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Long-Term Impact in Hepatitis C Virus Infection in Post Renal Transplantation

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ABSTRACT

Purpose: The authors have evaluated the impact of the kidney transplantation associated with chronic hepatitis C virus (HCV) infection, analyzing the complications, patients and graft survival. Methods: Retrospective study with 40 kidney transplant recipients with HCV infection and 40 kidney transplant recipients without HCV infection in the same post transplantation period. Results: The average follow-up after transplantation was 12.3 ± 4.5 years in patients with HCV infection and 12.5 ± 2.9 years in patients without HCV infection (p = 0.49). There was no statistical difference related to age and gender of the recipient nor donor age and type. The current renal function in patients with HCV infection was 47.3 ± 24.9 mL/min and 54.9 ± 27.2 mL/min in the HCV negative group (p = 0.54). The incidence of graft and patient survival was similar in both groups. The main cause of death in both groups was bacterial infection (10% in patients with HCV infection and 12.5% in HCV negative patients (p = 0.63). The most common complication in the two groups were acute allograft rejection and bacterial infection. The incidence of diabetes mellitus did not differ statistically in both groups. Abnormal liver enzymes levels and cirrhosis were observed only in patients with HCV infection. Conclusion: HCV infection did not impact patient or graft survival and post-transplant complications were similar in both groups during a mean follow-up period of 12 years.

Keywords: HCV; Kidney Transplantation; Chronic Kidney Failure

1. Introduction

The hepatitis C virus infection (HCV) is the main cause of chronic liver disease in patients with chronic kidney disease in dialysis treatment and post-transplantation. The prevalence of HCV varies according to regions and countries, ranging from 3% to 80% in patients on dialysis treatment and 10% to 41% in kidney transplant recipients [1-3].

Patients with end-stage renal disease and HCV infection in transplant waiting list show a higher mortality risk compared to those submitted to renal transplant (Tx) and this risk increases with time [3-5].

Although there were improvements in the result of the kidney transplant, some publications have shown that chronic liver disease secondary to HCV infection represents one of the main causes of morbidity and mortality in immunocompromised patients [6].

It is controversial in medical literature if HCV has detrimental effects on patients and graft survival [7-11]. The purpose of this study was to observe the impact of chronic HCV infection in renal transplant recipients, compared to matched HCV negative patients. The pre-liminary data of this study were published previously [12].

2. Methods

Forty patients with HCV infection and forty patients without HCV infection submitted to renal transplant in our institution were selected retrospectively and analyzed. The HCV positive (HCV+) patients had been submitted to liver biopsy prior to renal transplantation, and none presented active chronic hepatitis or cirrhosis. The control patients (HCV–) had also been transplanted in our institution and were selected using demographic characteristics in order to closely resemble the HCV+ patients. The following variables were analyzed: age, gender and race of the receivers, donor types, HLA profile, time of the transplantation, current kidney function, graft and patient survival, time and cause of graft loss or death, immunosuppressive drugs and complications. The presence of anti-HCV antibodies was tested before and many times after transplantation, using Elisa method of first generation, in the period from 1990 to 1992, second generation from 1992 to 1997 and third generation after that. The renal function was evaluated by the creatinine clear-

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ance through the formula of Cochroft-Gault. HCV phenotype determination was not done because this constitutes a retrospective study. The cause of the renal insufficiency could not be established in 37 patients (46.2%); 26 patients (32.5%) had chronic glomerulonephritis; five patients (12.5%) had adult polycystic kidney disease; five patients (12.5%) had hypertensive nephrosclerosis; four patients (1.0%) had chronic interstitial nephritis; two patients (0.5%) had diabetic nephropathy and one patient (0.25%) had Alport's disease.

3. Statistical Analysis

For comparison of quantitative variables the Mann-Whitney test was used. When the analysis involved qualitative variables the Qui-Square test or the accurate test of Fisher were used, with the level of significance of 5%, ($p = 0.05$). Actuarial curves of graft and patients survival were performed using the Kaplan-Meier method.

4. Results

The follow-up after transplantation was 12.3 ± 4.5 years in patients with HCV infection and 12.5 ± 2.9 years in HCV negative patients ($p = 0.49$). **Table 1** shows the demographic characteristics of both groups. There was no statistical difference related to age and gender of the recipient nor donors' age, gender and if the donor was living or deceased. The incidence of haploidentical HLA was higher in patients without HCV infection ($p = 0.05$). The current renal function in patients with HCV infection was 47.3 ± 24.9 mL/min/1.73m^2 and 54.9 ± 27.2 mL/min/1.73 m^2 in the HCV negative group ($p = 0.48$). Time, measured in months, until the graft loss was 36.1 ± 3.1 in patients with HCV infection and 47.7 ± 40.6 in the HCV negative group ($p = 0.67$). Death was the main cause of graft loss in both groups (HCV+: 14 patients, HCV–: 13 patients), followed by interstitial fibrosis/tubular atrophy (IFTA) which was more commun in HCV negative patients (30.0% versus 15.5%) ($p = 0.03$) (**Table 2**). Patient survival was 65% in patients with HCV infection and 67.5% in HCV negative patients ($p = 0.545$) (**Figure 1**) and patients with HCV infection died earlier (18.0 ± 30.2 months × 49.8 ± 58.7 months, $p = 0.03$). Graft survival was similar in both groups, 30% in HCV positive patients and 40% in patients without HCV infection ($p = 0.24$) (**Figure 2**).

The main cause of death in both groups was bacterial infection: 10.0% in patients with HCV infection and 12.5% in the HCV negative group ($p = 0.63$) (**Table 3**). There was no statistical difference related to immunosuppressive therapy in both groups ($p = 0.87$), predominating the following protocol: cyclosporine (CSA), azathioprine (AZA) and prednisone (PRED) (**Table 4**).

The initial immunosuppressive therapy dose in both groups was similar and consisted of CSA (8 mg/kg/day), TAC (0.2 mg/kg/day), AZA (2 mg/kg/day), mycophenolate mofetil (MMF) (2.0 g/day), PRED (0.5 mg/kg/day). **Table 5** shows the immunosuppressive treatment dose in both groups at the time of final analysis. Steroid withdrawal was not performed.

Table 1. Dem ographic profile and major outcomes.

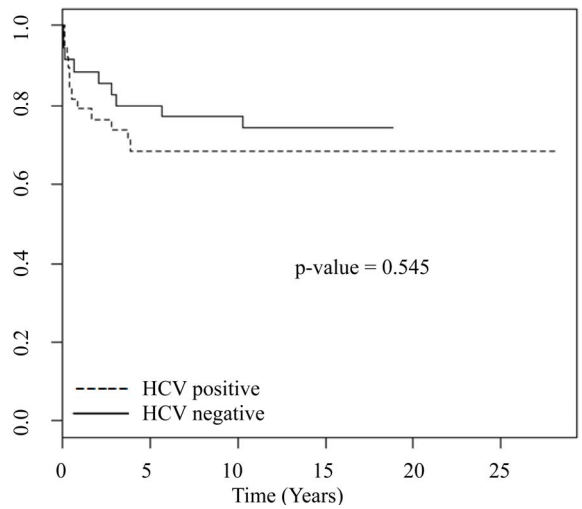
	HCV+	HCV–	p-value
Age (recipient)	37.3 ± 17.3	32.8 ± 12.4	0.09
Age (donor)	32.0 ± 10.3	33.8 ± 12.5	0.4
Gender (M, F)	31/10	27/13	0.31
Race (W, MU, BL)	28/6/6	38/1/1	0.08
Type of donor (RLD, NRLD, DD)	17/1/22	2/23/2015	0.11
HLA (HD, HI, I, NA)	3/8/0/29	4/16/2/18	0.05
Follow-up (years)	12.3 ± 4.5	12.5 ± 2.9	0.49
Current creatinine clearence (mL/min/1.73cm^2)	47.3 ± 24.9	54.9 ± 27.2	0.48
Graft loss	28 (70%)	34 (85%)	0.48
Death	14 (35%)	13 (32.5%)	0.22

M = Male; F = Female; W = White; MU = Mulatto; BL = Black; RLD = Related living donor; DD = Deceased donor; HD = Haplo different; HI = Haplo identical; I = Identical; NA = Not analyzed.

Table 2. Causes and time until graft loss.

	HCV+	HCV–	p-value
Time until graft loss (months)	36.1 ± 3.1	47.7 ± 40.6	0.67
Cause of graft loss—death	14 (35%)	13 (32.5%)	1.00
Cause of graft loss—IFTA	6 (15.02)	12 (30.0%)	0.03
Cause of graft loss—others	21 (52.5%)	15 (37.5%)	0.04

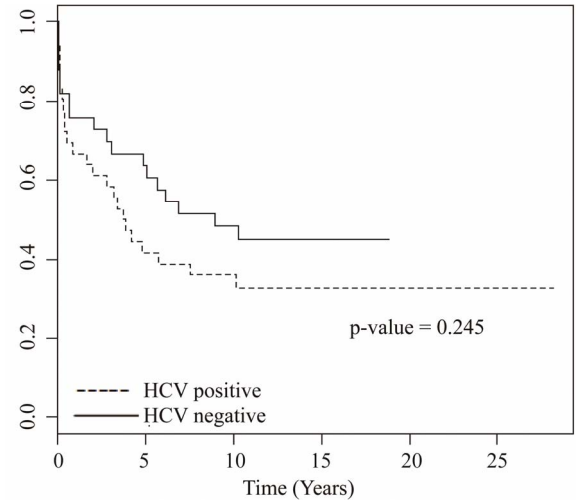
IFTA = Intersticial fibrosis tubular atrophy.



Patients at risk

	Year 1	Year 5	Year 12
HCV–	37	32	27
HCV+	31	26	26

Figure 1. Patient survival.



Patients at risk

	Year 1	Year 5	Year 12
HCV–	31	24	18
HCV+	26	16	13

Figure 2. Graft survival.

Table 3. Time until death and its causes.

	HCV+	HCV–	p
Time until death (months)	18.0 ± 30.2	49.8 ± 58.7	0.03
Death cause—bacterial infections	5	4	0.63
Death cause—lung cancer	1	0	-
Death cause—pulmonary hemorrhage	0	1	-
Death cause—retroperitoneal hemorhage	1	0	-
Death cause—lymphoma	1	0	-
Death cause—others	2	2	-
Death cause—undetermined	4	6	-

Table 4. Immunosuppressive therapy.

Type	HCV+	HCV–	p-value
CSA + AZA + PRED	29 (72.5%)	28 (70.0%)	0.87
CSA + AZA + PRED + OKT3	5 (12.5%)	7 (17.5)	0.4
CSA + AZA + PRED + BAS	1 (2.5%)	1 (2.5%)	1.0
CSA + MMF + PRED	3 (7.5%)	2 (5.0%)	0.85
CSA + SRL + PRED	1 (2.5%)	1 (2.5%)	1.0
TAC + MMF + PRED	1 (2.5%)	1 (2.5%)	1.0

CSA = Cyclosporine; AZA = Azathioprine; OKT3 = Orthoclone; BAS = Basiliximab; SRL = Sirolimus; TAC = Tacrolimus; PRED = Prednisone.

Table 5. Maintenance dose of immunosuppressive agents in HCV+ and HCV– patients.

Immunosuppressor	HCV	Mean	Standard deviation	p-value
CSA	–	2.65	0.32	0.00
	+	2.10	0.14	
AZA	–	1.25	0.23	0.00
	+	0.77	0.14	
TAC	–	0.035	0.02	0.77
	+	0.036	0.01	
PRED	–	0.09	0.04	0.48
	+	0.085	0.02	
MMF	–	15.4	12.1	0.62
	+	16.8	13.2	

The incidence of acute rejection was 35% in the HCV positive group and 25% in patients without HCV in-fection (p = 0.26) and the most common complication in both groups was acute cellular rejection and bacterial infection. The incidence of new onset diabetes mellitus did not differ statistically. Abnormal levels of liver enzymes (AST, ALT and GGT) and cirrhosis were observed only in patients with HCV infection (**Table 6**).

5. Discussion

The natural history of the HCV hepatitis in post-renal transplantation has not been well established. Some authors believe that the immunosuppressive therapy facilitates the viral proliferation and aggravates the liver disease [13,14]. However, an increase in viremia may not be associated with a higher risk of liver disease after the renal transplant [6,15,16]. According to the literature, the poorer outcomes after kidney transplantation in patients with HCV infection are mainly due to liver disease and bacterial infection [7,13,14,17]. In the long-term, death has been attributed to complications of chronic liver disease in 8% to 28% of the cases [1,5]. In the present study, the main cause of death in both groups was bacterial infection. In the HCV positive group, only one patient had liver cirrhosis and in three individuals abnormal liver enzymes levels were detected. Several publications with longer follow-ups have demonstrated that mortality was significantly higher in HCV positive patients [9,18]. In this study, patients survival in both groups was similar, but death occurred earlier in patients with HCV infection. However, one must take into account the small sample size which is a limitation of the present study.

Graft survival was similar in both groups, which is in accordance with some publications in literature [14, 19-22]. If patients with HCV infection have a greater risk of the acute cellular rejection is controversial, with some publications showing a higher incidence of rejection in patients with HCV infection when compared to a HCV-negative control group [13,23,24,27]. In the present study, however there was no statistical difference in the incidence of the acute allograft rejection comparing both

Table 6. Post-transplant complications.

Type	HCV+	HCV–	p-value
Acute rejection	14 (35.0%)	10 (25.0%)	0.36
Bacterial infections	9 (22.5%)	10 (25.0%)	0.79
Acute tubular necrosis	9 (22.5%)	6 (15.0%)	0.39
Nephrotoxicity od CSA	6 (15.0%)	6 (15.0%)	1.00
Cytomegalovirus	3 (7.5%)	1 (2.5%)	0.61
Abnormal levels of liver enzymes	2 (5.0%)	0	0.47
NODAT	5 (12.5%)	1 (2.5%)	0.2
Cirrhosis	1 (2.5%)	0	0.00

groups. The prevalence of new onset diabetes mellitus in the present study was low and without statistical differences between the groups, in contrast with other studies that report a greater risk of this condition in HCV positive patients [25,26,28]. Cyclosporine was the main calcineurin-inhibitor used and in this study, and is reportedly less diabetogenic than tacrolimus, expecially in patients with HCV infection [29]. This could also explain the low incidence of complications in HCV positive patients. Ony two patients received tacrolimus, a potentially diabetogenic drug specially in patients with HCV infection.

6. Conclusion

This study showed that the HCV infection did not impact on patient or graft survival in this non-concurrent cohort. The small sample size limits firm conclusions of the real burden of HCV infection on the renal transplant population. Post-transplant complications (bacterial infection, acute allograft rejection and chronic liver disease) were similar in both groups.

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