 100 mg in two patients, and Ledipasvir 90 mg + Sofosbuvir 400 mg in two patients. The choice of the DAAS was made by the hepatologists according to their institution protocol. All patients were treated for 12 weeks. The follow-up included a clinical and laboratory evaluation after the first, third, and the sixth months. We evaluated serum creatinine, estimated glomerular filtration range (eGFR), blood urea nitrogen (BUN), 24-h proteinuria, viral load by means of HCV RNA, Alaline Amino Transferase (ALT), Aspartate Amino Transaminase (AST), total bilirubin, alkaline phosphatasis, gammaglutamiltransferasis (GGT), cyclosporine (Cya) or tacrolimus (Fk) trough levels, and the dose of Cya and Fk. Subjective side-effects (diarrhea, headache, weakness, pruritus) were evaluated by reviewing the medical records of the patients and interrogating the patients during the visit.

Statistical analysis: Comparisons were made using Student's t-test for paired samples and Wilcoxon's rank-sum test when appropriate. The noncontinuous variables were compared using the χ^2 test or Fisher's exact test as appropriate and the log rank test for survival analysis. All the tests were performed using SPSS software.

Results

We analyzed seven patients that were treated with a complete course of therapy of 12 weeks. Table 1 depicts the characteristics of the patients. The virus genotype was 1b in four patients and 1a in the other three patients, as shown in Table 2. Viremia was cleared in all patients within 8 weeks from the start of therapy with DAAs.

Blood level of Cya or Fk remained substantially stable in all the patients except in one patient for whom it was necessary to reduce the dose of Cya of 10 mg. No other dose adjustment was required in any other patient.

None of the parameters that we evaluated had a statistically significant variation, with the exception of ALT, which decreased from 38 ± 11,189 to 1500 ± 8025 (P-value: 0.02) after 12 weeks of treatment with DAAs. Renal function remained stable throughout the course of the therapy (see Table 1).

None of the patients reported symptoms related to DAA side-effects like diarrhea, headache, weakness, or pruritus.

Discussion

Our study shows that DAAs are safe and effective in kidney transplant recipients. Viremia was cleared in all treated patients, and none of the patients had to stop the course of therapy because of serious adverse effects or drug intolerance. The use of DAAs had no influence on the parameters of renal function and the blood levels of immunosuppressive drugs except in one patient, but it is hard to ascertain whether this slight dose reduction (10 mg/daily) was needed because of any interaction between DAAs and Cya. This finding is

Table 1. Patients characteristics.

Patient	Sex	Age	HCV genotype	Cause of ESKD	DAAS
1	M	70	1b	IgA GN	Daclatasvir 60 mg + Sofosbuvir 400 mg
2	F	62	1a	HCV MPGN	Daclatasvir 60 mg + Sofosbuvir 400 mg
3	M	65	1b	Unknown	Daclatasvir 60 mg + Sofosbuvir 400 mg
4	F	64	1b	ADPKD	Ledipasvir 90 mg + Sofosbuvir 400 mg
5	F	61	1a	ADPKD	Ledipasvir 90 mg + Sofosbuvir 400 mg
6	M	54	1b	Nephroangiosclerosis	Sofosbuvir 600 mg + Velpatasvir 100 mg
7	m	49	1b	Extracapillary GN	Sofosbuvir 600 mg + Velpatasvir 100 mg

IgA GN: IgA glomerulonephritis, HCV MPGN: HCV-related membranoproliferative glomerulonephritis, ADPKD: autosomal dominant polycystic kidney disease, Extracapillary GN: Extracapillary glomerulonephritis, DAAS: direct-acting antiviral drugs, HCV: Hepatitis C virus, ESKD: End Stage Kidney Disease.

Table 2. Variation of the parameters at the beginning and after 12 weeks of therapy with Direct Acting Antivirals (DAA). Parameters are expressed as means and standard deviation.

Parameter	T0	T12	P
Creatinine (mg/dL)	1.21 ± 0.2	1.32 ± 0.2	0.23
Azotemia (g/L)	0.57 ± 0.76	0.57 ± 0.076	0.46
Creatinine clearance (mL/min)	62.45 ± 16.0	57.55 ± 28.1	0.6
Alt (U/L)	38 ± 11,189	15.00 ± 8.0	0.02
Ast (U/L)	25 ± 6.5	20 ± 7.8	0.59
Bilirubin (mg/dL)	0.42 ± 0.19	0.41 ± 0.1	0.76
GGT (U/L)	59.40 ± 63.5	39.40 ± 25.5	0.39
PAL (U/L)	105.20 ± 64.5	97.00 ± 43.4	0.6
Proteinuria 24 h (g/24 h)	0.44 ± 0.3	0.43 ± 0.3	0.81
CyAlevels (ng/mL)	96.50 ± 4.9	79.00 ± 2.8	0.19
FK levels (ng/mL)	10.05 ± 1.9	8.85 ± 1.9	–
HCV RNA (Ui/mL)	2258703.23 ± 3458997.0	0	0.22
Hemoglobin (g/dL)	12,257 ± 1.1	12.47 ± 1.5	0.58

GGT: Gamma Glutamyl transferasis; PAL: alkaline phospatasis

in contrast with the literature, since different studies showed pharmacological interactions between calcineurin inhibitors and DAAs. A review by Chute et al. reported that on average, 97 of 287 patients (34%) in 10 retrospective series required calcineurin inhibitor dose adjustments during or shortly after DAA therapy (2). Colombo et al. randomized 114 adult patients at least 6 months after kidney transplantation to receive 12 or 24 weeks of Sofosbuvir + Ledipasvir 400 mg/90 mg combination therapy. They observed that 18% of patients required adjustment in immunosuppressive medications, in the absence of documented episodes of acute rejection (1). The study by Fernandez et al. reported that 55% of patients required calcineurin inhibitors (CNI) dose adjustment, 16% experienced an increase in serum creatinine by more than 25% on DAAs therapy, observing three episodes of acute humoral rejection; however, adverse events specifically attributed to this regimen were not reported (3). Morales et al. enrolled 32 renal transplant recipients treated with Sofosbuvir-Ledipasvir, and 25% of them required CNI adjustment (4). Eisenberger et al. enrolled 15 renal transplant recipients treated with Sofosbuvir-Ledipasvir, and 53% of them required CNI dose adjustment (5).

All the patients included in our study reached a sustained virologic response at 12 weeks (SRV 12), defined as an undetectable HCV RNA 12 weeks after the completion of DAAs treatment (6). Likewise, several studies of DAAs used in kidney transplant recipients reported remarkable success rates. In the MAGELLAN-2 trial, 20 kidney transplant recipients received glecaprevir-pibrentasvir, and all were cured (7). Colombo et al. obtained SVR in 100% of the patients (1). Sawinsky et al. reported SVR in 100% of the patients, while 45% required CNI adjustments; there were no episodes of rejection (8). Bhamidimarri et al. reported 25 cases of transplantation of kidneys from hepatitis C-positive donors into HCV-infected recipients, followed by early initiation of direct-acting antiviral therapy. They observed SVR in 96% of patients, 52% required CNI adjustment, and four cases of antibody-mediated rejection on DAA treatment was reported (9). Lubetzky et al. reported SVR in 97% of cases, 19% had worsening proteinuria during or shortly after therapy with DAAs, 6% had eGFR decline below 20 mL/min, and 6% required CNI adjustment (10).

We did not observe any serious adverse events related to antiviral therapy to prove that DAAs have been well tolerated in all patients included in our study. Many other studies have confirmed the safety of DAAs in renal transplant recipients. In the trial by Colombo et al., adverse events experienced by more than 10% of those receiving Sofosbuvir-Ledipasvir were headache, weakness, and fatigue (1). In the MAGELLAN-2 study, participants commonly reported fatigue (22%), headache (22%), nausea (12%), pruritus (12%), and diarrhea (10%) (7).

It is necessary to point out some limitations of our study; first of all, the number of patients enrolled is clearly too

limited to process a valid statistical analysis and obtain statistically significant results. Furthermore, the study is retrospective and not controlled, and blood and urinary values were provided by different laboratories, located in different cities. Our cohort of patients is quite heterogeneous for age and transplant age.

Of note, we observed an alteration of GGT in two patients, of whom one had a history of gallbladder hydrops, episodes of cholangitis, and hepatic cysts infections, responsible for cholestasis, and the other patient had an advanced HCV-related liver fibrosis. Moreover, in both patients, the alteration of this parameter was pre-existing to DAAs therapy, stable during therapy, and persistent after therapy discontinuation.

Conclusion

In our study, DAAs resulted in a safe and effective antiviral therapy in kidney graft recipients, and they are set to revolutionize the natural history of HCV infection in transplant patients. Our study did not detect any significant variations in the blood levels of immunosuppressants, providing reassuring results, supported also by many other studies in the literature. Larger studies with longer follow-ups are needed to verify the efficacy of DAAs in transplant recipients in the long term, in particular to understand the risk of recurrence of viremia after years of treatment, and any link with the use of a particular immunosuppressant.

References

1. 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. http://dx.doi.org/10.7326/M16-1205
2. Chute DF, Chung RT, Sise ME. Direct-acting antiviral therapy for hepatitis C virus infection in the kidney transplant recipient. Boston, MA: Department of Medicine, Gastrointestinal Unit, Massachusetts General Hospital; and Boston, MA: Department of Medicine, Division of Nephrology, Massachusetts General Hospital. 2018.
3. 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;66:718–23. http://dx.doi.org/10.1016/j.jhep.2016.12.020
4. 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). [e12941]. http://dx.doi.org/10.1111/ctr.12941
5. 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;101:980–6. http://dx.doi.org/10.1097/TP.0000000000001414
6. Ortiz GA, Trivedi HD, Nader C. Pharmacokinetics and drug interactions of medications used to treat hepatitis C virus infection in the setting of chronic kidney disease and kidney transplantation. Hemodial Int. 2018;22:S22–35. http://dx.doi.org/10.1111/hdi.12648
7. Reau N, Kwo P, Rhee S, Brown RS, Agarwal K, Angus P, et al. LBO-03-MAGELLAN-2: Safety and efficacy of glecaprevir/pibrentasvir in liver or renal transplant adults with chronic hepatitis C genotype 1–6 infection. J Hepatol. 2017;66:S90–1. http://dx.doi.org/10.1016/S0168-8278(17)30444-0
8. 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. http://dx.doi.org/10.1111/ajt.13620
9. 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. Transplant Int. 2017;30:865–73. http://dx.doi.org/10.1111/tri.12954
10. 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;101:1704–10. http://dx.doi.org/10.1097/TP.0000000000001618