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End-Stage Liver Disease and Liver Transplantation: Role of Lamivudine Therapy in Patients With Chronic Hepatitis B

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Chronic infection with hepatitis B virus (HBV) is a common cause of advanced liver disease, including end-stage liver disease. Liver transplantation is generally regarded as the treatment of choice for decompensated cirrhosis. Although long-term prophylaxis with hepatitis B immune globulin (HBIg) has improved significantly the outcome after transplantation, about 20–36% of transplant recipients still develop recurrent hepatitis B and have reduced survival. Moreover, HBIg prophylaxis has a number of disadvantages, including high cost, difficulty in administration and tolerability problems. Lamivudine, an oral nucleoside analogue, is a potent inhibitor of HBV replication and has been investigated in end-stage liver disease and liver transplantation. Treatment with lamivudine results in suppression of viral replication, and clinical improvement and stabilisation of some patients with end-stage liver disease, leading to increased pre-transplant survival as well as a reduced need for transplantation. Prophylaxis with lamivudine is also effective in preventing recurrent HBV infection and graft reinfection after transplantation, although a combination of lamivudine plus HBIg is preferable to prevent the emergence of YMDD variant HBV (tyrosine-methionine-aspartate-aspartate amino acid motif of HBV polymerase). Lamivudine is also effective for the treatment of recurrent hepatitis B after transplantation, based on improvement in virological parameters of infection as well as clinical and histological manifestations of disease. In all of these clinical settings, lamivudine is well tolerated and dose reduction is not required. In conclusion, lamivudine has a potential role for the treatment of patients with hepatitis B-related end-stage liver disease, for prophylaxis in patients undergoing liver transplantation, and in the treatment of recurrent or de novo HBV infection after transplantation. ***J. Med. Virol. 61:403–408, 2000.*** © 2000 Wiley-Liss, Inc.

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection is a common cause of advanced liver disease, including decompensated end-stage liver disease (ESLD). Prognosis is poor: 5-year survival rates decrease from 84% in patients with compensated cirrhosis to 14% in patients with decompensated disease [De Jongh et al., 1992]. Moreover, patients with compensated chronic hepatitis B associated with active viral replication are more likely to have progressive disease and a poorer prognosis than patients in a low replicative state [De Jongh et al., 1992]. Ultimately, many patients with advanced HBV infection become potential candidates for liver transplantation.

Until recently, HBV infection was regarded as a relative contraindication for liver transplantation, due to poor long-term outcome post-transplantation. Recurrent HBV infection was the most common cause of death occurring more than 60 days after liver transplantation in patients who underwent this procedure for end-stage hepatitis B [Todo et al., 1991]. In fact, the 5-year survival rate in HBV-infected patients undergoing transplantation was about 50%, substantially lower than in any other group of transplanted patients, except those with hepatic malignancies [Terrault, 1999]. Although the precise mechanism of recurrent hepatitis B post-transplantation is incompletely understood, increased levels of HBV replication and altered host responsiveness are probable contributory factors.

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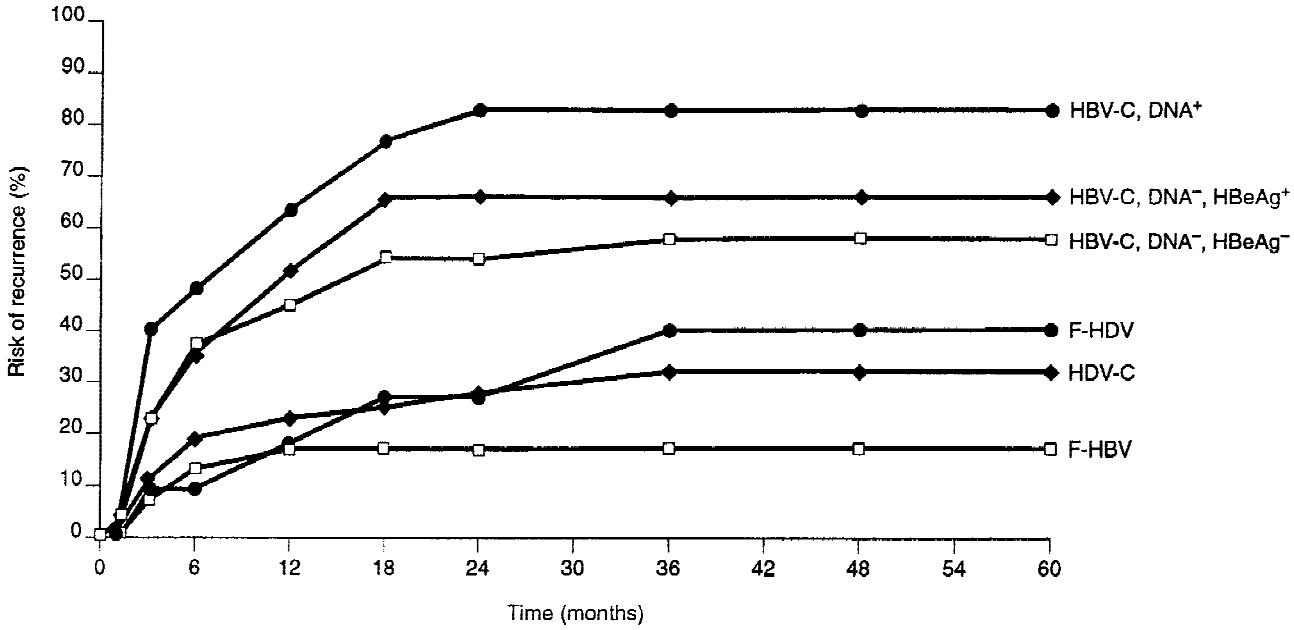

Fig. 1. Actuarial risk of recurrence of hepatitis B virus (HBV) infection as indicated by the detection of hepatitis B s antigen (HBsAg), according to type of liver disease and pre-transplantation viral replication status. HBV-C, HBV-related cirrhosis; HDV, hepatitis D virus; F-HDV, fulminant HDV; HDV-C, HDV- related cirrhosis; F-HBV, fulminant HBV; DNA+, presence of HBV DNA; DNA−, absence of HBV DNA. Reproduced with permission from Samuel et al., 1993.

FACTORS INFLUENCING RECURRENT HBV INFECTION

Retrospective analysis [Samuel et al., 1993] showed conclusively that patients with evidence of active viral replication before transplantation were at increased risk of recurrent HBV infection (Fig. 1) and mortality. Factors predictive of a lower risk of recurrent infection and mortality were the absence of hepatitis B e antigen (HBeAg), the absence of HBV DNA, the presence of hepatitis D superinfection and the presence of fulminant hepatitis before transplantation. Other early reports suggested that patients with pre-core mutant disease and Asian patients were more likely to have recurrent HBV infection and poorer outcome, although more recent reports have not confirmed these initial observations [Ho et al., 1997; Naumann et al., 1997].

ISSUES IN IMMUNOPROPHYLAXIS

In a large study [Samuel et al., 1993], long-term administration of hepatitis B immune globulin (HBIg) before and after transplantation substantially reduced the incidence of recurrent HBV infection to 36% at 2 years of follow-up (Fig. 2) and resulted in improved survival. Several studies [König et al., 1994; McGory et al., 1996; Terrault et al., 1996] confirmed subsequently the efficacy of long-term HBIg therapy for prophylaxis against recurrent HBV infection in liver transplant recipients.

HBIg is now well established as prophylaxis for recurrent HBV infection in liver transplant recipients. Yet, despite a favourable long-term outcome after transplantation, HBV recurrence rates are still about 20–36% [Samuel et al., 1993; Terrault, 1999], with evidence of residual virus (HBV DNA) in the serum and liver of most patients [Terrault, 1999]. Passive immunoprophylaxis with HBIg is not as effective in patients who receive transplants at a time of high rates of viral replication [Samuel et al., 1993], with HBV reinfection occurring in up to 90% of patients who are HBV DNA-positive before transplantation [Van Thiel et al., 1997]. In addition, HBIg prophylaxis is expensive (US $30,000–50,000 per year) [Keeffe EB, personal communication], unavailable periodically, poorly tolerated in some patients and cumbersome to administer.

POTENTIAL ROLE OF LAMIVUDINE

Lamivudine, a nucleoside analogue, is a potent inhibitor of HBV replication [Chang et al., 1992; Furman et al., 1992]. Lamivudine is the first effective oral treatment for patients with chronic hepatitis B [Dienstag et al., 1998; Lai et al., 1998; Schiff et al., 1998]. It is well tolerated [Leung et al., 1998], and no reduction in dosage is required in patients with impaired liver function [Johnson et al., 1998].

There is now promising evidence that lamivudine is well tolerated and beneficial in the management of patients with hepatitis B-related ESLD before and after liver transplantation, as part of a prophylactic regimen for recurrent HBV infection. Moreover, lamivudine may prove useful in the stabilisation of graft function and the control of disease progression in transplant recipients who subsequently develop recurrent hepatitis B.

Lamivudine may also be associated with substantial cost savings. Administration of lamivudine, 100 mg/day, before and after liver transplantation (without

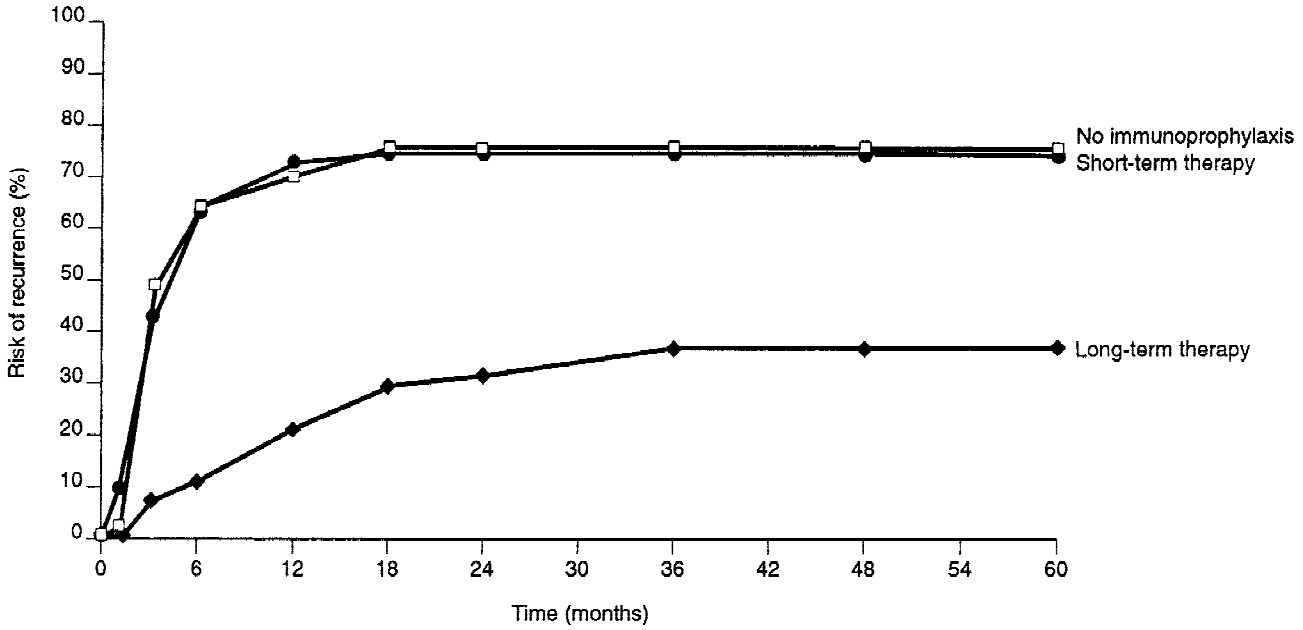

Fig. 2. Actuarial risk of recurrence of hepatitis B virus (HBV) infection, according to the duration of passive prophylaxis with hepatitis B immune globulin. Reproduced with permission from Samuel et al., 1993.

concomitant use of HBIg) costs US $1576 per year [Glaxo Wellcome Inc., unpublished data], substantially less than the US $30,000–50,000 for HBIg therapy alone.

TREATMENT OF ESLD

Although interferon (IFN) alpha therapy has been previously the standard therapy for patients with HBV infection, IFN alpha therapy is generally contraindicated in patients with advanced liver disease, particularly in those with decompensated disease who demonstrate a poor response to therapy [Hoofnagle et al., 1993]. Moreover, IFN alpha therapy is complicated in these patients by the need for careful titration and by serious side effects, particularly exacerbation of the underlying HBV infection and bacterial infections including pneumonia and peritonitis. Liver transplantation is currently the only option for patients with decompensated ESLD secondary to chronic hepatitis B.

LAMIVUDINE IN ESLD

The safety and efficacy of lamivudine has been evaluated in patients with ESLD resulting from chronic infection with HBV (i.e., HBV DNA-positive) in the setting of clinical studies of the therapeutic role of lamivudine before and after liver transplantation [Sponseller et al., 1998; Van Thiel et al., 1997; Villeneuve et al., 1997; Yao F, personal communication]. After prolonged treatment with lamivudine 100 mg daily (in early studies some patients received 150 mg/day), all patients became HBV DNA-negative (as assessed by polymerase chain reaction) despite concomitant use of immunosuppressant therapy, and some patients also became HBeAg-negative [Sponseller et al., 1998; Yao F, personal communication]. Most patients remained HBV DNA-negative during prolonged follow-up. This suppression of viral replication was associated with clinical improvement, as demonstrated by significant decreases in serum aminotransferases, bilirubin and alpha-fetoprotein concentrations, and improvements in Child-Pugh scores and functional status [Sponseller et al., 1997; Yao F, personal communication]. Lamivudine was well tolerated and dose modifications were generally not required.

In a multicentre study in the US and Canada, 27 patients with HBV-associated ESLD who did not undergo anticipated liver transplantation were treated with lamivudine 100 mg orally once daily ([Perrillo et al., 1999b]). The median duration of treatment was 762 days (range, 5–1128 days). Treatment resulted in disease stabilisation in many patients, with improvements in signs of hepatic decompensation affording prolonged periods of pre-transplantation survival. The results indicated that in some patients, lamivudine treatment may obviate or delay the need for liver transplantation.

YMDD variant HBV (tyrosine-methionine-aspartate-aspartate amino acid motif of HBV polymerase) has been observed in a small proportion of patients with advanced disease [Villeneuve et al., 1997; Yao F, personal communication]. The effect of the presence of YMDD variant HBV on lamivudine treatment of transplant patients is unclear at present. Studies in other patient groups, however, have indicated that patients may continue to derive clinical benefit from lamivudine treatment despite the emergence of the YMDD variant HBV [Atkins et al., 1998; Lai et al., 1998; Tassopoulos et al., 1999].

Thus, lamivudine seems to have a role in the stabilisation of disease for many patients with ESLD as a result of chronic hepatitis B, who are considered generally as potential candidates for liver transplantation. Improvement in the manifestations of hepatic decompensation resulted in increased pre-transplantation survival and even obviated the need for transplantation in some patients.

PROPHYLAXIS IN LIVER TRANSPLANTATION

HBIg prophylaxis is expensive, cumbersome to administer, poorly tolerated in some patients, and associated with HBV recurrence rates of about 20–36% [Samuel et al., 1993; Terrault, 1999]. Lamivudine has been investigated as a potential therapeutic option for HBV prophylaxis before liver transplantation. In various open-label studies of patients with advanced hepatitis B-related liver disease undergoing liver transplantation [Grellier et al., 1996; Markowitz et al., 1996; Perrillo et al., 1999c], lamivudine was administered before and after transplantation. Efficacy was assessed by improvement in serological markers of HBV. In the largest of these studies, 47 of the enrolled patients underwent liver transplantation [Perrillo et al., 1999c]. Of the 34 patients with available data at week 52 after transplantation, 24 (71%) had lost hepatitis B surface antigen (HBsAg). Of the 10 (29%) patients who were HBsAg-positive, seven were also HBV DNA-positive. Analysis carried out for five of the seven HBV DNA-positive patients showed that three had detectable YMDD variant HBV.

Of the 26 patients (55%) who were HBV DNA-positive at entry to the study, 18 had available data at week 52. Of these 18, eight (44%) were HBsAg-positive at week 52, and six of the eight were also HBV DNA-positive. Twenty-one patients (45%) were HBV DNA-negative at study entry, and for 16 of these patients data were available at week 52: two (13%) of the patients were HBsAg-positive, one of whom was also HBV DNA-positive.

The results of this study indicated that although markers of HBV reinfection were observed in some patients, most patients were clinically stable at 1 year after transplantation. Similar findings were observed in other studies [Grellier et al., 1996; Markowitz et al., 1996]. In all studies, lamivudine therapy was generally well-tolerated.

Thus, although lamivudine monotherapy is effective for prophylaxis against hepatitis B recurrence after transplantation, viral breakthrough and development of YMDD variant HBV do occur.

COMBINATION THERAPY: LAMIVUDINE AND IMMUNOPROPHYLAXIS

Mechanistic evidence suggests that the combination of lamivudine with HBIg may be synergistic in this setting. Because lamivudine is a potent inhibitor of viral replication, it is less likely that the viral binding capacity of HBIg would be overwhelmed and there would be little pressure to select for HBIg-resistant mutations. In addition, HBIg may provide humoral immunity and therefore limit viral spread, and indirectly inhibit viral replication, thereby reducing the likelihood of YMDD variants emerging.

Various studies [Dodson et al., 1998; Han et al., 1998; Markowitz et al., 1998; Marzano et al., 1999; Roche et al., 1999] have investigated the combination of lamivudine and HBIg given long-term as prophylaxis against the recurrence of hepatitis B in patients undergoing liver transplantation. All of these studies demonstrated that prophylaxis with the combination of HBIg and lamivudine was highly effective in preventing recurrent HBV infection in the graft. After transplantation, the majority of patients remained seronegative for HBsAg or HBV DNA (median follow-up, 5–35 months). Furthermore, only one patient [Marzano et al., 1999] had evidence of escape mutants with the combined regimen. These data suggest that the synergistic actions of combined lamivudine and HBIg prophylaxis outweigh any theoretical disadvantages of cross-resistance.

The optimal dose regimen for lamivudine and HBIg combination prophylaxis remains the subject of ongoing investigation. To minimise the disadvantages associated with HBIg therapy—high cost, limited availability, variable tolerability and patient inconvenience due to mode of administration (intramuscular or intravenous)—the efficacy and tolerability of the combination of short-term HBIg and long-term lamivudine therapy has been investigated [Terrault et al., 1998]. Of 52 patients studied, 29 patients received HBIg monotherapy as long-term prophylaxis and 23 patients received lamivudine with short-term HBIg given for 6 months after transplantation. At 2 years' follow-up after transplantation, there was no evidence of HBV recurrence in patients who received combination prophylaxis, whereas 22% of patients who received HBIg monotherapy developed recurrent infection; patient survival in the two groups was 90% and 81%, respectively. Thus the combination of lamivudine with short-term HBIg was at least as effective in preventing HBV recurrence as HBIg monotherapy. Given the substantial cost associated with long-term HBIg monotherapy, the combination of short-term HBIg and long-term lamivudine would be an effective and less costly alternative for HBV prophylaxis. Pharmacoeconomic analyses [Pasha et al., 1998] suggest that combined short-term HBIg and lamivudine prophylaxis may even be cost effective in this setting.

TREATMENT OF RECURRENT HBV INFECTION POST-TRANSPLANTATION WITH NUCLEOSIDE ANALOGUES

Despite effective prophylaxis with HBIg, lamivudine or a combination of these treatments, between 20% and 36% of patients still develop recurrent or de novo HBV infection after transplantation [Samuel et al., 1993; Terrault, 1999]. In this setting, the infection induces frequently aggressive and accelerated disease, such as fibrosing cholestatic hepatitis, leading to liver failure.

TABLE I. Relative Potency of Nucleoside Analogues for Recurrent Hepatitis B Virus Infection Post-Transplantation

Drug	Dose (route of administration)	Antiviral potency
Ganciclovir	7.5–10 mg/kg (intravenous)	++
Famciclovir	500–750 mg three times daily (oral)	+++
Lamivudine	100 mg/day (oral)	++++

To date, there is no effective therapy for post-transplantation hepatitis B. IFN alpha has limited efficacy in this setting and is poorly tolerated [Perrillo, 1993]. Attention has subsequently focused on the use of the nucleoside analogues (ganciclovir, famciclovir and lamivudine). Ganciclovir was the first of these agents to be used in this setting; however, efficacy was limited by its relatively modest antiviral activity and treatment was cumbersome because of the need for intravenous administration [Gish et al., 1996]. In addition, histological improvement with famciclovir has not been well-documented [Krüger et al., 1996]. On the basis of the relative antiviral potency of the three agents (Table I), lamivudine would be expected to be the most effective and would offer practical advantages.

Preliminary studies [Ben-Ari et al., 1997; Andreone et al., 1998; Nery et al., 1998] indicated that the use of lamivudine was a promising therapeutic approach in this setting. In one of these studies [Andreone et al., 1998] early initiation of lamivudine treatment, after the detection of HBsAg post-transplantation, induced sustained inhibition of viral replication. Patients became HBV DNA-negative rapidly (within 8 weeks), with subsequent normalisation of serum aminotransferase levels within 24 weeks for all patients. Serum HBsAg loss occurred 12–60 weeks after the initiation of therapy in 7 out of 12 patients (64%).

These promising results were subsequently confirmed in a large, multicentre study [Perrillo et al., 1999a]. Fifty-two transplant recipients received lamivudine, 100 mg/day, for 1 year after a diagnosis of recurrent HBV. At follow-up, 60% of patients had lost detectable serum HBV DNA, and 31% of the initially positive patients had lost HBeAg. Not only did lamivudine therapy result in the loss of markers of viral replication and an improvement in the hepatic biochemical profile (serum aminotransferase levels normalised in 71% of patients), but treatment was also associated with a significant improvement in, or stabilisation of, liver histology, specifically with respect to portal, periportal and lobular necrosis. This effect was most pronounced in patients who experienced a substantial decrease in intrahepatic hepatitis B core antigen. Although YMDD variants were detected in 27% of patients, there was no consistent evidence that the presence of such variants was associated with the progression of hepatic disease. Serum aminotransferase levels after breakthrough often remained below pretreatment values, and there was a sustained improvement in histology relative to the baseline.

Overall, these data indicate that lamivudine is an effective oral therapy for the treatment of hepatitis B after liver transplantation.

CONCLUSION

The evidence available indicates that lamivudine has a potential role in the setting of hepatitis B-related ESLD, liver transplantation and the treatment of recurrent or de novo HBV infection after transplantation. Lamivudine is effective in suppressing HBV replication, and may result in disease stabilisation and improved pre-transplant survival in patients with ESLD. The combination of lamivudine and HBIg is an effective prophylaxis against recurrent hepatitis B after transplantation, leading to improved graft and patient survival. Furthermore, lamivudine is effective in treating recurrent hepatitis B after transplantation, with clearance of virological parameters of infection associated with significant clinical and histological improvement. Lamivudine is well tolerated in these patient populations during prolonged periods of use. As well as an excellent efficacy–tolerability profile, lamivudine therapy offers the practical advantages of ease of administration and relatively low cost, particularly when compared with HBIg. Lamivudine fulfils an important role in the management of decompensated liver disease for prophylaxis in patients undergoing liver transplantation, and for treatment of recurrent HBV infection after transplantation.

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