

Controversies Regarding the Hepatitis B Immune Globulin Prophylaxis (HBIG) for Liver Transplantation Recipients

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INTRODUCTION

Hepatitis B virus (HBV) infection is among the top ten causes of death worldwide due to chronic liver disease^[1] and accounts for an estimated 370 million chronic infections^[2]. Approximately 10-15% of infected patients progress to chronic liver disease^[3], and 3% will develop hepatocellular carcinoma (HCC)^[4]. The ultimate interventional option for the end stage liver disease for chronic carriers is liver transplantation, however, this has been challenged by a recurrence rate of 80-100% of HBV infection^[5], leading to rapid progression to cirrhosis and death. With the utilization of hepatitis B immunoglobulin (HBIG), this frequency has been reduced dramatically depends on the dose, route and the presence of antiviral prophylaxis. In this paper we reviewed the current knowledge about the role of HBIG alone or in combination with antivirals and how they influence the outcome of liver transplantation.

METHOD

We performed a literature of review by search of National Library of Medicines PubMed and (NCBI) bibliographies of papers and journals from 2000 to April 2014 on the describing the efficacy of HBIG for the prophylaxis against HBV recurrence after LT in association with several factors using the MeSH terms: HBIG dose, HBIG route, HBIG monotherapy, HBIG combination therapy and finally HBIG and new nucleos (t) ide analogous (NA). We classified the selected papers which contained enough data alphabetically.

We included all cross sectional and prospective or retrospective cohort studies comparing the use of HBIG, antivirals, or both for prevention of recurrent HBV infection in liver transplanted patients. Due to the huge amounts of the data, results from some aspects of above criteria were published elsewhere^[6] mainly focused on the route of injection and dosage of HBIG liver in transplant settings. Herein, we focused mainly on the different types of HBIG therapy in

ABSTRACT

Despite the impressive progress that has been made in developing highly effective prophylaxis regimen against HBV recurrence after liver transplantation which reduces the risk of recurrence to 30% in patients with chronic hepatitis B and to less than 10% in patients with fulminant liver failure, however, the effectiveness of such prophylactic options in preventing recurrence of hepatitis B virus (HBV) depends upon the dosage, route of administration, duration of treatment, type of anti-virals and the viremic status at the time of transplantation. This review will discuss the current status of the topic and consider the developments that made for liver pre- and post-transplantation. The ultimate efficacy of hepatitis B immunoglobulin (HBIG) for the prophylaxis against HBV recurrence after LT in relation to variable factors has been discussed in this review. Moreover, different regimen options based on using either concomitant nucleos (t) ide analogues (NA) and HBIG or drug monotherapy etc discussed.

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Key words: HBIG; Liver transplantation; Nucleos (t) ide analogues; HBV recurrence

the era of new NA drugs.

ROLE OF HBIG IN THE PROPHYLAXIS

Over the past two decades, prophylactic treatment for the prevention of HBV re-infection following liver transplantation involves passive immunity offered by low- to high-dose HBIG alone or in combination with an antiviral NA has been suggested as a gold standard regimen^[7], which reduces the risk of recurrence to 30% in patients with chronic hepatitis B and to less than 10% in patients with fulminant liver failure^[7-10]. This strategy has led to the concomitant improvement in graft and overall survival rates. Despite being effective as an immunomodulator for HBV infection prophylaxis, however, the effectiveness of HBIG in preventing recurrence of HBV depends upon multiple factors: dosage, route, type of therapy, duration of HBIG, HBV DNA levels pre-LT etc. Also, there is currently no consensus over those factors for prevention and/or suppression recurrence of HBV post-LT and yet have not been standardized and tend to vary widely from one transplant center to another^[11-15]. Some of those important controversial factors include:

1. Route of HBIG administration.

As a standard procedure, high dosage of HBIG requires intravenous (IV) administration. As an accepted alternative for intravenous route, intramuscular injection (IM) of HBIG has been studied in many reports worldwide. Regarding the limited volumes that can be given per IM injection, only patients with low HBIG requirements are suited for intramuscular HBIG administration^[16,17]. Currently, switching from intravenous HBIG during anhepatic and a few days post-LT (which usually involved the application of high-dosage) to IM route for either short term or indefinitely has been using widely in different centers (Table 1). Subcutaneous (SC) HBIG either alone or in combination with NA to prevent recurrent HBV infection before LT has been reported only in few studies (Tables 1 and 2). Low recurrence rate, lower dosage of HBIG (500 to 1,000 IU), self-administration by the patients, low drug adverse effects, stability of anti-HBs levels were the advantages^[18-23].

In a cost-effectiveness analysis by Dan *et al* the overall cost for intravenous HBIG for the first and subsequent years were 108,300 and 51,300 US Dollar, respectively. However, the same calculation for intramuscular HBIG for the first and subsequent years were 80,000 and 90,00-10,000 US Dollars, respectively^[24].

2. HBIG doses (low dose versus high dose).

During 1990s, numerous reports from US and European centers have shown the benefit of continuous use of high-dose HBIG post liver transplantation that dramatically reduced the incidence of recurrent HBV infection^[25-27], prior to the availability of effective antiviral therapy^[10]. However, selection of surface protein mutants, high costs and patients in compliance have limited the efficacy of this application^[7,16,28-31]. Therefore, HBIG at lower doses (300-800 IU) and conversion of intravenous to intramuscular route have been used instead^[32-50] (Table 1). Combination of low-dose HBIG with NA resulted in lower costs as well as similar recurrence and survival rates with high dosage regimen^[34,51].

3. Duration of therapy

Many centers worldwide have employed lifelong prophylaxis by the administration of either low or high HBIG dose in combination with NAs^[7,52-54] despite no significant differences for HBV recurrence 5 years after LT for different HBIG regimens^[52]. However, the cost of

such treatment is very high and, in recent years, several centers have used short-term HBIG in combination with indefinite nucleos(t)ide analogue therapy^[30,38,50]. Discontinuation of HBIG after some defined interval and continuing treatment with new antivirals alone have been applied by some centers with a promising results indicating no rate of recurrence^[55-57] (Table 1).

4. Type of HBIG Therapy (mono vs combination with NA).

Although some studies showed that high-dose HBIG monotherapy to be equivalent to the combination regimen for prevention of HBV post-LT^[21,58], combination therapy have become a common strategy to reduce HBV recurrence rate post-LT and the efficacy has been investigated extensively^[30,32,37,40,45,48,49,51] (Table 1). Development of new antiviral agents and the use of HBIG plus antiviral NA have decreased the risk of recurrent hepatitis and death in transplant recipients by decreasing the amount of circulating virus at the time of transplant and by prolonging the half-life of HBIG^[10,59]. Generally, HBIG plus antiviral NA combination prophylaxis consists of antiviral agents administered pre-transplantation (especially in HBV-DNA-positive patients) to reduce the viral load, followed by high (IV) or low (IM) dose (2,000 to 10,000 IU) during the anhepatic phase and a combination of long term antiviral NA and high (IV) or low (IM) dose (400 to 10,000 IU HBIG) with different intervals following transplantation (Table 1)^[21,60].

5. Pre-LT HBV DNA levels.

a: Early recurrence: Typically, early recurrence graft infection (80% to 100%) in the absence of prophylaxis occurs between 6 and 12 months after LT^[5]. Several reports have noted that serum HBV DNA level at the time of transplant would be an important predictor of the half-life of HBIG^[10,17,61] and different high levels of pre-operative viral load (>104 copy/mL) have been suggested to be a risk factor for graft HBV re-infection^[32,52,62-64]. Lenci *et al* showed that patients without detectable HBV DNA in the liver before transplantation have a low risk of HBV recurrence^[7,65] and long-term follow-up studies confirmed that recurrence rates differed with HBV DNA titers prior to antiviral therapy^[34,45]. Neff *et al*^[13] found that none of the 51 patients with undetectable HBV DNA pre-LT experienced evidence of HBV viral recurrence post-LT regardless of the different prophylactic strategy^[30,50]. However, following studies showed that suppression of HBV-DNA in serum does not indicate clearance of the virus from hepatocytes^[46,66] and the long half-life of cccDNA in reinfecting hepatocytes is responsible for viral recurrence following OLT^[67-71]. Therefore, the authors suggested the complete withdrawal of prophylaxis with caution.

b: Late recurrence: Late recurrences are usually caused by the emergence of mutations caused by the selection pressure of HBIG on the surface protein^[28,29,72,73]. Moreover, the emergence of YMDD variants following NA resulted in HBV reinfection following LT as a result of selection pressure of the drugs on the polymerase protein. However, in contrast to HBIG, this emergence being variable according to the type of drug regimen, in a range being highest (16%) to lowest (0%) following lamivudine and entecavir combination therapy. On the other hand, higher occurrence of resistance have been reported following monotherapy with either HBIG (0% to 71%) or NA (lamivudine) (0% to 39.7%)^[74,75] (Table 1). Further, multiple drug/HBIG variants have been reported in patients receiving both interventions (especially in combination with lamivudine)^[72,73,76,77]. Obviously with current new NA agents like adefovir, entecavir, tenofovir, etc, the recurrence rate decreased to 0% to 12.9% (Tables 1-3). However, there are only limited data available for these new

Table 1 Summary of studies for prevention of HBV recurrence after liver transplantation using either HBIG or nucleos(t)ide analogues alone or in combination regimen.

Author	Sample No	Pre-operative Regimen	First week Post Operative	Long Term Post Operative	Antiviral therapy	HBV Recurrence Rate	Mean Follow Up Period
Angus/2008 ^[32]	32	I-(16): ADV/LAM No HBIG II-(18): (800 IM) HBIG + LAM	II- 800 IM	400 IM	LAM+ADV	0	22
Avolio/2008 ^[106]	47	I-5 (No HBIG) II- (16) 10,000 IV III- (26) 10,000+ LAM	5,000 IV	400-1560/m	LAM	I-3 (75) II-3 (30) III-2 (9)	120
Angus/2000 ^[51]	32	2,000 (IM)	400-800 (IM)	400-800 IM/m	LAM	0	18
Anselmo/2002 ^[33]	166	I-28: 10,000 IV II-20 LAM I-89: 10,000 IV +LAM IV-29: No Px	2,000 IV	1,560- Monthly	LAM	I-13 (48) II-13 (67) III-10 (11) II-23 (82)	29
Anderson/2007 ^[107]	123	I-(17): 2,000 IM+LAM II-(46): 1,0000 IV+LAM III-(44): 10,000IV Short Term IV-(16) No Px	I-(17):IM II-(46):IV III-(44):IV	I-(17): IM Indef II-(46): IV Long Term III-(44): No	LAM	I-1 (5.9) II-8 (19.5) III-34 (77) IV-11 (68.7)	60
Alonso/2003 ^[108]	6	2,000 IM	2,000 IM	2,000 IM	-	1 (16.6)	12
Brock/2011 ^[109]		I-(61)HBIG II-(116) LAM III-(66)HBIG+LAM IV-(509) No Px	NA	NA	LAM	I-0 II-7 (6) III-0 IV-21 (4)	23
Buti/2003 ^[110]	29	I-(20) LAM II-(15)HBIG 10,000 IV+LAM	5,000 IV	2,000 IM (18 m)	LAM	I-1 (7) II-3 (20)	83
Ben-Ari/2004 ^[111]	24	I- (24) 10,000 IV II- (9) 10,000+ LAM	10,000 IV	10,000 IV Indef	LAM	I-6 (25) II-1 (11)	48.1
Chun/2010 ^[112]	209	I-(11%) Mono: 10,000-20,000 IV II- (89%) 10,000-20,000+LAM	10,000 IV	10,000 IV Indef	LAM	I-3 (13) II-19 (10.2)	36.8
Dadson/2000 ^[113]	25	10,000 IV	10,000 IV	I-(3) 1,000 IM (2 Year) II- (6) 1,000 IM Indef III- (16) LAM	LAM	I-1(33) II- 0 III-0	73
Dehghani/2013 ^[114]	49	LAM+HBIG (??) IM	NA	IM Indef	LAM	0	96
Dickson/2006 ^[59]	30	10,000	10,000	5,000-10,000 IV/W	LAM	1 (3.3)	24
Dumortier/2003 ^[115]	60	I-(43) 10,000 IV II-(17) 10,000 IV+LAM	10,000 IV	10,000 IV	LAM	I-10 (23) II-0	98
Degertekin/2010 ^[116]	181	HBIG+NA (Variable)	(Variable)	(Variable)	LAM/ADV/ENI/TEN	13 (6.9)	42
Di Paolo/2004 ^[117]	11	HBIG 5,000+LAM	5,000	2,000 (on demand)	LAM	0	22
Faust/2003 ^[118]	12	HBIG 10,000 IV +LAM	10,000 IV	2,000 IM Indef	LAM	1 (8.3)	36
Freshwater/2008 ^[99]	42	I-(10) LAM mono II-(24) 10,000+LAM III-6 10,000+LAM+ADV	5,000	5,000 Indef	LAM/ ADV	I-8 (80) II-15 (62.5) III-0	160
Fabrega/2003 ^[119]	7	10,000 IV+LAM	10,000	No HBIG	LAM	0	23
Feretti/2004 ^[120]	28	HBIG 10,000 IV+LAM	10,000 IV	1,200 IM	LAM	1 (8.3)	20
Filipponi/2010 ^[121]	18	I-(7) 2,000 IM II-(11) 2,000 IM+LAM	2,000 IM	2,000 IM (6 m)	LAM	0	47
Gane/2013 ^[55]	20	HBIG 800 IM+LAM+ADV	900	No HBIG	ADV	0	57
Han/2000 ^[35]	71	Com(59): 10,000 IV+LAM Mono (12): 10,000 IV	10,000 IV	10,000IV Monthly Indefi	LAM	Comb: 0 Mono: 3 (25)	22
Han/2003 ^[122]	59	I-10,000 IV+LAM (Pre) I-10,000 IV+LAM (Post)	10,000 IV	1560 IM	LAM	I-0 II-0	87.5
Honaker/2002 ^[123]	27	I-(4): No Px II-(14) 10,000 Iv III-(9) 10,000 IV+LAM	10,000 IV	10,000-40,000 IV/m	LAM	I-100 II- 3(21) III-0	72
Iacob/2008 ^[124]	42	10,000+LAM	10,000	2,500 IV On demand	LAM	2 (4.8)	30.9
Jiang/2010 ^[125]	254	2,000 IM+LAM	800 IM	800-1,200 IM Indef	LAM	14 (5.5)	41.2
Jain/2005 ^[126]	28	10,000 IV (4 Days)+LAM	No HBIG	No HBIG	LAM	3 (10.7)	36
Jiao/2007 ^[127]	84	I-(55) 2,000 IM+LAM II-(28) LAM	800	400-1,200 IM Indef	LAM	I-3 (5.4) II-7(25)	37
Karademir/2006 ^[128]	40	4,000 IM+LAM	2,000 IM	1,200-2,000 IM Indef	LAM	0	16
Kwon/2006 ^[129]	28	I-(20) 10,000 IV II-(8) Mono 4,000 IV	I-10,000 IV/7D II-4,000 IV/3D	I-10,000 IV+ LAM	LAM	I-3 (15) II-0	NA
Lee/2000 ^[130]	26	I (12) HBIG 10,000 IV II (14)LAM	10,000 IV	10,000 (1st Year), 2,000 IV Indef	LAM	0	21.8
Lee/2004 ^[131]	14	10,000 IV	10,000 IV	10,000 IV	-	3 (21.4)	39.7
Lu/2004 ^[85]	17	I: (3) HBIG 1,000+LAM II (14)LAM	1,000	1,000 (NA)/Indef	LAM	I-1 (33.3) II-2 (14.2)	18
Lu/2008 ^[39]	122	8,000 IV I-111 (No recurrent) II- 11 (recurrent)	800 IM	800 IM for 1 Y	LAM	I-0 II- 7 (63.6)	12
Loss/2003 ^[132]	14	10,000+LAM	No	No	LAM	1 (7)	33
Manzarbeitia/2002 ^[133]	24	10,000 IV	10,000 IV	10,000 IV	-	2 (8.3)	25.6
Marzano/2005 ^[62]	177	I-(98) 10,000 IV II-(73) 10,000 IV+LAM & LAM+ADV	5,000 IV	5,000 IV	LAM/ ADV	I-9 (9) II-6 (8)	44
Marzano/2001 ^[36]	33	10,000 IV+LAM	5,000 IV	5,000 IV Indef	LAM	1 (3)	30
Nery/2003 ^[14]	60	I-(26) LAM mono II-(16) 10,000 IV+LAM III-(18) No Px	10,000 IV	10,000 IV Indef	LAM	I-0 II- 0 III- 2 (11)	23.5

Table 1 Summary of studies for prevention of HBV recurrence after liver transplantation using either HBIG or nucleos(t)ide analogues alone or in combination regimen.

Author	Sample No	Pre-operative Regimen	First week Post Operative	Long Term Post Operative	Antiviral therapy	HBV Recurrence Rate	Mean Follow Up Period
Pan/2011 ^[58]	18	I-HBIG (1) II-HBIG + LAM (3) III-LAM (no HBIG) (8) IV- No Px (6)	NA	NA	LAM	I-0 II-0 III-0 IV- 1 (16.6)	49
Park/2002 ^[134]	61	I- (31) 10,000 IV II- (30) LAM + 10,000 (1 week)	I-10,000 IV	I-10,000 IV Indef	LAM	I-1 (3.2) II-3 (10)	43
Prakaso/2006 ^[135]	12	No	No	No	LAM	0	21
Roque-Afonso/2002 ^[136]	22	I-16: 5,000-10,000 II-4: No Px. III-2: HBV vaccine	5,000-10,000	5,000-10,000 IV	-	I-1(6.2) II-4 (100) III-0	45
Rosenau/2001 ^[137]	21	10,000 IV+LAM	10,000 IV	2,000 IV Indef	LAM	2 (9.5)	20.1
Seehofer/2002 ^[138]	39	10,000 IV+LAM	10,000 IV	1,500-2,000 IV Indef	LAM	1 (2.5)	27
Sousa/2003 ^[139]	17	I- (17) 10,000 IV II- (10) 10,000 IV + LAM	10,000 IV	10,000 IV/Indef	LAM	I-17 (100) II-0	71
Steinmuller/2002 ^[53]	206	I-(102) 10,000 IV mono II-(51) 10,000 IV + LAM III-(53) 10,000IV+ FAM	10,000	1,500-2,000 IV /2-4 W Indef	LAM	I-16(16) II-4 (8) III-0	NA
Singham/2010 ^[20]	12	3,120 IU SC+LAM	-	Repeated SC within 3m	LAM	0	NA
Suehiro/2005 ^[40]	22	10,000	2,000	2,000/two m	LAM	0	38.5
Sugawara/2003 ^[140]	18	10,000 IV+LAM	10,000 IV	3,000-5,000 Infef	LAM	0	19
Targhetta/2006 ^[42]	42	10,000 IV	10,000 IV	1,600/m	LAM	7 (16.6)	96
Takaki/2007 ^[41]	23	-	200/kg	2,000 for 1 year	LAM	0	57
Umeda/2006 ^[43]	38	200 U/Kg	200 U/Kg	1,000 Indef	-	9 (23.7)	35
Wang/2004 ^[44]	66	I- (2) LAM mono II- (63) 4,000 IV+LAM III-(3) 4,000 IV+ADV	1,000 IV	400 twice/W IM	LAM & ADV	I-1(50) II-2 (3) III-0	18
Xi/2009 ^[100]	120	I-(30) 2,000 IM+ENT II-(90) 2,000 IM+LAM	1,600 IM	800 IV/W	LAM/ENT	I-0 II-10 (11)	34
Xie/2010 ^[136]	160	I-(107) HBIG+LAM II-(10) HBIG+ENT III-(43) HBIG	-	400 IM	LAM/ADV/ENT	I-17 (15.8) II-1 (10) III-0	38.5
Yilmaz/2008 ^[48]	16	I-10,000 IV (Mono): (15) II-HBIG+LAM/ADV (10)	1,500 IV	1,500 IM	LAM & ADV	I-8 (53) II-0	42
Yi/2007 ^[141]	203	I- (95) 10,000-20,000 IV II- (108) LAM + 10,000	10,000 IV	10,000/Indef	LAM	I -(6) 6.3 II-(12) 13.8	26.8
Yan/2006 ^[142]	51	20 g IV	5 g IV+IM	5 g IM Indef	LAM	2 (3.9)	14
Yang/2007 ^[143]	392	HBIG+LAM HBIG+Ganciclovir	800 IM	800 IM	LAM	16 (4)	19.4
Yoshida/2007 ^[46]	60	I-(26) LAM II-(34) HBIG(10,000) IV+LAM	10,000 IV	10,000 IV (6 M)	LAM	I -4 (15) II-6 (18)	67
Yu/2001 ^[144]	15	I-(6) LAM+HBIG II-(9) LAM	-	1,000 IM	LAM	I-1(16.6) II-0	20
Yuefeng/2011 ^[145]	15	10,000 IV+ LAM	2,500 IV	2,500 IM Indef	LAM+ADV	2 (13.3)	86
Zheng/2006 ^[30]	165	I-114: 2,000 IM+LAM II- 51: only LAM	400-800	800 monthly Indef +LAM	LAM	I: 16 (14) II: 21 (41)	20
Zhu/2003 ^[146]	24	I-(15) LAM II-(9): LAM+HBIG 2,000	1,000	1,000 Indef	LAM	I-2 (13) II-0	17

ENT: Entecavir; ADV, Lamivudine, LAM; Adefovir, FTC, Emtricitabine; TDF, Tenofovir; FAM, Famciclovir; GAN, Ganciclovir; SC, subcutaneously; NA, not identified; Px, Prophylaxis; IV, Intravenous; IM, Intramuscular; Indef, Indefinitely.

©: No details for HBIG administration.

Author	Sample No	Pre-operative Regimen	First week Post Operative	Long Term Post Operative	Antiviral therapy	HBV Recurrence Rate	Mean Follow Up Period
Compos-Varela/2011 ^[38]	49	I-(7): 4,000/w for 1 month II-Comb (NA +HBIG: -(38):LAM - (2) ETV -TDF+FTC (1) -LAM+ADV (1)	4,000 IM	4,000 IM/W: 3 W 2,000/m/Indef	LAM + New NA	HBIG Alone: 5/7 (71%) HBIG Comb: 3 (7%). -1 (33%) under ETV	37-54
Cai/2012 ^[147]	252	HBIG 1000 IM+ I: LAM (189) II: ENT (63)	400 IM	Maintenance Indef	ETV	I: 18(9.5%) II:0	41.2
Di Costanzo/2013 ^[22]	135	6,000 IV Switched to SC+New NA	-	-	LAM/ ADV/ LAM+ADV/ENT/ LdT	0	NA
Gao ^[103]	253	HBIG 2000 IM I-84: ENT II-169: LAM	-	400-1,000/Indef	ETV/LAM	I-0 II-16 (9.4%)	72
Hwang/2011 ^[97]	1524	I -10,000 IV+NA II-10,000 IV	10,000 IV	10,000 IV/m Indef	ENT/ADV (Res)	I-No Rec II-106 (7.3%)	57
Hwang/2008 ^[98]	639	10,000 IV	10,000 IV	10,000 IV/m	LAM/ADV/ENT/ Cluvidine (post)**	6.4	53
Hu/2012 ^[148]	67	HBIG at low dose on demand 67 ETV	-	HBIG at low dose on demand	ETV	2 (3%)	NA
Ishigami/2011 ^[149]	4	[10,000 IV] / [10000/day IV 4 ETV	-	[1,000-2,000]	4 ETV	0	64
Kim/2013 ^[104]	154	ENT+ 10,000 IV (first month)	10,000 IV	Maintenance Indef	ETV	5 (3.2%)	28
Jiménez-Pérez/2010 ^[93]	8	HBIG+ENT+TDF	NA	LOW IM	ENT+TDF	No Rec	8
McGonigal/2013 ^[101]	4	10,000 IV ENT/LAM/TEN ²	10,000 IV	3,000 IM	TDF-FTC	0	9
Perrella/2012 ^[56]	14	HBIG®+ENT/LdT/TEN/ LAM+ADV	-	-	-	0	6
Perrakis/2013 ^[100]	19	10 000 IV I:LAM mono (8) II:LAM+ADV (4) III:ENT+TEN (2) IV:ENT (1) V:ADV (1)	2,000	10,000 IV Indef	LAM/ENT/ ADV/ TEN (Res)	3 (15.7%) I:2 (25%) II: 1 (25%)	47
Perrillo/2013 ^[150]	65	HBIG ¹ + ENT (26), LAM (22), ADV (12), TNF+PegINF (1) None (12)	NA	Monthly dose	New NA	2/61 (3.2%) One LAM+ADV One no antiviral therapy	6
Roche/2010 ^[28]	77	A- HBsAg+: HBIG (10,000/7 D) mono (n=11) B-HBsAg+: HBIG (10,000/7/ D) +combination NA (n=10) C-HBsAg:-HBIG (5,000/7 D) (n=45) D-HBsAg-: No Px. (n=11)	A- 10,000 B- 10,000 C- 5,000 D- No Px.	10,000 IV 6-12 doses/Y	LAM + ADV+ENT+TEN	-No Rec in A & B (n=21). -Rec in 8/45 (17.7%) C. -Rec in 7/11 (64%) of D	59
Tanaka/2012 ^[102]	152	2,000 IV	2,000 IV/IM	2,000 IM (one year)+NA	LAM only: 97 LAM+ADV:16 ADV:1 TDV:4 ETV:3	9 (9.2%) only in LAM only group	
Teperman/2010 ^[57]	33	HBIG ¹ TDF+FTC	NA	Only for 24 weeks	TDF + FTC(cont after HBIG withdrawal)	0	24
Ueda/2013 ^[151]	26	I: LAM+ HBIG (63) II: ETV +HBIG (26) 10,000 IV	10,000	1,000 Indef	ETV	I: 3 (4.7%) II:0	25.1
Varghese/2014 ^[105]	7	10,000 IV	1,000-14,000	3,000	ETV	0	24
Xie/2010 ^[95]	160	I-(107) HBIG+LAM II-(10) HBIG+ENT III-(43) HBIG	-	400 IM	LAM/ADV/ENT**	I-(17) 15.8% II-(1) 10% III-No Rec	38.5
Xi/2009 ^[100]	120	I-(30) 2,000 IM+ENT II-(90) 2,000 IM+ LAM	1,600 IM	800 IV/W	LAM/ENT	I-No Rec II-10 (11%)	34
Yasunaka/2011 ^[46]	32	200 U/kg	2,000	2,000 inde until anti-HBs<100	LAM+ADV+ENT	No Rec±	38

ENT: Entecavir; ADV, Lamivudine, LAM; Adefovir; FTC, Emtricitabine; TDF, Tenofovir; FAM, Famciclovir; GAN, Ganciclovir; SC, subcutaneously; NA, not identified; Px, Prophylaxis; IV, Intravenous; IM, Intramuscular; Indef, Indefinitely.

±: cccDNA was positive in 57% of patients. Indef: Indefinitely.

¹:. the details of HBIG regimen were not available.

²: All 4 patients switched to FTC/TDF after transplantation.

Table 3 Summary of studies for prevention of HBV recurrence after liver transplantation using NA without HBIG.

Author	Sample No	Pre-operative Regimen	Antiviral therapy	HBV Recurrence Rate	Mean Follow Up Period
Chotiyaputta/2010[78]	18	I-LAM (10) II-ENT (8)	ENT	0	75
Gane/2007[34]	147		LAM	4	62
Genzini/2010[88]	19	LAM:11 LAM+ADV:3 ENT:5	-	0	19.5
Holt/2002[152]	12	LAM Mono	LAM	No Rec	38
Fung/2011[42]	80	ENT	ENT	18 (22.5%)	26
Fung/2013[41]	362	I:LAM (176) II:ENT (142) III:LAM+ADV (44)	New NA	I:36 (20.4%) II:1 (0.7%) III:5 (11.3%)	53
Schiff/2007[87]	80	I-(23)ADV mono II-(57)HBIG+ADV I:LAM+ADV: 19 II:ENT:42	LAM-ADV*	I-0% II-0%	12
Wadhawan/2013[90]	75	III: TEN:12 IV:ENT+TEN:2	ADV/ENT/TEN	6 (8%)	21

ENT: Entecavir; ADV, Lamivudine, LAM; Adefovir, FTC, Emtricitabine; TDF, Tenofovir; FAM, Famciclovir; GAN, Ganciclovir; SC, subcutaneously; NA, not identified; Px, Prophylaxis; IV, Intravenous; IM, Intramuscular; Indef, Indefinitely.

antiviral NAs and further studies needed to test their effectiveness as part of combination therapy with HBIG and/or monotherapy strategies^[78-80].

6. Anti-HBs target levels

Despite there is no consensus regarding sustained levels of anti-HBs following HBIG administration before and after LT, it is widely accepted that anti-HBs plasma titers should not fall below 100 IU/L during HBIG therapy. Protection against HBV recurrence seems to obtain better with higher anti-HBs levels (300-500 IU/L)^[81,82]. The proposed levels ranges from >70 to >500 IU/mL among centers. Furthermore, serum HBsAb levels monitoring after HBIG injections is also controversy among centers and the need for an intensive care of the level of anti-HBs (and subsequent frequent reinjection) to prevent HBV recurrence are still unclear^[13,30,50]. The ideal method for establishment of anti-HBs variability in response to HBIG administration would be through individualized dosing proportional to anti-HBs levels obtained in a timely fashion interpatiently^[59].

PROPHYLAXIS WITH NA

1. NA monotherapy

Among the NAs, lamivudine was the first that introduced as a monotherapy before and after LT for prophylaxis against HBV recurrence post-LT especially in certain patients such as those who were HBV-DNA-negative and at low risk of re-infection^[36,75,83]. Subsequently, there was a dramatic decrease of the HBV recurrence rate in patients receiving lamivudine (LAM) monotherapy (3 years post-LT recurrence rate of 40%)^[75,84].

Unfortunately a recurrence rate of 3.8 to 40% at 2 years post-LT have been reported by multiple centers as a consequence of drug-resistance phenomenon caused by the emergence of mutants in the highly conserved motif YMDD within the polymerase^[30,72,73,77,85]. Lu *et al* investigated two groups of LT recipients receiving lamivudine (in combination with HBIG) at long and short term periods. The longer period-group (mean 698.5 days) showed 9% HBV recurrence compared to 0% for shorter period group (mean 36.9 days)^[39]. Moreover, others showed that in patients on lamivudine monotherapy, high viral load pretransplantation could be a predictor for the development of posttransplantation lamivudine resistance^[51,74]. Therefore, long term LT prophylaxis using lamivudine

monotherapy has been not recommended, particularly in replicative patients^[30,35,84,86].

The data on using new NA monotherapy for prophylaxis in the absence of HBIG are few. Adefovir (ADV) monotherapy has been used by few studies with encouraging results (Tables 1-3)^[87]. The rate of recurrence after LT was 0%. Similarly, entecavir, Telbivudine monotherapy^[78,88-91] pre-and post LT resulted in 0% to 8% HBV recurrence rate (Table 2). Only one study found a relatively high rate of recurrent HBV infection (22.5%) using ENT^[91] (Table 3). Based on experience in non-transplant patients, telbivudine can be substituted for lamivudine. Similar to lamivudine, telbivudine should not be used as monotherapy, and if used it should be combined with adefovir or tenofovir to minimize the risk of drug resistance^[10].

2. Rescue therapy

During the new NA era for the prophylaxis against HBV recurrence following LT, many centers have been using these drugs only in the case of drug resistance following lamivudine administration as either add-on or switching approaches in combination with HBIG as rescue therapy^[13,37,45,49,92-97] (Table 4). ADV has been at the top of this list for only cases who acquired HBV reinfection due to LAM-resistance. Schiff *et al*^[94] reported a survival of one-year 84% for pre-LT and 93% for post-LT patients with no cases of ADV-resistance in patients who experienced HBV recurrence after LT. HBV DNA was undetectable at week 144 in 78% of cases. Longer follow up study showed a 3 year sustained survival of 87% in these patients group^[87]. Also, entecavir showed promising results for these patients with no cases of recurrence^[38,88,93,98]. However, despite entecavir is an ideal antiviral agent in nucleoside-naïve patients for its potent antiviral effects, low rate of drug resistance, and lack of nephrotoxicity, as entecavir-resistant mutations are more likely to be selected in the presence of lamivudine-resistant mutations, some authors have not recommended this drug in patients with lamivudine-resistant HBV^[10]. Other new NA agents like Emtricitabine (FTC), Tenofovir (TDF); Famciclovir (FAM)^[13,28,38,93] (Table 4) showed to be effective for lamivudine-resistant variants following liver transplantation. However, the sample sizes in these studies on the effectiveness of new NA agents were too small to make a definite conclusion.

3. NA combination therapy

New NAs including adefovir, entecavir, tenofovir, and telbivudine

Table 4 Summary of studies for prevention of HBV recurrence after liver transplantation using NA as rescue therapy.

Author	Sample No	Pre-operative Regimen	Antiviral therapy	Mean Follow Up Period
Akyildiz/2007 ^[37]	209	2,000 IM+ 2,000 IV	LAM ADV+LAM	18
Donataccio/2006 ^[92]	19	I-(6)short term (10 D): 10,000 IV II-(8) Indefinite: 10,000 IV III-(5) No Px:	LAM & ADV	34
Hwang/2011 ^[97]	1524	I -10,000 IV+NA II-10,000 IV	ENT/ADV	57
Neff/2004 ^[13]	92	I- HBV DNA (-): LAM II- HBV DNA (-): 10,000 IV+LAM III- HBV DNA(+): LAM IV- HBV DNA(+): 10,000 IV +LAM	LAM TNV/ADV	14
Jiménez-Pérez/2010 ^[93]	4	HBIG+ENT+TDF 10,000 IV	ENT+TDF	8
Perrakis/2013	19	I:LAM mono (8) II:LAM+ADV (4) III:ENT+TEN (2) IV:ENT (1) V:ADV (1)	LAM/ENT/ADV/TEN	47
Roche/2010 ^[28]	1	HBIG+ENT	ENT	65
Schiff/2003	324	HBIG	ADV	56.1
Xie/2010	19	I-(17) HBIG+LAM II-(1) HBIG+ENT III-(1) HBIG+ADV	LAM/ADV/ENT	38.5
Wong/2007 ^[49]	21	I-(15) 10000 IV+NA II-(6) 10000 IV	LAM & ADV	18
Woo/2008 ^[45]	165	NO HBIG	ADV	40

ENT: Entecavir; ADV, Lamivudine, LAM; Adefovir; FTC, Emtricitabine; TDF, Tenofovir; FAM, Famciclovir; GAN, Ganciclovir; SC, subcutaneously; NA, not identified; Px, Prophylaxis; IV, Intravenous; IM, Intramuscular; Indef, Indefinitely.

are antiviral agents of choice for the treatment of HBV. However, due to lack of data and despite some few studies that showed their effectiveness when they included in the prophylactic regimen^[38,93,96] (Table 3), combination of NAs without the concomitant use of HBIG is generally not recommended. Further, comparison of trails that used a combination of antivirals compared with a combination of HBIG plus either NA alone showed that both regimens provides equivalent protection against recurrent HBV infection after LTx with fewer side effects and lower cost^[32,88]. Furthermore, treatment with adefovir plus lamivudine before LTx and the addition of HBIG after LTx has shown to prevent graft reinfection^[7,87,94,99].

Due to the potential nephrotoxicity, tenofovir is not an ideal drug in the transplant setting in nucleoside naïve patients but tenofovir alone or in combination with a nucleoside, lamivudine, emtricitabine, telbivudine or entecavir, is recommended for patients with lamivudine resistance^[10].

4. HBIG+NA prophylaxis

As it shown in the table 1, the incidence of de novo HBV was ranged from zero to 2.7% in patients receiving LAM-only prophylaxis versus zero to 20% in those receiving HBIG plus LAM combination therapy. Thus, both prophylactic treatment strategies were associated with HBV breakthrough post-LT.

Following lamivudine, adefovir has been introduced as more potent NA antiviral for post-LT prophylaxis. Although the sample size of the patients-studied was low in compare with Lam-receiving patients, the reported recurrence after prophylaxis with ADV was 0%^[44,87,99]. Among new NAs, entecavir, telbivudine, tenofovir and emtricitabine have been used with 0% recurrence rate (Table 2)^[22,46,56,93,95,100-105].

5. NAs cross-regimen

There are some recommendation regarding switching from HBIG monotherapy or combination therapy to NAs monotherapy (Tables 1-2). Patients without virus replication at the time of LTx, with at least 2 years of HBIG treatment and those who are negative for HBV

DNA by polymerase chain reaction before stopping HBIG seem to be the best candidates to switch to a monotherapy with NAs^[7,13,28,49,74]. In a study by Xie *et al.*, of 17 patients who experienced HBV recurrence after LT, 12 switched from LAM+HBIG to adefovir plus lamivudine. HBV DNA fell below 103 copy/mL in 10 cases after 6 months (one case died due to HCC) and subsequently in one patient who switched to entecavir^[95].

CONCLUDING REMARKS

Despite the absence a consensus on prophylaxis against HBV reinfection following liver transplantation, in an attempt to determine an optimal regimen for HBIG administration that can be more cost-effective, convenient, and widely-accepted alternative approaches have been studied including: lower HBIG doses, the use of intramuscular or subcutaneous HBIG rather than the intravenous route, non-HBIG forms of anti-HBs, and low-dose or short-term HBIG in combination with antivirals and tailoring HBIG administration guided by plasma concentrations rather according to a fixed time schedule. The choice of options depend on the availability of antivirals and cost of HBIG regimen. Regarding new NA monotherapy, due to the lack of adequate data, for a definite conclusion more prospective, cohort studies needed though the available results are optimistic.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests and received no financial support.

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