Transpl Int (2000) 13 [Suppl 1]: S31–S33

F.N. Özdemir
S. Sezer
G. Güz
Z. Arat
M. Turan
M. Haberal

Is hepatitis C virus infection a risk factor for panel-reactive antibody positivity?

F.N. Özdemir (✉) · S. Sezer · G. Güz · Z. Arat
Başkent University Faculty of Medicine, Department of Nephrology, Fevzi Çakmak Bulvarı, Sokak No: 45 Bahçelievler-06490 Ankara, Turkey
Tel.: + 90-312-2126868
Fax: + 90-312-2237333

M. Turan
Başkent University Faculty of Medicine, Department of Biochemistry, Ankara, Turkey

M. Haberal
Başkent University Faculty of Medicine, Department of General Surgery, Ankara, Turkey

Abstract Patients with high levels of panel-reactive antibody (PRA) represent an increasingly large group in the waiting lists for cadaveric renal transplantation. Hepatitis C virus (HCV) infection has been found to be associated with a high prevalence of positivity of autoimmune serological tests. We planned this study to evaluate the effect of HCV positivity on the PRA levels in our hemodialysis (HD) patients. We included 38 HCV-infected (group I: 20 male,18 female patients, mean duration of HD 73.6 ± 50.6 months) and 43 hepatitis marker-negative (group II: 23 male, 20 female patients, mean duration of HD 22.2 ± 22.4 months) HD patients. The PRA positivity ratio and number of transfusions were not significantly higher in group I than in group II (PRA ABC; 28.9%, %19.4, $P > 0.05$, PRA DR; 21.8%, 20.9, $P > 0.05$, respectively, and blood transfusions 7.0 ± 5.7, 6.6 ± 5.2, respectively, $P = 0.06$). HD duration correlated significantly with PRA positivity in our patients (PRA-positive patients: 56.1 ± 57.9 months, PRA-negative patients: 43.3 ± 41.9 months, $P = 0.021$). In conclusion, HD duration was found to be the main factor affecting PRA sensitivity independently of HCV positivity and blood transfusion.

Key words Hepatitis C virus · Infection · Panel-reactive antibody · Transplantation · Blood transfusion

Introduction

Preoperative assessment of panel-reactive antibody (PRA) levels in patients scheduled to undergo cadaveric kidney transplantation gives information about allogenic sensitization. High PRA levels are known to predict acute rejection and poor graft outcome [1]. Waiting lists for cadaveric renal transplantation now include an increasing number of end-stage renal disease (ESRD) patients with high PRA levels. As a consequence, more questions are being asked about the factors that influence these levels. Three common elements that are known to have roles in allogenic sensitization are blood transfusion, pregnancy, and transplantation [2, 3].

Hepatitis C virus (HCV) infection is the most common cause of viral hepatitis in dialysis patients [4]. Research has revealed that HCV infection is associated with a broad spectrum of autoimmune diseases. The prevelance of autoimmune disease with positive serological testing is high in patients with hepatitis C virus infection [5, 6]. This finding has led to the suggestion of a possible link between HCV positivity and PRA levels in renal failure patients. The aim of this study was to investigate the possible relationship between HCV positivity and PRA levels in our hemodialysis (HD) patients. We also tested for the effect of number of blood transfusions and duration of HD on PRA positivity.

Materials and methods

Patients

The study was performed at the Başkent University Hemodialysis Center in Ankara. We enrolled 84 patients who were on a dialysis program entailing dialysis with cuprophan membranes three times

weekly. We divided the HD patients into two groups. Group I included 38 HCV-infected patients (20 male, 18 female, mean age 46.0 ± 11.7 years, mean HD duration 73.6 ± 50.6 months), and group II was made up of 43 hepatitis marker-negative patients (23 male, 20 female, mean age 45.2 ± 15.3 years, mean HD duration 22.2 ± 22.4 months). All patients were receiving treatment three times per week using standard cuprophane membranes. Patients with a history of pregnancy or transplantation, and those who were on interferon treatment were excluded from the study.

Methods

Anti-HCV was investigated using a third-generation ELISA test (Axsyon; Abbot, USA), that detects antibodies and localizes them to three different regions of the HCV DNA sequence: HCr43 (core structural protein and nonstructural protein NS3), c22 (codes for NS3 and NS4), C100–3 (nonstructural protein NS3 and NS4), and NS5 (putative HCV nonstructural protein NS5). HCV-RNA was detected using the reverse transcriptase-polymerase chain reaction (RT-PCR), and PRA testing was done using the One Lambda system (Lambda Cell Trayô, 21001 Kiltridge street, Canoga Park, CA 91303–280). A PRA level above 30% was considered positive.

Blood transfusion information was obtained from the patient, the dialysis unit, and hospital blood bank records.

This study was performed in accordance with the ethical standards laid down in an appropriate version of the 1964 Declaration of Helsinki. All the patients gave informed consent prior to their inclusion in the study.

Statistical analysis

All values were expressed as mean ± SD, and statistical analysis was done using the program SPSS for Windows. Differences in the parameters of the two groups were evaluated using the Student's *t*-test. Chi-square analysis was used for categorical values. The criterion for statistical significance was $P < 0.05$.

Results

We found no significant difference in PRA positivity between our HCV-infected patients (group I) and those who were negative for hepatitis markers (group II) (PRA ABC 28.9% and 19.4%, respectively, with $P > 0.05$; PRA DR 21.8% and 20.9%, respectively, with $P > 0.05$; Table 1). The groups also did not differ statistically with regard to mean number of blood transfusions received (7.0 ± 5.7, 6.6 ± 5.2, respectively, $P = 0.06$; Table 1). Patient age, gender, and HD duration were analyzed for their effect on PRA positivity. HD duration was positively correlated with PRA positivity in our patients, independent of HCV status and the number of blood transfusions received (HD duration 56.1 ± 57.9 months in PRA-positive, and 43.3 ± 41.9 months in PRA-negative patients; $P = 0.021$; Table 2). We found no significant relationship between PRA positivity and age or gender.

Table 1 The relationship between hepatitis C virus *(HCV)* positivity and panel-reactive antibody *(PRA)* positivity in our hemodialysis patients

	HCV (+)	HCV (–)	*P*
PRA ABC (+) (%)	28.9	19.4	> 0.05
PRA DR (+) (%)	21.8	20.9	> 0.05
Mean no. of blood transfusions	7.0 ± 5.7	6.6 ± 5.2	> 0.05

Table 2 The relationship between PRA positivity and age, gender, mean number of packed red blood cell transfusions received, and hemodialysis duration of hemodialysis *(HD)* in our HD patients

	PRA (+)	PRA (–)	*P*
Mean age (years)	42 ± 15	44 ± 14	> 0.05
Gender (M/F)	11/9 (1.2)	32/29 (1.1)	> 0.05
No. of blood transfusions	9.4 ± 11.7	7.3 ± 6.9	> 0.05
HD duration (months)	56.1 ± 57.9	43.3 ± 41.9	0.021

Discussion

PRA screening has been accepted as part of mandatory screening for patients scheduled to undergo renal transplantation. Pre- and posttransplantation PRA levels have been found to be associated with increased incidence of hyperacute or acute graft rejection and graft loss [1, 7]. The overall 1-year and 5-year graft survival rates for sensitized kidney transplant recipients are lower than those for nonsensitized patients. A study by Özdemir et al. showed that recipient presensitization was a stronger predictor of graft loss than other known risk factors, including cause of donor death, HLA mismatches, donor age, and year of transplantation [6]. High pretransplantation PRA levels have also been correlated with the need for posttransplantation dialysis, which is an indicator of poor graft outcome. Investigation has shown that the majority of highly sensitized patients have received fewer than 10 blood transfusions and that most patients who suffer graft loss have not been sensitized through transfusion. These findings have raised the possibility that other factors may be important in allogeneic sensitization. Studies on the race factor have underlined the effect of HLA group on PRA levels. HLA antigen, which differs according to race and ethnic background, might play a role in protecting or triggering PRA sensitization.

HCV infection is associated with various immunologic manifestations, both clinically and in the laboratory. Since HCV is a major complication for patients on dialysis, studies have focused on immunological disorders in these individuals. Autoimmune serological testing of renal transplant recipients afflicted with HCV has revealed prevalence of 60% for RF, 53% for ANA, and 26% for SMA [5]. Interferon therapy has been found

to trigger autoimmune disorders in HCV-positive patients [8].There is not yet enough evidence about the exacerbation of autoimmunity by interferon therapy in HD patients, and this topic is currently under investigation [9].

HCV positivity has been found to be associated with previous blood transfusions, mode of therapy, and duration of dialysis. We postulated that HCV infection might have an effect on PRA sensitization, but found no statistically significant relationship to support this theory. In this study, the major factor influencing PRA positivity was duration of HD (which was independent of HCV infection and number of blood transfusions received). Our results were similar to those obtained in our preceding study on comparison of panel-reactive antibody levels with clinical and laboratory parameters in patients with renal failure [10]. A possible explanation for this is that longer duration of HD involves a greater probability of exposure to antigenic stimulants, such as drugs and incompatible dialysis membranes. This exposure may trigger PRA sensitization. .

In conclusion, our study shows that HD duration is an important determinant of PRA positivity. Although HCV infection is associated with many autoimmune disorders, we found no relationship between HCV infection and PRA positivity in HD patients.

References

1. Monteiro F, Buelow R, Mineiro C, Rodrigues H, Kalil J (1997) Identification of patients at high risk of graft loss by pre- and posttransplantation monitoring of anti-HLA class I IgG antibodies by enzyme-linked immunoabsorbent assay. Transplantation 63: 542
2. Lazda VA, Gaddis PJ, Stormoen BM, Fabrega AJ, Pollak R (1993) Presensitization and frequency of positive crossmatches in black and nonblack renal transplant candidates. Transplant Proc 25: 2411
3. Kerman RH, Kimball PM, Van Buren CT, et al (1992) Influence of race on crossmatch outcome and recipient eligibility for transplantation. Transplantation 53: 64
4. Pereira BJG(1999) Hepatitis C virus infection in dialysis: a continuing problem. Artif Organs 23: 51–60
5. Clifford BD, Donahue D, Smith L, et al (1995) High prevalence of serological markers of autoimmunity in patients with chronic hepatitis C. Hepatology 21: 613–619
6. Özdemir FN, Turan M, Sezer S, et al (1998) Prevalence of serological markers of autoimmunity in hemodialysis patients with hepatitis C virus. Transplant Proc 30: 848–849
7. Cosserat J, Cacoub P, Bletry O (1996) Immunological disorders in C virus chronic hepatitis. Nephrol Dial Transplant 11 [Suppl 4]:31–35
8. Kerman RH, Susskind B, Buelow R, et al (1996) Correlation of Elisa-detected IgG and IgA anti-HLA antibodies in pretransplant sera with renal allograft rejection. Transplantation 62: 201–205
9. Rostaind L, Oksman F, Izopet J, et al (1996) Serological markers of autoimmunity in renal transplant patients before and after alpha-interferon therapy for chronic hepatitis C. Am J Nephrol 16: 478–483
10. Sezer S, Özdemir FN, Turan M, et al (1998) Comparison of panel reactive antibody levels with clinical and laboratory parameters in end-stage renal disease patients. Transplant Proc 30: 844–845