

Renal transplantation in patients with hepatitis C virus antibody. A long national experience

Jose María Morales¹, Roberto Marcén², Amado Andres¹, Beatriz Domínguez-Gil³, Josep María Campistol⁴, Roberto Gallego⁵, Alex Gutierrez⁶, Miguel Angel Gentil⁷, Federico Oppenheimer⁴, María Luz Samaniego⁸, Jorge Muñoz-Robles⁹ and Daniel Serón¹⁰

¹Hospital 12 de Octubre, Madrid, Spain, ²Hospital Ramon y Cajal, Madrid, Spain, ³Organización Nacional de Trasplantes, Madrid, Spain, ⁴Hospital Clinic, Barcelona, Spain, ⁵Hospital Dr Negrin, Las Palmas, Spain, ⁶Hospital Miguel Servet, Zaragoza, Spain, ⁷Hospital Virgen del Rocío, Sevilla, Spain, ⁸Statistical Department of Pfizer, Madrid, Spain, ⁹Medical Department of Pfizer, Madrid, Spain and ¹⁰Hospital Vall d' Hebrón, Barcelona, Spain

Correspondence and offprint requests to: Jose M. Morales; E-mail: jmorales@h120.es

Abstract

Background. Renal transplantation is the best therapy for patients with hepatitis C virus (HCV) infection with end-stage renal disease. Patient and graft survival are lower in the long term compared with HCV-negative patients. The current study evaluated the results of renal transplantation in Spain in a long period (1990–2002), focusing on graft failure.

Methods. Data on the Spanish Chronic Allograft Nephropathy Study Group including 4304 renal transplant recipients, 587 of them with HCV antibody, were used to estimate graft and patient survival at 4 years with multivariate Cox models.

Results. Among recipients alive with graft function 1 year post-transplant, the 4-year graft survival was 92.8% in the whole group; this was significantly better in HCV-negative vs HCV-positive patients (94.4% vs 89.5%, $P < 0.005$). Notably, HCV patients showed more acute rejection, a higher degree of proteinuria accompanied by a diminution of renal function, more graft biopsies and lesions of *de novo* glomerulonephritis and transplant glomerulopathy. Serum creatinine and proteinuria at 1 year, acute rejection, HCV positivity and systolic blood pressure were independent risk factors for graft loss. Patient survival was 96.3% in the whole group, showing a significant difference between HCV-negative vs HCV-positive patients (96.6% vs 94.5%, $P < 0.05$). Serum creatinine and diastolic blood pressure at 1 year, HCV positivity and recipient age were independent risk factors for patient death.

Conclusions. Renal transplantation is an effective therapy for HCV-positive patients with good survival but inferior than results obtained in HCV-negative patients in the short term. Notably, HCV-associated renal damage appears early with proteinuria, elevated serum creatinine showing chronic allograft nephropathy, transplant glomerulopathy and, less frequently, HCV-associated *de*

novo glomerulonephritis. We suggest that HCV infection should be recognized as a true risk factor for graft failure, and preventive measures could include pre-transplant therapy with interferon.

Keywords: hepatitis C; proteinuria; renal function; renal transplantation

Introduction

Renal transplantation is the best therapeutic option for hepatitis C virus-positive (HCV) patients with end-stage renal disease [1,2]. However, graft and patient survival are lower in most series comparing with patients without HCV infection [3–5]. In fact, HCV infection is an independent risk factor for mortality, and also for graft loss [5,6]. In this way, although the presence of HCV-related post-transplant complications such as glomerulonephritis and diabetes can contribute to graft loss, why HCV infection negatively influences graft survival is unknown. In spite of these, results after renal transplantation in HCV patients are better than those obtained in HCV patients in the waiting list [1,3].

We previously published the influence of HCV infection on late graft loss in Spain including the period 1990–98, demonstrating that HCV infection was an independent risk factor for graft loss and mortality [5]. In this way, the decreasing incidence of the prevalence of HCV infection was an important factor together with the low incidence of acute rejection to improve the results from 1990 to 1998 in our country. Now, we extended the data of chronic allograft study to include the year 2002 that represents a time with modern immunosuppression. We analysed the results of renal transplantation in HCV patients during the period 1990–2002 focusing on graft loss and their causes. We also compared two periods, 1990–94 vs 1998–2002.

Materials and methods

Sources of data

The data on recipients were collected from individual transplant centres participating in the Spanish Chronic Allograft Nephropathy Study Group, which comprised 34 out of 38 adult kidney transplant centres in Spain and 96% of all adult kidney transplant recipients in Spain who were alive with a functioning graft at 1 year post-transplant, during the studied years (1990, 1994, 1998 and 2002).

Study population

According to the Spanish National Transplant Organization (ONT), total cases of transplanted patients in the years 1990, 1994, 1998 and 2002 were 6901 (source: www.ont.msc.es), of which 5060 (73.3% of total) transplants were included by the 34 centres participating in the study. The inclusion criteria were to be recipients of a single organ with a functioning graft at 1 year post-transplant and more than 2 years of follow-up. We found 89 (1.8%) patients younger than 18 years. Furthermore, 91 (1.8%) cases were excluded for having an inferior graft survival at 1 year. Eighty-six (1.7%) patients were not included because no data were available for monitoring, and therefore, the total number of patients analysed was 4842 (95.7%).

Distribution of patients according to the serology for hepatitis C and B virus was the following: 97.5% of patients ($n = 4304$) did not have hepatitis B virus, of which 13.6% ($n = 587$) presented HCV+ and the remaining 86.4% ($n = 3717$) HCV-.

Methods

For the following analysis, we have taken into account all evaluable patients not showing HBV+ ($n = 4304$), disaggregated by the year of transplantation: 1990–94 ($n = 1659$, 38.5%) vs. 1998–2002 ($n = 2645$, 61.5%). To avoid the need to adjust survival per year of transplant, given that monitoring of patients is significantly higher in those transplanted between 1990 and 1994 than in those transplanted between 1998 and 2002 (and as its follow-up varies from 16–12 years to 8–4 years, respectively), graft and patient survival were examined during the first 4 years after transplantation. Thus, patients whose graft or patient survival was more than 4 years were only assessed until the fourth year after transplantation.

Definitions

The glomerular filtration rate (GFR) was estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation: $eGFR$ (mL/min/1.73 m²) = $\exp(5.228 - 1.154 \times \ln(\text{SCr}) - 0.203 \times \ln(\text{age}) - (0.299 \text{ if female}) + (0.192 \text{ if black}))$. Induction was considered whether the immunosuppressive was ALG/ATG or OKT3 or anti-IL-2R.

HCV infection was defined by the presence of HCV antibody (ELISA2/3).

Statistical analysis

Statistical treatment of data was done with the support of SPSS version 17.0. Continuous variables were described using measures of central tendency (mean, median) and measure of dispersion (standard deviation, minimum and maximum). Categorical variables were described as absolute and relative frequency.

The survival function was evaluated by Kaplan–Meier, Cox regression and log-rank test, to study graft and patient survival, as well as the association between graft and patient survival and the presence of HCV+ or the cohort (transplanted in 1990–94 or 1998–2002).

Results

Donor and recipient characteristics

Mean donor age was 42.39 ± 16.9 (range 12–86) years that was significantly higher in HCV-negative 42.77 ± 16.9 than HCV-positive patients 39.98 ± 16.31 years ($P < 0.001$). Donor age significantly increased in the period

1998–2002, 45.35 ± 16.81 vs 37.56 ± 15.9 in 1990–94 ($P < 0.001$) in all patients and separated in HCV+ and HCV- patients.

Mean recipient age was 46.6 ± 13.27 (range 18–78) years; this also was significantly higher in HCV-negative 46.8 ± 13.3 years than HCV-positive patients 45.2 ± 12.8 years ($P < 0.005$). Recipient age increased significantly in the period 1998–2002, 48.21 ± 13.4 vs 44.1 ± 12.6 years in 1990–94 ($P < 0.001$) in all patients and separately in HCV+ and HCV- patients.

Gender was 62.2% males and 37.8 females without differences according to HCV status.

Re-transplantation was more frequent in 1998–2002 than 1990–94 (13.2% vs 10.6%, $P < 0.05$). In the subpopulation of HCV+ patients, the frequency of re-transplants was higher than HCV- patients (32.4% vs 9%, $P < 0.001$) and notably was significantly higher in the modern period (51.2% vs 21.8%, $P < 0.001$) in HCV-positive patients.

Pre-transplant panel-reactive antibodies (PRA) were significantly higher in HCV+ than HCV-negative patients (7.54 vs 3.79, $P < 0.01$), and the subpopulation of HCV-positive PRA was higher in those transplanted in 1998–2002 (10.68% vs 5.83%, $P < 0.01$). The percentage of patients with PRA >50% was higher in the HCV+ group (4.4% vs 2%, $P < 0.05$).

Time on dialysis was higher in HCV+ patients (6.86 ± 5.3 vs 2.64 ± 2.89 year, $P < 0.001$) and in those transplanted in 1998–2002 HCV+ (8.4 ± 5.9 vs 5.9 ± 4.3 year, $P < 0.001$) but not in the HCV- subpopulation.

HLA mismatching DR and B was higher in the modern era: 38.6% vs 29.1% ($P < 0.001$) had two incompatibilities in the HLA-B, and 11.3% vs 4.4% ($P < 0.001$) had two mismatches in HLA-DR. In the subpopulation of HCV, the same happened with the locus DR.

The percentage of pre-transplant diabetes was low in the whole group (5.5%), showing a higher frequency in HCV-negative vs HCV-positive patients (5.9% vs 3.4%, $P < 0.05$). Interestingly, pre-transplant diabetes was higher in the modern era in HCV-negative (6.8% vs 4.1%, $P < 0.001$) and HCV-positive patients comparing with the 1990–94 period (6.3% vs 1.7%, $P < 0.001$).

Immunosuppression

Induction therapy was more frequent in HCV+ patients (39.8% vs 34.1%, $P < 0.05$). ALG/ATG was preferentially used in 63% of them. Cyclosporine was used in 71.2%, MMF in 49%, and tacrolimus in 25% without differences in HCV subpopulations. However, cyclosporine was more used in HCV-positive patients (81.3% vs 69.5%, $P < 0.005$).

Prevalence of HCV infection was decreasing progressively from 27.7% in 1990 to 5.9% in 1998 ($P < 0.001$), as we demonstrated in the previous analysis [5].

Delayed graft function, acute rejection, renal function and proteinuria

Delayed graft function was higher in HCV-positive patients 38.5% vs 29.4%, $P < 0.001$, but with no difference between periods.

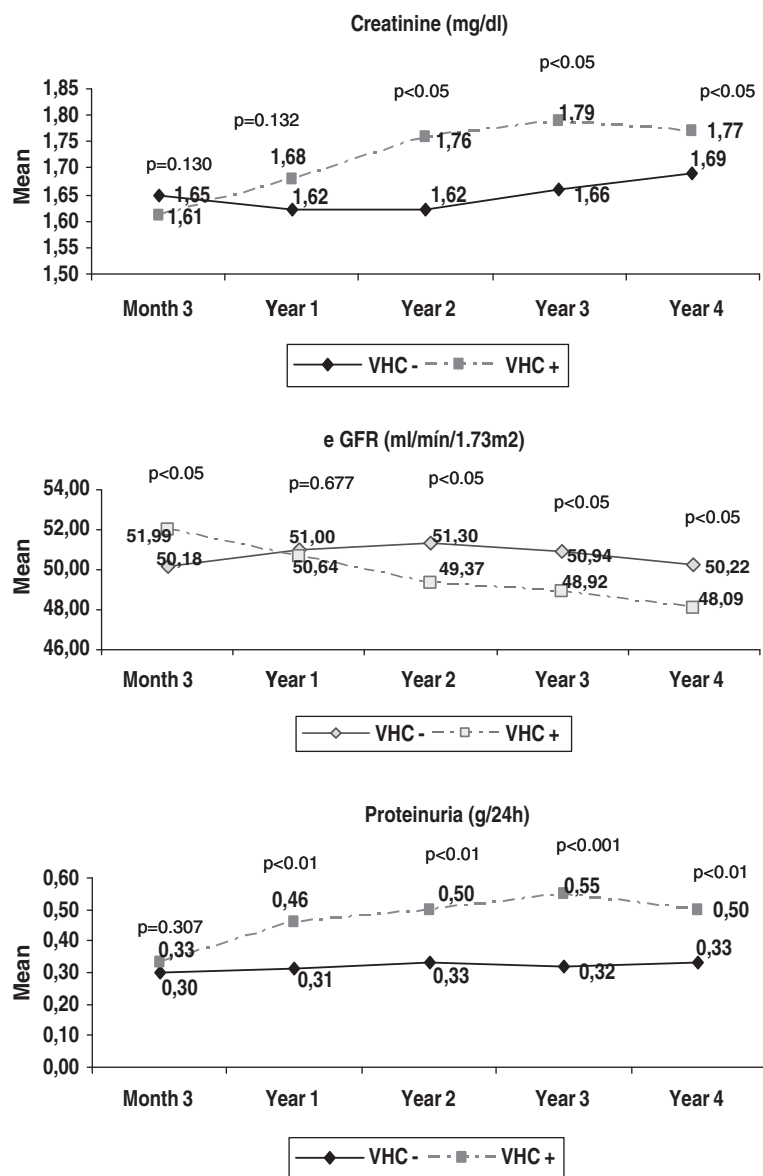


Fig. 1. Renal function and proteinuria.

Acute rejection was more frequent in HCV+ patients 32.5% vs 27.3%, $P < 0.01$. Patients transplanted in 1990–94 suffered more acute rejection episodes than those transplanted in the modern era (39.1% vs 21%, $P < 0.001$), as well as in the two subpopulations HCV negative (39.8% vs 20.6%, $P < 0.001$) and HCV positive (36.6% vs 25.2%, $P < 0.01$). It is interesting to note that acute rejection in HCV patients was higher than HCV-negative patients in the modern era (25% vs 20.6%, $P < 0.01$). The majority of acute rejection episodes were in the first year (84.6%).

Mean values of eGFR were lower in HCV+ vs HCV- patients from the second year post-transplant. From the first year, there was a much better GFR in the whole group transplanted in the period 1998–2002, including both HCV+ and HCV- patients. Serum creatinine (SCr) showed higher mean values in HCV+ vs HCV- patients from the second

year post-transplant. From the first year, SCr was lower in the whole group transplanted in the modern era, including both HCV+ and HCV- patients.

Mean values of proteinuria were higher from the first year in HCV+ vs HCV- patients. Proteinuria was lower in the whole group of patients transplanted in the modern era, but only in the second and in the third years post-transplant (see evolution of eGFR, creatinine and proteinuria in Figure 1).

Interestingly, the percentage of patients with at least one graft biopsy during these 4 years was higher in HCV+ versus HCV- group: 34.6% vs 25%, $P < 0.05$. The indications of biopsy were worsening of renal function and/or proteinuria in both groups of patients. Transplant glomerulopathy and *de novo* glomerulonephritis were more frequent in HCV patients (Table 1).

Table 1. Pathological lesions of graft biopsies

Diagnosis	HCV(-) n = 463	HCV(+) n = 140	ALL n = 603
Transplant glomerulopathy	23 (5.0%)	16 (11.4%)	39 (6.5%)
<i>De novo</i> GN	24 (5.2%)	13 (9.3%)	37(6.1%)
Normal	22 (4.8%)	2 (1.4%)	24 (4.0%)
CAN Ia	65 (14.0%)	16 (11.4%)	81 (13.4%)
CAN Ib	43 (9.3%)	5 (3.6%)	48 (8.0%)
CAN IIa	60 (13.0%)	21 (15.0%)	81 (13.4%)
CAN IIb	52 (11.2%)	18 (12.9%)	70 (11.6%)
CAN IIIa	27 (5.8%)	8 (5.7%)	35 (5.8%)
CAN IIIb	17 (3.7%)	5 (3.6%)	22 (3.6%)
Others	57 (12.3%)	12 (8.6%)	69 (11.4%)
Acute rejection	35 (7.6%)	15 (10.7%)	50 (8.3%)
Recurrent disease	38 (8.2%)	9 (6.4%)	47 (7.8%)
	<i>P</i> < 0.05		

GN, glomerulonephritis; CAN, chronic allograft nephropathy.

Graft survival

Graft loss during the 4 years of follow-up was 7.2%, but significantly higher in HCV+ vs HCV- patients: 12.1% vs 6.4%, *P* < 0.001. Therefore, graft survival was 92.8% across the whole group. There were no differences in graft survival in HCV+ patients comparing the period 1990–94 vs 1998–2002: 87.5% vs 93%, *P* = 0.084. However, in HCV- patients, graft survival was significantly better in the modern period: 95.3% vs 92.9%, *P* < 0.005. Causes of graft loss are displayed in Table 2.

In the univariate analysis: donor age, recipient age, acute rejection, HCV positivity, cohort (year of transplantation), pre-transplant PRA, acute tubular necrosis, post-transplant diabetes at 1 year, therapy with steroids, induction, tacrolimus, cyclosporine, anti-IL2 R, value of proteinuria, serum creatinine, eGFR, total cholesterol, systolic (SBP) and diastolic blood pressure (DBP), and body weight were statistical significant factors for graft survival. These factors

Table 2. Causes of graft loss and Cox regression analysis for graft loss

Causes of graft loss at the fourth year after renal transplantation			
	HCV(-) n = 227	HCV(+) n = 70	All n = 297
Biopsy-proven CAN	61 (30%)	22 (34.4%)	83 (30%)
No biopsy-proven CAN	68 (33.5%)	20 (31.3%)	88 (33%)
Death with functioning graft	10 (4.9%)	3 (4.7%)	13 (4.9%)
<i>De novo</i> glomerulonephritis	6 (3%)	4 (6.3%)	10 (3.7%)
Late acute rejection	13 (6.4%)	6 (9.4%)	19 (7.1%)
Recurrent original disease	16(7.9%)	4 (6.3%)	20 (7.5%)
Non-compliance	9 (4.4%)	0 (0)	9 (3.4%)
Others	20 (9.9%)	5 (2.8%)	25 (9.4%)
	<i>P</i> = NS		
Cox-regression analysis: factors for graft failure.			
	<i>P</i> -value	OR	CI 95% OR Low-high
Serum creatinine at 1 year	<0.001	1.937	1.563–2.401
Proteinuria at 1 year	<0.001	1.360	1.272–1.454
SBP at 1 year	<0.01	1.013	1.005–1.021
Body weight at 1 year	<0.001	0.974	0.961–0.987
GFR at 1 year	<0.001	0.969	0.952–0.987
Acute rejection	<0.05	1.439	1.031–2.009
Recipient age	<0.01	0.982	0.970–0.995
Hepatitis C antibody	<0.001	1.702	1.264–2.291
Transplantation 1998–2002	<0.01	0.676	0.525–0.871

were introduced in the Cox regression model analysis showing that only serum creatinine and proteinuria at 1 year, acute rejection, HCV positivity, and SBP were independent risk factors for graft loss, while body weight, GFR, recipient age and year of transplantation were protective factors for the graft (Table 2).

Patient survival

During the first 4 years of follow-up, 4.3% of the whole group died, showing a decrease of death in the modern era: 3.7% vs 5.2%, *P* < 0.05. Mortality was higher in HCV+ vs HCV-: 6.1% vs 4%, *P* < 0.05, but there was no difference in both periods: 1990–94 6.4% vs 5.7% (*P* = NS) in 1998–2002.

Patient survival in the whole group was 96.3% showing a significant difference between HCV-negative and HCV-positive patients: 96.6% vs 94.5%, *P* < 0.05. Causes of death are represented in Table 3. Ages of the patients who died were higher in both groups, HCV+ and HCV-, in the period 1998–2002.

In the univariate analysis, donor age, recipient age, acute rejection, HCV+, proteinuria, serum creatinine, GFR, SBP, DBP and treatment with steroids were associated factors with mortality. Cox regression analysis including all significant data in the univariate demonstrated that serum creatinine and SBP at 1 year, HCV+ and recipient age were independent risk factors for patient death (Table 3).

Discussion

In the present national study performed in Spain, we show the results of renal transplantation in patients with hepatitis C antibody compared with patients HCV- in the period 1990–2002. At 4 years after transplantation, graft and patient survival were lower than HCV-negative patients, and

Table 3. Causes of mortality and Cox regression analysis for patient death

Causes of death at the fourth year after renal transplantation			
	HCV(-) n = 149	HCV(+) n = 36	All n = 185
Heart disease	32 (25.4%)	11(59.3%)	43 (27.9%)
Neoplasia	30 (23.8%)	1 (3.6%)	28 (18.2%)
Infection	27 (4.4%)	6 (4.4%)	36 (23.4%)
Liver disease	1 (0.8%)	2 (7.1%)	3 (1.9%)
Others	36 (28.6%)	8 (28.6%)	44 (28.6%)
	<i>P</i> < 0.05		

Risk factors for mortality at the fourth year after renal transplantation: Cox regression analysis			
	<i>P</i> -value	OR	CI 95% OR Low-high
Serum creatinine at 1 year	<0.001	1.905	1.573–2.306
Diastolic blood pressure	<0.05	1.016	1.000–1.032
Hepatitis C antibody	<0.05	1.684	1.110–2.557
Recipient age	<0.001	1.064	1.048–1.081

remarkably, HCV+ patients exhibited a greater degree of proteinuria and lower renal function from the first post-transplant year. Comparison among the two periods showed no difference in survival figures or renal function and/or proteinuria in the two cohorts of HCV-positive patients. Fortunately, the prevalence of HCV infection in our patients is decreasing progressively.

Graft survival at 4 years was lower in HCV patients, and HCV infection was an independent risk factor for graft loss at short time after transplantation. This is an interesting finding because, in most series, graft survival is lower in the long term [3,4,6]. In addition, proteinuria was higher, and renal function was lower after the first year, which explains why these patients were biopsied more frequently than HCV-negative patients. Also, the presence of HCV-associated GN and transplant glomerulopathy were more frequent in HCV patients. In this way, we showed that HCV infection seems to be a risk factor for transplant glomerulopathy as has been recently described by the group of the Mayo Clinic in protocol biopsies [7]. In addition, acute tubular necrosis and acute rejection rate were more frequent in HCV patients; particularly, acute rejection was higher in the modern era. This incidence of acute rejection could be explained because hyperimmunized and re-transplants were more frequent in the HCV+ population [8], because in low risk patients, the presence of acute rejection is lower compared with HCV-negative patients [9]. These factors, acute rejection, hyperimmunization and re-transplantation are risk factors for chronic rejection and transplant glomerulopathy. Therefore, it is reasonable to think that HCV-positive patients could have an increased risk for chronic humoral rejection and graft failure.

The presence of proteinuria is important because it is well known that HCV infection is an independent risk factor for proteinuria [5,10]. We demonstrated that proteinuria is higher than in the HCV- population, and accompanied by a concomitant diminution of renal function after the first

year. These factors *per se* are risk factors for allograft failure [5,6] and clinically represent the early damage of the allograft, mainly by chronic allograft nephropathy. So, in protocol biopsies at 6 months, HCV infection was an independent risk factor for graft loss [11] and for transplant glomerulopathy [7]. Our data demonstrated that HCV infection is associated with early greater rates of proteinuria, lower renal function, chronic rejection, *de novo* GN and graft loss. Therefore, HCV infection may be included as a true risk factor for graft loss and chronic allograft nephropathy/chronic rejection. In this way, pre-transplant treatment with interferon could decrease the incidence of chronic allograft nephropathy [12].

Patient survival at 4 years in the whole group transplanted in 1990–2002 is excellent. As expected, patient survival was lower in HCV+ patients compared with HCV negative, but in spite of this mortality can be considered low taking into consideration the presence of the chronic condition of HCV infection. The most important series demonstrated that, in the short term, patient survival is similar to non-infected renal transplant patients, and in the long term, mortality is higher in HCV+ patients [3,6,13,14]. Notably, in our series, mortality is earlier and more elevated at 4 years, very similar to recently published American findings [15]. In patients transplanted in the modern era, mortality was a little bit lower than in 1990–94 but without statistical differences. Cardiovascular, infections and neoplasia were the most frequent causes of death in our patients, and liver disease was higher in HCV+. Cox regression analysis showed that, once again, HCV+ was an independent risk factor for mortality at 4 years together with recipient age, Scr and DBP at 1 year. Therefore, a good blood pressure control and an improvement of renal function are mandatory to improve this early mortality. In these patients, the presence of post-transplant diabetes, proteinuria and a lower renal function are cardiovascular risk factors that could explain why heart disease is the first cause of death. Also, the longer time on dialysis and the presence of arterial hypertension could also contribute.

The main limitation of this study was that we have no information of HCV RNA at transplantation and in the follow-up. Also, there is no information about liver enzyme values or liver biopsy. Therefore, because we do not know how many patients had viraemia and if they had liver fibrosis, we cannot demonstrate the role of liver disease in survival figures [16]. In spite of this, our work is the longest numerically and in follow-up in renal transplant patients showing the role of HCV infection on early graft failure.

In summary, renal transplantation is an effective therapy for patients with HCV infection, with survival figures that are good but inferior to those obtained in HCV-negative patients in the short term. Notably, HCV-associated renal damage appears early with proteinuria and elevated serum creatinine showing chronic allograft nephropathy, transplant glomerulopathy and less frequently HCV-associated *de novo* GN. We suggest that HCV infection should be recognized as a true risk factor for graft failure, and preventive measures could include pre-transplant therapy with interferon in viraemic patients [17].

Conflict of interest statement. None declared.

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