How to manage the dialysis patient with chronic viral hepatitis who is considered for renal transplantation

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Introduction

Chronic liver disease is an important cause of late morbidity and mortality in renal transplant patients. Several aetiological factors may be involved, but infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) are certainly the most frequent causes of chronic liver damage in these patients.

The prevalence of HBsAg at the time of transplantation was high in the past, as high as 45% in some series [1]. After preventive measures were adopted HBV infection has become less frequent in dialysis patients and has become almost exceptional after vaccination and erythropoietin were made available. Although in most cases HBV infection is acquired during haemodialysis, transmission of the virus through the graft or perioperative blood transfusions might also be expected. Positivity for HBsAg at the time of transplantation is usually associated with the presence of chronic hepatitis as shown by histological studies even in the absence of abnormal serum transaminases [1].

The prevalence of anti-HCV in renal transplant patients, as assessed by second-generation immunoassays, ranges between 10 and 25% [2–4]. However, the polymerase chain reaction (PCR) revealed HCV infection in about 17% of the ELISA II negative patients [4]. The HCV infection is usually acquired during haemodialysis, but transmission via transplanted organs, again, is also possible. Although the HCV infection exposes renal recipients to chronic abnormal liver function tests, some 30–54% of patients with anti-HCV (ELISA II) [3,4] and 51% of HCV RNA positive recipients [2] can be expected to maintain normal liver function tests throughout their post-transplant follow-up. It has been well demonstrated that serum transaminases may be normal or fluctuating even in ELISA II or HCV RNA-positive subjects with an underlying chronic active hepatitis (CAH). Thus only liver biopsy gives reliable information on the state of chronic liver damage in HCV-infected patients.

Outcomes for liver function and patient survival

The prognostic significance of histological features in HBsAg-positive renal recipients is still controversial. Most of the available studies were done in patients treated with azathioprine and steroids. In a mean follow-up of 4.5 ± 4.3 years Rao et al. [5] did not

References


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observe any worsening in patients with steatosis or chronic persistent hepatitis (CPH). On the contrary, histological lesions had progressed to advanced damage or cirrhosis in patients with CAH at the initial biopsy. Parfrey et al. [6] reported progression to CAH and cirrhosis also in patients with morphological benign forms followed for a mean of 7 years.

Pirson et al. [7] reported that neither patient nor graft survival were negatively affected by HBsAg positivity in the first 2–3 years post-transplantation in patients treated with azathioprine and prednisone. In the long-term, however, a number of patients developed liver failure and eventually died of extrahepatic sepsis. In our experience with azathioprine-treated patients followed-up for at least 1 year, the 16-year patient survival rate was significantly better (75 versus 59%, P = 0.03) for the 186 HBsAg-negative than the 55 HBsAg-positive patients. The mortality rate for liver failure and/or sepsis was 16% for HBsAg-positive versus 3% for HBsAg-negative patients. Nevertheless, several patients still had functioning grafts and were in good clinical condition after 16 years or more. The outcome of HBsAg-positive patients taking cyclosporin is not clear yet. In a group of 300 cyclosporin-treated patients followed-up for at least 1 year we found no difference in the patient survival rate at 10 years (93 versus 94%) between 24 HBsAg-positive and 276 HBsAg-negative patients. However, the mortality rate from liver failure and/or sepsis was 4% for HBsAg-positive versus 0.7% for HBsAg-negative patients.

Few morphological data are available concerning HCV-positive renal recipients. Roth et al. [2] observed CPH in 40%, CAH in 50% and cirrhosis in 10% of HCV–RNA-positive patients biopsied 41–92 months after transplantation. Chan et al. [8] observed ‘minimal change’ in 53%, chronic lobular hepatitis in 8% and CAH in 38% of biopsies performed 39 ± 31 months after transplantation. The total histological score was negatively correlated with the duration of dialysis. Finally, a progressive worsening of liver damage was documented in repeat biopsies by Morales et al. [3] in 78% of ELISA-II-positive kidney recipients. Of them, 73% developed CAH and 27% cirrhosis over a period of 24–144 months after transplantation. The continuing advances in diagnostic assays of hepatitis C infection make it difficult to evaluate the preliminary results regarding the impact of HCV on the outcome of renal transplant patients. Early studies showed that the presence of anti-HCV at the time of transplantation does not adversely affect the patient and graft survival, at least in the short term. Roth et al. [2] found no differences at 5 years between RIBA-II-positive and -negative patients with regard to either patient (81 versus 80%) and graft survival (63 versus 63%). There were no deaths due to liver failure in these patients. However, further studies and longer follow-ups are needed to corroborate the current opinion.

**Selection of candidates for transplantation**

Whether or not the few HBsAg-positive dialysis patients should be excluded from a kidney transplant programme is still controversial. Only one small study has compared the clinical outcomes of HBsAg-positive dialysis and transplant patients [9]. The clinical outcome of 22 HBsAg-positive renal transplant patients treated with azathioprine was poorer than those of 31 HBsAg-positive dialysis patients. Chronic liver disease developed in 100% of transplant patients compared to 29% of dialysis patients. The overall mortality (64 versus 19%) and death of liver disease (36 versus 3%) were higher in transplant patients over a period of 10 years following the detection of HBsAg. Decisions about renal transplantation into HBsAg-positive patients should be based on the liver histology and on the markers of replication in serum.

HBsAg-positive patients with CAH are likely to have a high risk of cirrhosis after transplantation, whereas patients with morphologically benign forms of chronic liver disease might be expected to have a better outcome. Since chronic carriers of HBV may have CAH by biopsy even when liver enzymes are normal, liver biopsy is recommended whether or not liver function tests are normal. The indication for liver biopsy becomes mandatory if there is an even minimal but persistent increase in serum aminotransferases. The evaluation of HBeAg and/or HBV DNA in serum or in liver samples may also be helpful for selecting candidates for kidney transplantation and for assessing the aetiology of the liver disease in HBsAg-negative patients with chronic hepatitis. In fact, HBsAg-positive transplant patients without active viral replication prior to transplantation have better survival than patients with signs of viral replication [10]. Thus HBsAg-positive patients may be considered good candidates for renal transplantation, provided that there is no CAH and markers of viral replication are not detectable.

Candidates for transplantation with documented HCV infection and abnormal or fluctuating serum ALT should also undergo liver biopsy to assess the liver involvement and the degree of the hepatic damage precisely. For HCV-positive patients with normal liver enzymes, only a liver biopsy can confirm histological liver damage. However, all precautions should be taken before performing liver biopsies in uraemic patients, who may have haemostatic abnormalities. The available data suggest that HCV-positive dialysis patients with CPH or mild activity by liver biopsy may be accepted for renal transplantation. Although an unfavourable outcome of the liver disease cannot be completely excluded in the long term, for most patients with stable renal transplant function a good quality of life may be expected for many years. There are not sufficient data to determine whether HCV-infected patients with biopsy-proven advanced CAH or early cirrhosis should be transplanted or should remain on dialysis. As it is a common experience, however, that the course of liver disease is often progressive in immunosuppressed patients, we feel that such patients should be excluded from renal transplantation.
How should immunosuppressive therapy in transplant patients with chronic liver disease be handled?

Immunosuppressive therapy may enhance viral replication and exacerbate or accelerate the progression of chronic hepatitis B and C. A late reduction in the dosage of azathioprine seems not to cause any changes in the natural course of chronic hepatitis B, and therefore an early reduction in the dosage of the drug might be a possible approach for such patients. Corticosteroids seem to be particularly harmful, in that they favour viral replication. To avoid or minimize this risk the maintenance doses of prednisone should be kept as low as possible from the time of transplantation. As there is growing evidence that cyclosporin alone may lead to excellent graft survival, steroid-free immunosuppression might be tried for HBsAg-positive and/or HCV-positive patients. This is even more justified since HBsAg-positive and/or HCV-positive patients have a lower immunological reactivity. Unfortunately, however, no specific trial with such an immunosuppressive patients with viral infection has been done. Although immunosuppressive therapy should be kept as low as possible after transplantation, it cannot be ignored that rapid reduction of immunosuppressive therapy in patients with deteriorating liver function might accelerate liver damage in some cases. This paradoxical response is probably due to the fact that while immunosuppressive agents may protect from the autoimmune response to virus, in some cases an abrupt reduction or discontinuation of immunosuppressive therapy might lead to cytolysis and further destruction of the livers.

During immunosuppressive therapy, levels of serum HBV DNA may be a useful non-invasive method for monitoring both viral replication and progression of liver disease in patients with HBV. In some cases, however, one cannot manage patients properly without resorting to periodic liver biopsies in order to assess the activity and progression of liver damage. A decline in HBV DNA levels in patients with established CAH may reflect either reversal to CPH or the onset of cirrhosis [9].

Therapeutic approaches to eradication of viral replication are not available for patients with renal transplants. New antiviral agents such as adenine arabinoside 5'-monophosphate, prostaglandin E, and famciclovir are still under investigation. Although interferon-2 seems to be effective against chronic active hepatitis C, most investigators agree that this drug should be used with caution in kidney recipients in view of the observation that occurrence of relapses cannot be totally excluded and that there may well be graft rejection, especially in those patients with impaired graft function. It is paradoxical that for those who develop end-stage liver cirrhosis as a consequence of renal transplantation the only hope rests on transplantation of the liver.

References

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Delayed referral for dialysis

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Introduction

Age and non-renal comorbidity dominate survival in end-stage renal disease [1]. Modifiable factors include extracellular volume/blood pressure control [2], nutrition and solute clearance [3]. Experience of renal replacement therapy in elderly and 'complicated' patients, with inherently reduced survival, has sharpened awareness of morbidity and quality of life as complementary outcomes. Timely referral of patients with chronic renal failure to a nephrologist optimizes conservative management, including dialysis planning. Unfortunately many patients suffer a needlessly rough journey on the road to dialysis.