
Leading article

Hepatitis B virus infection and liver transplantation

Hepatitis B virus (HBV) infection is the commonest cause of chronic liver disease worldwide, and as such, remains an important indication for liver transplantation. Whereas transplantation is an effective treatment for patients with liver failure due to acute and chronic liver diseases, there are subgroups of patients, such as those with HBV infection, who have historically done poorly with transplantation. The five year survival rate for patients undergoing liver transplantation with hepatitis B infection is 50% in the absence of specific prophylactic treatments, compared with survival rates of 70%–85% for patients with alcoholic or cholestatic liver diseases.¹ Reduced graft and patient survival in patients with pretransplant HBV infection is largely related to the development of recurrent liver disease.^{2,3} Thus efforts to improve the outcome of HBV infected patients undergoing liver transplantation have focused on strategies to prevent reinfection. In recent years, several new treatments have become available which are improving the outcome of this patient group, lending a sense of optimism to clinicians caring for patients with this disease.

Natural history of post-transplantation infection

Early series from the United States and Europe suggested that the level of viral replication before transplantation was important in determining the risk of recurrent disease.^{2,4,5} In a series of 334 patients from 17 different European centres, risk of reinfection, defined by the presence of HBsAg in serum, was highest in patients with HBV related cirrhosis (mean (SE), 67 (4)%), lowest in patients with fulminant hepatitis B (17 (7)%), and intermediate for patients with HDV related infection (40 (16)% for fulminant HDV and 32 (5)% for HDV related cirrhosis).³ Within the subgroup of patients with chronic HBV related cirrhosis, risk of reinfection was also related to the level of viral replication before transplantation, with 83 (6)% of those who were HBeAg positive and HBV DNA positive (by hybridisation assay) developing recurrent infection compared with 58 (7)% of patients who were negative by both assays. The natural history of infection was generally not changed by retransplantation.⁶ In a United States series of 20 patients retransplanted for recurrent HBV infection, only one long term survivor was identified.⁶ Of the patients dying within the first 60 days after transplantation, sepsis was the most common cause of death. Of those dying after 60 days, death from recurrent HBV infection was common (n=8), with death from sepsis being less common (n=2). Thus in the absence of specific prophylactic therapy, retransplantation for recurrent HBV infection has an extremely poor prognosis. The availability of prophylactic hepatitis B immunoglobulin has changed this outcome, so that good results are now achievable.^{7,8} New treatments to prevent reinfection (see later) are changing our approach to the patient requiring retransplantation for recurrent HBV infection.

Pathology and pathogenesis

Most recipients of liver transplants who become HBsAg positive after transplantation have evidence of histological disease and, in general, the histological features are similar to those seen in non-transplant patients.⁹ The rate of histological progression is accelerated in some patients, with cirrhosis developing within two years of transplantation. Additionally, a rare histological variant called fibrosing cholestatic hepatitis has been described, which is typified by the presence of periportal and perisinusoidal fibrosis, ballooned hepatocytes with cell loss, pronounced cholestasis, and a paucity of inflammatory activity.^{9,10} Immunohistochemical stains show high cytoplasmic expression of viral antigens, suggesting that liver injury is due to a direct cytopathic effect of the virus. The clinical course is rapidly progressive and the outcome is usually fatal.⁹⁻¹¹ The pathogenesis of HBV related liver damage in the post-transplant patient is incompletely understood. Several mechanisms have been proposed. In immunocompetent patients, the primary mechanism of liver injury is immune mediated and the main target of this immune response is HBeAg expressed on the surface of the hepatocyte. Viral peptides in association with class I HLA antigens on the hepatocyte are presented to cytotoxic T cells expressing identical HLA antigens and the interaction of the HLA associated viral antigen with the cytotoxic T cell triggers an immune mediated response which results in tissue injury. In recipients of liver transplants, HLA antigens of the donor liver and recipients are not matched and hence the effectiveness of the cytotoxic T cell response in liver injury is less clear. The type and amount of immunosuppression may directly influence viral replication, and hence the degree of liver damage (see later). A direct cytopathic effect of HBV has been shown in transgenic mice which overproduce pre-S1.¹² Large amounts of pre-S1 lead to inhibition of secretion of HBsAg from the endoplasmic reticulum and the accumulation of viral proteins which are, in turn, directly injurious to liver cells. The findings in the transgenic mouse model are best paralleled by the findings in the fibrosing cholestatic variant of hepatitis B in humans.^{10,13} Immunohistochemical stains demonstrate large amounts of viral antigen with hepatocytes in association with hepatocyte necrosis and minimal inflammatory activity. Finally, specific viral mutations may be important in the pathogenesis of HBV infection post-transplantation. Mutations in the pre-core region with failure of HBeAg production have been associated with a particularly aggressive form of post-transplant HBV infection.¹⁴

Treatment strategies

The management strategies for patients with hepatitis B infection undergoing liver transplantation include: (a) patient selection; (b) modification of immunosuppression,

(c) passive immunoprophylaxis; and (d) pretransplantation and post-transplantation antiviral treatment.

PATIENT SELECTION

As previously highlighted, the rate of recurrent HBV infection is dependent on the level of viral replication before transplantation.^{3 5 15} Thus patients who have acute, fulminant hepatitis B or D, chronic HDV infection, or chronic HBV infection without detectable HBeAg or HBV DNA have a lower risk of reinfection and are considered better transplant candidates than patients with chronic HBV infection who have actively replicating virus.¹⁶ Selection of patients based upon their pretransplantation replicative state remains operational in many transplant programmes, but the availability of new treatments may be obviating the need for selection on this basis. Coexisting hepatocellular carcinoma is not uncommon in patients with HBV infection referred for liver transplantation. The presence of large lesions (greater than 5 cm in diameter) is associated with poor long term prognosis irrespective of HBV infection.¹⁷

MODIFICATION OF IMMUNOSUPPRESSION

In non-transplant patients with chronic hepatitis B infection, immunosuppression has been associated with reactivation of quiescent infection and, in some cases, with rapidly progressive disease.¹⁸ Steroids have a deleterious effect, which may be related to the presence of a corticosteroid responsive promoter region in the HBV genome, the activation of which leads to increased viral replication.^{19 20} Rapid reduction in the dose of corticosteroids in liver transplant recipients with HBV infection is common practice in many transplant programs, although the efficacy of this approach is not proven. Reduced doses of prednisolone do not seem to increase the risk of rejection.²¹ Further studies are needed to determine the independent contribution of specific immunosuppressive agents to the risk of recurrent disease. The dose and type of immunosuppression used may be less important when prophylactic hepatitis B immunoglobulin or pre-emptive antiviral treatment are being used concomitantly.

PASSIVE IMMUNOPROPHYLAXIS

Several series have shown the effectiveness of hepatitis B immunoglobulin (HBsIg) in reducing the rate of recurrent HBV infection after transplantation.^{3 8 22-24} In a large multicentre study from Europe, the rate of recurrent HBV infection after three years was only 30% in patients receiving long term prophylactic HBsIg treatment (for at least six months) compared with 67% in those given no prophylaxis.³ In most centres, HBsIg is given during the anhepatic phase and daily for the first week after transplantation. Subsequent schedules of administration vary from centre to centre but in most European centres, the frequency of HBsIg administration is determined by the titre of anti-HBs in serum. Administration of HBsIg at intervals sufficient to achieve anti-HBs titres of 100–500 IU/l has resulted in overall rates of recurrence of 20–50%. The patients represented at the higher end of this range are those with markers of active viral replication before transplantation.^{15 22 23 25 26} At the University of California, San Francisco, HBsIg is given on a fixed monthly schedule after the initial week of infusions.⁸ The monitoring of patients is simplified because anti-HBs titres are not used to determine the frequency of dosing and the rate of recurrence is acceptable (17% at two years).⁸ Moreover,

the high anti-HBs titres which are achieved with this regimen (mean titre=1275 mIU/ml, SD 531 mIU/ml) seem to override the adverse effects of pre-transplantation active viral replication on risk of recurrence.^{8 24} Long term HBsIg treatment seems to be important. In the multicentre European study, the risk of recurrence was 36 (4)% in patients receiving at least six months of HBsIg, but was substantially higher (74 (5%) in those receiving treatment for two months or less.³ Recurrent infection has been documented in patients in whom HBsIg was discontinued after one year.¹⁶ Despite the clear efficacy of prophylactic HBsIg therapy, this treatment has limitations. The major disadvantages are high cost and limited availability. Treatment with HBsIg in the United States adds \$10 000–\$50 000 to the first year's charges for a liver transplant and \$5000–\$20 000 to each subsequent year. With the many HBV patients who are potential candidates for liver transplantation, supply of HBsIg has not kept pace with the demand. With other therapeutic agents on the horizon (see later), the use of long term, high dose HBsIg treatment will likely diminish.

ANTIVIRAL TREATMENTS PRETRANSPLANTATION AND POST-TRANSPLANTATION

Antiviral drugs may be used as: (1) pre-emptive treatment, in which the primary goal is prevention of graft reinfection after transplantation; or as (2) post-transplant treatment for patients with overt recurrence of HBV infection, in which the primary goal is to stabilise graft function and control disease progression. Pre-emptive treatment is an attempt to decrease HBV replication to undetectable levels, with the implication that once achieved, this will substantially reduce the rate of post-transplant infection. In some cases, successful treatment before transplantation may delay or even obviate the need for liver transplantation. Pre-emptive treatment begins before transplantation and continues for variable duration after transplantation.

Interferon- α

Interferon- α (IFN- α) is an effective antiviral agent in immunocompetent patients with chronic hepatitis B, resulting in a loss of HBeAg and HBsAg more often (20% and 6%, respectively) than in patients given no treatment.²⁷ It has been used both before and after liver transplantation.^{2 28-30} In a controlled study pre-emptive IFN- α failed to reduce the rate of HBV reinfection.²⁹ However, rates of recurrence were lower in treated patients who lost HBV DNA prior to transplantation, than in those with ongoing viral replication, suggesting that loss of HBV DNA before transplantation is an important therapeutic end point for pre-emptive treatment.²⁹ In a few studies, IFN- α treatment before transplantation has been associated with stabilisation of liver disease and postponement of the need for transplantation.^{29 31} A major limitation of giving IFN- α before transplantation has been its poor tolerability in patients with decompensated disease. Dosage reduction is frequent, which in turn, limits the antiviral efficacy of the drug. There have been no controlled trials examining the efficacy of interferon in the treatment of HBV infection post-transplantation. In a series of 14 liver transplant patients with recurrent HBV, HBV DNA but not serum alanine aminotransferase concentrations fell with IFN- α treatment.²⁸ Loss of HBV DNA (by hybridisation assays) was seen in four, loss of HBeAg in two, and loss of HBsAg in one patient with treatment.²⁸ A theoretical risk associated with use of IFN- α in patients with transplants is that enhanced HLA expression on

epithelial cells of the bile duct by IFN- α could lead to allograft rejection. The magnitude of this risk (if any) is controversial.^{28-30 32-35} Conflicting results regarding risk of rejection may be related to: (1) the duration of time between transplantation and initiation of IFN- α treatment; (2) the frequency of previous episodes of rejection; (3) the type of concomitant immunosuppression; and (4) the total dose of IFN- α given. At the present time, the risk of acute rejection associated with post-transplantation IFN- α usage cannot be quantified.

Nucleoside analogues

Nucleoside analogues such as lamivudine and famciclovir have engendered much enthusiasm in the transplant setting. Both drugs have potent anti-HBV activity and are given orally.^{36 37} Lamivudine, the (-) enantiomer of 2'-deoxy-3'-thiacytidine, inhibits the reverse transcriptase of HBV by interfering with synthesis of the proviral DNA chain from viral RNA. Unlike other dideoxynucleosides, lamivudine does not inhibit and is not incorporated into mitochondrial DNA, which has been associated with major toxicities with other nucleoside analogues.³⁸ In the first randomised, placebo controlled, dose ranging study conducted in North America and Europe, lamivudine at doses of 100 mg/day and higher for 28 days, produced a greater than 98% reduction in circulating HBV DNA during treatment.³⁹ Although a breakthrough of HBV DNA did not occur during treatment, HBV DNA rebound was found in most patients after discontinuation of lamivudine.³⁹ In a second randomised study, the efficacy of lamivudine was evaluated over a narrower range of doses (25, 100 and 300 mg daily) and for a longer duration (12 weeks).⁴⁰ Concentrations of HBV DNA fell in all patients on treatment and became undetectable by hybridisation assays in 100% of patients receiving 100 and 300 mg/day. In the follow up period, 81% of patients experienced a rebound, with HBV DNA concentrations again becoming detectable. However, in six (19%) patients including some who had previously failed to respond to IFN- α treatment, a sustained suppression of HBV DNA was associated with normalisation of alanine aminotransferase and loss of HBeAg in four of six patients. Preliminary data on the use of lamivudine in recipients of liver transplants are available.^{41 42} In four patients given 100 mg lamivudine daily for at least four weeks before transplantation, serum HBV DNA concentrations were undetectable or borderline positive (by bDNA assay) in all patients post-transplantation, all post-transplant biopsy specimens were negative for HBsAg and HBeAg on immunostaining, and two patients became HBsAg negative. Prospective trials using lamivudine in transplant recipients are ongoing. Famciclovir, the prodrug for penciclovir, is a guanosine analogue which inhibits HBV DNA and viral protein synthesis. By contrast with other drugs within the family of guanosine analogues, such as acyclovir and ganciclovir, famciclovir has good bioavailability after oral administration (about 80%).⁴³ In a pilot study by Kruger *et al.*, 12 liver transplant recipients with HBV reinfection were treated with famciclovir (500 mg thrice daily) for a mean duration of 13.5 months (range 3-30 months).⁴⁴ Dosage adjustment was required for patients with renal insufficiency. Concentrations of HBV DNA decreased by 55%-100% during famciclovir treatment in nine of 12 patients. Two responders seroconverted from HBeAg to anti-HBe and one patient also became HBV DNA by polymerase chain reaction. In three patients, a sustained decrease in the concentrations of HBV DNA did not occur after at least three months of treatment. No significant adverse effects were noted with treatment periods up to

30 months. A multicentre, randomised trial in currently underway to evaluate further the effectiveness of famciclovir in preventing recurrent HBV infection in liver transplant recipients (as pre-emptive treatment).

The future

The management of HBV infected patients referred for liver transplantation is undergoing an exciting period of change. The positive impact of HBsIg immunoprophylaxis on post-transplant outcome is clearly established but limitations of cost and availability have provided the impetus to find alternatives. The preliminary results with the nucleoside analogues, lamivudine and famciclovir, are encouraging and the final results of the clinical trials which are now in progress are eagerly awaited. Unconsidered issues include (1) the optimal duration of treatment necessary to achieve appropriate treatment end points; (2) elucidation of the mechanisms of treatment failure or "breakthrough"; (3) evaluation of the cost efficacy of specific drug treatments given either alone or in combination. Clinical and virological "breakthroughs" during treatment have been described with HBsIg,^{8 22-24} IFN- α , lamivudine^{42 45 46} and famciclovir.⁴⁴ The aetiology of these breakthroughs is under investigation. Preliminary evidence suggests that mutations in the HBV genome facilitate the "escape" of HBV from the inhibitory effects of the specific treatment, in some cases.⁴⁵⁻⁴⁷ Full information on the frequency and the clinical consequences of these breakthroughs is awaited. Future therapeutic strategies will likely include several drugs given either concomitantly or sequentially. As more therapeutic options become available, studies on the most cost effective strategy will be needed to guide clinicians in their decision making.

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