Review

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Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: A systematic review

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Background & Aims: Chronic hepatitis B patients are at increased risk for hepatocellular carcinoma (HCC). The effect of medium-term nucleos(t)ide analogue therapy on HCC incidence is unclear; therefore, we systematically reviewed all the data on HCC incidence from studies in chronic hepatitis B patients treated with nucleos(t)ide analogues.

Methods: We performed a literature search to identify studies with chronic hepatitis B patients treated with nucleos(t)ide analogues for $\geqslant$24 months.

Results: Twenty-one studies including 3881 treated and 534 untreated patients met our inclusion criteria. HCC was diagnosed in 2.8% and 6.4% of treated and untreated patients, respectively, during a 46 (32–108) month period ($p = 0.003$), in 10.8% and 0.5% of nucleos(t)ide naive patients with and without cirrhosis ($p < 0.001$) and in 17.6% and 0% of lamivudine resistance patients with and without cirrhosis ($p < 0.001$). HCC developed less frequently in nucleos(t)ide naive patients compared to those without virological remission (2.3% vs 7.5%, $p < 0.001$), but there was no difference between lamivudine resistance patients with or without virological response to rescue therapy (5.9% vs 8.8%, $p = 0.466$).

Conclusions: Chronic hepatitis B patients receiving medium-term nucleos(t)ide analogue therapy had a significantly lower incidence of HCC compared to untreated patients but treatment does not completely eliminate the risk of HCC. Among the treated patients, cirrhosis, HBeAg negative at baseline and failure to remain in virological remission were associated with an increased risk of HCC.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide [1]. Its incidence is high in Eastern Asia and sub-Saharan Africa [1,2], and increasing in several Western low incidence areas [3]. HCC usually develops in patients with pre-existing chronic liver disease, mostly cirrhosis [1,2]. The risk for developing HCC varies according to the etiology of liver disease with chronic hepatitis B virus (HBV) infection being globally the most frequent underlying cause [1,2].

The prognosis of HCC is extremely poor, because therapeutic interventions are generally ineffective in advanced stages [4]. Screening programs have been applied to detect HCC in early stages. However, screening programs with determinations of serum alpha-fetoprotein levels and ultrasonography every 6–12 months are rather unsatisfactory, with HCC detected in early stages in less than 50% of cases [5]. Thus, development of prevention strategies is imperative.

The efficacy of primary prevention programs based on the universal HBV vaccination of all newborns has already become apparent in many high endemic Asian countries, where HCC incidence among children have declined by 70% [6]. However, approximately 400 million people who are chronically infected with HBV will not benefit from immunisation and remain at increased risk for HCC [7]. Given that the HCC risk is particularly high in the presence of cirrhosis and/or persistent high viral replication [1,2,8], antiviral therapy could be a rational approach to prevent this complication in such patients.

The current therapeutic options for patients with chronic HBV infection may be summarized into treatment with standard or pegylated interferon-alpha (IFNα), a drug with antiviral, immunomodulatory and perhaps antitumoral activities, and treatment with oral nucleos(t)ide analogues [9–11]. The effect of IFNα on HCC incidence in patients with chronic hepatitis B has been evaluated in several studies and meta-analyses. Most of the data suggest that IFNα treatment may decrease overall HCC incidence with a more marked effect in sustained responders. The effect is more evident in Asian than in European studies possibly related to the lower incidence of HCC in European patients [12–17]. The effect of oral antiviral therapy on HCC incidence, however, has not been clarified. Therefore, we systematically reviewed all the data on HCC incidence from studies in patients with chronic hepatitis B with or without cirrhosis who were treated with medium-term nucleos(t)ide analogues.

Search strategy and selection criteria

Medline/Pubmed from January 1998 to April 2009 was searched to identify all medical literature included under the search text

Keywords: Hepatitis B; Hepatocellular carcinoma; Antivirals; Nucleoside analogues; Nucleotide analogues; Lamivudine.

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Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; IFNα, interferon-alpha.

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terms: "hepatitis B" and "cancer", "carcinoma" and "therapy", "treatment", "lamivudine", "adefovir", "entecavir"; "telbivudine", "tenofovir". In addition, a manual search of all relevant review articles and of the retrieved original studies was performed.

All studies published in English as full papers were included, if they fulfilled all of the following criteria: (1) were randomised trials or observational cohort studies, (2) had adult patients with chronic hepatitis B and/or cirrhosis (compensated or decompensated), (3) the patients were treated with nucleos(t)ide analogues for a mean/median duration of at least 24 months, and (4) data on the incidence of HCC was available. Studies including patients with HBV and hepatitis D or C and/or human immunodeficiency virus co-infections were excluded.

The literature search was performed by two independent reviewers (G.V.P., P.L.), who determined which studies could be potentially included. Two lists of selected papers were compared for concordance and discrepancies, were discussed, and, if necessary, arbitrated by a third reviewer (A.L.). Each study in the list of selected papers was evaluated by two independent reviewers (G.V.P., S.M.) in order to determine whether it fulfilled all the inclusion criteria. The same two independent reviewers (G.V.P., S.M.) extracted data from the selected papers according to a predefined form. Two data summary tables were compared for concordance and a minor discrepancy was identified in only one study.

Studies and patient characteristics

There were 672 studies initially identified from the literature search. Of these, 422 were excluded because they did not include chronic hepatitis B patients treated with nucleos(t)ide analogues, 198 had a mean/median follow-up of <24 months and 31 did not report HCC data. Therefore, only 21 studies were included in the final list [18–38]. Studies were considered to be of high quality for this review if they fulfilled three of the following five criteria: (a) provided definitions for HCC diagnosis, (b) described HCC screening at baseline, (c) described HCC surveillance during therapy, (d) provided HCC data separately in patients with and without cirrhosis, and (e) provided HCC data in relation to virological response. According to these criteria, 14 studies were characterized to be of high [19–22,24–27,29,32,35–38] and 7 to be of low quality [18,23,28,30,31,33,34]. Ten studies were considered as large [18,20,22,26,29,32,33,36–38] and 11 as small [19,21,23–25,27,28,30,31,34,35] if the total number of patients was more than 100 or less than 100, respectively.

In total, there were 3881 chronic hepatitis B patients with or without cirrhosis who were treated with nucleos(t)ide analogues (from 20 to 998 patients in each study). Of these, 1280 (33%) had cirrhosis, 888 (69%) had compensated and 162 (13%) decompensated cirrhosis, while the severity of cirrhosis was not reported in 230 (18%) patients. Roughly half (49.2%) of the patients were hepatitis B e antigen (HBeAg) positive (1909/3881) (Table 1).

The mean or median age of the patients was between 30 and 40 years in three studies [18,23,32], between 40 and 50 years in 10 studies [21,22,24,25,29,31,34,36–38] and in the non-cirrhotic patients of one additional study [20], and ⩾50 years in 7 studies [19,26–28,30,33,35] and in the cirrhotic patients of one study [20]. Most patients were males (79.7%) and the majority was Caucasians (50.6%) or Asians (48.0%). HCC screening at baseline was reported to be performed in 15 studies including 2807 patients [18,19,21,22,24–27,29,32,34–38] and HCC surveillance during therapy (mostly by alpha-fetoprotein and/or abdominal ultrasound) at least every 6 months in 11 of these studies including 1553 patients [19,21,22,25–27,32,35–38], while HCC screening and/or surveillance were not described or performed in the remaining studies (Table 2). It should be noted that the proportion of cirrhotic patients was significantly higher in studies with than without reported strategies for HCC surveillance (650/1553 or 41.9% vs 630/2328 or 27.1%, $p < 0.001$).

Sixteen studies included nucleos(t)ide naive chronic hepatitis B patients with lamivudine monotherapy used initially in 14 [18–22,24–28,32,34–36], emtricitabine in one [23] and adefovir in the remaining study [29]. Five studies included patients with lamivudine resistance treated with adefovir monotherapy or adefovir and lamivudine combination therapy [30,31,33,37,38]. The mean or median duration of follow-up was 24–36 months in 10 studies [20–23,26,28,30,31,37,38] and >36 months in 11 studies [18,19,24,25,27,29,32–36] (Table 3).

Three of the 21 studies included not only treated but also untreated chronic hepatitis B patients followed for at least 24 months. Of note, 215 untreated controls were included in the only randomised controlled trial [22], 195 historical untreated controls were included in a cohort study [26] and 124 untreated patients were included in a single center study [32]. The untreated patients in the second study were younger, had lower baseline ALT levels and longer follow-up compared to the treated patients, while the untreated patients in the third study had similar characteristics as the treated patients in that study (Tables 1–3).

Incidence of HCC and timing of HCC diagnosis

In total, 168 (4.3%) chronic hepatitis B patients receiving nucleos(t)ide analogue therapy were diagnosed to have HCC during a mean/median follow-up of 40 (24–102) months (Table 4). In 10 studies including nucleos(t)ide naive patients that provided data on the timing of HCC diagnosis, HCC was diagnosed within the first year of treatment in 25 (22.7%) patients and after the first year in 85 (77.3%) of 110 cases [19,20,22,23,25–29,35,36]. In 5 studies including patients with lamivudine resistance, 13 patients had HCC at the onset of adefovir and/or lamivudine therapy, 9 were diagnosed within the first year, and 18 after the first year of rescue therapy for lamivudine resistance [30,31,33,37,38].

Risk factors for HCC

Patients naive to nucleos(t)ide analogues

In the 16 studies including nucleos(t)ide naive patients, HCC was diagnosed in 126 (3.8%) of 3287 cases during a mean/median follow-up of 42 (24–102) months [18–29,32,34–36]. In the three studies with untreated controls [22,26,32], which were all of high quality and large, HCC was detected significantly less frequently in treated (22/779 or 2.8%) than in untreated patients (34/534 or 6.4%, $p = 0.003$). The incidence of HCC was significantly higher in untreated patients (34/534 or 6.4%) compared to both treated patients remaining in virological remission (9/353 or 2.5%,

Table 1. Baseline characteristics of chronic hepatitis B (CHB) patients who were treated or not treated with nucleos(t)ide analogues.

Reference	Study design	Primary study question	Patients *n*	Severity of CHB *n*	HBeAg pos./neg.
Lok, 2003 [18]	MC, RE, data from clinical trials	Safety of long-term LAM	998	CHB: 944 Compensated Cirr: 54	998/0
Andreone, 2004 [19]	SC, PR cohort study	HCC risk in cirrhotic patients under LAM	22	Compensated Cirr: 22 (Child A/B: 16/6)	0/22
Di Marco, 2004 [20]	MC, RE cohort study	Clinical outcome of chronic HBV patients under LAM 656	656	CHB: 353 Compensated Cirr*: 198 Decompensated Cirr*: 105	0/656
Gaia, 2004 [21]	SC, RE cohort study	Clinical and virological impact of long-term LAM	94	CHB: 72 Compensated Cirr: 22	0/94
Liaw, 2004 [22]	PR, RA controlled trial	Efficacy of LAM in advanced CHB	Treated: 436 Untreated: 215	CHB (Ishak's stage 4): 176 Compensated Cirr: 260 (Child A/B: 416/20) CHB (Ishak's stage 4): 76 Compensated Cirr: 139 (Child A/B: 197/18)	252/184 124/91
Gish, 2005 [23]	Phase II trial	Safety & efficacy of emtricitabine	98	CHB: 98	77/21
Moskovitz, 2005 [24]	SC, RE cohort study	Response to long-term LAM	71	CHB: 40 Compensated Cirr: 31	38/33
Acuta, 2005 [25]	SC, PR cohort study	Long-term efficacy of LAM	20	CHB: 20	9/11
Papatheodoridis, 2005 [26]	MC, RE cohort study	Outcome under long-term LAM	Treated: 201 Untreated: 195	CHB: 137 Compensated Cirr: 64 CHB: 127 Compensated Cirr: 68	0/201 0/195
Di Marco, 2005 [27]	SC, RE cohort study	HBV DNA suppression & course under LAM	59	Cirr: 59 (Child A/B/C: 45/9/5)	12/47
Manolakopoulos, 2006 [28]	MC, RE cohort study	Prediction of response to long-term LAM	79	CHB: 52 Compensated Cirr: 27	0/79
Hadziyannis, 2006 [29]	MC, PR cohort study	Long-term efficacy of ADV in HBeAg-negative CHB	125	CHB: 95 Compensated Cirr†: 30	0/125
Rapti, 2007 [30]	SC, RA controlled trial	Efficacy of ADV LAM-resistance CHB	42	CHB: 26 Compensated Cirr: 16	0/42
Buti, 2007 [31]	SC, RE cohort study	Response to ADV in LAM-resistance patients	54	CHB: 34 Compensated Cirr: 20	29/25
Yuen, 2007 [32]	SC, PR cohort study	Efficacy of long-term LAM in HBeAg-positive CHB	Treated: 142 Untreated: 124	CHB: 142 CHB: 124	142/0 124/0
Lampertico, 2007 [33]	SC, PR cohort study	Efficacy of LAM + ADV in LAM-resistance CHB	145	CHB: 39 Cirr: 106	21/124
Wong, 2008 [34]	SC, PR/RE cohort study	Efficacy of long-term LAM in HBeAg-positive CHB with severe exacerbation	60	CHB††: 17 Compensated Cirr††: 43	60/0
Kilic, 2008 [35]	SC, PR cohort study	Efficacy of long-term LAM in HBeAg-negative decompensated cirr	68	Cirr: 68 (Child A/B/C: 35/22/11)	0/68
Nishida, 2008 [36]	MC, PR cohort study	Efficacy of long-term LAM in CHB with or without cirr	158	CHB: 87 Compensated Cirr: 28 Decompensated Cirr: 43	96/60
Akuta, 2008 [37]	SC, RE cohort study	Efficacy of and HCC incidence during ADV + LAM in LAM-resistance CHB	183	CHB: 127 Cirr: 56	109/74
Idilman, 2009 [38]	SC, RE cohort study	Efficacy of 6 months ADV + LAM followed by ADV alone in LAM-resistance CHB	170	CHB: 142 Compensated Cirr: 28	68/102

MC: multicenter, SC: single center, PR: prospective, RE: retrospective, RA: randomised, Cirr: cirrhosis, LAM: lamivudine, ADV: adefovir.
* Compensated and decompensated Ci: Child A and B/C, respectively.
† Histological cirrhosis or bridging fibrosis.
†† Twenty-nine patients with severe acute exacerbation of CHB (CHB: 16, Ci: 13).

$p = 0.015$) as well as treated patients with virological breakthroughs or no response (12/426 or 2.8%, $p = 0.016$) (Tables 4 and 5).

Among the treated patients, HCC developed significantly more frequently in patients with cirrhosis (114/1054 or 10.8%) compared to chronic hepatitis B patients without cirrhosis (12/2233 or 0.5%) (p <0.001) (Fig. 1). The higher HCC rate in patients with cirrhosis vs those without cirrhosis was also observed in studies with high (108/928 or 11.6% vs 11/1122 or 1.0%, p <0.001) [19–22,24–27,29,32,35,36] and low quality (6/124 or 4.8% vs 1/1111 or 0.1%, p <0.001) [18,23,28,34] as well as in large (70/782 or 9.0% vs 10/1934 or 0.5%, p <0.001) [18,20,22,26,29,32,33,36–38] and small studies (44/272 or 16.2% vs 2/299 or 0.7%, p <0.001) [19,21,23–25,27,28,30,31,34,35]. In 12 studies providing data on the HCC incidence in relation to the severity of cirrhosis [18–22,24,26–29,34,36], HCC was diagnosed in 78 (10.0%) of 779 patients with compensated and 18 (12.2%) of 148 patients with decompensated cirrhosis ($p = 0.522$) (Table 5).

Table 2. Baseline characteristics of chronic hepatitis B (CHB) patients who were treated or not treated with nucleos(t)ide analogues.

Reference	Patients *n*	Age* years	Sex M/F	Race C/A	ALT* IU/L	Serum HBV DNA	HCC screening	
							At baseline	On therapy
Lok, 2003 [18]	998	32	760/238	243/714	1.6 × ULN	79 pg/ml	aFP + U/S	Unknown
Andreone, 2004 [19]	22	53	18/4	22/0	192	16 pg/ml	aFP + U/S	aFP + U/S
Di Marco, 2004 [20]	CHB: 353	47	279/74	353/0	2–5 × ULN	NA	Unknown	Unknown
	Ci: 303	52	268/35	303/0	2–5 × ULN	NA		
Gaia, 2004 [21]	94	46	75/19	94/0	3 × ULN	1–10 pg/ml	U/S	U/S
Liaw, 2004 [22]	Treated: 436	43	370/66	0/426	70	11.7 mEq/ml	aFP + U/S	aFP + U/S
	Untreated: 215	44	182/33	0/215	68	21.5 mEq/ml		
Gish, 2005 [23]	98	36	69/29	9/86	66	7.6 $\log_{10}$ cp/ml	Unknown	Unknown
Moskovitz, 2005 [24]	71	47	53/18	33/38	NA	NA	U/S	Unknown
Acuta, 2005 [25]	20	44	16/4	0/20	100	32 × 10^6 gEq/ml	U/S	U/S
Papatheodoridis, 2005 [26]	Treated: 201	52	167/34	201/0	98	2 × 10^6 cp/ml	aFP + U/S	aFP + U/S
	Untreated: 195	49	160/35	195/0	68	4.5 pg/ml		(in cirrhotics)
Di Marco, 2005 [27]	HBeAg+: 12	54	10/2	12/0	163	1.3 × 10^7 gen./ml	aFP + U/S	aFP + U/S
	HBeAg−: 47	52	42/5	47/0	216	1.4 × 10^7 gen./ml		
Manolakopoulos, 2006 [28]	79	50	64/15	79/0	110	6 $\log_{10}$ cp/ml	Unknown	Unknown
Hadziyannis, 2006 [29]	125	47	103/22	87/34	100	7 $\log_{10}$ cp/ml	aFP + U/S	Unknown
Rapti, 2007 [30]	42	56	39/3	42/0	123	8 × 10^6 cp/ml	Unknown	Unknown
Buti, 2007 [31]	54	51	44/10	54/0	113	7 $\log_{10}$ cp/ml	Unknown	Unknown
Yuen, 2007 [32]	Treated: 142	34	106/36	0/142	65	8.7 $\log_{10}$ cp/ml	aFP†	aFP†
	Untreated: 124	33	90/34	0/124	49	6.8 $\log_{10}$ cp/ml		
Lampertico, 2007 [33]	145	56	122/23	145/0	58	6 $\log_{10}$ cp/ml	Unknown	Unknown
Wong, 2008 [34]	††(a) 29	39	25/14	0/29	1135	8 $\log_{10}$ cp/ml	U/S	Unknown
	††(b) 31	44	31/0	0/31	76	7.3 $\log_{10}$ cp/ml		
Kilic, 2008 [35]	68	52	51/17	68/0	104	4 × 10^3 IU/ml	aFP + U/S	aFP + U/S
Nishida, 2008 [36]	158	49	101/57	0/158	105	6.8 $\log_{10}$ cp/ml	aFP + DCP + U/S	aFP + DCP + U/S
Akuta, 2008 [37]	183	47	150/33	0/183	130	7.3 $\log_{10}$ cp/ml	U/S	U/S
Idilman, 2009 [38]	170	43	130/40	170/0	100	7 $\log_{10}$ cp/ml	aFP + U/S	aFP + U/S

M/F: males/females, C: Caucasians, A: Asians, HCC: hepatocellular carcinoma, Ci: cirrhosis, NA: not available, aFP: alpha-fetoprotein, DCP: des-γ-carboxy-prothrombin, U/S: ultrasound.

* Mean or median values.

† U/S at baseline in patients with albumin <3.5 g/dl and during follow-up in patients with aFP elevations.

†† (a) Patients with severe acute exacerbation of CHB, (b) CHB patients without severe acute exacerbation.

In 10 studies providing data on the HCC incidence in relation to virological response, HCC was diagnosed in 64 (7.5%) of 852 patients with virological non-response or breakthrough but also in 23 (2.3%) of 982 patients in virological remission (p <0.001) [19–22,25–29,32] (Table 5, Fig. 1). The HCC rate was significantly lower in patients remaining in virological remission vs those not in remission in studies with high quality (23/943 or 2.4% vs 63/1115 or 5.7%, p <0.001) [19–22,25–27,29,32], while only one of the studies with low quality provided such data [28]. Similarly, the HCC rate was significantly lower in patients remaining in virological remission in both large (20/856 or 2.3% vs 39/704 or 5.5%, p = 0.002) [20,22,26,29,32] and small studies (3/126 or 2.4% vs 25/148 or 16.9%, p <0.001) [19,21,25,27,28]. The sensitivity of the HBV DNA assay used in each study did not affect the association between virological response and HCC development. HCC was diagnosed more frequently in patients with virological non-response or breakthrough than in those in virological remission from studies using sensitive HBV DNA assays (lower limit of detection ⩽1000 cp/ml) (43/594 or 7.2% vs 13/564 or 2.3%, p <0.001) [19,21,22,26–29,32] as well as studies using insensitive HBV DNA assays (lower limit of detection ⩾100,000 cp/ml) (21/258 or 8.1% vs 10/418 or 2.4%, p = 0.001) [20,25]. In two studies with only cirrhotic patients followed for a median of 42–44 months, HCC was also detected significantly less frequently in cirrhotics compared to those without virological remission (3/36 or 8.3% vs 17/45 vs 37.8%, p = 0.004) [19,27].

HCC was reported to develop at a higher rate in studies with regular HCC surveillance compared to those without (6.6% vs 2.3%, p <0.001); in studies including patients with a mean/median age ⩾50 compared to those including <50 years (6.0% vs 2.8%, p <0.001); and in studies with almost exclusively (>85%) HBeAg-negative patients compared to studies with mostly HBeAg-positive patients (5.5% vs 0.5%, p <0.001) (Table 5). The incidence of HCC did not differ significantly between studies including almost exclusively (>85%) Caucasian or Asian patients (6.1% vs 4.9%, p = 0.283) (Table 5). The effect of gender could not be determined, as males represented the majority of patients in all studies.

Patients with lamivudine resistance

In five studies including patients with lamivudine resistance treated with adefovir with or without continued lamivudine for a mean/median period of 30 (24–42) months [30,31,33,37,38], HCC was diagnosed in 42 (7.1%) of 594 cases (Tables 4 and 5). Since only two of the five studies were classified to be of high quality and both studies did not provide HCC data in relation to the presence of cirrhosis or virological response, subgroup analyses according to the quality of the studies were not performed for patients with lamivudine resistance.

In the four studies which provided data on the HCC incidence in patients with lamivudine resistance in relation to the presence of cirrhosis [30,31,33,38], HCC was reported to develop exclusively in cirrhotic patients (30/170 or 17.6% vs 0/241 or 0%, p < 0.001) (Fig. 1). In the four studies providing data on the HCC incidence in relation to virological response to rescue therapy [30,31,33,37], HCC was detected in 21 (20.2%) of 104 patients with viremia and in 19 (5.9%) of 320 patients in virological

Table 3. Treatment characteristics in chronic hepatitis B (CHB) patients receiving nucleos(t)ide (NUC) analogue therapy.

Reference	Type of patients	Initial therapy		Maintained virological response (VR)*, *n*	No VR or breakthroughs *n*	Rescue therapy**, Type: *n*	Duration of study follow-up, months	VR during rescue therapy, *n*
		Type	Duration months					
Lok, 2003 [18]	NUC naive	LAM	48 (0–77)	NA	NA	None	48 (0–77)	–
Andreone, 2004 [19]	NUC naive	LAM	42 (12–74)	9	13	None	42 (12–74)	–
Di Marco, 2004 [20]	NUC naive	LAM	24 (1–66)	407	249	None	24 (1–66)	–
Gaia, 2004 [21]	NUC naive	LAM	33 (12–54)	40	54	None	33 (12–54)	–
Liaw 2004 [22]	NUC naive Untreated	LAM	32 (0–42)	227	209	None	32 (0–42) 32 (0–42)	–
Gish, 2005 [23]	NUC naive	Emtricitabine	24	41	36	None	24	–
Moskovitz, 2005 [24]	NUC naive	LAM	40 (12–60)	19	52	None	40 (12–60)	–
Acuta, 2005 [25]	NUC naive	LAM	102 (80–104)	11	9	Other† + LAM: 3 IFN: 2	102 (80–104)	3
Papatheodoridis, 2005 [26]	NUC naive Untreated	LAM	46 (12–95)	92	109	ADV: 26, ADV + LAM: 53	46 (12–95) 73 (12–162)	66
Di Marco, 2005 [27]	NUC naive	LAM	44 (11–78)	27	32	None	44 (11–78)	–
Manolakopoulos, 2006 [28]	NUC naive	LAM	31 (6–56)	39	40	ADV ± LAM: 20	31 (6–56)	NA
Hadziyannis, 2006 [29]	NUC naive	ADV	45–57	96	29	LAM ± ADV: 11	45–57	NA
Rapti, 2007 [30]	LAM resistance	LAM	32 (12–84)	0	42	ADV: 14, ADV + LAM: 28	38 (9–53)	12 months: 30/42
Buti, 2007 [31]	LAM resistance	LAM	33 ± 23	0	54	ADV: 28, ADV + LAM: 26	30 ± 16	38
Yuen, 2007 [32]	NUC naive Untreated	LAM	90 (27–128)	34	108	None	90 (27–128) 108 (31–127)	–
Lampertico, 2007 [33]	LAM resistance	LAM	NA	0	145	ADV + LAM: 145	42 (12–74)	108
Wong, 2008 [34]	NUC naive	LAM	††(a) 42 (12–85) ††(b) 46 (12–101)	21 NA	8 NA	ADV: 7 NA	42 (12–85) 95 (42–101)	5
Kilic, 2008 [35]	NUC naive	LAM	45 ± 18	48	20	ADV + LAM: 20	50 ± 19	NA
Nishida, 2008 [36]	NUC naive	LAM	40 ± 13	NA	Breakthroughs: 78	ADV + LAM: NA	40 ± 13	NA
Akuta, 2008 [37]	LAM resistance	LAM	35 (7–130)	0	183	ADV + LAM: 183	26 (6–54)	144
Idilman, 2009 [38]	LAM resistance	LAM	36 (6–108)	0	170	ADV + LAM × 6 months – ADV: 170	24	12 months: 84/141

LAM: lamivudine, ADV: adefovir, IFN: interferon-alfa, NA: not available.

* Virological response defined as undetectable HBV DNA with lower limit of detection of HBV DNA assays 35–1000 copies/ml in 15 studies [19,21,22,24,26–34,36,37] and a wide range of sensitivities in other studies (400 or 4700 copies/ml [35], 2000 copies/ml [38], 4700 copies/ml [23], 100,000 copies/ml [20] and ⩾0.7 mEq/ml [18,25]).

** The main therapy in studies with LAM-resistance patients [30,31,33,37,38].

† IFN in 2 and glycyrrhizin in 1 patient.

†† (a) Twenty-nine patients with severe acute exacerbation of CHB and (b) 31 CHB patients without severe acute exacerbation.

remission (p <0.001). This difference in HCC incidence, however, was not statistically significant when the 13 patients with HCC at the onset of adefovir therapy were excluded (8/91 or 8.8% vs 19/320 or 5.9%, p = 0.466) (Table 5 and Fig. 1). Similar findings were observed when only large studies were included in the analyses [33,37,38].

Comparisons between nucleos(t)ide naive patients and patients with lamivudine resistance

The cumulative HCC rate was significantly higher in patients with lamivudine resistance compared to that in all nucleos(t)ide naive patients (42/594 or 7.1% vs 126/3287 or 3.8%, p = 0.001) (Table 5). It should be noted that the proportion of patients with cirrhosis was lower in studies with nucleos(t)ide naive patients than those including patients with lamivudine resistance (1054/3287 or 32.1% vs 226/594 or 38.0%, p = 0.005) (Table 1). Among cirrhotics, HCC developed significantly more frequently in patients with lamivudine resistance than in those who were nucleos(t)ide naive (30/170 or 17.6% vs 114/1054 or 10.8%, p = 0.015) (Table 5). The median duration of follow-up was shorter in studies of patients with lamivudine resistance ranging from 24 to 36 months in four studies and exceeded 36 months in only one (20.0%) study, while it exceeded 36 months in 10 (62.5%) of 16 studies with nucleos(t)ide naive patients (p = 0.149) (Table 3).

When all 14 studies with nucleos(t)ide naive or lamivudine resistance patients and data on HCC incidence in relation to virological response were taken into account [19–22,25–33,37], HCC was found to develop in 85 (8.9%) of 956 patients with detectable viremia and in only 42 (3.2%) of 1302 patients in virological remission (p <0.001). HCC developed more frequently in patients in virological remission after initiation of rescue therapy for lamivudine resistance (19/320 or 5.9%) than in patients remaining in virological remission under the initial nucleos(t)ide therapy (23/982 or 2.3%, p = 0.003).

Discussion

The results of our systematic review show that the medium-term risk of HCC is significantly lower in chronic hepatitis B patients receiving effective oral antiviral therapy. In three studies including untreated controls, HCC developed in 2.8% of treated and in 6.4% of untreated chronic hepatitis B patients (p = 0.003). Although only one of these three studies was randomised [22], the untreated controls had many similar characteristics with the treated patients in the second study [26] and were selected to match the treated patients in the third study [32]. It should be noted that treatment significantly reduced the HCC incidence in the only randomised trial [22]. Given the benefits of antiviral therapy, it is unethical not to offer treatment to chronic hepatitis B patients who meet treatment criteria. These data therefore represent the best evidence supporting the efficacy of nucleos(t)ide

Table 4. Development of hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB) patients who were treated with nucleos(t)ide analogues or remained untreated.

Reference		Patients with HCC, *n/N*					Patients with HCC, *n/N*		Timing of HCC diagnosis after treatment onset, months
		Total	CHB	Cirrhosis			Virological remission		
				All	Comp.	Decomp.	Yes	No	
Lok, 2003 [18]		0/998	0/944	0/54	0/54	0/0	NA	NA	–
Andreone, 2004 [19]		11/22	0/0	11/22	11/22	0/0	1/9	10/13	Median: 34 (9–58) [3 cases within first year]
Di Marco, 2004 [20]		31/656	4/353	27/303	21/198*	6/105*	10/407	21/249	[5 cases within first year]
Gaia, 2004 [21]		7/94	1/72	6/22	6/22	0/0	NA	NA	Median: 30 (8–39)
Liaw, 2004 [22]	Treated:	17/436	0/176	17/260	17/260	0/0	8/227	9/209	[3 cases within first year]
	Untreated:	16/215	NA	NA	NA	0/0	–	–	[2 cases within first year]
Gish, 2005 [23]		1/98	1/98	0/0	0/0	0/0	NA	NA	[1 case within first year]
Moskovitz, 2005 [24]		3/71	0/40	3/31	3/31	0/0	NA	NA	NA
Acuta, 2005 [25]		0/20	0/20	0/0	0/0	0/0	0/11	0/9	–
Papatheodoridis, 2005 [26]	Treated:	4/201	0/137	4/64	4/64	0/0	1/92	3/109	10, 33, 54, 60
	Untreated:	15/195	1/127	14/68	14/68	0/0	–	–	48 (8–157)
Di Marco, 2005 [27]		9/59	0/0	9/59	NA	NA	2/27	7/32	Median: 13 (6–28) [4 cases within first year]
Manolakopoulos, 2006 [28]		1/79	0/52	1/27	1/27	0/0	0/39	1/40	14
Hadziyannis, 2006 [29]		6/125	1/95	5/30	5/30	0/0	1/96	5/29	112–219 [1 case at 12 months]
Rapti, 2007 [30]		3/42	3/26	3/16	3/16	0/0	2/30	1/12	13–35
Buti, 2007 [31]		2/54	0/34	2/20	2/20	0/0	1/38	1/16	[1 case within first year]
Yuen, 2007 [32]	Treated:	1/142	1/142	0/0	0/0	0/0	0/34	1/108	NA
	Untreated:	3/124	3/124	0/0	0/0	0/0	–	–	NA
Lampertico, 2007 [33]		23/145†	0/39	23/106†	NA	NA	6/108	17/37†	†Median: 12 (3–38) [6 cases within first year]
Wong, 2008 [34]		5/60	0/17	5/43	5/43	0/0	NA	NA	NA
Kilic, 2008 [35]		9/68	0/0	9/68	NA	NA	NA	NA	6–84 [1 case within first year]
Nishida, 2008 [36]		21/158	4/87	17/71	5/28	12/43	NA	NA	[6 cases within first year]
Akuta, 2008 [37]		12/183	NA	NA	NA	NA	10/144	2/39	Median: 14 (1–54) [3 cases within first year]
Idilman, 2009 [38]		2/170	0/142	2/28	2/28	0/0	NA	NA	0, 12

Comp: compensated, Decomp: decompensated, NA: not available, *n/N*: *n* the number of cases with HCC in each group and *N* total number of cases (with and without HCC) in each group.

* Compensated and decompensated cirrhosis: Child A and B/C, respectively.

† Twelve patients had HCC at the onset of adefovir and lamivudine and were not taken into account in timing of HCC after treatment onset.

analogue therapy in reducing the incidence of HCC in chronic hepatitis B patients.

Achievement of virological remission after the initial treatment course was found to be extremely important for the reduction of HCC incidence. In studies including nucleos(t)ide naive patients, HCC developed significantly less frequently in patients remaining in virological remission than in those with virological breakthrough or no response (2.3% vs 7.5%, $p < 0.001$). This finding is in agreement with the well known association between levels of HBV replication and HCC risk [8]. It is not surprising that viral suppression decreased but did not eliminate the risk of HCC in chronic HBV patients because HBV DNA may have already integrated into the host genome before the onset of treatment and may have already resulted in genomic alterations and/or chromosomal instability [39,40]. Furthermore, in patients who have been infected for a long time or who have already progressed to cirrhosis, malignant transformation of hepatocytes may be present before the onset of treatment. Finally, some of the tumours may have been present at the start of treatment and were not detected by routine clinical evaluations. The latter hypothesis is in agreement with the finding that approximately one fourth (23%) of HCC cases in nucleos(t)ide naive patients were diagnosed within the first year of treatment.

The rate of HCC was significantly higher in lamivudine resistance than in nucleos(t)ide naive patients (7.1% vs 3.8%, $p = 0.001$) despite a shorter duration of follow-up. This is partly related to the more frequent presence of cirrhosis among patients with lamivudine resistance, but even among cirrhotics, the incidence of HCC was significantly higher in patients with lamivudine resistance than in those who were nucleos(t)ide naive (18% vs 11%, $p = 0.015$). Achievement of virological response did not seem to significantly reduce the HCC risk in patients with lamivudine resistance, as HCC was detected in 9% of such patients with and in 6% of those without detectable viremia during rescue therapy ($p = 0.466$). These data suggest that the maintenance of viral suppression over a long period of time is needed to reduce the risk of HCC. It has also been suggested that mutations associated with lamivudine resistance, in particular, changes at position 181 of the reverse transcriptase domain of the HBV polymerase have direct oncogenic potential [41,42].

It is well known that the HCC risk is highest among untreated chronic HBV patients with cirrhosis and that severe fibrosis and cirrhosis predispose to the development of HCC [1,2,4]. Our data show that the risk of HCC remains high in cirrhotic patients receiving nucleos(t)ide analogue therapy. HCC developed in 11% of cirrhotic and in only 0.5% of non-cirrhotic chronic hepatitis B patients who were naive to nucleos(t)ide agents ($p < 0.001$) and

Table 5. Incidence of hepatocellular carcinoma (HCC) in chronic hepatitis B patients who were treated or not treated with oral antivirals.

Subgroups of patients	Studies, *n* [References numbers]	Mean/Median follow-up (months)	No. of patients	Patients with HCC	*p* value
Nucleos(t)ide naive patients	16 [18–29,32,34–36]	42 (24–102)	3287	126 (3.8%)[1]	
Treatment effect					0.003
Treated	3 [22,26,32]	46 (32–90)	779	22 (2.8%)	
Untreated	3 [22,26,32]	73 (32–108)	534	34 (6.4%)	
Presence of cirrhosis					<0.001
No cirrhosis	13 [18,20–26,28,29,32,34,36]	40 (24–102)	2233	12 (0.5%)	
Cirrhosis	13 [18–22,24,26–29,34–36]	40 (24–52)	1054	114 (10.8%)[2]	
Severity of cirrhosis					0.522
Compensated cirrhosis	12 [18–22,24,26–29,34,36]	40 (24–52)[#]	779	78 (10.0%)	
Decompensated cirrhosis	3 [20,27,36]	24 (12–36)[#]	148	18 (12.2%)	
Virological response	10 [19–22,25–29,32]	39 (24–102)			<0.001
Virological remission			982	23 (2.3%)[3]	
No virological remission[¶]			852	64 (7.5%)	
HCC surveillance					<0.001
No	7 [18,20,23,24,28,29,34]	40 (24–52)	2087	47 (2.3%)	
Yes	9 [19,21,22,25–27,32,35,36]	42 (32–102)	1200	79 (6.6%)	
Mean/median age					<0.001
<50 years	10 [18,21–25,29,32,34,36]	42 (24–102)	2202	61 (2.8%)	
⩾50 years	6 [19,20,26–28,35]	39 (24–45)	1085	65 (6.0%)	
HBeAg status (>85% of patients)					<0.001
HBeAg positive	3 [18,32,34]	48 (44–90)	1200	6 (0.5%)	
HBeAg negative	7 [19–21,26,28,29,35]	39 (24–45)	1245	69 (5.5%)	
Race (>85% of patients)					0.283
Caucasians	7 [19–21,26–28,35]	36 (24–45)	1179	72 (6.1%)	
Asians	6 [22,23,25,32,34,36]	42 (24–102)	914	45 (4.9%)	
Patients with lamivudine resistance	5 [30,31,33,37,38]	30 (24–42)	594	42 (7.1%)[4]	
Presence of cirrhosis	4 [30,31,33,38]	31 (24–42)			<0.001
No cirrhosis			241	0	
Cirrhosis			170	30 (17.6%)[5]	
Virological response during rescue therapy	4 [30,31,33,37]	31 (26–42)			0.466
Virological remission			320	19 (5.6%)[6]	
No virological remission[¶]			91	8 (8.8%)	

1 vs 4, $p = 0.001$; 2 vs 5, $p = 0.015$; 3 vs 6, $p = 0.003$.

[#] The duration of follow-up was not provided separately for patients with compensated and decompensated cirrhosis in one study [27].

[¶] Virological non-response or breakthrough.

in 18% of cirrhotic and 0% of non-cirrhotic patients with lamivudine resistance ($p < 0.001$). The effect of the severity of cirrhosis (compensated vs decompensated) on HCC risk could not be evaluated because of the small number of patients.

Other factors found to be associated with the risk of HCC were older age, regular HCC surveillance and inclusion of HBeAg negative cases. Older age is a well known risk factor for HCC [1,2,4], but the higher HCC rate in the studies with mean/median age ⩾50 years vs <50 years might be, at least partly, related to the higher proportion of cirrhotic patients in the studies with older patients. Indeed, cirrhosis was present in a higher percent of patients in studies with mean/median age ⩾50 years (543/1085 or 50% vs 511/2202 or 23%, $p < 0.001$) (Table 1). The association between HCC risk and HCC surveillance may be related to a higher proportion of patients with cirrhosis in studies with HCC surveillance. The proportion of nucleos(t)ide naive patients with cirrhosis was significantly higher in studies which reported regular HCC surveillance [19,21,22,25–27,32,35,36] than those which did not [18,20,23,24,28,29,34] (566/1200 or 47% vs 488/2087 or 23%, $p < 0.001$). The association between HCC risk and HBeAg-negative status may be related to the older age and more frequent presence of cirrhosis in HBeAg-negative patients. The proportion of patients with cirrhosis was significantly higher in studies with almost exclusively HBeAg negative [19–21,26,28,29,35] than studies with predominantly HBeAg-positive patients [18,32,34] (536/1245 or 43% vs 97/1200 or 8%, $p < 0.001$) (Table 1).

In conclusion, medium-term nucleos(t)ide analogue therapy significantly reduces but it does not completely eliminate the risk of HCC, particularly in patients with pre-existing cirrhosis. Patients with cirrhosis undergoing antiviral treatment should continue to undergo HCC surveillance. Maintenance of virological remission is important for the reduction of HCC risk. Our findings suggest that HCC risk is increased in patients who experience virologic breakthrough even if HBV replication is subsequently suppressed by rescue therapy. This observation provides further evidence that lamivudine is not an optimal first-line treatment for chronic hepatitis B, as it is associated with very high rates of drug resistance during long-term treatment. Our study is limited by the poor quality of many of the included studies, the heterogeneous patient populations, the variations in treatment regimens and patient monitoring, the differences in definitions of response, and the wide range in sensitivity of HBV DNA assays used to assess virological response and the different duration of follow-up. In addition, because incidence of HCC was not a primary outcome in these studies, details regarding screening of HCC at baseline and HCC surveillance during therapy, diagnostic criteria of HCC and timing of HCC diagnosis were not specified in most studies. Nevertheless, the large number of patients and the results of subgroup analyses reinforce the validity of our conclusions. The vast majority of the current data on HCC risk in chronic hepatitis B patients treated with nucleos(t)ide analogues come from studies on lamivudine. It is anticipated that the newer nucleos(t)ide analogues, such as entecavir and tenofovir, will fur-

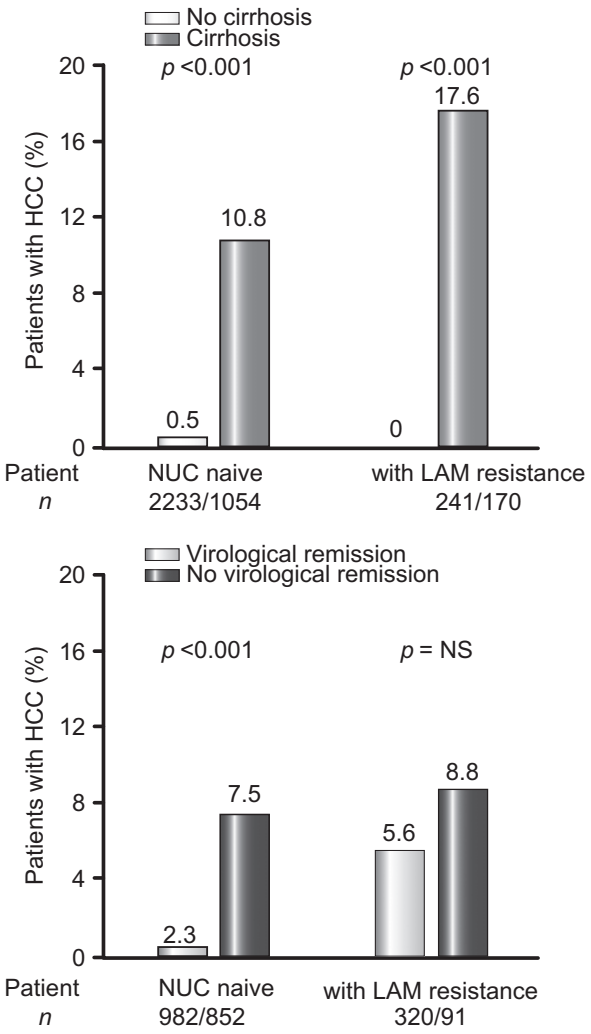

Fig. 1. Incidence of hepatocellular carcinoma (HCC) in chronic hepatitis B patients who were treated with nucleos(t)ide analogue(s) (NUC) for a mean/median of 40 (24–102) months in relation to the presence of cirrhosis, virological remission, and development of lamivudine (LAM) resistance.

ther reduce the HCC incidence given their greater potency and better resistance profiles.

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References

[1] El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007;132:2557–2576.
[2] Schafer DF, Sorrell MF. Hepatocellular carcinoma. Lancet 1999;353:1253–1257.
[3] El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999;340:745–750.
[4] Okuda K. Hepatocellular carcinoma. J Hepatol 2000;32:225–237.
[5] Maringhini A, Cottone M, Sciarrino E, Marceno MP, La Seta F, Fusco G, et al. Ultrasonography and alpha-fetoprotein in diagnosis of hepatocellular carcinoma in cirrhosis. Dig Dis Sci 1988;33:47–51.
[6] Chang MH, You SL, Chen CJ, Liu CJ, Lee CM, Lin SM, et al. Decreased incidence of hepatocellular carcinoma in hepatitis B vaccinees: a 20-year follow-up study. J Natl Cancer Inst 2009;101:1348–1355.
[7] Maddrey WC. Hepatitis B: an important public health issue. J Med Virol 2000;61:362–366.
[8] Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65–73.
[9] Lok ASF, McMahon BJ. Chronic hepatitis B. Hepatology 2007;45:507–539.
[10] Papatheodoridis GV, Manolakopoulos S, Dusheiko G, Archimandritis AJ. Therapeutic strategies in the management of patients with chronic hepatitis B. Lancet Infect Dis 2008;8:167–178.
[11] European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B. J Hepatol 2009;50:227–242.
[12] Craxi A, Di Bona D, Camma C. Interferon-a for HBeAg-positive chronic hepatitis B. J Hepatol 2003;39:S99–S105.
[13] Papatheodoridis GV, Manesis E, Hadziyannis SJ. The long-term outcome of interferon – a treated and untreated patients with HBeAg-negative chronic hepatitis B. J Hepatol 2001;34:306–313.
[14] Lampertico P, Del Ninno E, Vigano M, Romeo R, Donato MF, Sablon E, et al. Long-term suppression of hepatitis B e antigen-negative chronic hepatitis B by 24-month interferon therapy. Hepatology 2003;37:756–763.
[15] Lin SM, Yu ML, Lee CM, Chien RN, Sheen IS, Chu CM, et al. Interferon therapy in HBeAg positive chronic hepatitis reduces progression to cirrhosis and hepatocellular carcinoma. J Hepatol 2007;46:45–52.
[16] Yuen MF, Hui CK, Cheng CC, Wu CH, Lai YP, Lai CL. Long-term follow-up of interferon alfa treatment in Chinese patients with chronic hepatitis B infection: the effect on hepatitis B e antigen seroconversion and the development of cirrhosis-related complications. Hepatology 2001;34:139–145.
[17] Sung JJ, Tsoi KK, Wong VW, Li KC, Chan HL. Meta-analysis: treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. Aliment Pharmacol Ther 2008;28:1067–1077.
[18] Lok AS, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. Gastroenterology 2003;125:1714–1722.
[19] Andreone P, Gramenzi A, Cursaro C, Biselli M, Camma C, Trevisani F, et al. High risk of hepatocellular carcinoma in anti-HBe positive liver cirrhosis patients developing lamivudine resistance. J Viral Hepat 2004;11:439–442.
[20] Di Marco V, Marzano A, Lampertico P, Andreone P, Santantonio T, Almasio PL, et al. Clinical outcome of HBeAg-negative chronic hepatitis B in relation to virological response to lamivudine. Hepatology 2004;40:883–891.
[21] Gaia S, Marzano A, Smedile A, Barbon V, Abate ML, Olivero A, et al. Four years of treatment with lamivudine: clinical and virological evaluations in HBe antigen-negative chronic hepatitis B. Aliment Pharmacol Ther 2004;20:281–287.
[22] Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004;351:1521–1531.
[23] Gish RG, Trinh H, Leung N, Chan FK, Fried MW, Wright TL, et al. Safety and antiviral activity of emtricitabine (FTC) for the treatment of chronic hepatitis B infection: a two-year study. J Hepatol 2005;43:60–66.
[24] Moskovitz DN, Osiowy C, Giles E, Tomlinson G, Heathcote EJ. Response to long-term lamivudine treatment (up to 5 years) in patients with severe chronic hepatitis B, role of genotype and drug resistance. J Viral Hepat 2005;12:398–404.
[25] Akuta N, Suzuki F, Suzuki Y, Sezaki H, Hosaka T, Someya T, et al. Favorable efficacy of long-term lamivudine therapy in patients with chronic hepatitis B: an 8-year follow-up study. J Med Virol 2005;75:491–498.
[26] Papatheodoridis GV, Dimou E, Dimakopoulos K, Manolakopoulos S, Rapti I, Kitis G, et al. Outcome of hepatitis B e antigen-negative chronic hepatitis B

on long-term nucleos(t)ide analog therapy starting with lamivudine. Hepatology 2005;42:121–129.
[27] Di Marco V, Di Stefano R, Ferraro D, Almasio PL, Bonura C, Giglio PM, et al. HBV-DNA suppression and disease course in HBV cirrhosis patients on long-term lamivudine therapy. Antivir Ther 2005;10:431–439.
[28] Manolakopoulos S, Bethanis S, Elefsiniotis J, Karatapanis S, Triantos C, Sourvinos G, et al. Lamivudine monotherapy in HBeAg-negative chronic hepatitis B: prediction of response-breakthrough and long-term clinical outcome. Aliment Pharmacol Ther 2006;23:787–795.
[29] Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. Gastroenterology 2006;131:1743–1751.
[30] Rapti I, Dimou E, Mitsoula P, Hadziyannis SJ. Adding-on versus switching-to adefovir therapy in lamivudine resistant HBeAg-negative chronic hepatitis B. Hepatology 2007;45:307–313.
[31] Buti M, Elefsiniotis I, Jardi R, Vargas V, Rodriguez-Frias F, Schapper M, et al. Viral genotype and baseline load predict the response to adefovir treatment in lamivudine-resistant chronic hepatitis B patients. J Hepatol 2007;47:366–372.
[32] Yuen MF, Seto WK, Chow DH, Tsui K, Wong DK, Ngai VW, et al. Long-term lamivudine therapy reduces the risk of long-term complications of chronic hepatitis B infection even in patients without advanced disease. Antivir Ther 2007;12:1295–1303.
[33] Lampertico P, Vigano M, Manenti E, Iavarone M, Sablon E, Colombo M. Low resistance to adefovir combined with lamivudine: a 3-year study of 145 lamivudine-resistant hepatitis B patients. Gastroenterology 2007;133:1445–1451.
[34] Wong VW, Wong GL, Tsang SW, Hui AY, Chim AM, Yiu KK, et al. Long-term follow-up of lamivudine treatment in patients with severe acute exacerbation of hepatitis B e antigen (HBeAg)-positive chronic hepatitis B. Antivir Ther 2008;13:571–579.
[35] Kilic ZM, Kuran S, Akdogan M, Cicek B, Oguz D, Odemis B, et al. The long-term effects of lamivudine treatment in patients with HBeAg-negative liver cirrhosis. Adv Ther 2008;25:190–200.
[36] Nishida T, Kobashi H, Fujioka S, Fujio K, Takaguchi K, Ikeda H, et al. A prospective and comparative cohort study on efficacy and drug resistance during long-term lamivudine treatment for various stages of chronic hepatitis B and cirrhosis. J Gastroenterol Hepatol 2008;23:794–803.
[37] Akuta N, Suzuki F, Kawamura Y, Yatsuji H, Sezaki H, Suzuki Y, et al. Virological response and hepatocarcinogenesis in lamivudine-resistant hepatitis B virus genotype C patients treated with lamivudine plus adefovir dipivoxil. Intervirology 2008;51:385–393.
[38] Idilman R, Kaymakoglu S, Oguz OF, Ahishali E, Bektas M, Cinar K, et al. A short course of add-on adefovir dipivoxil treatment in lamivudine-resistant chronic hepatitis B patients. J Viral Hepat 2009;16:279–285.
[39] Shafritz DA, Shouval D, Sherman HI, Hadziyannis SJ, Kew MC. Integration of hepatitis B virus DNA into the genome of liver cells in chronic liver disease and hepatocellular carcinoma. Studies in percutaneous liver biopsies and post-mortem tissue specimens. N Engl J Med 1981;305: 1067–1073.
[40] Laurent-Puig P, Legoix P, Bluteau O, Belghiti J, Franco D, Binot F, et al. Genetic alterations associated with hepatocellular carcinomas define distinct pathways of hepatocarcinogenesis. Gastroenterology 2001;120:1763–1773.
[41] Warner N, Locarnini S. The antiviral drug selected hepatitis B virus rtA181T/sW172* mutant has a dominant negative secretion defect and alters the typical profile of viral rebound. Hepatology 2008;48:88–98.
[42] Lai MW, Yeh CT. The oncogenic potential of hepatitis B virus rtA181T/surface truncation mutant. Antivir Ther 2008;13:875–879.