Hepatitis C in transplantation

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Introduction

Liver disease is an important cause of morbidity and mortality after renal transplantation. Transplant recipients are potentially at risk of acquiring viral hepatitides from transmission within dialysis units, blood products or organ donors [1]. The cloning of hepatitis C virus (HCV), the major cause of parenterally transmitted non-A, non-B hepatitis (NANBH), and development of tests for antibody to HCV and HCV RNA [2,3], have opened avenues to study the transmission of infection by organ transplantation, and its role in post-transplantation liver disease.

Transmission by organ transplantation

The transmission of HCV by organ transplantation was unequivocally demonstrated by studies from the New England Organ Bank [4,5]. Among recipients of organs from anti-HCV positive donors, the prevalence of liver disease, anti-HCV and HCV RNA are 15–100%, 32–100% and 57–96% respectively [6]. These differences in the rate of transmission reported by different centres could be because clinical and laboratory evidence of liver disease and anti-HCV testing underestimate the transmission of HCV among organ recipients. Hence failure to test for HCV RNA could erroneously suggest a low rate of transmission of infection. Further, a lower prevalence of HCV RNA among anti-HCV positive cadaver organ donors at some centres could explain a lower rate of transmission by anti-HCV positive donors. Currently, several organ procurement organizations restrict the use of anti-HCV positive donors to life-saving transplants (heart, liver or lung). Nonetheless, despite the transmission of HCV by infected organs, at 3.5 years, donor HCV infection does not adversely affect patient or graft survival, leading several authors to argue against a ban on these donors [7].

Prevalence of markers of HCV infection among cadaver organ donors

In a national collaborative study of 3078 cadaver organ donors from eight organ procurement organizations in the US, the prevalence of anti-HCV by ELISA 1 and ELISA 2 and HCV RNA was 5.1, 4.2 and 2.4% respectively [8]. The prevalence of anti-HCV among positive organ donors, the prevalence of liver disease, anti-HCV and HCV RNA are 15–100%, 32–100% and 57–96% respectively [6]. These differences in the rate of transmission reported by different centres could be because clinical and laboratory evidence of liver disease and anti-HCV testing underestimate the transmission of HCV among organ recipients. Hence failure to test for HCV RNA could erroneously suggest a low rate of transmission of infection. Further, a lower prevalence of HCV RNA among anti-HCV positive cadaver organ donors at some centres could explain a lower rate of transmission by anti-HCV positive donors. Currently, several organ procurement organizations restrict the use of anti-HCV positive donors to life-saving transplants (heart, liver or lung). Nonetheless, despite the transmission of HCV by infected organs, at 3.5 years, donor HCV infection does not adversely affect patient or graft survival, leading several authors to argue against a ban on these donors [7].
clinical consequences, at least in the short-term. Until cadaver organ donors was severalfold higher than the 0.6% prevalence among healthy blood donors in the US. Anti-HCV positive cadaver organ donors were more likely to be male, with a history of alcohol or drug abuse, elevated blood alcohol levels, a positive toxic screen, hepatitis B core antibody, and antibody to CMV. These characteristics are consistent with known epidemiological features of high-risk populations exposed to parenterally transmitted viruses. The sensitivity and negative predictive value of ELISA 2 were 100%. Therefore a ban on ELISA 2-positive donors would eliminate transmission of HCV infection. Although the specificity of ELISA 2 was 98.1%, due to the low prevalence of infection, the positive predictive value was only 55%. Consequently, a ban on ELISA 2-positive donors would waste organs from 45% of ELISA 2 positive, or 1.8% of all donors [6].

One strategy to minimize waste would be to identify clinical or laboratory characteristics that differentiate anti-HCV positive donors with and without HCV RNA. Some authors suggest that anti-HCV positive donors without history of drug abuse or homosexual lifestyle, absence of anti-HBs or anti-HBc, and normal serum ALT levels are at low risk of transmitting disease. However, in the US National Collaborative Study, these characteristics did not distinguish anti-HCV positive donors with and without HCV RNA. Thus there are no ‘low-risk’ anti-HCV-positive cadaver organ donors. The RIBA 2, which has been suggested as a confirmatory test in blood donors, also did not distinguish ELISA 2-positive organ donors with and without HCV RNA. Hence, newer confirmatory tests with an even greater specificity need to be developed in order to reduce organ waste.

Transplantation of kidneys from anti-HCV-positive donors into recipients with pretransplantation HCV infection

Even if anti-HCV positive but HCV RNA negative donors could be identified and utilized, 2.4% of cadaver organ donors that test positive for HCV RNA would remain unsuitable for transplantation of non-life saving organs. The use of kidneys from anti-HCV-positive donors in recipients with pre-existing HCV infection could potentially eliminate both the need for confirmatory testing in donors with anti-HCV and discarding of organs from anti-HCV positive donors. In a prospective study from Spain, there were no differences in the post-transplantation prevalence of liver disease, graft or patient survival between anti-HCV positive renal transplant recipients who received organs from anti-HCV positive vs negative donors [9]. More recently, Widell and colleagues [10] have demonstrated that among HCV RNA positive recipients of kidneys from HCV RNA-positive donors, the viral genotype present post-transplantation could be that from the recipient, donor, or both. These data suggest that superinfections do occur, but may not have serious clinical consequences, at least in the short-term. Until the completion of large clinical trials, transplantation of organs from anti-HCV positive donors into anti-HCV-positive recipients remains an experimental treatment.

Impact of pre-transplantation HCV infection on post-transplantation outcomes

Kidney transplantation is associated with a 2–30-fold increase in HCV RNA titre. However, transplant recipients with HCV infection can harbour HCV RNA in the serum despite the absence of abnormalities in liver function or antibodies to HCV, and the titre of HCV RNA does not differ between patients with and without post-transplantation liver disease [11]. These data suggest that factors other than the viral load determine the risk of liver disease among transplant recipients with HCV infection. Controversy exists regarding the impact of pre-transplantation HCV infection on clinical outcomes after transplantation [11–15]. Studies from the New England Organ Bank and the Medical College of Wisconsin show that pretransplantation HCV infection is associated with an increased risk of adverse outcomes after renal transplantation [11,12]. In the New England Organ Bank study, recipients with pre-transplantation anti-HCV had a 5-fold increased risk of post-transplantation liver disease, 3.3-fold increased risk of death, and 9.9-fold increased risk of death due to sepsis [11]. In sharp contrast, several other studies have shown that although the prevalence of liver disease is high, the presence of anti-HCV at the time of renal transplantation does not adversely affect graft or patient survival after transplantation [13–15]. This difference in survival might reflect differences in the severity of pretransplantation HCV infection among patients in different studies. In the New England Organ Bank study, 61% of patients with anti-HCV prior to transplantation had a history of liver disease prior to transplantation compared to only 3% in the University of Miami study, in which anti-HCV was not associated with an increased mortality [11,14]. More accurate assessment of the severity of pretransplantation liver disease, for example liver biopsy, would be necessary to address this question. Indeed, pretransplantation liver histology has been shown to be a good predictor of adverse post-transplantation outcomes [16]. Alternatively, the differences in survival between anti-HCV-positive and negative recipients in different studies may be due to differences in completeness of follow-up. Less complete follow-up could possibly fail to identify patients who died. Finally, the virulence of the virus differs between strains of the virus and the differences in the distribution of various strains could possibly explain differences in the results obtained from different geographical regions. These results raise the question whether anti-HCV-positive patients on dialysis should be offered renal transplantation as opposed to continuing dialysis. This question can only be answered by comparing outcomes among anti-HCV-
positive patients who continue on dialysis with those who undergo transplantation. Meanwhile, properly informed patients should be allowed to make the choice.

References

Hepatitis G virus: an old, but newly discovered hepatotropic virus — is it of interest for the nephrologist?

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History

The history of the lately discovered hepatitis G or GB viruses goes back to the year 1967 [1]. At that time Deinhardt and coworkers reported on an infectious agent in the serum of a 34-year-old surgeon with initials GB. The serum was taken from the patient on the third day of an icterus that he had acquired during his convalescence. The agent in the serum of a 34-year-old surgeon with initials GB. The agent was expected that the sample obtained on the third day of an icterus that he had acquired during his convalescence. The agent was expected to be a virus [2]. Deinhardt never identified the infectious organism in the GB agent.

Molecular biology

Finally, Simons and coworkers published two flavivirus like genomes in April 1995, that they had discovered in the GB agent [2]. They used a subtractive polymerase chain reaction (PCR) method, and representational difference analysis, to compare large DNA sequences for the presence of different genes. To do this they performed a nucleic acid extraction from the plasma of a tamarin before and after infection with the GB agent. It was expected that the sample obtained after infection contained RNA or DNA from the infectious agent. This method allowed selective amplification of these sequences and 76 DNA clones were obtained. Eleven clones contained new sequences and 7 of these were further studied. Using rt-PCR they investigated the plasma of tamarins for the presence of these sequences. Indeed, they could be found in samples from infected but not from uninfected animals. Furthermore, it had to be an RNA-virus since these...