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REVIEW ARTICLE

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Treatment of hepatitis B and C after liver transplantation. Part 1, hepatitis B

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Abstract The outcome of OLT for HBV-related liver disease is dependent on the prevention of allograft re-infection. Over the past decade, major advances have been made in the management of HBV transplant candidates. The advent of long-term hepatitis B immune globulin (HBIG) administration as a prophylaxis against HBV recurrence, and the introduction of new antiviral agents against HBV infection, such as lamivudine (LAM), were a major breakthrough in the management of these patients. Results of OLT for HBV infection are similar to those achieved with other indications. Pre-OLT antiviral treatment such as LAM can suppress HBV replication before OLT and thus decrease the risk of re-infection of the graft. Combination prophylaxis with LAM and HBIG after transplantation highly effectively reduces the rate of HBV re-infection, even in HBV replicative cirrhotic patients. The optimal HBIG protocol in the LAM era is yet to be defined: dosing of HBIG, routes of administration, and possibility of stopping HBIG. Several antiviral drugs have been developed for the management of HBV infection on the graft, so outcome is currently good.

Keywords Hepatitis B · Liver transplantation · Antiviral therapy · Hepatitis B immune globulin

Introduction

Of orthotopic liver transplant patients (OLT), 5% to 10% have HBV-associated chronic or fulminant liver disease. Historically, in the absence of prevention, the spontaneous risk for HBV re-infection after OLT is approximately 80% related to the initial liver disease and the presence of HBV replication at time of transplantation [1, 2]. HBsAg reappearance was associated with HBV infection of the graft and poorer survival. Patients will develop acute liver failure, fibrosing cholestatic hepatitis, chronic hepatitis, or cirrhosis. Over the past years, major advances have been made in the management of HBV transplant candidates. The advent of long-term hepatitis B immune globulin (HBIG) administration as a prophylaxis of HBV recurrence and the introduction of new antiviral agents against HBV infection were a major breakthrough in the management of these patients [3, 4].

HBV re-infection is the consequence of either an immediate re-infection of the graft due to circulating HBV particles or a re-infection of the graft from HBV particles coming from extrahepatic sites, or both. In patients receiving HBIG, HBV re-infection may be the consequence of HBV overproduction coming from extrahepatic sites [5], of too low a protective titre of anti-HBs antibody, or of emergence of escape mutants.

Several effective antiviral drugs have been developed for the management of HBV disease of the graft, so the outcome is now good. Less frequently, HBV infection could be acquired in the peri-transplantation period. In this review, current knowledge on prevention and treatment of HBV graft infection after liver transplantation is discussed.

Prevention of HBV recurrence

Hepatitis B immune globulins monoprophylaxis

The mechanisms by which HBIG protects the transplanted liver against HBV re-infection are poorly understood. One hypothesis suggests that HBIG protects naive hepatocytes against HBV released from extrahepatic sites through the blocking of a putative HBV receptor. There is evidence for a dose-dependent response to HBIG treatment [3, 4]. The administration of HBIG during a short-term post-transplantation period gave disappointing results [1, 2, 3]. The Hanover group subsequently adjusted HBIG dosages to maintain the anti-HBs titre at 100 IU/l for 6 months after OLT [6]. This group showed that the rate of HBV recurrence significantly increased following discontinuation of HBIG after 6 to 12 months of therapy. We, and others, adopted an indefinite immunoprophylaxis [7]. Patients received 10,000 IU during the anhepatic phase, then 10,000 IU daily during the 6 post-operative days; then, the level of anti-HBs was assessed weekly, and 10,000 IU of HBIG were re-administered if anti-HBs was < 100 IU/l.

In a European multicentre study there was a dramatic decrease in the rate of HBV recurrence, from 75% in patients receiving no or short-term administration of HBIG to 33% in those receiving long-term administration of HBIG ($P < 0.001$) [3]. Recurrence of HBV occurred in 67% of patients who had undergone transplantation for HBV cirrhosis, in 40% of those who had undergone transplantation for fulminant hepatitis B-delta, in 32% of those who had undergone transplantation for HDV cirrhosis, and in 17% of those who had undergone transplantation for fulminant hepatitis B [3]. The HBV recurrence rate was dependent on the presence of HBV replication assessed by both HBeAg and HBV DNA by a conventional hybridisation technique at the time of transplantation [3]. These results were confirmed by other clinical trials in the USA and Europe and by long-term follow-up studies (Tables 1 and 2) [8, 9, 10, 11, 12, 13, 14, 15].

For HBV DNA-positive patients, the rate of HBV re-infection could be reduced by the use of higher HBIG doses and maintenance of a serum anti-HBs level > 500 IU/l or by the use of pre-OLT and/or post-OLT supplemental antiviral therapy. Several reports that used very high doses of HBIG and maintenance titres > 500 IU/l showed promising results [9, 16]. HBV recurrence occurred in 0%–15% and 16%–35% of patients who had undergone transplantation for both non-replicative and replicative HBV cirrhosis, respectively (Tables 1 and 2) [8, 16, 17, 18, 19].

Taking into consideration the inter-patient and intra-patient variations in the pharmacokinetics of HBIG, monitoring of serum anti-HBs levels is required. An alternative approach has been proposed by Terrault et al. in which a fixed monthly dose of 10,000 IU HBIG is given intravenously, irrespectively of preoperative viral replication status [9]. Most data support long-term intravenous administration of HBIG. Efforts to use intramuscular HBIG have been motivated by substantial cost benefit and unavailability of intravenous HBIG, but experience with the intramuscular route of HBIG is limited. HBIG administration had a very satisfactory safety record, and adverse events observed are usually minor and rare. Immune reactions have been reported but are easily prevented by steroids, antihistamine drugs and slower infusion. Long-term HBIG administration has several drawbacks: (a) HBIG administration is expensive, but the cost depends greatly on the country

Table 1 Frequency of HBV recurrence after liver transplantation for non-replicative HBV cirrhosis

Authors [references]	Patients (*n*)	[a]Prevention of HBV recurrence	Rate of HBV recurrence (%)	Follow-up (months)
O'Grady [2]	9	Short-term HBIG	78	40
Samuel [3]	15	None	67	36
	13	Short-term HBIG	92	36
Koenig [15]	5	Short-term HBIG	100	31
Devlin [14]	9	Short-term HBIG	78	18
Lerut [10]	3	Short-term HBIG	100	60
Muller [12]	14	HBIG > 100 IU/l (6–12 months)	28	24
Samuel [7]	24	Long-term HBIG > 100 IU/l	29	24
Samuel [3]	37	Long-term HBIG > 100 IU/l	38	36
Koenig [15]	17	Long-term HBIG > 100 IU/l	17.6	22
Devlin [14]	9	Long-term HBIG > 100 IU/l	33	18
Roche [8]	52	Long-term HBIG > 100 IU/l	36.9	120
Lerut [10]	9	Long-term HBIG > 100 IU/l	30	60
Gugenheim [17]	30	Long-term HBIG > 500 IU/l	15.2	60
McGory [16]	9	Long-term HBIG > 500 IU/l	0	24

[a]Prevention of HBV recurrence with short-term or long-term HBIG to maintain anti-HBs levels > 100 IU/l or > 500 IU/l

Table 2 Frequency of HBV recurrence after liver transplantation for replicative HBV cirrhosis

Authors [references]	Patients (*n*)	Prevention of HBV recurrence[a]	Rate of HBV recurrence (%)	Follow-up (months)
O'Grady [2]	11	Short-term HBIG	100	15
Samuel [3]	16	None	75	36
	14	Short-term HBIG	71	36
Koenig [15]	1	Short-term HBIG	100	12
Devlin [14]	11	Short-term HBIG	91	18
Nymann [19]	4	None	100	17
Lerut [10]	7	Short-term HBIG	100	60
Muller [12]	9	HBIG > 100 IU/l (6–12 months)	89	24
Samuel [7]	16	Long-term HBIG > 100 IU/l	96	24
Samuel [3]	47	Long-term HBIG > 100 IU/l	70	36
Koenig [15]	15	Long-term HBIG > 100 IU/l	73	22
Devlin [14]	6	Long-term HBIG > 100 IU/l	94	18
Roche [8]	30	Long-term HBIG > 100 IU/l	79	60
Lerut [10]	8	Long-term HBIG > 100 IU/l	37.5	60
McGory [16]	19	Long-term HBIG > 500 IU/L	16	18
Nymann [19]	10	Long-term HBIG > 500 IU/L	30	17
Sawyer [18]	26	Long-term HBIG > 500 IU/L	35	36
Roche [8]	10	Long-term HBIG > 500 IU/L and antiviral drugs	20	60

[a]Prevention of HBV recurrence with short-term or long-term hepatitis B immune globulin (HBIG) to maintain anti-HBs levels > 100 IU/l or > 500 IU/l

and the manufacturer [4]; (b) HBIG administration remains constraining because of the need for close monitoring of the level of anti-HBs antibody and frequent re-injection; (c) the HBV re-infection rate remains high in patients with HBV replication at the time of transplantation.

Pre-transplantation antiviral therapies

Until recently, the presence of HBV replication was considered a contraindication to OLT by most centres. Thus, the main goal of antiviral therapy is to suppress HBV replication prior to OLT and decrease the risk of re-infection. However, candidates for OLT are difficult to treat because of the severity of the liver disease. The ideal treatment in this setting would have rapid and potent antiviral action without inducing deterioration of liver function.

Interferon alpha

A major limitation to the use of interferon (IFN) before OLT has been its poor tolerability in cirrhotic patients. In a controlled study we used IFN in 22 cirrhotic patients awaiting OLT compared with 26 non-treated patients. HBIGs were used after OLT. INF failed to reduce the rate of HBV recurrence [20]. However, in those patients who were HBV DNA-negative by PCR in serum, the risk of recurrence was low. In one report, the use of INF prior to OLT was shown to reduce the rate of HBV re-infection [21].

Famciclovir

Famciclovir has modest activity against HBV [22] and was used successfully in a small study before and after OLT in combination with HBIG [23].

Lamivudine

Lamivudine (LAM) is well tolerated even in decompensated cirrhosis, which it achieves by inducing a loss of HBV DNA by molecular hybridisation in 90% of patients [24, 25, 26, 27, 28, 29, 30]. However, viraemia will occur in 80% following cessation of therapy, and development of mutations in the YMDD motif of the HBV DNA polymerase gene increased with treatment duration. Villeneuve et al. [25] report on 35 patients with severely decompensated HBV cirrhosis and replicative HBV infection who were treated with LAM 100 at 150 mg/day. Within 6 months after treatment initiation, seven patients underwent OLT, and five others died. Of 23 patients who were treated for at least 6 months, there was a slow but marked improvement in liver function in 22. The rate of development of resistance to LAM was 25% at 2 years.

Other studies confirmed the slow improvement (3 to 6 months) of hepatic function in patients with decompensated cirrhosis and replicating HBV treated with LAM [26, 27, 28], which may confer a survival advantage [29]. Fontana et al. [30] found, in a retrospective multicentric study that included 309 patients, that LAM did not improve overall pre-OLT or OLT-free survival. However, a subset of patients with less advanced liver

failure may derive clinical benefit from LAM treatment. The baseline Child–Pugh score was the only variable significantly associated with death before OLT and was also a significant predictor of OLT-free survival [30]. In a prospective multicentre study reported by Fontana et al. 154 patients listed for OLT received LAM for a median of 16 months [31]. The majority of deaths, 78%, occurred within the first 6 months of therapy. The estimated actuarial 3-year survival rate of patients who survived at least 6 months was 88% on continued treatment. Elevated serum bilirubin, creatinine levels and the presence of detectable serum HBV DNA were strong and independent predictors of 6-month mortality. Virological response to LAM was similar in both survivors and non-survivors. The severity of liver disease at induction of therapy is a better predictor of early mortality than the virological response to LAM. Thus, patients with advanced liver failure should be prioritised for OLT, irrespectively of the antiviral response.

A question that emerges is when to initiate therapy in patients listed for OLT. Prolonged administration of LAM is usually necessary to obtain significant clinical benefits, but the risk for developing drug-resistant mutations increases with the duration of treatment and may be associated with increasing liver failure. New antiviral agents such as adefovir dipivoxil may serve as "rescue" therapy for patients with LAM resistance [32]. Schiff et al. used adefovir, administered at doses of 10 mg/day for a median of 18 weeks to 128 patients with decompensated cirrhosis who failed LAM therapy pre-OLT [33]. A median reduction of serum HBV DNA levels of 2.2 log after 4 weeks and 4.1 log after 24 weeks, associated with improvement in Child score, was observed.

Cases of liver transplantation in patients with YMDD mutants were reported, with controversial results. In two cases, recurrence of HBV was successfully prevented by administration of a prophylaxis combining HBIG and LAM [34, 35]. In contrast, two studies reported five cases of HBV recurrence after transplantation in patients with YMDD mutants, despite the same combination prophylaxis [36, 37]. This suggests that transplantation should be either contraindicated or performed only after use of new antiviral treatment in case of emergence of HBV escape mutations before transplantation. The use of adefovir, first line in patients with liver cirrhosis and awaiting liver transplantation, has not been reported and is under evaluation.

Post-transplantation antiviral therapies

Lamivudine monotherapy

The administration of LAM alone pre-OLT and post-OLT showed promising results after 1 year, with only one case of HBV recurrence out of ten patients [38]. A longer follow-up time showed, however, a recurrence rate of 5/10 due to the emergence of escape mutations in the YMDD motif of the polymerase gene [39]. These mutations were observed mainly in patients with high-level viral replication prior to drug exposure. Similar results were reported in other studies, with HBV recurrence in 22.6%–50% of patients [28, 40, 41] (Table 3). These patients developed HBV recurrence with YMDD mutants and sometimes had a severe clinical outcome [42]. A low rate of breakthrough infection was observed by Lo et al [43]. They described the appearance of serum anti-HBs antibodies after OLT in 21 of 50 Chinese patients with hepatitis B that were receiving LAM monoprophylaxis. The authors hypothesise that this increase of anti-HBs Ab level is the consequence of active production arising from donor lymphocytes. Because the follow-up time in this series is short, definite conclusions on the persistence of anti-HBs Ab and its protective efficacy cannot be drawn. These findings should be confirmed in studies carried out in the West.

In conclusion, the administration of LAM alone as a prophylaxis after liver transplantation is probably insufficient, particularly in replicative patients. Future studies are needed to assess the efficacy of adefovir monotherapy or in combination with LAM pre- and post-OLT.

Combination of lamivudine and HBIG

Several groups developed a more rational approach by giving LAM before, and a combination of LAM and HBIG after, OLT. The initial results were very encouraging, demonstrating disappearance of HBV DNA prior to OLT and absence of HBV recurrence [24]. In these studies the HBV recurrence rate at 1–2 years was $< 10\%$ [24, 36, 44, 45, 46, 47, 48, 49, 50, 51] (Table 4). In addition, HBV DNA was found to be negative by PCR in most cases 1 year after OLT. LAM co-administration may reduce the overall amount of HBIG needed after transplantation [36, 44].

The good results of combination treatment may be the consequence of a synergistic effect with reduction of the production of HBsAg by LAM with a decreased rate of escape mutations in the preS/S and YMDD regions. Passive immunoprophylaxis protocols utilised in different centres are heterogeneous regarding both dosing and routes of administration of HBIG (Table 4). The major limitation of IV HBIG protocols is its cost. Therefore, high doses of HBIG appear unnecessary for the majority of patients that are receiving combination therapy. Han et al. [52] showed that conversion from i.v. to i.m. HBIG in combination with LAM resulted in absence of HBV recurrence in 58 of 59 (98%) treated patients. Taking efficacy and cost-effectiveness into consideration, i.m.

Table 3 Prevention of HBV recurrence with LAM monotherapy before and after liver transplantation (*NA* not available)

Authors [references]	Patients (*n*)	Pre-treatment virological status of transplant patients HBV DNA positive	Pre-treatment virological status of transplant patients HBeAg positive	Duration of treatment before OLT (months)	HBV DNA-positive at time of OLT	Transplantation (*n*)	HBV recurrence [*n* (%)]	Follow-up (months)	Death related to HBV recurrence
Grellier [38][a]	17	8	4	2 (1.2–5.6)	0	12	5 (50)	32 (16–51)	2
Mutimer [39][a]	23	9	11	NA	3	17	5 (29.4)	37 (22–50)	2
Malkan [41]	13	3	2	8 (1–31)	0	13	4 (30.7)	22 (4–37)	2
Lo [40]	31	11	18	1.6 (0.03–20.4)	6	31	7[b] (22.6)	16 (6–47)	0
Perillo [28]	77	26	24	2.1 (0.03–20.9)	6	47	17 (36.1)	38 (2.7–48.5)	1

[a]These two studies report common patients
[b]Six of these patients were HBsAg positive, HBV DNA negative by PCR

HBIG plus LAM seems to be superior to i.v. HBIG plus LAM. The optimal HBIG protocol in the LAM era is yet to be defined.

Guidelines and future prospects

Patients considered as OLT candidates should be further subdivided into those with active viral replication and those without. For patients without viral replication, there is no evidence that preoperative antiviral therapy is useful. These patients should receive HBIG 10,000 IU daily for 7 days, including the anhepatic period, and then indefinitely every 6–8 weeks to maintain anti-HBs titres > 100–150 IU/l. For patients with viral replication, LAM therapy should be started before OLT. Patients with advanced liver failure should be prioritised for OLT, irrespectively of the antiviral response. Patients who developed resistance to LAM may respond to adefovir dipivoxil. Patients who become HBV DNA negative (by molecular hybridisation) could undergo transplantation. After undergoing transplantation, these high-risk patients should receive a combination of HBIG 10,000 IU daily for 7 days and then indefinitely in association with antiviral therapy (LAM ± adefovir) (Fig. 1).

Discontinuation of HBIG

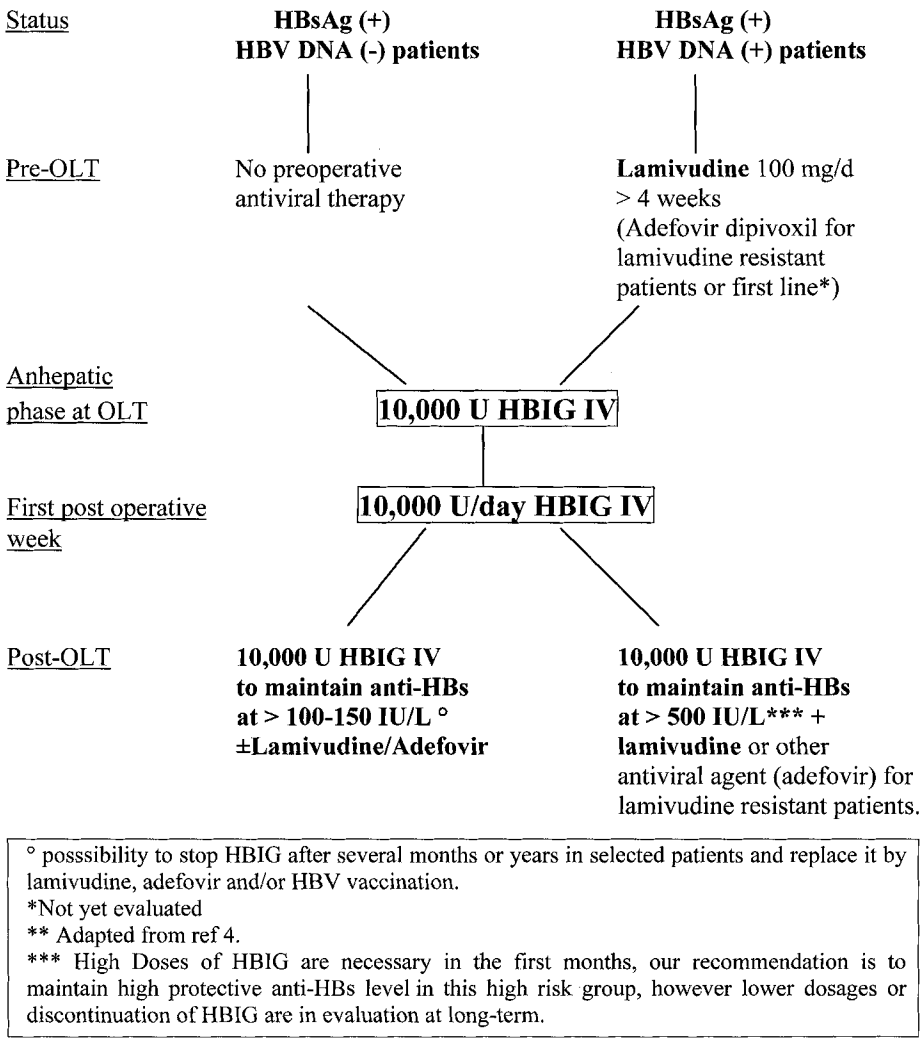
Future prospects, especially in patients without HBV replication before transplantation, are the possibility to stop HBIG and to replace it by LAM or vaccination or both. The aims are to reduce the long-term costs and the constraints of HBIG administration. In a recent study, HBIG administration was discontinued in a selected group of 17 patients and replaced by HBV vaccination [53]. The authors claimed good results with anti-HBs production and absence of HBV re-infection. However, the antibody level was low and declining with time in most patients. These results were confirmed with a longer follow-up time [54] and in another study [55]. Conflicting results were reported by Angelico et al. using a triple course of hepatitis B vaccination in 17 patients that had undergone transplantation for HBV cirrhosis after cessation of HBIG [56]. Anti-HBs > 100 IU/l was observed in only two patients (12%). Patient populations, methods, definitions of vaccine response and immunogenicity of vaccine were different in these studies.

Two studies compared the HBV re-infection rate in a group of transplant patients randomised to receive HBIG or LAM after a period of administration of HBIG [57, 58]. In the study by Naoumov et al. [58] 24 patients were selected on a low-risk HBV re-infection basis (i.e. absence of detectable HBV DNA at time of

Table 4 Prevention of HBV recurrence after liver transplantation with LAM and anti-HBs Ig (HBIG) (*NA* not available)

Authors [references]	Patients (*n*)	Pre-treatment virological status of transplant patients HBV DNA$^+$	Pre-treatment virological status of transplant patients HBeAg$^+$	HBV DNA-positive at OLT	Transplantation (*n*)	Prevention of HBV recurrence pre-OLT duration (months)	Prevention of HBV recurrence post-OLT	HBV recurrence [*n* (%)]	Follow-up (months)
Markowitz [24]	14	5	1	1	14	LAM 3 (0.7–7.8)	LAM[a] + HBIG i.v	0	13
Yao [45]	10	9[b]	6	2	10	LAM 8.6 (1–22)	LAM + HBIG i.m.[c]	1 (10)	15 (10–21)
Yoshida [46]	7	4	NA	0	7	LAM NA	LAM + HBIG i.m.[d]	0	17 (13–21)
Angus [47]	37	36	19	NA	37	LAM 3.2	LAM + HBIG i.m	1 (2.7)	18 (5–45)
Marzano [44]	33	26	7	0	26[e]	LAM 4.6 (0.6–14.1)	LAM + HBIG i.v.[f]	1 (4)	30 ± 8
McCaughan [48]	9	9	0	NA	9	0	LAM + HBIG i.m.[g]	0	17 (9–24)
Rosenau [36]	21	11	3	5[k]	21	LAM 4.6 (0.06–14.1)	LAM + HBIG i.v.[i]	2 (9.5)	21 (2.4–49.1)
Roche [50]	15	15	5	4	15	LAM 4.6 (0.3–13)	LAM + HBIG i.v.[j]	1 (6.6)	15 (3–36)
Han [49]	59	NA	NA	NA	59	LAM NA	LAM + HBIG i.v.[k]	0	15 (1–61.8)
Seehofer [37]	17	17	9	5	17	LAM 10.6 (1–28)	LAM + HBIG i.v.[l]	3 (18)	25 (9–49)
Gane [51]	107	79	39	35	107	LAM 2 (0.5–3.5)	LAM + HBIG i.m.[m]	4 (3.7)	26 (0.5–76)

[a]LAM initiated at OLT in four patients, HBIG 80,000 IU first month then 10,000 IU per month
[b]One patient developed LAM resistance
[c]Patients HBV DNA-positive: 80,000 IU i.v. + 3,300 IU i.m. first month then 1,480 IU i.m. per month; patients HBV DNA-negative: 10,000 IU i.v. + 4,400 IU i.m. first month then 1,480 IU i.m. per month
[d]43,400 IU i.m. first month then 4,300–6,800 IU i.m. per month
[e]Seven patients did not undergo transplantation: four died from liver failure, three had improved liver function
[f]46,500 IU i.v. first month then 5,000 IU i.v. per month
[g] 8,260 i.m. First month then 400 IU i.m., per month
[h]two patients have YNOD mutation before OLT
[i]45,000 IU i.v. first week then reinjection to maintain anti HBs > 500 IU/L until day 14, then > 200 IU/L
[j]80,000 IU i.v. first month then 10,000 IU i.v. per month
[k]80,000 IU i.v. first week then 10,000 IU i.v. per month
[l]80,000 IU i.v. first week then 1,500-2,000 IU i.v. to maintain anti-HBs > 100 IU/L
[m]400-800 IU i.v. first week then monthly thereafter



° posssibility to stop HBIG after several months or years in selected patients and replace it by lamivudine, adefovir and/or HBV vaccination.
*Not yet evaluated
** Adapted from ref 4.
*** High Doses of HBIG are necessary in the first months, our recommendation is to maintain high protective anti-HBs level in this high risk group, however lower dosages or discontinuation of HBIG are in evaluation at long-term.

Fig. 1 Guidelines for patients considered as OLT candidates

transplantation and no HBV re-infection after a minimal follow-up period of 6 months after transplantation). After 1 year, the HBV re-infection rate was not significantly different: 2/12 and 1/12 patients in the LAM and HBIG groups, respectively. However, HBV DNA was detected by PCR in the serum of patients without HBV recurrence in 2/11 patients in the HBIG group and in 5/10 patients in the LAM group. This should keep us alert. Indeed, the follow-up time of these studies is limited, around 1–2 years, and it has been clearly shown that the risk of escape mutations with LAM increases with time.

HBIG withdrawal has also been explored in patients that receive combination prophylaxis. Buti et al. included 29 patients that were HBV DNA-negative (12 spontaneously and 17 LAM-induced) at the time of OLT [59]. HBIG doses were 10,000 IU i.v. during the anhepatic phase and on the first postoperative day, followed by 5,000 IU/day until day 7 and then 4,000 IU i.m. weekly until the end of the first month. Then, patients were randomised to receive either LAM monotherapy (14 patients) or LAM plus HBIG at 2,000 IU i.m. monthly (15 patients) until month 18. None of the patients developed HBV recurrence during the study period. Indeed, HBV DNA was positive by PCR at month 18 in three patients who had received HBIG + LAM and in one patient who had received LAM monotherapy. Polymerase mutants were detected in three of these four patients.

It is important to determine which patients can stop HBIG: patients without replication at the time of transplantation, minimum delay of several months post-transplantation, negative HBV DNA by PCR before stopping HBIG. The drawbacks of the discontinuation of HBIG are: (a) the possibility of recurrence of HBV infection after cessation of HBIG; (b) the persistence of HBV DNA in serum, liver or peripheral blood mononuclear cells in 50% of HBV transplant patients who are HBsAg negative on HBIG long-term administration at 10 years [8] or on combination pro-

phylaxis with HBIG and LAM [44, 58]; (c) the inability to identify patients who have cleared HBV post-transplantation. An alternative approach would be to maintain HBIG at lower dosage in combination with antiviral treatment.

Liver transplantation in patients with HDV liver cirrhosis

Patients chronically infected with HBV and HDV are less at risk of HBsAg reappearance than patients infected with HBV alone. The rate of HBsAg reappearance in patients with HBV-HDV cirrhosis was 50%–60% in those who did not receive long-term HBIG [2] and 17% in those receiving long-term HBIG [3]. The HBV recurrence rate in these patients is probably lower overall, because almost all patients are HBV DNA-negative at time of liver transplantation and HDV has an inhibitory effect on HBV replication.

In contrast, HDV re-infection is frequent and was observed in 80% of cases in the first post-transplantation months [60]. The course of HDV re-infection varies, depending on whether HBsAg reappears or not. In the few cases where HBsAg reappeared, it was associated with a combined HBV-HDV replication, the development of acute, then chronic, hepatitis [60, 61]. HBV–HDV recurrence is, in general, less severe than HBV recurrence alone [3]. In the patients who remained HBsAg negative after transplantation, the amount of HDAg in the liver graft was low, and the liver graft remained histologically normal. In the long term, HDV markers progressively disappeared from liver and serum [61]. The hypotheses for explaining the presence of HDV replication in HBsAg negative patients are: (a) HBV markers could be present but not detectable; (b) HDV is present in the hepatocytes in the absence of HBsAg but cannot replicate or has a low replication level; (c) the level of HDV RNA in the liver is much lower in patients without than with HBsAg, and this low level of HDV may explain the absence of liver graft lesions.

In conclusion, the risk of HBsAg reappearance after liver transplantation in HBV–HDV cirrhotic patients who received long-term HBIG is low.

Use of hepatitis B core antibody-positive donors for transplantation

Donors previously exposed to HBV provide an opportunity to expand the donor pool. However, previous or latent HBV infection in the donor liver may be reactivated in the recipient after OLT. Frequency of organ-donor anti-HBcAb positivity is around 15% in the USA [62]. Indeed, a high false-positive rate of anti-HBcAb results by enzyme-linked immunoassay was reported. When the liver donor is positive only for anti-HBsAb, the organ does not transmit HBV to the recipient [63]. In recipients of anti-HBcAb ± HBsAb positive livers, the frequency of HBV transmission ranges from 33% to 100% [62, 63, 64, 65]. Several, but not all, studies have shown that recipients negative for anti-HBcAb ± HBsAb have a greater risk for HBV acquisition than those who have markers of previous exposure [62, 63]. HBV DNA detected in donor liver tissue also has been linked to a greater risk of HBV transmission [66]. Anti-HBcAb positive livers should first be offered to suitable HBsAg positive recipients, and secondly to HBsAb positive recipients. Prophylactic regimens for naive HBV recipients remain to be defined. Several possibilities have been explored, including HBIG alone [67], HBIG plus LAM [68] and LAM monotherapy [69], with promising results. Further studies are necessary to confirm these results in a larger cohort of transplant recipients. Due to the shortage of grafts, there is now a tendency to use these grafts in selected recipients with a prophylaxis to avoid HBV transmission.

Treatment of HBV graft infection

Treatment of HBV graft infection is indicated: (1) in case of recurrent HBV infection in patients without prevention; (2) in case of recurrent HBV infection despite prevention with HBIG and/or LAM; (3) in patients with "de novo" HBV infection. Selection of therapy for HBV infection depends on treatments previously received by the patients (i.e. no therapy, HBIG alone, LAM alone, or HBIG and LAM in combination). In the context of protocols that include LAM as prophylaxis, post-transplantation HBV breakthrough involves resistant HBV species. The treatment of HBV graft infection is difficult because of the high level of viral B replication, the ongoing immunosuppressive treatment, and the rapid evolution of graft disease. Rapid reduction in the immunosuppression, mainly corticosteroids, is common practice in many transplant programmes, although the efficacy of this approach is not proven.

Interferon is not very efficient in this setting, and there is a risk of graft rejection [70]. Ganciclovir [71, 72] and famciclovir [73] displayed modest activity against HBV. New nucleoside analogs such as LAM [48, 73, 74, 75, 76, 77, 78, 79, 80, 81] and adefovir dipivoxil are promising, since they have a potent antiviral effect and are well tolerated. The advent of these agents poses a considerable change in the outcome of liver transplant patients infected with HBV. The main disadvantage of these methods of treatment is that all these antiviral agents should be used for long periods of time.

Furthermore, there is a risk of rebound viral replication when these agents are suspended. LAM is the most widely used nucleoside analog, due to a more

Table 5 LAM treatment of hepatitis B after transplantation (*NA* not available)

Author [references]	Patients (*n*)	Pre-treatment HBV DNA$^+$	Pre-treatment HBeAg$^+$	Treatment duration (months)	HBV DNA-negative [*n* (%)]	Seroconversion HBe [*n* (%)]	Seroconversion HBs [*n* (%)]	Breakthrough (n(%))
Andreone [78][a]	11	11	2	17 (8–27)	11 (100)	2 (100)	1 (9)	3(27)
Ben Ari [77]	8	8	5	36 (24–50)	8 (100)	1 (12.5)	0	5(62.5)
Perillo [74]	52	47	45	12	32 (68)	5 (11)	2 (4)	14(27)
McCaughan [48]	10	10	0	12.4 (1–30)	NA	0	0	6(60)
Nery [76]	11	10	NA	15 (13–21)	9 (90)	NA	NA	2(22)
Roche [75]	16	16	10	15.5 (1–30)	13 (81)	3 (30)	3 (18.7)	6(50)
Fischer [79]	12	12	NA	10.5 (5–43)	10 (83)	NA	NA	3(30)
Rayes [73]	41	41	NA	12 to 36	31 (75.6)	NA	NA	14(45)
Malkan [80]	15	14	6	21.2 (4–39)	14 (100)	0	1 (6.6)	2(14.2)
Fontana [81]	33	29	24	21 (4–36)	22 (72)	1 (3)	0	13(45)

[a]Reports treatment of acute HBV re-infection of the graft

potent antiviral effect than ganciclovir and famciclovir. LAM 100 mg/day is well tolerated, and a rapid loss of HBV DNA in serum has been achieved. In a multicentre study on 52 HBV DNA-positive transplant patients, LAM for 1 year resulted in 60% loss of HBV DNA in serum, 11% HBe seroconversion, 4% HBs seroconversion and a histological improvement [74].

Those results were confirmed in other studies showing no HBV DNA in 68% to 100% of patients and HBe seroconversion in 3% to 30% of patients treated for periods of 12 to 36 months (Table 5). Prolonged therapy (i.e. for more than 6 months) is associated with the development of breakthrough (i.e. rise in serum HBV DNA and ALT levels) due to the emergence of HBV escape mutants in 14% to 62% of patients (Table 5) and clinical deterioration in some cases [74, 81]. Thus, with longer follow-up periods, it seems likely that the majority of treated patients would develop HBV DNA breakthrough. Molecular analysis of mutations observed during LAM or famciclovir monotherapy has shown changes in the gene for the viral DNA polymerase (B and/or C domains). Thus, famciclovir-resistant viruses may not be sensitive to LAM. If antiviral drugs are stopped, the wild-type HBV becomes the dominant viral population, but re-treatment is associated with the development of resistant mutants at an accelerated rate [82].

Bock et al. [83] have recently reported severe post-transplantation HBV disease in patients receiving combination prophylaxis with LAM and HBIG, related to a drug-dependent enhanced replication of LAM-resistant HBV mutants. HBV sequence analysis of these patients showed both mutations in the "a-determinant" of the envelope and the YMDD motif (domain C) of the polymerase protein. In vitro experiments indicated that combinations of mutations enhance replication in vitro in the presence of LAM. Thus, it was suggested that continuation of lamivudine could be deleterious in these patients. The prevalence of patients with LAM-resistant HBV infection will continue to increase because of the increasing number of patients treated with LAM prior to or after transplantation.

Fortunately, new HBV antivirals such as adefovir dipivoxil are effective in viral suppression of LAM-resistant variants [33, 84]. The use of adefovir at a dose of 10 mg/day may be limited by toxicity possibly associated with impaired renal function. Schiff et al. reported on 121 patients treated with adefovir, 10 mg/day for a median of 33 weeks (1–88 weeks) [33]. Treatment for 48 weeks resulted in a significant decline in HBV DNA levels by 4 log copies/ml. Dose reductions are required if creatinine clearance is less than 50 ml/min, whereas no dose adjustment is needed for hepatic dysfunction.

Successful treatment by adefovir for hepatic failure, such as cholestatic fibrosant hepatitis resulting from LAM-resistant HBV, was reported [84, 85, 86, 87]. For

these patients, sustained inhibition of replication was not achieved with high-dose LAM, ganciclovir or famciclovir treatment. It is not known if patients treated for LAM resistance with adefovir need to continue on LAM, but it seems better to continue both drugs for some period after the initiation of adefovir. In contrast to the experience with LAM during pivotal studies, no patients developed evidence of viral resistance to therapy.

However, Angus et al. described recently the case of a patient who developed virological resistance to adefovir therapy following the development of a novel mutation in the HBV polymerase gene [88].

Experience with entecavir [89] or tenofovir [90] is limited, but these antivirals seem effective in the treatment of LAM-variants in transplant patients.

Historically, liver retransplantation for HBV recurrence was highly controversial and was considered as a contraindication due to the high risk of recurrence on the second graft and to overall poor results [91]. The advent of HBIG and new antiviral agents has changed this outcome, so that good results are now achievable [92].

Survival of patients undergoing transplantation for HBV cirrhosis

In the absence of prophylaxis of HBV re-infection, the 5-year survival rate is only 40%–60%. In 206 patients receiving adequate immunoprophylaxis, results of OLT for HBV infection in Berlin are similar to those achieved with other indications. Survival rates at 1, 5 and 10 years were 91%, 81%, 73%, respectively [93]. In the multivariate analysis for patient survival, presence of hepatocellular carcinoma and HBV recurrence was associated with lower survival rates. In our own series, the 10-year survival rate of patients who underwent transplantation for HBV and HDV, for cirrhosis, was 70.9% and 89%, respectively [8].

Conclusions

Over the past decade major advances have been made in the management of HBV transplant candidates. The advent of long-term HBIG administration as a prophylaxis of HBV recurrence was a major breakthrough. With the use of LAM before transplantation and a combination of LAM and HBIG after transplantation it is possible to reduce the rate of HBV re-infection in HBV-replicative cirrhotic patients. Future research should: (a) test new protocols using lower HBIG doses given intravenously or intramuscularly, alone, or in combination with antiviral agents; (b) identify patients in whom HBIG prophylaxis can be stopped safely; (c) evaluate new antiviral agents against LAM-resistant HBV mutants.

Currently, treatment of post-liver transplantation hepatitis B is a less pressing clinical problem than it has been in the past. However, in the context of protocols that include LAM as prophylaxis, post-transplantation HBV breakthrough involves LAM-resistant variants. New HBV antivirals, such as adefovir dipivoxil, entecavir or tenofovir, are effective in viral suppression of LAM-resistant variants. Future prospects should compare combination of antivirals to monotherapy and define duration of therapy and criteria for safe discontinuation of the drug.

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