Hepatitis B virus and liver transplantation

D. Samuel

Centre HépatoBiliaire, Université Paris Sud, Hôpital Paul Brousse, 94800 Villejuif, France.

Introduction

Liver disease due to hepatitis B (HBV), is affecting many patients candidates for liver transplantation. Viral recurrence after liver transplantation is a major issue. Acute or chronic liver disease on the graft secondary to viral reinfection may lead to graft failure, retransplantation or death (1,2).

The spontaneous risk for HBV reinfection after transplantation is around 80 per cent (3,4). HBV reinfection is the consequence of either an immediate reinfection of the graft due to circulating HBV particles or of a reinfection of the graft from HBV particles coming from the extrahepatic sites. The latter mechanism is mainly involved in the reinfection of the graft of patients receiving anti-HBs immunoglobulins (5). In patients receiving anti-HBs Ig, HBV reinfection may be the consequence of HBV overproduction coming from extrahepatic sites, or of a too low protective titer of anti-HBs Ig, or of emergence of escape mutants. This latter mechanisms is probably important since mutations in the pre S/S genome of HBV and in the "a" determinant have been described (6). We have shown in a patient with HBV reinfection that the HBV strain predominant after reinfection was the strain predominating in the mononuclear cells of this patient before liver transplantation (7). These mechanisms of escape mutation are not exclusive, since HBV reinfection was shown with a non mutated form of HBV.

Role of the initial liver disease and of the pretransplant viral B replication level on HBV recurrence after liver transplantation

HBV infection recurrence was shown to be higher in patients with viral B cirrhosis than with viral B-Delta cirrhosis and with fulminant hepatitis B (8). This was later confirmed in a European multicenter study which showed that recurrence of HBV occurred in 67% of patients transplanted for HBV cirrhosis, 40% of those transplanted for HDV fulminant hepatitis, 32% of those transplanted for HDV cirrhosis, and 17% of those transplanted for HBV fulminant hepatitis (9).

The pretransplant HBV DNA status detected using conventional hybridisation technique was the best accurate predictor of HBV recurrence after transplantation (9,10). In the multicenter European study, HBV recurrence rate was 83% in HBV DNA and HBeAg positive HBV-cirrhosis ; 66% in HBV DNA negative and HBeAg positive HBV-cirrhosis ; and 58% in HBV DNA and HBeAg negative HBV-cirrhosis ($p = 0.05$) (9).

Graft lesions due to HBV

HBV reinfection is characterized by appearance of HBsAg in serum, and is associated with reappearance of HBV DNA in serum. After HBsAg reappearance, HBV replication level is usually high and high amount of HBV particles are present in the graft (1,2,11). HBV reinfection have a major impact on graft and patient survival (9). Indeed in the absence of HBV reinfection, graft histology remains normal (8). In contrast, almost all patients with HBV reinfection will develop graft disease (2,8). In most cases, acute lobular hepatitis will occur with an evolution to chronic active hepatitis. In some cases, acute liver failure can be observed. This severe evolution is probably related to the high amount of HBsAg, HBeAg and HBcAg present in the nuclei and the cytoplasm of the hepatocytes. A particular form named fibrosing cholestatic hepatitis have been described by the group at King's College, it is characterized clinically by a severe outcome leading to graft failure within months, and histologically by a cholestatic pattern, with few necrosis, rapid development of fibrosis, enormous amount of HBsAg and HBeAg in the liver (12,13).

Prevention of HBV graft reinfection

The administration of anti-HBs Ig during the anhepatic phase and short term posttransplantation period gave disapointing results since most of the patients developed HBV reinfection (3). In contrast the long-term administration of high doses of anti-HBs Ig reduces drastically the rate of HBV recurrence (8,9,10,14). Our own protocol of long-term passive immuno prophylaxis was based on the principle of an indefinite administration of anti-HBs Ig. Our patients received 10000 IU/l during the anhepatic phase then 10000 IU/l of anti-HBs Ig every day during the 6 post-operative days, then the level of anti-HBs was assessed weekly and 10000 IU of

Correspondence : D. Samuel, Centre Hépatobiliaire Hôpital Paul Brousse, 12 Av. P. V. Couturier, 94800 Villejuif, France.
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anti-HBs Ig were readministered when anti-HBs was less than 100 IU/l. Using this protocol, the overall actuarial rate of reappearance of HBsAg was 17%, 26%, and 27% at 1, 3 and 10 years respectively. The 10-year recurrence rate of HBV infection was significantly higher in patients with viral B cirrhosis (55%) than in those with fulminant hepatitis (7%) or with viral B-Delta cirrhosis (16%) ; it was significantly higher in patients with viral B cirrhosis who were serum HBV DNA positive before transplantation than in those who were HBV DNA negative (80% vs 27%). Recent reports using very high doses of anti-HBs Ig, and maintainance titers over 500 IU/l showed promising results event in patients who were HBV DNA positive before transplantation (15). More recently the administration of lamivudine alone (without concommitent administration of anti-HBs Ig) after transplantation, gave promising results at one year with only 1 case of recurrence out of ten (16). However the rate of escape mutations with HBV reinfection was 50% with a longer follow-up. Combination of HBIG and lamivudine seems promising.

Antiviral treatment prior to transplantation

The presence of HBV replication was considered as a contraindication to transplantation by most centers (17, 18). Thus an antiviral treatment in order to clear HBV DNA from serum is logical. However, patients candidates to liver transplantation are difficult to treat because of the severity of the liver disease. Alpha recombinant interferon is difficult to manage in this setting and did not reduce HBV recurrence after transplantation (19). It should be emphasized that when patients were HBV DNA negative by PCR in serum the risk of viral B recurrence is low suggesting that a prolonged course of treatment or a more potent antiviral agent may have a place for the treatment of these patients. Lamivudine (3TC) give very good results however if treatment is prolonged, the risk of viral breakthrough before transplantation is high.

Treatment of graft infection with HBV

The treatment of HBV infection of the graft is difficult due to the high level of viral B replication, the ongoing immunosuppressive treatment and the rapid evolution of graft disease. Interferon has been used subsequently to transplantation but has not been shown to be effective in a study from Pittsburgh (20). In a study from Terrault *et al.*, 14 transplanted patients with recurrent hepatitis B infection were treated with recombinant alpha interferon 3 million units 3 times weekly for a mean period of 23 weeks. Four out of 14 have a complete virological response with loss of HBV DNA from serum. Among the 10 non responders, one patient developed chronic rejection, and was retransplanted, 3 were retransplanted for recurrent hepatitis B, 3 died and 3 are alive with persistence of serum HBV DNA (21). ARA AMP decrease viral B replication but its antiviral effect is transient (22). Nucleoside analogues such as Ganciclovir (23), Famciclovir (24), Lamivudine, are promising in this setting, since they do not augment the risk of rejection, they have a potent antiviral effect, and are well tolerated. The more potent agent is undoubtly lamivudine. Indeed in a recent report 90% of the HBV reinfected patients became HBV DNA negative at 2 months, at one year 60% are still HBV DNA negative and the rate a breakthrough was 27% (25). All these antiviral agents should be used for long period of time. Indeed there is a high risk of rebound of viral replication when these agents are stopped.

Survival of patients transplanted for HBV cirrhosis

In the absence of prophylaxis, of HBV reinfection, the 10-year survival is low between 40 and 50%, and HBV related deaths are frequent after 6 months post-transplant. In patients receiving adequate immunoprophylaxis, the 10 year survival is similar to patients transplanted for other liver diseases. In our own series, The 10 year survival of patients transplanted for HBV cirrhosis was 72%.

Conclusion

The prevalence of HBV recurrence after liver transplantation is higher in patients with viral B cirrhosis than in patients with viral B-D cirrhosis or fulminant hepatitis B and is related to the presence of HBV replication prior to transplantation. Long term passive anti-HBs immunoprophylaxis is the best current way for prevention of HBV reinfection and improve long term survival. New nucleoside analogues such as Lamivudine are a promising approach for patients with viral B replication before transplantation. These patients are now candidates to transplantation providing they receive antiviral treatment before transplantation and combination of anti-HBs passive immunoprophylaxis and antiviral treatment after transplantation.

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