Impact of hepatitis C virus infection in renal transplant recipients

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Objectives: The impact of hepatitis C virus (HCV) infection on the success of renal transplant is controversial. We assessed the effect of HCV infection on graft and patient survival in renal allograft recipients. Methods: We retrospectively analyzed medical records of renal allograft recipients who were transplanted between June 1990 and March 2004. Patients were divided into those positive and negative for anti-HCV antibody. Graft and patient survival were compared between the groups. Results: Of 126 patients studied (median age 34.5 years, range, 16-60; 111 men), 35 were positive for anti-HCV antibody. In seven patients, the antibodies were detected for the first time after renal transplant. Mean patient and graft survival duration in the anti-HCV negative group was longer (55 [SD 2] months [95% CI, 51-58]) than in the anti-HCV positive group (50 [SD 4] months [95% CI, 43-58]) (p<0.05). Twenty-two patients died – 8 (22.8%) in the anti-HCV positive group and 14 (15.3%) in the negative group. In the anti-HCV positive group, infections were the cause of death in 5 patients and 3 patients died of liver cell failure. In the anti-HCV negative group, corresponding figures were 13 and one. Conclusion: HCV infection is a bad prognostic indicator for patient and graft survival duration in renal transplant recipients. Infections are the commonest cause of death in renal transplant recipients. [Indian J Gastroenterol 2005;24:151-154]

Methods

We retrospectively analyzed medical records of patients who had undergone renal transplant elsewhere between June 1990 and March 2004, and had been referred to our center for follow up. The time interval between renal transplant and referral to us ranged from 2 to 48 months (median 11 months). All clinical events were recorded till the time of death, loss to follow up, completion of five years since transplantation, or June 2004, whichever occurred earlier. All patients had received grafts from living donors and were receiving azathioprine and prednisolone (before December 1990) or prednisolone, cyclosporine and azathioprine (after December 1990) as primary immunosuppressive drugs. If cyclosporine or azathioprine toxicity was suspected, the offending agent was withdrawn and patients were continued on two drugs. In some, azathioprine was substituted with mycophenolic mofetil.

All patients were screened for anti-HCV antibody (in the later part of the study kits from LG Life Sciences, Korea were used; the other kits used were from MBS Medical Biological Sciences, Italy, and Zhongshan Biotech, China) and HBsAg (Sanofi Diagnostic Pasteur, France). Serum HCV RNA PCR was done in patients who could afford this test. The two-step RT-PCR method was used; the first step involved reverse transcription from RNA to complementary DNA and the second step involved amplification of DNA by PCR. The sense primer used was 5’-GAC ACT CCA CCA TAG AT-3’ (1-20) and the anti-sense primer was 5’-GGT GCA CGG TCT ACG AGA CCT-3’ (323-303). These tests were carried out after referral to our center. Liver function tests were performed in all patients who tested positive for anti-HCV or HBsAg; when abnormal, these were repeated at least once a month.

No transplant patient received therapy for hepatitis C infection before or after renal transplant.

The cause of death was categorized as liver disease, sepsis or others. Only those infections serious enough to require hospitalization were included.
for analysis. Acute allograft rejection was defined by biopsy or clinically after a positive response to anti-rejection therapy. An allograft was considered to be lost if the patient died with a functioning graft or if the patient returned to dialysis, or had a second transplant.

Comparison of qualitative variables was done using the $\chi^2$ test, and for quantitative variables Student’s $t$ test was used. All values are expressed as mean (SD) unless otherwise specified. Patient survival was estimated using the Kaplan-Meier method; inter-group comparison was done using the log rank test. The relative risk of graft loss and death was calculated using Mantel-cox chi square test. Statistical calculations were done using statistical package SPSS 12.0.

### Results

Of 126 patients (median age 34.5 years, range, 16-60; 111 men) with renal transplantation referred to us, 35 tested positive for anti-HCV antibody; 28 had anti-HCV antibodies prior to transplantation, and in 7 anti-HCV antibodies had been detected for the first time after transplant, though the exact duration since transplantation was not available. The median follow-up duration for all patients, and for HCV-positive and HCV-negative patients, was 31, 24 and 40 months, respectively.

Sixty-seven patients were followed up to 5 years (19 anti-HCV positive and 48 anti-HCV negative). No patient was lost to follow up in either group. In 37 patients (HCV positive 11, HCV negative 26) the end point of follow up was June 2004.

Table 1 shows the pre-transplant characteristics in the anti-HCV positive and negative patients. The duration of dialysis was significantly longer in the anti-HCV positive patients. Of the 23 anti-HCV positive patients who were tested for HCV RNA, 21 tested positive, as did one of the two anti-HCV negative patients who underwent this test.

The post-transplant events are shown in Table 2. Mean (SD) duration of patient and graft survival in the anti-HCV negative patients was 55 (2) months (range 2 to 60 months), and in the anti-HCV positive patients was 50 (4) months (range 6 to 60 months); this difference was significant (Fig. 1 and 2). Twenty-seven patients lost renal grafts, 9 in the anti-HCV positive and 18 in the anti-HCV negative group.

In the anti-HCV positive group ALT was raised (>40 IU/mL) in 23 patients; 18 of these had serum albumin level <3.5 g/dL. Esophageal varices were documented in 5 patients. HBsAg was detected in nine of the 35 patients with anti-HCV antibodies. The pattern of infections requiring hospitalization was similar in the two groups (Table 3).

Twenty-two patients died, 8 (22.8%) in the anti-HCV positive group and 14 (15.3%) in the anti-HCV negative group. In the former group, in-
Infections were a cause of death in 5 patients and 3 patients died of liver cell failure. In the anti-HCV negative group, 13 patients died of infections and one of liver cell failure. This difference was not significant. Five patients with raised ALT and 3 with normal ALT levels died (p=ns). The relative risk of graft loss and death at 5 years post transplant was 2.88 and 3.2, respectively.

Discussion
During the past few years, several clinical trials have addressed the issue of survival in HCV-infected renal transplant recipients. The results are conflicting and difficult to interpret. Whereas some studies have shown lower patient survival in infected recipients,7-10 others have shown similar survival rates.11-14 Recent studies have shown that HCV-infected patients who clear their viremia with interferon therapy in the pre-transplant period have overall outcome close to HCV-negative recipients in the post-transplant period.15 In our study, the relative risk of death at five years post transplant was 3.2 times greater in the anti-HCV positive group. Infections and liver cell failure were the cause of death.

Pereira et al8,9 noted increased risk of death and of deaths due to infection in anti-HCV positive renal allograft recipients. These findings are at variance with that reported by Aggarwal et al,11 where in a prospective follow up of almost 30 months, no difference in mortality was seen in anti-HCV positive compared to anti-HCV negative transplant patients. The shorter duration of follow up may have been one of the reasons.

A number of factors could explain the difference in results of various studies.16 The presence of anti-HCV antibodies does not necessarily imply the presence of HCV infection.17 False positive results have been reported with older assays. Secondly, the antibody may have been acquired passively from blood transfusion, in which case it would disappear over few weeks. Lastly, antibodies to HCV may persist after the viral RNA has disappeared. Conversely, among renal transplant patients, serological responses to HCV may be delayed or sometimes absent.17 Thus the use of anti-HCV positivity as sole indicator of HCV infection may be fallacious. Significantly, some patients may seroconvert after renal transplant. Because of the shorter history of infection in these patients, their prognosis would be better than in those who acquired the infection before the transplant.17,18

Our clinical records showed anti-HCV antibodies after renal transplant for the first time in seven patients. These may represent fresh seroconversion, but there could be other reasons. The antibody test used in the pre-transplant period may not be sensitive enough or the antigen used in the assay system could not detect the antibody response to the particular genotype.17 Second, it is possible that at the time of renal transplant, the patient may be in the window period between infection and seroconversion.17

Liver disease in patients with HCV infection may range from no injury to chronic hepatitis or cirrhosis.16 Most studies have not taken this into account while calculating patient survival. Mahmoud et al16 reported that HCV-infected renal transplant patients with elevated liver enzyme levels had lower survival. We however did not find any such difference. This is not surprising, as chronic hepatitis characteristically has a fluctuating course with multiple peaks and troughs in ALT levels, and patients with normal ALT.
levels may have severe histological lesions. Because severity of liver disease is a strong predictor of liver failure and death after transplant, there is merit in performing liver biopsy in anti-HCV positive patients awaiting renal transplant.

About one-fourth of our patients with HCV infection had co-existing hepatitis B virus infection. Hepatitis B virus infection is known to be associated with higher mortality rate in the post renal transplant period. This could have contributed to the higher mortality in our patients.

The higher mortality in some studies is also explained on the basis of increased alcohol intake, age of acquiring infection above 40 years, male sex, genotype, and immunosuppression used. Most of our patients were male, less than 40 years of age, and were not alcohol dependent. While we did not study this, the most common genotype in northern India is genotype 3, which carries a better prognosis.

The limitations of our study were that it was a retrospective study in which all the variables in the pre and early post transplant period that could affect graft and patient survival were not known. The use of anti-HCV positivity as sole indicator of HCV infection may have been fallacious. Some patients seroconverted after renal transplant; however, there was no difference between these patients and others. Because severity of liver disease is a strong predictor of liver failure and death after transplant, there is merit in performing liver biopsy in anti-HCV positive patients awaiting renal transplant. Lastly, the proportion of patients followed up was widely different in the two groups.

We conclude that HCV-positive compared with HCV-negative renal transplant patients have lower recipient and graft survival duration. There may be a case for attempting to clear the viremia in the pre-transplant period.

References