Impact of Hepatitis C Virus Infection on Short-Term Outcomes in Renal Transplantation

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Hepatitis C virus is an RNA virus with 6 known genotypes. Prevalence of hepatitis C virus infection in the world is almost 3%. In patients undergoing hemodialysis, prevalence of hepatitis C virus positivity is reported to be from 1%-54% depending on the methods used for detection. Liver disease in kidney transplant recipients has been attributed to hepatitis B virus, hepatitis C virus, Epstein-Barr virus, cytomegalovirus, ethanol, hemosiderosis, and drugs such as azathioprine and cyclosporine A. Hepatitis C virus infection is currently the main cause of chronic liver disease in this group, and it may affect allograft outcome. Whether hepatitis C virus infection after renal transplantation adversely affects graft and patient survival remains controversial. Several series have reported no impact on short- and long-term patient and graft survival. In fact, comparative studies using different immunosuppressive protocols are not available. The differences in the results of these studies may be explained by confounding factors, for example, differences in immunosuppressive protocols, study design, methodology of diagnosing hepatitis C virus infection, and differences in hepatitis C virus genotypes. Treatment protocols for hepatitis-C-virus–associated liver disease should be considered before renal transplantation. Nevertheless, transplantation is the best option for patients with hepatitis C virus with end-stage renal disease, and less hepatotoxic immunosuppressive agents may decrease the incidence of posttransplant liver disease in patients with hepatitis C virus. This review will discuss the studies with specific emphasis on the impact of hepatitis C virus infection on short-term outcome in renal transplantation.

Key words: *Glomerulonephritis, Acute tubular necrosis, Genotype, Interferon, Acute humoral rejection*

Hepatitis C virus (HCV) is a single-strand RNA virus of the Flaviviridae family, with 6 known genotypes. The prevalence of HCV infection in the world is almost 3% [1]. In patients undergoing hemodialysis, prevalence of HCV seropositivity is reported to be from 1%-54% depending on the method used for HCV detection [2]. Liver disease in kidney transplant recipients has been attributed to hepatitis B virus (HBV), HCV, Epstein-Barr virus (EBV), cytomegalovirus (CMV), azathioprine, cyclosporine A, ethanol, or hemosiderosis [3]. HCV infection is currently the main cause of chronic liver disease in this group [4].

Impact of HCV Infection on Acute Rejection

The incidence of acute rejection in recipients who are HCV-positive is a controversial issue. Some authors have found a higher frequency of acute rejection in recipients who are HCV-positive compared with recipients who are HCV-negative. Meier-Kriesche and colleagues have reported their results from a study of 73,707 patients. Acute rejection within the first 6 months after transplantation was significantly more frequent in patients who were HCV-positive compared with those who were HCV-negative (32.2% vs 24.6%, $P < 0.01$) [5]. In a retrospective analysis of 227 patients receiving renal transplantation, Ozdemir and coworkers found that the presence of the HCV antibody produced adverse effects on graft survival in 29 recipients

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who were HCV-positive compared with 198 recipients who were HCV-negative. Early acute rejection was 17% in those who were HCV-positive and 47% in those who were HCV-negative ($P > 0.05$). The number of late acute rejection episodes was significantly greater in those who were HCV-positive (80%) compared with those who were HCV-negative (45%) ($P < 0.03$) [6]. In contrast, Corell and coworkers reported a significantly lower rate of acute rejection in 118 patients who were HCV-positive (28%) compared with 229 patients who were HCV-negative (40%) ($P < 0.025$). This is despite having a significantly higher proportion of patients who, immunologically, were at high risk (30.5% vs 11.8%) [7]. The lower rate of rejection may be explained by a reduction of naive T-helper cells in patients who are HCV-positive in association with altered T-cell proliferative responses to mitogens. The combination of a low incidence of acute rejection and a high prevalence of infections may be explained by the immunodeficiency state during HCV infection.

Dr. Shafiei Sabet and colleagues followed 509 patients who had undergone renal transplantation at Dr. Shariati's University Hospital in Tehran, Iran, from March 1995 to January 2000. Anti-HCV was checked by ELISA II at least once before transplantation in all patients. Thirty-eight patients were HCV-positive. A control group was selected from recipients who were HCV-negative and matched for age, sex, donor type, pretransplantation dialysis duration, cytotoxic antibody status, and immunosuppressive regimen. Thirty-eight renal transplant recipients who were HCV-positive and 46 matched renal transplant recipients who were HCV-negative were evaluated retrospectively for patient survival, graft function, and liver function tests at the time of discharge, and at 6, 12, and 24 months after renal transplantation. Patients who tested positive for hepatitis B surface antigen were excluded from the study in both groups. Patients who lost their grafts owing to urologic and vascular complications also were excluded. The immunosuppressive protocol consisted of cyclosporine, azathioprine, and prednisolone in both groups. Episodes of mild and severe rejection and acute renal failure were found in 5.3%, 13.2%, and 0% of patients who were HCV-positive, respectively. These figures for patients who were HCV-negative were 10.9%, 2.2%, and 7%, respectively. In this study, there was no significant short-term difference in the outcome of renal transplantation between patients who were HCV-positive and those who were HCV-negative, except for a higher (although not statistically significant) incidence of chronic and severe acute rejection [8].

Impact of HCV Infection on Graft and Patient Survival after Renal Transplantation

Whether HCV infection after renal transplantation adversely affects graft and patient survival remains controversial. Ozdemir has reported graft loss as a result of chronic rejection in 68% of recipients who were HCV-positive versus 47.8% in those who were HCV-negative ($P < 0.001$) [6]. A study by Dr. Shafiei Sabet and coworkers revealed 2-year survival rates in both groups of patients to be 100%. Graft failure was seen in 5% of patients who were HCV-positive and 0% of those were HCV-negative, which was not statistically significant [8]. In a study by Hestin and coworkers, 322 consecutive renal allograft recipients were studied. Before transplantation, 9.6% of the recipients were anti-HCV-antibody positive. One- and 5-year graft survival rates were significantly worse in patients with proteinuria (90.7% and 41.1%) than they were in patients without proteinuria (95.6% and 91.8%, $P < 0.00001$). Despite the strong association between HCV infection and proteinuria, patient and graft survival rates in recipients who were anti-HCV-positive and those who were anti-HCV-negative were similar [9].

In a large study by Meier-Kriesche and coworkers, data from the United States Renal Data System from October 1988 through June 1998 were analyzed. In the 73,707 recipients studied, the overall incidence of death was significantly lower in recipients who were hepatitis-C-antibody positive after transplantation compared with those who were hepatitis-C-negative ($P = 0.02$). Although the incidence of cardiovascular death was significantly lower in patients in the hepatitis-C–positive group compared with patients in the hepatitis-C–negative group ($P = 0.001$), infectious death and gastrointestinal death were both significantly more frequent in patients in the hepatitis-C–positive group ($P = 0.043$ and $P = 0.03$ respectively). There was a significantly higher number of male patients in the hepatitis-C–positive group compared with the hepatitis-C sero-negative group (70% vs 60.1%, $P < 0.01$). Patients in the hepatitis-C–positive group displayed a significantly longer pretransplant dialysis time ($P < 0.01$) and a significantly lower incidence of living donations ($P < 0.01$) [5]. Conversely, Miguel

and coworkers studied 335 renal transplant recipients on quadruple immunosuppressive therapy who had received kidneys from cadaveric donors. Graft survival rates were significantly lower in patients who were HCV-positive (90.6%, 68.3%, and 51% at 1, 5, and 10 years, respectively) [10]. Patient survival rates were 96.4%, 87.0%, and 71.9% in patients who were HCV-positive at 1, 5, and 10 years, compared with 98.2%, 96.0%, and 90.0% in patients who were HCV-negative [10].

Pereira and colleagues and The New England Organ Bank Hepatitis C Study Group concluded that HCV infection at the time of referral for transplantation is associated with an increased risk of death, irrespective of whether patients remain on dialysis or undergo transplantation. Transplantation has a beneficial rather than an adverse effect on long-term survival in patients who are anti-HCV positive [11]. A role for heavy immunosuppression is suggested by the observation that quadruple therapy with monoclonal or polyclonal antibodies is associated with more frequent instances of liver disease [12]. Although comparative studies using different immunosuppressive protocols are not available, current information regarding survival figures, incidence of acute rejection, and infectious complications suggests that immunosuppression should be adjusted depending on liver histology. Acute humoral rejection is reported in renal transplant recipients with hepatitis C who are receiving interferon-alpha antiviral therapy [13]. To prevent this serious complication, preemptive treatment options including interferon in the dialysis period to achieve improvement of fibrosis are suggested [14].

Batty and colleagues have reported another study of 33,479 patients transplanted from July 1994 to June 1997 from the USRDS data. They concluded that recipients with HCV had increased mortality and hospitalization rates compared with other transplant recipients [15]. The lower graft survival rates in patients who are HCV-positive may reflect lower patient survival and the presence of HCV-associated glomerulonephritis. Cruzado and coworkers studied the incidence of glomerulonephritis in 78 HCV-positive recipients of renal allografts from December 1992 to December 2000. They treated 15 patients with interferon, 1 of whom developed proteinuria. Twelve of 63 patients (19%) not treated with interferon developed de novo glomerulonephritis (9 membranoproliferative, 3 membranous). The authors concluded that all HCV–RNA positive candidates for renal transplantation should receive interferon treatment prior to transplantation [16]. However, in study by Hetin and coworkers [9], the presence of anti-HCV antibodies was strongly associated with proteinuria (relative risk [RR] = 5.36, 95% confidence interval [CI] = 2.49-11.51) in the graft. Despite this strong association between HCV infection and proteinuria, patient and graft survival rates in recipients who were anti-HCV-positive and those who were anti-HCV-negative were similar.

A definitive conclusion cannot be made from the literature regarding the short- and long- term impact of HCV infection in renal allograft recipients. Most of the studies are retrospective reports from single-center experiences based on small numbers of patients, with possible center-specific factors. The patient populations studied were heterogeneous with respect to different immunosuppressive protocols. The methodologies for detecting HCV infection were different. Although long-term survival rates are lower in graft recipients who are HCV-positive compared with those who are HCV-negative in most of the above studies, kidney transplantation remains the best option for patients with end-stage renal disease who are HCV-positive, because survival, even short-term, would be substantially lower on a waiting list than on dialysis owing to the high cardiovascular mortality with the latter [17].

Conclusions

Differences in the results of the various studies may be explained by confounding factors, for example, differences in immunosuppressive protocols, study design, methodology used to diagnose HCV infection, and differences in HCV genotypes. Other factors that should be considered are duration of pretransplant dialysis, age of recipients, previous transplantation, and history of smoking and alcohol abuse. Nevertheless, transplantation remains the best option for patients with end-stage renal disease who are HCV-positive. Immunosuppressive regimens should be kept at the lowest dosages possible, and quadruple immunosuppressive protocols for recipients of renal allograft who are HCV-positive should be avoided if possible. Finally, patients with end-stage renal disease should be given the chance to make an informed choice between continuing maintenance dialysis or receiving renal transplantation.

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