

Trends in the Management of Hepatitis B Virus Infection after Liver Transplantation

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SUMMARY

Post-transplant hepatitis B virus (HBV) recurrence occurs in the majority of patients transplanted for HBV liver disease, if left untreated. Post-transplant prophylaxis with hepatitis B immune globulin (HBIG) has significantly reduced HBV recurrence rates, but it is rather ineffective in patients with chronic liver disease and pre-transplant detectable serum HBV-DNA by hybridization assays. Moreover, long-term HBIG administration increases the cost of post-transplant medical therapy and may be associated with emergence of escape HBV mutants. Lamivudine is the first antiviral agent to be widely used in the management of HBV transplant patients. Pre-transplant lamivudine therapy lowers HBV viremia, decreasing the risk of post-transplant HBV recurrence, but to try and minimize virologic breakthroughs due to resistant HBV strains, it should be started within the prior to 6 months the anticipated timing of transplantation, which is often difficult in practice. Prophylactic post-transplant lamivudine monotherapy is associated with progressively increasing HBV recurrence rates, but combined therapy with lamivudine and HBIG at relatively low dosage is currently the most effective approach in this setting, even in HBV-DNA positive patients, who also receive lamivudine in the pre-transplant period. The most frequent therapy for post-transplant HBV recurrence is lami-

vudine, but the increasing resistance rates represent a challenging problem. Adefovir dipivoxil is currently the most promising agent amongst those tried for lamivudine resistant HBV strains. All these advances in anti-HBV therapy have made HBV liver disease an indication for liver transplantation, irrespective of viral replication status, a complete turn around from 10 years ago.

Key words: hepatitis B virus, liver transplantation, hepatitis B immune globulin, nucleoside analogues, lamivudine, adefovir, entecavir, viral resistance, YMDD mutants

INTRODUCTION

Despite significant recent progress in the prevention of hepatitis B virus (HBV) infection by vaccination, HBV is still responsible for more than 300 million cases of chronic liver disease worldwide and is classified among the top 10 lethal infectious diseases with an annual death rate of approximately 1 million.¹ Chronic HBV carriers constitute a population with high morbidity and mortality from chronic liver disease, including hepatocellular carcinoma (HCC).² Thus, orthotopic liver transplantation (OLT) may be the only therapeutic option for a proportion of HBV infected patients with advanced or terminal stage liver disease. It is currently estimated that, in the United States and Europe, 5% to 10% of patients undergoing OLT have HBV/related liver disease.³

Early experience with liver transplantation of patients with HBV/related liver disease, with no immunoprophylaxis or its use short-term, was rather discouraging, with an extremely high rate of graft loss due to the almost universal and frequently aggressive HBV recurrence.^{4,6} Thus, HBV/related liver disease was initially considered a relative or even absolute contraindication for liver transplantation in many centres³ and the proportion of liver

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transplants performed for HBV/related cirrhosis declined from 5.8% in 1990 to 3.6% in 1993.⁷ However, the use of long-term hepatitis B immune globulin (HBIG) significantly decreased the post-transplant HBV recurrence rate and improved the prognosis for HBV transplant patients⁸ resulting in revision of the transplant policy and allowing OLT for HBV/related liver disease.^{3,9} Although HBIG remains the gold standard for prevention of post-transplant HBV recurrence, newer antiviral agents, mainly nucleoside analogues, are currently used or evaluated, as monotherapy or in combination with HBIG, in an effort to further improve the outcome, treat HBIG failures, and/or reduce the need for the use of the expensive HBIG preparations.¹⁰ This review focuses on the management of HBV/related liver transplant patients, reviewing the efficacy of newer antiviral agents, alone or in combination with HBIG.

Natural history of post-transplant HBV recurrence

Post-transplant HBV recurrence or graft reinfection, expressed by the reappearance of HBsAg, occurs in the majority of patients transplanted for HBV/related liver disease, if left untreated.^{4,5,8} The risk of HBV graft reinfection is closely related to the pre-transplant HBV replication status and type of liver disease. The HBV recurrence rate is higher among patients with HBV/related chronic liver disease and lower among patients with acute fulminant hepatitis B or hepatitis D virus (HDV) co-infection.^{5,8} In particular, among patients with HBV/related chronic liver disease, the HBV recurrence rate is highest in those with pre-transplant detectable HBeAg and/or high serum HBV-DNA levels.^{5,8}

The clinical manifestations of post-transplant HBV recurrence resemble those observed in non-transplant patients, but with a more rapidly progressive course.⁵ Fibrosing cholestatic hepatitis, a particularly lethal and unique syndrome for transplant patients, may also develop in up to 20-25% of cases with HBV recurrence.^{6,11} It is well established that steroids directly stimulate HBV replication,¹² while immunosuppression often results in exacerbation of chronic HBV infection in non-transplant patients and may induce a rapidly progressive course.¹³ Although it is reasonable, and is common practice, to withdraw steroids early after OLT in HBV transplant patients,¹⁴ or even not use them at all,¹⁵ the efficacy of such an approach on the incidence or severity of HBV recurrence has not been documented. In the current era of obligatory preemptive post-transplant anti-HBV prophylaxis, however, the effects of dosage and types of different immunosuppressive agents (cyclosporin or tacroli-

mus with or without azathioprine or recently mycophenolate), if any, appear to be less important and remain uninvestigated.

Retransplantation is the only therapeutic option for patients with HBV recurrence and graft failure. Although initial results for HBV retransplanted patients were relatively poor,¹⁶ it seems that aggressive antiviral treatment and/or patient selection can result in satisfactory (>80%) long-term survival rates.¹⁷

Passive Immunoprophylaxis

The efficacy of HBIG is associated with the pre-transplant type of liver disease and viremic status as well as with the dose and duration of HBIG treatment. The rate of HBV reinfection under HBIG prophylaxis is <10% in patients transplanted for fulminant acute hepatitis B, 10-20% in those transplanted for HBV and HDV cirrhosis and >20% in those transplanted for HBV cirrhosis.³ In particular, among patients transplanted for HBV cirrhosis, HBIG immunoprophylaxis is less effective in those with pre-transplant detectable compared to undetectable serum HBV-DNA by hybridization assays [20-35% and 30-80% post-transplant HBV recurrence rates respectively³], and higher HBIG doses are usually needed for pre-transplant viremic patients.^{18,19} Moreover, recurrence of HBV is usually observed shortly after cessation of HBIG treatment in transplant patients treated with HBIG for short periods,⁸ but it develops infrequently in those receiving long-term HBIG treatment.^{8,20} However, the ideal duration of post-transplant HBIG prophylaxis remains unknown. Since HBV-DNA can often be detected in the liver, serum, or peripheral mononuclear cells of HBsAg-negative patients on long-term prophylactic HBIG therapy,²¹⁻²³ it seems that HBIG may only rarely lead to eradication of HBV infection and therefore indefinite HBIG prophylaxis is probably required. Besides duration, several practical questions about the ideal dosage, the frequency and the mode of HBIG administration also remain to be answered.

The most widely accepted recommendations for HBIG prophylaxis depend on the patient's pre-transplant viremic status.³ In patients without pre-transplant detectable serum HBV-DNA by conventional hybridization assays, HBIG treatment starts with intravenous administration of 10,000 U during the anhepatic phase and is followed by 10,000 U daily for the first 6 to 7 days and then by 10,000 U every 4-8 weeks or whenever needed to maintain anti-HBs titers above 100-150 mIU/ml. More aggressive protocols are recommended for patients with detectable serum HBV-DNA pre-transplant, who are

usually transplanted only after clearance of HBV viremia by lamivudine. In the latter setting, HBIG treatment during the first post-transplant week is the same as that recommended for pre-transplant non-viremic patients, but has often been followed by more frequent HBIG doses of 10,000 U every 2-4 weeks or whenever needed to maintain anti-HBs titers above 500 mIU/ml.³ Since long-term HBIG treatment is extremely expensive, several variations in its administration protocol have been tried in order to reduce cost. The most cost-effective approach seems to be the individual tailoring of HBIG administration.³ Taking into consideration that the clearance of HBIG varies significantly among different patients and among different HBIG preparations and that it generally decreases with time after transplant, it is obvious that intervals between HBIG injections may significantly vary from patient to patient and may decrease with time after transplant, if a HBIG protocol based on monitoring of anti-HBs titers instead of fixed monthly HBIG doses is used.

Intramuscular HBIG administration has also been tried in an effort to reduce the cost of long-term HBIG prophylaxis, but no long-term data for such an approach are currently available.²⁴⁻²⁶ Intramuscular compared to intravenous HBIG administration significantly reduces the cost of HBIG prophylaxis without adding side effects, except for local reactions to the injection sites, and appears to be equally effective for prevention of post-transplant HBV recurrence, particularly if it is used in combination with lamivudine as described below.²⁷

Another recently reported strategy in an effort to reduce the cost is the substitution of HBIG by anti-HBV vaccination.²⁸ Double-dose recombinant anti-HBV vaccine was given to 17 low-risk HBV transplant patients who had undetectable serum HBV-DNA before transplant by a hybridization assay (but HBV-DNA by PCR – negative: 13, -positive: 1, -not done: 3) and had received HBIG for at least 18 months after transplant without evidence of HBV recurrence; no HBV recurrence was observed in the 14 who developed anti-HBs after vaccination, during a median follow-up of 14 months.²⁸ Based on these data, it could be suggested that in selected liver transplant recipients, long-term HBIG prophylaxis may be safely substituted by anti-HBV vaccination, which is a more cost-effective strategy in the prevention of post-transplant HBV recurrence. However, in a more recent study, a highly reinforced anti-HBV vaccination resulted in development of anti-HBs in only 12-18% of 17 patients.²⁹ Therefore, greater numbers of patients and longer follow-up periods are required before the long-term ef-

ficacy of such approaches for HBIG substitution can be determined.

Besides cost, another disadvantage of long-term HBIG administration has been associated with emergence of escape mutant HBV strains, a phenomenon observed in many other cases of long-term selective immunologic pressure on chronic viral infections.³⁰⁻³² Mutations in the HBV surface gene have been identified in about 50% of patients who were on HBIG prophylaxis for at least 6 months before therapeutic failure.^{31,33} The most frequent mutation is a substitution of glycine to arginine at amino acid 145, which is within the neutralizing “a” determinant of HBsAg.³² The clinical significance of such breakthrough escape mutants has not been completely clarified, but there are some reports showing that the emergence of HBV escape strains is progressively increasing with the prolongation of HBIG administration and is associated with increased rates of graft failure.³³ In cases of failure of HBIG prophylaxis, HBsAg becomes detectable in serum, HBV viremia levels increase, and histological disease usually develops.³³ Since wild HBV usually dominates over the escape mutant strains in case of HBIG withdrawal,³⁴ there is no consensus about continuation or not of HBIG therapy after the emergence of an escape mutant HBV strain.³

Preemptive therapy with antiviral agents

Pre-transplant

Preemptive therapy with antiviral agents is an alternative approach to prevent post-transplant HBV recurrence, which frequently starts during the pre-transplant period in order to lower or clear the viral load at the time of OLT.¹⁴ The use of preemptive antiviral therapy was rather limited until the late 1990s. Interferon- α (IFN α), which was the only available therapeutic option for chronic hepatitis B in the non-transplant setting until a few years ago, is usually contraindicated or causes intolerance and therefore could not be used in patients with decompensated cirrhosis.^{35,36} Thus, cirrhotic patients with detectable HBV viremia were frequently excluded from transplant lists because of the high risk of post-transplant HBV recurrence even with HBIG prophylaxis.^{3,8}

Lamivudine [(-)-2',3'-dideoxy-3'-thiacytidine or 3TC], a cytosine analogue with quite potent antiviral activity against HBV, seems to be an ideal drug for short-term therapy of patients with HBV decompensated cirrhosis, since it is very well tolerated, achieves complete inhibition of HBV replication in the majority of cases and may stabilize or even improve liver function.^{37,38} Lamivudine monotherapy is widely used in the pre-transplant period

in the effort to inhibit HBV replication, clear HBV viremia and reduce the risk of subsequent graft reinfection.^{10,39,40} There are, however, two major drawbacks to the wide use of lamivudine in the pre-transplant setting. First, the possible improvement or stabilization of liver function under therapy may result in temporary withdrawal of the patients from transplant lists or prevent them from being upgraded to a higher status, thus reducing their chances of a timely transplantation.^{37,41} Second, the prolongation of lamivudine therapy has been associated with progressively increasing rates of virologic breakthroughs^{37,38,42,43} that may worsen the post-transplant outcome by increasing the probability of HBV recurrence.⁴⁰

Virologic breakthroughs during lamivudine monotherapy are associated with emergence of HBV mutant strains resistant to lamivudine due to mutations within the YMDD motif of the HBV polymerase.⁴⁴ Currently, the post-transplant outcome of patients with pre-transplant HBV viremia due to YMDD mutant strains is not clear. It was initially reported that post-transplant HBV recurrence was not observed during the first 32 months after OLT in a patient with YMDD mutant strains during pre-transplant lamivudine therapy, who was treated with high dose HBIG and lamivudine after transplant.⁴⁵ However, two patients with pre-transplant YMDD mutant strains were subsequently observed to rapidly develop post-transplant HBV recurrence, despite combined prophylaxis with low dose HBIG and lamivudine.⁴⁶ Whether the dose of HBIG is an important factor for post-transplant HBV recurrence in patients who have already developed virologic breakthroughs during pre-transplant lamivudine therapy and what the risk of HBV recurrence is, precisely, in such patients must be evaluated in larger and properly designed studies. However, transplant centres may be reluctant to perform OLT in patients with HBV cirrhosis and detectable serum HBV-DNA irrespective of the type of HBV strains.⁴⁷ The recent availability of adefovir dipivoxil, a nucleotide analogue of adenosine esterified with two pivalic acid molecules, which is effective against both wild and lamivudine resistant HBV strains,^{48,49} is expected to ameliorate the consequences of lamivudine resistance.

Post-transplant

Lamivudine was first tried as monotherapy administered before and prophylactically after OLT, at a daily dose of 100 mg and gave promising short-term results in initial reports with small numbers of patients.^{50,51} However, it was subsequently shown that the efficacy of such a policy progressively declines with time with development of virologic breakthroughs and HBV recurrence in

about 40%-50% of cases at two years after OLT, and severe clinical outcomes in some patients.⁵²⁻⁵⁵ Thus, such an approach should be abandoned.

Prophylactic combined approach

Post-transplant prophylactic combined administration of HBIG and lamivudine has been recently tried in HBV transplant patients in an effort to improve the efficacy of post-transplant prophylactic monotherapy or to achieve similar results at a lower cost.²⁷ The overall efficacy of such a combined regimen appears to be superior to the efficacy of prophylaxis with any of the two agents alone. In particular, in 12 recent studies of prophylactic therapy with HBIG and lamivudine, post-transplant HBV recurrence was observed in only 7 (3%) of 233 HBV transplant patients during a mean follow-up of 13-22 months^{24,25,27,46,56-63} (Table 1). It should be mentioned that lamivudine monotherapy was given to viremic patients (81 out of 154 by hybridization assays) during the pre-transplant period in most of the above studies and thus serum HBV-DNA just before OLT remained detectable in only 34 by a hybridization assay.^{24,25,27,46,56-58,60,62} Of the 7 patients with post-transplant HBV recurrence, 3 had developed YMDD mutant HBV strains during the pre-transplant lamivudine therapy.^{46,58} In addition, only the combination of HBIG and lamivudine, and none of the two agents alone, has been found 100% to prevent de novo HBV infection after OLT with allografts from anti-HBc positive donors.^{64,65} In a more recent study with a longer mean post-transplant follow-up of 30 months, similar good results of the combined prophylactic approach were documented with good results with only 1 (4%) of 26 HBV transplant patients having HBV recurrence by a hybridization assay⁶⁶ (Table 1).

One particularly important aspect in all studies using combined HBIG and lamivudine prophylaxis is that such an approach achieved low HBV reinfection rates with a relatively low HBIG dosage, similar to current recommendations for non-viremic HBV transplant patients,³ and despite the fact that more than 50% of cases had detectable serum HBV-DNA by hybridization assays before pre-transplant administration of lamivudine.^{24,25,46,56,59,66} Moreover, in three of these studies, HBIG was given intramuscularly with similar good results.^{24,25,59} The addition of lamivudine reduces the cumulative amount of HBIG required to effectively prevent post-transplant HBV reinfection, possibly through suppression of HBV replication and HBsAg production.⁴⁷ Thus, the prophylactic post-transplant combination of HBIG and lamivudine preceded by short-term lamivudine therapy during the pre-transplant period appears to be the ap-

Table 1. Published studies using combination of hepatitis B immune globulin (HBIG) and lamivudine (LAM) for prevention of hepatitis B virus (HBV) recurrence after orthotopic liver transplantation (OLT) for HBV related chronic liver disease.

Study (1 st author, year)	Patient number	Patients with HBV-DNA (+)*, Baseline/at OLT	Pre-OLT therapy, LAM (mg)	Post-OLT HBIG dose (IU), [cumulative within 1 st month] -after the 1 st month	Post-OLT LAM (mg)	Mean follow-up (months)	HBV recurrence, n (%)	Survival (%)
Markowitz, 1998 ⁵⁶	14	5/1	150	[80,000]-10,000/month IV	150	13	0	93
Yao, 1999 ²⁴	10	9/2	150	[5,555 ¹]-1,111/3 weeks IM	150	16	1 (10)	90
Yoshida, 1999 ²⁵	7	4/0	100	[34,720]-2,170/1-4 weeks IM	100	18	1 (14)	86
McGaughan, 1999 ⁵⁷	9	6 ² /6 ²	0	Low dose (no details)	N.A.	17	0	89
Roche, 1999 ⁵⁸	15	15/4	100	No details-anti-HBs>500IU/L	100	16	1 (7)	93
Angus, 2000 ⁵⁹	32	N.A.	100	[3,200-6,300]-400 or 800/month IM	100	18	1 (3)	100 ⁸
Han, 2000 ²⁷	59	20/16	150	[80,000]-10,000/month IV	150	15	0	98
Lee, 2000 ⁶⁰	5	1/0	100	[26,000]-2,000/month IV ³	100	11	0	80
Andreone, 2000 ⁶¹	19	N.A.	100	[45,000]-5,000/month IV	100	17	1 (5)	95
Buti, 2000 ⁶²	12	9/0	100	[62,000]-2,000/month IV-IM ⁴	100	12	0	100
Marzano, 2001 ⁶⁶	26	9/0 ⁵	100	[60,000]-5,000/month IV	100	30	1 ⁷ (4)	92
Rosenau, 2001 ⁴⁶	21	12/5 ⁶	100-150	[40,000 - anti-HBs>500IU/L] -anti-HBs>100IU/L IV	100-150	20	2 (10)	90
Machicao, 2001 ⁶³	30	N.A.	N.A.	High dose	N.A.	22	0	97

*Serum HBV-DNA detectable by hybridization assays. N.A.: not available.

¹Plus 10,000 IV during anhepatic phase in all patients and another 70,000 IV during the first 7 days in 2 HBV-DNA positive patients

²Another 3 patients had detectable serum HBV-DNA by a polymerase chain reaction (PCR) assay

³One patient received 80,000 IU of HBIG during the first month, while another patient received only 2,000 IU of HBIG during the anhepatic phase and 4 IM injections of 650 IU each within the first 6 months after OLT

⁴IV for the first 4 weeks and IM thereafter; 5 of the 12 patients received HBIG only for the first 4 weeks after OLT

⁵Seven patients had detectable serum HBV-DNA by a PCR assay

⁶Two out of 4 patients tested had YMDD mutant strains, while another 3 patients had detectable serum HBV-DNA by a PCR assay

⁷Serum HBV-DNA was detected by PCR in another 61.5% (16 patients)

⁸Five patients, who died within month after OLT from unrelated to HBV causes, were not included in this survival estimation

Table 2. Published studies of lamivudine (LAM) therapy for hepatitis B virus (HBV) recurrence or de novo HBV infection after orthotopic liver transplantation (OLT).

Study (1 st author, year)	Patient Number	Baseline serum HBV-DNA (+)*, n (%)	Baseline HBsAg (+), n (%)	Mean duration of LAM (months)	Clearance of serum HBV-DNA, n (%)	Clearance of HBsAg, n (%)	Clearance of HBsAg, n (%)	YMDD mutants, n (%)
Andreone, 1998 ⁷⁰	11 ¹	11 (100)	2 (18)	16	8 (73) – 5 (45)	2 (100)	5 (45)	3 (27)
Nery, 1998 ⁷¹	11 ²	10 (91)	N.A.	25	8 (73) – N.A.	N.A.	N.A.	2 (18)
Perrillo, 1999 ⁷²	52	52 (100)	45 (87)	12	31 (60) – N.A.	14 (45)	3 (6)	14 (27)
Roche, 1999 ⁷³	16	16 (100)	10 (63)	16	7 (44) – N.A.	3 (19)	3 (19)	6 (40)
Balan, 1999 ⁷⁴	24	N.A.	N.A.	25	9 (37)	N.A.	N.A.	15 (63)
Malkan, 2000 ⁵³	15 ³	14 (93)	6 (40)	23	13 (87) – N.A.	N.A.	4 (27)	2 (13)
Seehofer, 2000 ⁷⁵	41 ⁴	41 (100)	N.A.	32	31 (76) – N.A.	N.A.	9 (22)	14 (34)
Fontana, 2001 ⁷⁶	31	29 (94)	23 (74)	20	11 (36) – N.A.	3 (9)	0	13/29 (45)
Ben-Ari, 2001 ⁸¹	8 ⁵	8 (100)	5 (63)	36	3 (38) – N.A.	1 (20)	0	5 (63)

*Serum HBV-DNA detectable by hybridization assays. N.A.: not available.

¹All patients had acute HBV recurrence; ²Three patients had de novo HBV recurrence and another two patients had been treated with famciclovir before start of LAM;

³Four patients had de novo HBV recurrence; ⁴22 patients had been treated with famciclovir therapy before start of LAM; ⁵Two patients had de novo HBV recurrence.

proach of choice in high-risk viremic HBV transplant patients, since it is associated with the lowest post-transplant HBV recurrence rate and probably has a reduced cost due to the low HBIG dosage.

Another strategy using preemptive combined therapy has been the withdrawal of HBIG administration after a certain period after OLT. In this context, the prophylactic combination of HBIG and lamivudine followed by maintenance lamivudine alone was reported to achieve similar results to HBIG prophylaxis in the short-term,⁶⁷ but long-term data about this approach are still lacking. In a recent trial, 24 HBV transplant patients, who had undetectable serum HBV-DNA before transplant by a hybridization assay and had received HBIG for at least 6 months after transplant without evidence of HBV recurrence, were randomized to continue with HBIG or receive lamivudine alone.⁶⁸ The HBV recurrence rate, as well as the proportion of patients with detectable serum HBV-DNA by PCR, were similar in the two groups at 12 months, while 8 of the 12 patients in the lamivudine group did not develop HBV recurrence during an additional follow-up of 6-22 months.⁶⁸ Similarly, HBV recurrence was not observed in any of 16 HBV transplant patients, who continuously received HBIG for two years and then switched over to lamivudine monotherapy for an additional period of up to 27 months.⁶⁹ Thus, it seems that post-transplant HBIG prophylaxis may be safely replaced by lamivudine after at least 6 months post-OLT in selected HBV transplant patients with low risk of HBV recurrence.⁶⁸

Treatment of post-transplant HBV recurrence

The primary targets of treatment of post-transplant HBV recurrence are the control of liver disease and stabilization of graft function. Lamivudine is currently the most frequently used agent for this indication (Table 2). In eight studies including about 200 patients with post-transplant HBV infection treated with lamivudine therapy for a mean of 12-25 months, serum HBV-DNA levels became undetectable by hybridization assays in the majority of them and no significant clinical manifestations were observed.^{53,70-76} Whether initiation of lamivudine therapy earlier after the diagnosis of HBV reinfection is associated with better outcomes, as suggested in some reports,^{70,77} remains to be determined. Lamivudine has also given promising results for the treatment of patients with fibrosing cholestatic hepatitis.^{78,79} However, the progressively increasing rates of resistance to lamivudine, which were reported to be 27% at 1-year,⁷² about 40% at 2-years^{76,80} and exceed 50% at 3-years of therapy,^{81,82} may cause problems in the long-term. Although

the clinical significance of resistance to lamivudine is not clear in both transplant and non-transplant patients and lamivudine resistant post-transplant reinfection cases have suggested the following of a relatively milder course than in cases with wild HBV recurrence,⁸³ the emergence of such HBV mutant strains has been associated with rapid development of advanced histological lesions and even liver failure and death in some HBV transplant patients.^{81,84,85}

Adefovir, a nucleotide analogue of adenosine, seems to be the most promising new anti-HBV agent and has recently been approved for the treatment of chronic HBV liver disease in several countries.⁸⁶ Adefovir, which is administered esterified with two pivalic acid molecules as adefovir dipivoxil, due to better oral bioavailability,⁸⁶ is generally well tolerated, although relatively high doses (60 or 120 mg daily) have been associated with an increased risk of nephrotoxicity after >20 weeks of the rapy.⁸⁷ Although nephrotoxicity is a potential adverse event that needs particular attention in transplant patients, the currently recommended daily dose of adefovir dipivoxil is 10 mg with reduction to 5 mg in case of low creatinine clearance. In particular in transplant patients with HBV recurrence, adefovir dipivoxil appears to be effective even against lamivudine resistant HBV strains.^{49,88} Entecavir is a carboxylic analogue of guanosine,⁸⁹ which has initially been found to suppress satisfactorily the HBV replication in non-transplant patients with chronic hepatitis B.⁹⁰

Several other nucleos(t)ide analogues have been evaluated for the treatment of subgroups of patients with HBV infection, including those with post-transplant HBV recurrence. Famciclovir, guanosine analogue, has been tried in transplant patients with HBV recurrence,⁹¹ but it has been found to be inferior to lamivudine.^{80,82,92} Ganciclovir, another guanosine analogue, was found to achieve reductions in both ALT and serum HBV DNA levels as well as improvement of liver histology.^{93,94} but the need for intravenous administration restricts its use as long-term therapy. In the pre-lamivudine era, IFNa was a common therapeutic option for patients with post-transplant HBV recurrence. The role of IFNa as first line treatment in this setting has currently almost disappeared due to both its low efficacy and a low but possible theoretic risk of graft rejection.^{95,96}

Treatment of HBV transplant patients with strains resistant to lamivudine

Since lamivudine is currently used widely in HBV transplant patients either as prophylactic therapy, alone or in combination with HBIG, or as treatment for HBV

recurrence, the numbers of transplant patients with HBV strains resistant to lamivudine are expected to increase with time and they may comprise the most challenging problem in this setting in the near future.⁹⁷ Several antiviral agents are currently evaluated as candidates for the treatment of HBV strains resistant to lamivudine.

Adefovir dipivoxil appears to be the most promising agent for the treatment of lamivudine resistant HBV mutant strains;⁴⁸ in two recent clinical trials, which included patients with decompensated HBV cirrhosis or post-transplant HBV recurrence, treatment with adefovir dipivoxil achieved significant reduction in serum HBV DNA levels and improvement of transaminase activity.^{49,88} Besides clinical trials, protocols of compassionate use of adefovir dipivoxil in HBV transplant or pre-transplant patients are currently running in many centers worldwide. In addition, adefovir dipivoxil in combination with HBIG effectively prevented HBV recurrence after OLT for fulminant liver failure resulting from lamivudine-resistant HBV stains in a renal transplant recipient.⁸⁵ Moreover, adefovir dipivoxil was recently reported to be a successful therapy in one case with post-transplant fibrosing cholestatic hepatitis and one with acute liver graft failure, both due to lamivudine-resistant HBV strains which had emerged during combined HBIG and lamivudine prophylaxis.^{98,99} Viral resistance to adefovir dipivoxil has not been reported to date.¹⁰⁰ Entecavir therapy has also given promising initial results against HBV strains resistant to lamivudine¹⁰¹ and shown to be effective in patients with chronic hepatitis B and resistance to lamivudine.¹⁰² Entecavir is currently being evaluated in clinical trials in the HBV transplant setting. Famciclovir is not a useful agent for this indication, since there is cross resistance with lamivudine.^{103,104}

Although IFNa has been almost abandoned as first line therapy of post-transplant HBV recurrence, it may still have a role, alone or in combination with other antiviral agents, as a second choice therapeutic option for such patients who develop resistance to lamivudine or other nucleoside analogues.¹⁴ The addition of IFNa to lamivudine therapy has been used for the treatment of a few transplant and non-transplant patients with HBV mutant strains resistant to lamivudine, showing promising initial results.^{105,106}

CONCLUSIONS

Prevention is always preferable to treatment of any infection. This is particularly important for patients transplanted for HBV/related liver disease, for whom there

are available safe and effective prophylactic agents. HBIG prophylaxis has significantly reduced the risk of post-transplant HBV recurrence and increased graft and patient survival. However, the high cost, low availability, HBIG failures, and emergence of escape mutant HBV strains have led to a search for alternative agents. The introduction of lamivudine gave the opportunity to transplant many viremic patients with HBV chronic liver disease by inducing effective inhibition of HBV replication during the pre-transplant period. The prophylactic post-transplant combination with HBIG and lamivudine appears to significantly reduce the risk of HBV recurrence and it is expected to improve the long-term outcome of pre-transplant viremic patients. All these advances have established a far more optimistic outlook for HBV transplant patients, and thus HBV/related liver disease is now a universal indication for OLT, irrespective of the initial replicative status of HBV.

The management of YMDD mutant HBV strains that progressively develop with time during lamivudine therapy represents the most challenging task for the near future, in transplant as well as non-transplant patients with chronic HBV infection. All such patients are candidates for newer antiviral drugs effective against YMDD mutant HBV strains. Whether *ab initio* combinations of drugs with complementary mechanisms of antiviral activity or sequential therapy with different antiviral agents represent the most cost-effective approach is currently unknown. However, long-term and maybe perennial prophylaxis for HBV transplant patients is required, which will be an added cost for these patients, since HBV eradication with therapy seems to be an almost impossible target for the time being and residual virus can be detected even after many years of post-transplant effective prophylaxis.²³

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