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The impact of hepatitis C virus infection on long-term outcome in renal transplant patients

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Background/aims: *The aim of this study was to determine the effect of hepatitis C virus infection on patient and graft survival and liver function in renal transplant patients.* ***Methods:*** *1811 renal transplant patients were included in this study. One hundred renal transplant patients (5.5%) were anti-hepatitis C virus-positive. We evaluated demographic, clinical, biochemical, and serological data of patients and compared patient and graft survivals between hepatitis C virus-positive and -negative renal transplant patients.* ***Results:*** *The median follow-up period was 35.7 months. One hundred (5.5%) patients were anti-hepatitis C virus- positive. There were no differences between anti-hepatitis C virus-positive and -negative renal transplant patients regarding age, etiology of renal disease, number of pre-transplant blood transfusions, and hepatitis B virus coinfection rate. Rate of graft loss in anti-hepatitis C virus-positive renal transplant patients was significantly higher than in anti-hepatitis C virus-negative patients (16.0% vs. 9.2%, p=0.026). Survival analysis revealed that patient survival was similar between anti-hepatitis C virus-positive and -negative renal transplant patients. Graft survival was lower in the anti-hepatitis C virus-positive group than in anti-hepatitis C virus- negative patients, especially after the fifth year of renal transplant (p<0.001). Thirty-three percent of anti-hepatitis C virus-positive patients were positive for hepatitis C virus RNA. Twenty-seven percent of anti-hepatitis C virus-positive patients had persistent alanine aminotransferase elevation. None of the patients developed cirrhosis during the follow-up period.* ***Conclusion:*** *Our findings suggest that hepatitis C virus infection in renal transplant patients does not adversely affect patient survival. Long-term graft survival seems to be lower in hepatitis C virus-positive compared to hepatitis C virus-negative renal transplant patients. Nevertheless, renal transplant can be considered as a safe and effective treatment modality in anti-hepatitis C virus-positive patients with end-stage renal disease.*

Key words: End-stage renal disease, hepatitis C virus infection, long-term survival, renal transplantation

Böbrek transplantasyonu yapılmış hastalarda HCV infeksiyonunun uzun dönem sonuçları

Amaç: *Bu çalışmada, böbrek transplantasyonu yapılmış hastalarda hepatit C virusu infeksiyonunun hasta ve graft sağkalımına, graft işlevine ve karaciğer hastalığına olan uzun dönem etkileri değerlendirilmiştir.* ***Yöntem:*** *Çalışma, 1 Ocak 1999 ile 31 Aralık 2009 tarihleri arasında merkezimizde böbrek transplantasyonu yapılmış 1811 hasta üzerinde yürütülmüştür. Hastaların tıbbi kayıtlarının retrospektif analizi yapılmıştır.* ***Bulgular:*** *Hastaların 100 ünde (%5.5) hepatit C virusu antikor pozitifliği saptanmıştır. Hepatit C virusu antikoru pozitif olan (n:100) ve olmayan (n:1711) hastaların demografik, klinik, biyokimyasal ve tedaviye ilişkin özellikleri karşılaştırılmış ve sağkalım analizleri yapılmıştır. Hastaların median izlem süresi 35,7 ay (%25-%75 lik aralık:18,8-63,9 ay) idi. Hepatit C virusu antikoru pozitif olan grupta kadın oranı (%42'ye karşın %32,1, p=0.031) daha yüksek, pretransplant diyaliz modalitesi ise ağırlıklı olarak hemodiyalizdi (p<0.001). Bu hastalarda total diyaliz süresi belirgin şekilde daha uzun bulundu (p<0.001). Hepatit C virusu antikoru pozitif ve negatif olan grup arasında yaş, böbrek yetmezliği etyolojisi ve hepatit B virusu ko-infeksiyonu açısından fark yoktu. Hepatit C virusu antikoru pozitif olan grupta graft kaybı oranı daha yüksekti (%16'ya karşın %9,2 p=0.026). Kaplan Meier sağkalım analizinde iki grup arasında hasta sağkalımları benzer olmasına karşın graft sağkalımının 5. yıldan sonra düşme eğiliminde (p<0.001) olduğu saptandı. Hepatit C virusu antikoru pozitif hastaların %33'ünde posttransplant dönemde hepatit C virusu RNA pozitif bulunurken %27'sinde persistan alanin aminotransferaz yüksekliği vardı. İzlem süresi içinde hiç bir hastada klinik olarak siroz saptanmadı.* ***Sonuç:*** *Bulgularımız, böbrek transplantasyonu hastalarında hepatit C virusu infeksiyonunun uzun dönemde hasta sağkalımını olumsuz etkilemediğini ancak graft sağkalımının daha düşük olduğunu göstermiştir. Bu sonuçlar, hepatit C virusu antikoru pozitif olan son dönem böbrek yetmezliği hastalarında böbrek transplantasyonunun güvenilir ve etkin bir renal replasman tedavisi olduğunu düşündürmektedir.*

Anahtar kelimeler: Kronik böbrek yetmezliği, hepatitis C virus infeksiyonu, uzun dönem sağkalım, böbrek transplantasyonu

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INTRODUCTION

Viral hepatitis is prevalent in patients with end-stage renal disease (ESRD) on renal replacement therapy (RRT) because the patients are exposed to the transmission risk factors such as blood transfusion and nosocomial factors, etc. Nevertheless, there has been a decrease in the prevalence of hepatitis B infection after the application of a vaccination program, isolation of infected patients and common use of erythropoiesis-stimulating agents (1-3).

However, hepatitis C virus (HCV) infection is still highly prevalent in both hemodialysis and renal transplant (RTx) patients in developing countries, including Turkey (4). RTx is considered as a treatment of choice in HCV-infected ESRD patients compared to dialysis treatment (5,6). However, the impact of HCV infection on graft and patient survival after RTx remains controversial. Several studies suggest that HCV infection could worsen both graft and patient survival rates (7) and increase the risk of post-transplant infections, sepsis and diabetes mellitus in HCV-positive kidney transplant recipients (8,9). On the other hand, some studies have documented that HCV infection did not change patient or graft survival significantly (10-12).

The purpose of this retrospective study was to determine the effect of HCV infection on patient-graft survival and on liver function in RTx patients.

MATERIALS AND METHODS

1811 RTx patients who were operated at Akdeniz University Organ Transplantation Center between January 1, 1999 and December 31, 2009 were included in the study. The medical reports of the patients were evaluated retrospectively. One hundred patients (5.5%) were serologically found to be HCV-positive. We evaluated demographic, clinical, biochemical, serological, and therapeutic data and compared patient and graft survivals between HCV-positive and -negative patients.

Acute rejection was diagnosed based on clinical and/or histological findings. Clinical acute rejection was considered when serum creatinine level increased by more than 20% of basal values for no other reason and if there was a response to anti-rejection therapy.

Graft loss was defined as return of the patient to dialysis or patient death. In the assessment of graft function, serum creatinine level (mg/dl) and estimated glomerular filtration rate (GFR) (ml/min/1.73m^2) with the modified four variable Modification of Diet in Renal Disease (MDRD) equation were taken into account. The criterion of pathologic proteinuria was defined as urine protein-creatinine-ratio >0.3.

Postoperative alanine aminotransferase (ALT) level and albumin levels were used as markers of liver function.

Anti-HCV antibodies were detected in sera by third generation enzyme immunoassays (Cobas Core Anti-HCV, Roche Diagnostics and AXSYM Anti-HCV, Abbott Laboratories), and HCV RNA was investigated in plasma samples by quantitative polymerase chain reaction (PCR) assays (Cobas Amplicor HCV monitor and Cobas TaqMan HCV, Roche Diagnostics).

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation if they followed a normal distribution and compared using Student *t* test. If not normally distributed, continuous variables were expressed as median values and 25th and 75th percentiles and compared using the Mann-Whitney test. Categorical variables were compared using the χ^2 test or the Fisher exact test, as appropriate. Patient and graft survivals after transplantation were calculated using Kaplan-Meier survival curves and compared using the log-rank test. A p value <0.05 was considered significant. The statistical analyses were performed using SPSS software version 16 (SPSS, Chicago, IL).

RESULTS

Demographic and Pre-transplant Clinical Characteristics

The median follow-up period of the 1811 RTx patients was 35.7 months (25th and 75th percentiles: 18.8-63.9). One hundred (5.5%) patients were anti-HCV-positive. It was found that anti-HCV positivity was more prevalent among female patients (p=0.041), and hemodialysis was the main RRT modality before RTx in HCV-positive patients (p<0.001). Moreover, the total duration of dialysis in HCV-positive RTx patients was significantly longer than in HCV-negative patients (p<0.001). There were no significant differences between HCV-positive and -negative patients with respect to age, etiology of renal disease, number of pre-transplant blood transfusions, and coinfection with hepatitis B virus (Table 1).

Table 1. Demographics and clinical features of patients before renal transplantation

Parameters	HCV (+) (n=100)	HCV (-) (n=1711)	P value
Female (%)	42	32.1	0.041
Age (years, mean±SD) (range)	37.0±10.8 (18-66)	35.4±13.1 (2-74)	0.15
Renal disease etiology (%)			
Diabetes mellitus	8	7.3	0.80
Hypertension	9	16.1	0.057
Chronic glomerulonephritis	19	13.8	0.15
Urologic causes	20	15.5	0.23
Polycystic kidney disease	3	4.3	0.52
Unknown	42	28.9	0.005
Last type of RRT (%)			<0.001
HD	88	71.9	
PD	3	13.0	
HD + PD	9	4.1	
Preemptive Tx	-	11.0	
Duration of RRT months, median (25^{th}-75^{th} percentiles)	60 (34-120)	17 (4-42)	<0.001
HBV coinfection (%)	4	3.2	0.64

HBV: Hepatitis B virus. HD: Hemodialysis. PD: Peritoneal dialysis. RRT: Renal replacement therapy. SD: Standard deviation. Tx: Transplantation.

Transplantation Characteristics

Median post-transplant follow-up periods in anti-HCV-positive and -negative groups were similar (38 (19-75) vs 35 (19-63) months). The rate of cadaveric-related transplant was higher in the anti-HCV-positive group compared to the -negative group (29.0% vs. 18.9%, p=0.013).

The rate of anti-thymocyte globulin (ATG) use in the HCV-positive group was higher than in the HCV-negative group (38.0% vs. 26.0%, p=0.008). ATG was mostly used for induction therapy in the anti-HCV-positive group and for acute rejection in the anti-HCV-negative group. Moreover, it was found that there was no difference between the groups with respect to immunosuppressive protocols. Additionally, the rate of acute rejection was found to be similar between the anti-HCV-positive and -negative groups.

It was found that the rate of graft loss was significantly higher in the anti-HCV-positive group than in the anti-HCV-negative group (16.0% vs. 9.2%, p=0.026). The causes of graft loss in the anti-HCV-positive group were as follows: primary nonfunction in 4 patients, acute rejection in 2 patients, chronic allograft nephropathy (CAN) in 6 patients, death in 3 patients, and hemophagocytic syndrome in 1 patient. There was no difference in the rate of development of new-onset post-transplant diabetes (Table 2). Based on the last visit results, serum creatinine and GFR levels were 1.18±0.43 mg/dl and 74.8±25.6 ml/min/1.73 m^2, respectively, in patients who did not develop graft loss in the anti-HCV-positive group. In the anti-HCV-positive group, the rate of pathologic proteinuria in patients with graft loss was found to be much higher than that of patients with good renal function (92.9% vs 32.5%; p<0.001).

Patient and Graft Survival

The median follow-up of patients was 35.7 months (25^{th} and 75^{th} percentiles: 18.8-63.9). Five percent of anti-HCV-positive patients and 2.9% of anti-HCV-negative patients died during the follow-up period (p=0.24). The causes of death in the HCV-positive patients were sepsis in 4 patients and cardiovascular event in 1 patient. On the other hand, the rate of graft loss in the anti-HCV-positive group was significantly high (16.0% vs. 9.2%, p=0.026). Survival analysis by the Kaplan-Meier method revealed a similar rate of patient survival in both groups. On the other hand, graft survival was lower in the anti-HCV-positive group (p<0.001). Patient and graft survivals are shown in Figure 1.

Liver Disease in Anti-HCV-Positive Patients

Thirty-three percent of anti-HCV-positive patients were also positive for HCV RNA. Furthermore, 27 (27%) of the anti-HCV-positive patients had an elevation of transaminase levels (ALT >80 IU/ml) for more than 3 months. None of the patients had developed cirrhosis of the liver during the follow-up. Liver biopsy was not performed in any patient after RTx. No significant relationship was found between high ALT levels and age, sex, HLA matching, donor type, use of ATG, immunosuppressive

Table 2. Transplantation-related features of patients

Parameters	HCV (+) (n=100)	HCV (-) (n=1711)	P value
Donor type (%)			
Living related	71	81.1	0.013
Cadaveric	29	18.9	
Immunosuppressive therapy* (%)			
CsA-based	31	22.6	0.057
Tac-based	50	39.2	0.036
mTOR inhibitor-based	17	38.2	<0.001
ATG use (%)			
Total	38	26.0	0.008
Induction therapy	27	10.5	<0.001
AR therapy	11	15.5	0.22
Acute rejection rate (%)	26	24.5	0.74
Graft loss (%)	16	9.2	0.026
PostTx DM (%)	7	8.0	0.72

CsA: Cyclosporine. Tac: Tacrolimus. ATG: Anti-thymocyte globulin. AR: Acute rejection. DM: Diabetes mellitus.

** Immunosuppressive therapy data is based on 1010 patients in the HCV-negative group.*

protocol, renal function, proteinuria, serum albumin, post-transplant diabetes mellitus, and patient and graft survival. The presence of HCV viremia was not found to be correlated with clinical and laboratory variables.

Four of the anti-HCV-positive patients were also positive for HBsAg. There was neither patient nor graft loss in this group. One of these patients had an increase in HBV DNA levels, but there was no deterioration in liver or graft function. These patients were on 100 mg/day of lamivudine therapy.

DISCUSSION

Hepatitis C virus (HCV) infection is the most common cause of chronic hepatitis and cirrhosis in patients with ESRD on RRT (1). HCV infection is frequently acquired prior to RTx. All of our patients acquired the infection during the pre-transplantation period. The risk of acquiring infection is determined by the duration of the dialysis, number of blood transfusions and nosocomial factors (1,2,13). In our study, the duration of dialysis in the HCV-positive group was longer compared to the HCV-negative group.

In our case series, the number of cadaveric transplants in the anti-HCV-positive group was higher than that of the anti-HCV-negative group (29.0% vs 18.9%, p=0.013). As a result, induction therapy with ATG was more frequent in this group. There was no difference in terms of maintenance immunosuppression between the two groups.

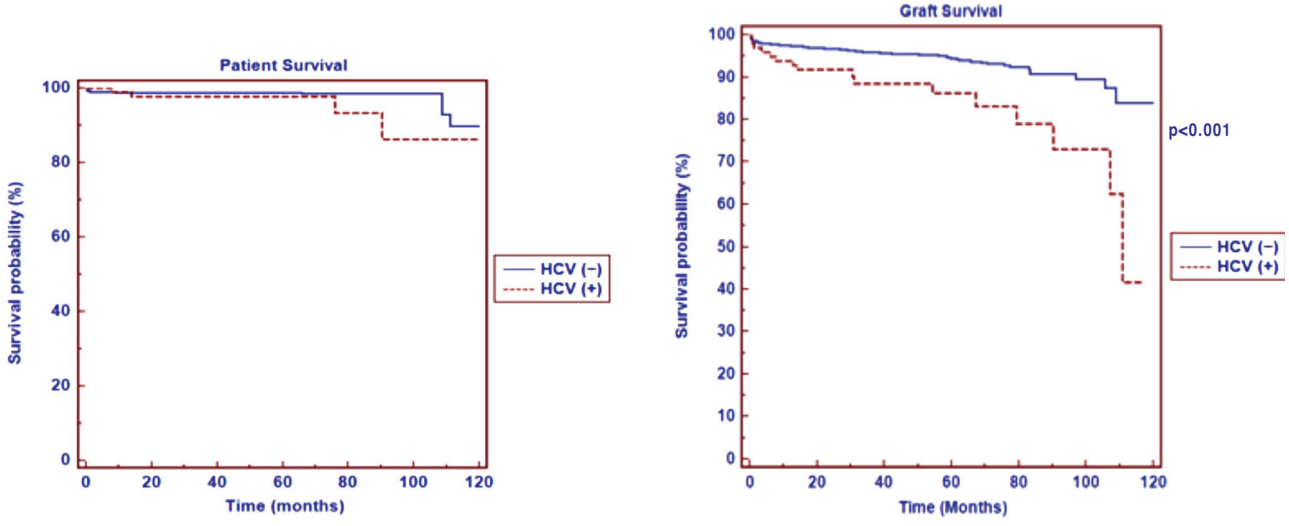

Figure 1. The comparison of patient and graft survival between HCV (+) and HCV (-) RTx patients.

Another concern is about the type of optimal immunosuppressive therapy in RTx patients with HCV infection. Many studies have been conducted on this topic, and previous studies revealed that cyclosporine caused stabilization and regression of fibrosis in anti-HCV- positive recipients by decreasing the viral replication (14,15). However, in our study, there was no difference in patient/graft survivals according to the immunosuppressive protocols. Additionally, there was no significant correlation between the different immunosuppressive drugs used such as tacrolimus, cyclosporine, everolimus, or sirolimus with transaminase elevation and viremia. These results are similar to the findings of Luan et al. (16), who did not observe a difference in liver function between patients receiving tacrolimus or cyclosporine. They also noticed that mycophenolate mofetil (MMF) was a safe and effective alternative drug and caused an increment in survival in anti-HCV-positive RTx patients. This result is consistent with many studies suggesting that MMF has positive effects on patient/graft survivals even though it increases HCV replication (17-19). In our center, we used MMF as a component of maintenance immunosuppressive therapy unless there was a complication or side effect of the medication. The reasonable results in the anti-HCV-positive patients can be related to this approach, but further studies must be carried out before making a final decision. It was also shown that induction therapy did not have a negative effect on patient/graft survivals or other parameters. There was no significant difference with respect to induction therapy type such as ATG, basiliximab or daclizumab use in a subgroup analysis.

Controversial results have been reported about the prevalence of acute rejection in anti-HCV- positive RTx patients. While some studies reported an increased rate of rejection (20,21), others concluded that there was no significant difference (22). In our study, there were similar overall rates of rejection episodes in the anti-HCV-positive and -negative groups. These results were in concordance with previous studies.

There are different opinions about the effects of HCV infection on patient and graft survivals. Some studies suggest that HCV infection adversely affects patient and graft survivals and that this is related to cardiovascular disease, post-transplant diabetes mellitus and infection/sepsis (10,23-25). In another group of studies, there was no difference between the groups in terms of patient/graft survivals (1,16,22). Our study revealed that there was no difference in patient survival between anti-HCV-positive and -negative groups over the 10-year study period, but graft survival was shorter in the 10th year in the anti-HCV-positive group. We diagnosed CAN based on clinical findings (such as proteinuria, deterioration of renal function, hypertension, and hyperlipidemia). Proteinuria was detected in the late period of transplantation with the appearance of hypertension and hyperlipidemia, which was informative regarding the diagnosis of CAN. It is well known that recurrent or de novo glomerulonephritis in RTx may lead to CAN. In our study, there was only one HCV-associated de novo glomerulonephritis case among six CAN cases. We cannot conclude that HCV infection may increase the rate of CAN by causing de novo glomerulonephritis in the transplant kidney based on our results. We believe that the lower graft survival in the anti-HCV-positive group in the long-term follow-up period may be related to the higher number of cadaveric transplants in this group.

Although in some of the previous studies, liver failure was reported to be one of the most important causes of mortality in RTx patients with chronic hepatitis C infection (10), none of our patients developed cirrhosis of the liver. There was no difference between the anti-HCV-positive and -negative patients in terms of development of post-transplant de novo diabetes mellitus.

In 27% of the anti-HCV patients, ALT levels were above two-fold of normal (>80 IU/ml), and none of the patients had developed liver failure or cirrhosis. This finding supports the results of other studies revealing that transaminase elevation in anti-HCV-positive RTx patients does not affect liver-related patient survival (25,26). Similarly, even though viral replication continued in 33.7% of patients, patient and graft survivals were not associated with elevated ALT level or type of immunosuppression. This result was compatible with the finding that even in the presence of an increase in HCV replication related to immunosuppression, there was no detrimental effect on liver function (27,28).

In conclusion, our findings suggest that HCV infection in RTx patients does not adversely affect patient survival, but the long-term graft survival is somewhat low. RTx seems to be a safe and effective modality of renal replacement in anti-HCV-positive patients with ESRD.

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