

Treatment of Recurrence of Hepatitis B in Transplant Patients

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1- Introduction

With significant improvements in immunosuppressive therapy and surgical techniques over the past two decades, liver transplantation has become the definitive and effective therapy for patients with end-stage liver disease with survival rates approaching 90%-95% and 65%-80% after 1 and 5 years of follow-up, respectively¹. Among several circumstances that may pose a threat to long-term survival, the greatest is likely the recurrence of the original liver disease². Although hepatitis B recurrence has been effectively contained by the use of combination therapy with hepatitis B immunoglobulin and lamivudine, there remains the possibility of post-transplantation HBV disease of the allograft. Fortunately in the past decade several effective drugs have been developed for the management of patients with HBV disease undergoing liver transplantation, so that outcomes with the patient group are now excellent and allograft infection poses a relatively minor threat to long-term survival.

In the United States and Europe, HBV disease accounts for fewer liver transplantations than HCV disease, yet the outcomes in 2002 are better for HBV than for HCV³. Treatment of hepatitis B after liver transplantation is less of a clinical problem today than it was a decade ago, largely due to effective interventions to prevent post-transplantation recurrence – namely high doses of hepatitis B immune globulin (HBIG) in combination with antivirals such as lamivudine. Historically, rates of recurrence of HBV were high (90 per cent) and the consequences of reinfection were devastating, such that HBV was considered a relative contraindication to liver transplantation. There has been a step-wise reduction in likelihood of recurrence with each intervention – down to 25 per cent with high dose HBIG alone, and even further reductions with HBIG plus lamivudine. With pre-transplantation lamivudine plus HBIG at low doses, rates of reinfection are as low as 10 per cent. In addition, post-transplantation HBV disease may occur in patients who were HBsAg negative prior to transplantation⁴. Thus treatment of HBV after liver transplantation remains an important, albeit relatively uncommon clinical dilemma.

A recent summary of a single clinical center's experience supports the excellent outcomes of patients undergoing liver transplantation for HBV-related liver disease⁵. A twenty-year experience in 206 patients spanning the period of evolution of HBV therapies has demonstrated an improvement in patient survival and a reduction in incidence of rates of recurrence. All patients received long-term immunoprophylaxis, maintaining trough anti-HBs at greater than 100 U/L. Since 1993, antivirals have been used prior to transplantation and for management of HBV reinfection. The one, five, and ten-year patient survival rates were 91%, 81%, and 73%. Survival was even good in patients with preoperative positive HBV DNA, detectable by hybridization-assays (78% 5-year survival), although preoperative positive hepatitis B e antigen (HBeAg) was associated with a worse survival than patients negative for HBeAg ($p < .05$)⁵. Two-year patient survival increased from 85% in 1988-1993, prior to availability of antivirals, to 94% since 1997, in which period patients received combination of hepatitis B immune globulin and lamivudine ($p < 0.05$). The 2-year recurrence rates in these two periods were 42% and 8% ($p < 0.05$). In summary, with currently available combination therapy, survival is excellent in patients undergoing liver transplantation for HBV disease, even in those with active pre-transplantation viral replication, and risk of recurrent disease of the allograft is low (less than 10 percent).

Thus in 2002, there are three categories of patients who are potential candidates for HBV therapy after liver transplantation: (i) those who have undergone liver transplantation in the pre-HBtg and/or lamivudine era; (ii) those who have undergone liver transplantation in the post-HBtg/lamivudine era and who have broken through treatment; (iii) those with apparent “de novo” acquisition of HBV⁴. Selection of therapy for post-transplantation recurrence likely depends on the category to which the patient belongs. For example, patients in the first category who have received either no therapy or HBtg alone, may have indolent infection or, if these patients have active liver disease, treatment options include lamivudine, entecavir or adefovir. These patients may have developed “vaccine escape mutants”⁶, but they are likely to be sensitive to all three antivirals (see below). As discussed above, the proportion of patients falling into the second category today is small, yet if these patients have “broken through” both HBtg and lamivudine, they are likely to have developed resistance and as such may be appropriate candidates for antivirals such as adefovir or entecavir that have activity against resistance variants. Finally patients that fall into the third category with “de novo” infection, are likely to be infected with virus that is sensitive to all currently available agents. The prevalence of de novo HBV hepatitis ranges from 2% to 8%, and is generally related to transmission from an HBsAg negative anti-HBc positive donor. The most significant factor associated with transmission is the serologic status of the recipient, so that the risk is almost null in patients who are anti-HBs positive, minor (\approx 10%) in those who are anti-HBs negative but anti-HBc positive, and high (\approx 50%-70%) in those without markers of previous exposure to HBV^{7,8}. Although there have been reports of severe progression⁹, the natural history of de novo hepatitis B is generally more benign than that described for recurrent hepatitis B. In this group, the greatest experience is with lamivudine.

2- Treatment of hepatitis B following liver transplantation

There have been series from both the U.S. and Europe showing the suppressive nature of lamivudine for the treatment of post-transplantation HBV disease¹⁰⁻¹². In Europe, the older literature included treatment with famciclovir for post-transplantation HBV disease, but recent European reports suggest that lamivudine is a superior antiviral in this setting¹². Treatment of HBV-related liver disease in transplant patients is difficult due to several reasons including the high levels of HBV replication and the ongoing immunosuppressive treatment. New nucleoside analogues are promising in this setting due to their potent antiviral effect and their lack of side effects. However, resistance is becoming an increasingly important problem.

Lamivudine is the most widely used nucleoside analogue¹⁰⁻¹². In most studies, liver transplant recipients with documented HBV recurrence (elevated serum ALT levels, and detectable HBsAg and HBV DNA) have been treated with lamivudine 100 mg daily (adjusted for renal function) with good tolerance and rapid loss of HBV DNA in serum. Good biochemical and virologic response have been achieved not only in patients with chronic hepatitis B following transplantation, but also in acute hepatitis B of the graft and even in the most severe cases of fibrosing cholestatic hepatitis¹³. Histologic improvements in the inflammatory grade are also achieved with therapy. In a multicenter study based on 52 patients with detectable DNA after liver transplantation, lamivudine for one year resulted in 60% loss of HBV DNA in serum and 31% “e” seroconversion¹⁰. Other studies have confirmed these results showing HBV DNA negativization in 68% to 100% of patients treated for periods of 12 to 36 months (table 1)¹⁰⁻¹⁷. The downside of this agent is the need for continuous treatment since relapse is the rule once the drug is discontinued. Prolonged therapy is associated with the potential development of breakthrough due to the emergence of HBV escape mutants, which has been shown to reach 50% or higher¹⁰⁻¹⁷.

Monotherapy with both lamivudine and famciclovir has resulted in the emergence of HBV variants that are resistant to these compounds^{10,18}. This resistance generally occurs after prolonged therapy (more than 6 months) and the appearance of resistant mutants is associated with a rise in serum HBV DNA and ALT levels, indicating a breakthrough in therapy. Molecular analysis of these mutations has shown changes in the gene for the viral DNA polymerase¹⁹⁻²¹. Because of the overlapping nature of the HBV open reading frames, nucleotide changes in the polymerase may result in amino acid changes not only in the polymerase

protein but also in the surface protein, which could in turn theoretically alter binding of HBsAg¹⁸. Resistance to lamivudine is associated with changes in both the B and C domains of the polymerase while those associated with famciclovir occur mainly in the B domain. When these drugs are stopped, the wild-type variant reemerges as the dominant viral population, but retreatment is again associated with the development of resistant mutants at an accelerated rate²¹. Lamivudine-induced mutations can also occur in the B domain of the polymerase, where changes have been described with famciclovir. Thus famciclovir resistant virus may not be sensitive to lamivudine, a situation recently described in several patients. The long-term rate of emergence of drug resistant-mutants and their implications in the natural history of HBV infection are under investigation. Although some cases of histological and clinical deterioration have been reported when drug resistant mutants develop, these are not consistently associated with hepatic disease progression¹⁸. It is possible that differences in the replicative competence or "fitness" of the mutants may account for these differences in outcome. In vitro and in vivo studies with adefovir have shown that lamivudine and famciclovir resistant variants remain sensitive to adefovir, suggesting that adefovir dipivoxil may be important in the treatment of HBV with or without resistance to other oral agents^{22,23}.

Lamivudine resistance post-transplantation has on occasion been associated with severe and even fatal post-transplantation disease in patients receiving combination therapy with lamivudine plus hepatitis B immune globulin²⁴. The molecular mechanisms associated with this severe recurrence may be a drug-dependent enhanced replication of lamivudine-resistant HBV mutants²⁴. HBV sequence analysis of these patients has revealed both mutations in the "a-determinant" of the envelope and the YMDD (tyrosine, methionine, aspartate, aspartate) motif (domain C) of the polymerase protein. Transfection experiments with replication competent vectors indicated that the "a-determinant" changes were not associated with resistance, whereas mutations in the YMDD motif conferred resistance to lamivudine. More importantly, variants in which combinations of mutations in the "a-determinant" and the YMDD motif from patients with a severe hepatitis were not only resistant to lamivudine treatment, but also showed enhanced replication in vitro in the presence of lamivudine. This observation suggests that severe and fatal hepatitis B infection can occur during lamivudine therapy and may be associated with certain HBV mutants selected during sequential nucleoside and HBsAg treatment. The lamivudine-enhanced replication shown by these mutants suggests that continuation of therapy with lamivudine could be deleterious in some patients.

Fortunately, the availability of new hepatitis B antivirals such as adefovir has resulted in viral suppression of lamivudine resistant variants²³ and even resolution of graft failure in these patients with lamivudine resistant variants^{25,26}. Thus far, resistance to adefovir has not been reported, but given the increased risk of developing variant viruses in these immune compromised patients, it is likely that resistance will be observed with prolonged exposure. It is not yet known whether patients who are treated for lamivudine resistance with adefovir post-transplantation need to continue on lamivudine, but given the potential for progressive liver disease with overt recurrence, it seems prudent to continue both drugs for some period after the institution of adefovir. Prospective studies comparing combination of antivirals to monotherapy are important, but given the small numbers of patients, such studies are unlikely to be performed. In addition, defining the length of antiviral therapy and more importantly the criteria required to stop therapy safely without risk of relapse is also a major goal.

For patients who have become HBsAg positive after liver transplantation despite therapy in the pre- and/or peri-transplantation period, possible interventions include adefovir or entecavir. Experience with adefovir (at a dose of 10 mg per day) has shown that this drug is viral suppressive but that treatment may be limited by toxicities, possibly associated with impaired renal function²³. Experience with entecavir is limited.

For patients with apparent "de novo" acquisition of HBV who have active viral replication and liver injury, treatment with lamivudine either alone or in combination should be instituted. The treatment regimen is similar to that described for recurrent hepatitis B. If started at early time-points, the results are generally better than those obtained with recurrent hepatitis B. Resistant mutants develop unfortunately at the same rate, and adefovir or entecavir may prove to be preferred therapy for the primary management of this disease. In addition, in order to avoid de novo HBV infection, two complementary approaches may be undertaken: (i) HBV vaccination prior to liver transplantation of all anti-HBs negative candidates. Accelerated vaccination

regimen with double doses (40 ug) has been adopted at 0, 1 and 2 months with a follow up vaccine at 6 months. Unfortunately, as with other immunosuppressed populations, the results of vaccination in these patients have been disappointing with response rates which barely reach 40%²⁷. A second course of vaccination may slightly increase these results. (ii) Anti-HBc determination of the donor with use of organs from anti-HBc positive donors only in recipients already infected with HBV. In order to obtain a maximum benefit from these organs while at the same time reducing the risk of HBV transmission, these organs may be used in special circumstances in recipients not infected with HBV. The following criteria should then be applied. Since the risk of HBV transmission is low if the recipient is anti-HBs and anti-HBc core positive^{7,8}, selection of an anti-HBs positive recipient may be sufficient without other interventions. However, there is concern that vaccine-induced immunity may not be as effective as innate immunity in preventing acquisition of HBV from an infected donor. Thus there may be a difference in risk of acquisition for a recipient who is anti-HBs positive without concomitant anti-Hbcore. Livers from anti-HBc(+) donors can be directed next to recipients with isolated anti-HBc although a low risk of HBV transmission appears to exist if no specific HBV prophylactic measures are taken^{7,8}. While initiating prophylaxis with HBIg and or lamivudine to all patients will prevent transmission, this strategy has the potential for treating a high proportion of recipients who would have never developed infection. When no individuals with the above criteria exist in the waiting list, anti-HBc (+) donors can be offered to naïve recipients with critical clinical situation or with hepatocellular carcinoma although, in such cases, prophylaxis of HBV infection with either lamivudine or HBIg or a combination of both agents is advisable given the high likelihood of HBV acquisition.

Fortunately, with effective preventive measures and the availability of “salvage therapy” for patients who fail combination lamivudine plus hepatitis B immune globulin, retransplantation for severe allograft disease is rarely necessary.

In summary, treatment of post-liver transplantation is a much less important clinical problem currently than it was historically. If the patient has been exposed to HBIg and/or lamivudine, the genotype of the infecting virus should be determined. Defining the sequence in the surface and polymerase genes are key. Experimental therapy with adefovir and/or entecavir may be indicated but intervention will likely be limited by concomitant renal insufficiency.

Table 1. Treatment of hepatitis B after transplantation

Author, number of patients	HBV DNA + pre-therapy (%)	HBeAg + pre-therapy (%)	HBV DNA negativization (%)	HBe seroconversion (%)	Treatment duration (months)
Andreone, 11	100	18	100	100	17 (8-22)
Nery, 11	100	NA	90	NA	15 (13-21)
Perrillo, 52	90	86	68	11	12
Malkan, 15	93	40	100	0	21 (4-39)
Ben-Ari, 8	100	62	100	20	36 (24-50)
Rayes, 41	100	NA	76	NA	12-36
Fontana, 33	94	75	72	4	21 (4-36)

References:

1. United Network for Organ Sharing Web Site. Available at www.unet.org. Accessed January 31, 2000.
2. Todo S, Demetris A, Van Thiel D, Teperman L, Fung JJ, Starzl TE. Orthotopic liver transplantation for patients with hepatitis B virus-related liver disease. *Hepatology* 1991; 13: 619-26.
3. Berenguer M, Wright TL. Antiviral therapy pre and post-transplantation. In: *Transplantation of the Liver*. Maddrey W, Sorrell M, Schiff E. Ed. Lippincott Williams & Wilkins. 2000: 343-360.
4. Chazouilleres O, Mamish D, Kim M, Carey K, Ferrell L, Roberts J, Ascher N, Wright TL. "Occult" hepatitis B viral infection: An important source of transmission to the liver transplant recipient. *Lancet* 1994;343:142-6.
5. Steinmuller T, Seehofer D, Rayes N, Muller AR, Settmacher U, Jonas S, Neuhaus R, Berg T, Hopf U, Neuhaus P. Increasing applicability of liver transplantation for patients with hepatitis B-related liver disease. *Hepatology*. 2002;35:1528-

35.

6. Terrault NA, Zhou S, McGory RW, Pruett TL, Lake JR, Roberts JP, Ascher NL, Wright TL. Incidence and clinical consequences of surface and polymerase gene mutations in liver transplant recipients on hepatitis B immune globulin. *Hepatology* 1998;28:555-561.
7. Prieto M, Gómez MD, Berenguer M, et al. De novo hepatitis B after liver transplantation from hepatitis B core antibody-positive donors in an area with high prevalence of anti-HBc positivity in the donor population. *Liver Transplantation* 2001; 7: 51-58.
8. Dickson RC, Everhart JE, Lake JR, Wei Y, Seaberg EC, Wiesner RH, et al. Transmission of hepatitis B by transplantation of livers from donors positive for antibody to hepatitis B core antigen. The National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database. *Gastroenterology* 1997;113:1668-1674.
9. Crespo J, Fabrega E, Casafont F, Rivero M, de las Heras G, de la Peña J, et al. Severe clinical course of de novo hepatitis B infection after liver transplantation. *Liver Transpl Surg* 1999;5:175-183.
10. Perrillo R, Rakela J, Dienstag J, Levy G, Martin P, Wright T, Caldwell S, Schiff E, et al. Multicenter study of lamivudine therapy for recurrent hepatitis B after liver transplantation. *Hepatology* 1999;29:1581-6.
11. Fontana RJ, Hann HW, Wright T, Everson G, Baker A, Schiff ER, Piely C, Anschuetz G, Riker-Hopkins M, Brown N. A multicenter study of lamivudine treatment in 33 patients with hepatitis B after liver transplantation. *Liver Transpl.* 2001 Jun;7 (6):504-10.
12. Rayes N, Seehofer D, Hopf U, Neuhaus R, Naumann U, Bechstein WO, Neuhaus P. Comparison of famciclovir and lamivudine in the long-term treatment of hepatitis B infection after liver transplantation. *Transplantation* 2001;71:96-101.
13. Al Faraidy K, Yoshida EM, Davis JE, et al. Alteration of the dismal natural history of fibrosing cholestatic hepatitis secondary to hepatitis B virus with the use of lamivudine. *Transplantation* 1997;64:926-8.
14. Nery JR, Wepler D, Rodriguez M, et al. Efficacy of lamivudine in controlling hepatitis B virus recurrence after liver transplantation. *Transplantation* 1998; 65:1615-21
15. Ben-Ari Z, Mor E, Shapira Z, Tur-Kaspa R. Long-term experience with lamivudine therapy for hepatitis B virus infection after liver transplantation. *Liver Transpl* 2001; 7: 113-7.
16. Andreone P, Caraceni P, Grazi GL, Belli L, Milandri GL, Ercolani G, et al. Lamivudine treatment for acute hepatitis B after liver transplantation. *J Hepatol* 1998;29:985-9.
17. Malkan G, Cattral M, Humar A, Al Asghar H, Creig P, Hemming AW, et al. Lamivudine for hepatitis B in liver transplantation. *Transplantation* 2000; 69: 1403-7.
18. Locarnini S. Hepatitis B virus surface antigen and polymerase gene variants: potential virological and clinical significance. *Hepatology* 1998; 27: 294-7.
19. Tipples GA, Ma MM, Fischer KP, Bain VG, Kneteman NM, Tyrrell DL. Mutation in HBV RNA-dependent DNA polymerase confers resistance to lamivudine in vivo. *Hepatology* 1996;24:714-7.
20. Allen M, Deslauriers M, Andrews C, Tipples GA, Walters KA, Tyrrell DL, et al. Identification and characterization of mutations in hepatitis B virus resistant to lamivudine. *Hepatology* 1998; 27: 1670-7.
21. Chayama K, Suzuki Y, Kobayashi M, Kobayashi M, Tsubota A, Hashimoto M, et al. Emergence and takeover of YMDD motif mutant hepatitis B virus during long-term lamivudine therapy and re-takeover by wild type after cessation of therapy. *Hepatology* 1998; 27: 1711-6.
22. Xiong X, Flores C, Yang H, Toole JJ, Gibbs CS Mutations in hepatitis B DNA polymerase associated with resistance to lamivudine do not confer resistance to adefovir in vitro. *Hepatology* 1998; 28:1669-73
23. Perrillo R, Schiff E, Yoshida E, Statler A, Hirsch K, Wright T, Gutfreund K, Lamy P, Murray A. Adefovir dipivoxil for the treatment of lamivudine-resistant hepatitis B mutants. *Hepatol* 2000;32:129-34.
24. Bock CT, Tillmann HL, Torresi J, Klempnauer J, Locarnini S, Manns MP, Trautwein C. Selection of hepatitis B virus polymerase mutants with enhanced replication by lamivudine treatment after liver transplantation. *Gastroenterology*. 2002 ;122:264-73.
25. Mutimer D, Feraz-Neto BH, Harrison R, O'Donnell K, Shaw J, Cane P, Pillay D. Acute liver graft failure due to emergence of lamivudine resistant hepatitis B virus: rapid resolution during treatment with adefovir. *Gut*. 2001;49:860-3.
26. Walsh KM, Woodall T, Lamy P, Wight DG, Bloor S, Alexander GJ. Successful treatment with adefovir dipivoxil in a patient with fibrosing cholestatic hepatitis and lamivudine resistant hepatitis B virus. *Gut*. 2001 ;49:436-40.
27. Chalasani N, Smallwood G, Halcomb J, Fried MW, Boyer TD. Is vaccination against hepatitis B infection indicated in patients waiting for or after orthotopic liver transplantation? *Liver Transpl Surg* 1998; 4: 128-132