REVIEW

Risk for hepatocellular carcinoma in the course of chronic hepatitis B virus infection and the protective effect of therapy with nucleos(t)ide analogues

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Author contributions: Both authors contributed to this manuscript.

Conflict-of-interest: None.

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Abstract

Hepatocellular carcinoma (HCC) is a major health problem worldwide, representing one of the leading causes of death. Chronic hepatitis B virus (HBV) infection (CHB) is the most important etiologic factor of this tumor, accounting for the development of more than 50% of the cases in the world. Primary prevention of HCC is possible by hepatitis B vaccination conferring protection from HBV infection. However, according to the World Health Organization Hepatitis B Fact sheet N° 204 (update of July 2014) globally there exists a large pool of > 240 million people chronically infected with HBV who are at risk for development of HCC. These individuals represent a target population for secondary prevention both of cirrhosis and of HCC. Since ongoing HBV replication in CHB is linked with the progression of the underlying liver disease to cirrhosis as well as with the development of HCC, effective antiviral treatment in CHB has also been evaluated in terms of secondary prevention of HCC. Currently, most patients with active CHB are subjected to long term treatment with the first line nucleos(t)ide analogues entecavir and tenofovir. These compounds are of high antiviral potency and have a high barrier to HBV resistance compared to lamivudine, adefovir dipivoxil and even telbivudine. Many studies have shown that patients under antiviral treatment, especially those in virological remission, develop less frequently HCC compared to the untreated ones. However, the risk for development of HCC cannot be eliminated. Therefore, surveillance for the development of HCC of patients with chronic hepatitis B must be lifelong or until a time in the future when new treatments will be able to completely eradicate HBV from the liver particularly in the early stages of CHB infection. In this context, the aim of this review is to outline the magnitude of the risk for development of HCC among patients with CHB, in the various phases of the infection and in relation to virus, host and environmental factors as evaluated in the world literature. Moreover, the benefits of antiviral treatment of CHB with nucleos/tide analogs, which have changed the natural history of the disease and have reduced but not eliminated the risk of HCC are also reviewed.

Key words: Chronic hepatitis B; Cirrhosis; Hepatocellular carcinoma; Hepatitis B virus; Treatment; Interferon; Lamivudine; Adefovir; Entecavir; Tenofovir; Virological

remission; Nucleos(t)ide analogues

Core tip: Hepatocellular carcinoma (HCC) represents a major health problem worldwide. It develops on the grounds of chronic liver disease, with chronic hepatitis B virus infection (CHB) being responsible for more than 50% of HCC worldwide. Currently, the vast majority of patients with CHB are being treated with nucleos(t)ide analogues, which have changed the natural history of the disease, reducing at a considerable extent its long-term consequences. However, although the risk of HCC has also been reduced, it has not been eliminated even after HBsAg loss or seroconversion. Therefore, constant surveillance, according to guidelines should never be omitted, unless new more potent treatment options are identified.

INTRODUCTION

Hepatocellular carcinoma (HCC) represents a major health problem, being one of the leading causes of death worldwide with 782000 new cases diagnosed in 2008 and highest incidence rates being reported in East/Southeast Asia, North and West Africa[1]. It is the 5th most common tumor in men accounting for 7.5% of the total number of tumors and the 9th most common in women (3.4% of the total number of tumors in them), while it stands as the 2nd commonest cause of death due to cancer in the world (746000 deaths in 2012)[2]. It has a very bad prognosis with a 14% 5-year survival from diagnosis, being worse than lung, esophagus or stomach cancer and better only in comparison to the 5-year survival of 6% of pancreatic cancer[3].

HCC usually develops on the grounds of chronic liver disease, particularly cirrhosis mainly due to the hepatitis B virus (HBV) or HCV, with HBV being responsible for more than 50% of the world cases of HCC, reaching 78% in areas of high HCC incidence[4,5]. Patients with chronic HBV infection (CHB) are at a 100-fold higher risk for developing HCC compared to healthy individuals while HBV cirrhotic patients are at an even higher risk[5,6].

From an historical point of view it is noteworthy that the link of HCC with chronic HBV infection was first pointed out in 1969 and 1970 in Europe, a geographical area in which HCC was previously thought to be extremely rare to practically non-existent. Up to those days the etiology of HCC was linked with exposure to aflatoxin which was particularly common in Sub-Saharan Africa, an area of high HCC incidence. Thus, it came out of a surprise when in 1970 2 clinical reports one from England and one from Greece published in Lancet pointed out that Australia antigen, a marker of HBV infection, already referred in those days as hepatitis associated antigen, prevailed in patients with cryptogenic chronic liver disease and cirrhosis and that a significant percentage of such patients developed HCC[7,8]. As stressed by Sherlock[9] in 1971 up to those early days the link between HBV infection and HCC had been missed by B.S.Blumberg the scientist who had discovered HBsAg. This is obvious by the content of a letter he published in 1969 in Lancet[10] despite his subsequent claims[11]. However, regardless of the early European data on the possible link between chronic hepatitis B in the development of HCC, it was only in the mid 1970s that the etiological role of chronic HBV infection in HCC was unequivocally established thanks to the large prospective studies of Beasley et al[6] in Taiwan. On the other hand, the early observations in Greece on the possible link between chronic HBV infection and HCC have stimulated further clinical research in the country aiming at the identification of risk factors, determinants and predictors of development of HCC[8,12-15]. They have also been followed by epidemiological studies with positive results disclosing an association between the prevalence of HBsAg in the various geographical departments of the Country and the incidence of HCC in the same areas.

To sum up, HCC is a major health problem especially in patients with chronic liver disease and mainly CHB with or without cirrhosis, established since the early 70s and therefore, the possible elimination of this risk with oral treatment is considerably important.

RISK FACTORS

The risk for development of HCC in CHB differs significantly between the various areas of the world being highest in Asian and African patients[16-20]. It is also higher in males than in females with CHB[21-23], in patients older than 40 years and in cirrhotics compared to non-cirrhotic ones[18,22,24]. Its incidence increases if the patient has a family history of HCC[25], if the viral load (HBV-DNA) is high[21,26,27], if the genotype of the infecting HBV is C[28,29] and if pre-core or basic core promoter mutations have developed[30,31]. The risk also increases in patients with heavy alcohol consumption[32,33], in those co-infected with HDV or/and HCV[34-37] and in those who consume unsafely stored crops (dietary exposure to aflatoxin)[38]. In the evaluation of the risk for HCC by variables of activity of HBV replication, a linear association with serum HBV-DNA levels has been proved, while, more recently, high levels of HBsAg (> 1000 IU/mL), even in patients with relatively low viral loads (2000-20000 IU/mL) have been reported to confer medium to high risk for HCC development[21,39,40]. As far

as baseline viral load is concerned, in a large prospective cohort study of 3653 patients, the cumulative incidence rate of HCC at the end of follow-up ranged from 1.3%, when baseline serum HBV-DNA was less than 300 copies/mL, to 14.89% for a viral load of $\geqslant$ 6log10 copies/mL[21].

PATHOGENETIC MECHANISMS IN HCC

Several molecular mechanisms have been implicated in the pathogenesis of HBV-linked HCC. In the 1980s the identification of integration of HBV-DNA into the genome of hepatocytes in patients with HCC, has been implicated in the development of HBV-related HCC with several HCC cases being reported harboring integrated HBV DNA sequences in the malignant hepatocytes while serum and non-malignant liver tissue was negative for any marker of active HBV infection[15]. The protein HBx and the epigenetic regulation of the minichromosome of covalently closed circular HBV DNA have also been implicated as factors contributing to chromosomal instability, to activation of cancer-related genes and to inactivation of protective genes. They have also been considered to interfere with cellular transcription and signal transduction through various pathways and cellular promoters[41-43]. Moreover, adaptive immune reactions developing as a consequence of chronic HBV infection result in release of cytokines and of growth factors leading to necrosis of hepatocytes and proliferation of fibroblasts, resulting in the development of fibrosis/cirrhosis. Furthermore, a high turnover of hepatocytes can confer to the host DNA certain mutations that are probably responsible for their malignant transformation[41-44]. In view of these crucial considerations regarding various factors in chronic active HBV infection with possible involvement in the development of HCC, it is reasonable that several studies have tried to evaluate the effect of antiviral treatment of CHB not only regarding prevention of disease progression to cirrhosis and its decompensation but also in terms of possible prevention from development of HCC and death, although HBV-DNA becomes integrated into the genome of hepatocytes of the patient, from the early phases of HBV infection, probably years before the start of treatment[45,46].

TREATMENT OF CHB

Currently, the great majority of patients with CHB are treated worldwide with nucleos(t)ide analogues (NAs). Finite courses of treatment with pegylated interferon (IFN) for 1 or 2 years also represent first line therapies both for HBeAg positive and HBeAg-negative patients and should be first applied to all patients eligible for therapy, provided, of course, that there are no contraindications and that IFN is tolerated without major side effects. The aim of such therapies is to achieve sustained virological response and subsequent HBsAg loss representing the closest to cure outcome of chronic HBV infection[46]. However, the frequency of such an effect, achieved even on the basis of response guided treatment, does not exceed 20% or at maximum 30%[47-49]. Thus, it is understandable why currently long-term NA therapy has turned out to be the number one first choice treatment of CHB. Prerequisite for the success of such long-term therapies is the use of compounds of robust antiviral potency and of high barrier to HBV resistance as are the current first line NAs entecavir (ETV) and tenofovir (TDF).

Long-term NA therapies reduce the incidence of unfavorable long-term outcomes of CHB (cirrhosis, decompensation of cirrhosis, liver transplantation) and can even lead to regression of advanced fibrosis/cirrhosis[50-53]. Thus, long-term therapy with these compounds represents a first-line recommendation of the treatment guidelines of the AASLD, EASL and APASL[46,54,55]. After all, the ultimate goal of therapy in CHB is to improve the quality of life and the survival of patients by preventing the progression of the underlying liver disease to cirrhosis, to decompensated cirrhosis, end-stage liver disease, to development of HCC and death[46].

THE EFFECT OF LONG-TERM TREATMENT WITH NAS ON THE DEVELOPMENT OF HCC

Lamivudine and adefovir dipivoxil

Most data is derived from the application of lamivudine (LAM), the first NA used for the treatment of CHB. The story begun with a breakthrough Asian study published ten years ago, showing that a single pill can change the natural history of CHB[56]. This study is the only randomized controlled clinical trial comparing the efficacy of treatment with lamivudine *vs* placebo on disease progression in a large number (*n* = 651) of patients with CHB and advanced fibrosis or cirrhosis with 58% of them being HBeAg-positive. Though the study was planned for a maximum of five years, it was terminated prematurely after 32.4 mo, since the difference between treated and untreated control patients became obvious from the first year of therapy and it was considered unethical to continue treating with placebo patients with advanced liver disease. The lamivudine arm showed cumulative development of HCC of 3.9% *vs* 7.4% in the placebo arm (*P* = 0.047), yet the clinical benefits for disease progression and HCC development were lost when resistance to the drug was developed (11% in patients with resistance *vs* 5% in placebo treated patients). Moreover, when HCC cases diagnosed in the first year of the trial were excluded, only a marginal difference could be detected (*P* = 0.052). It has, however, been implied, that if the study had continued for longer, then the difference in favor of lamivudine would have been more profound.

Following this initial study, many more were conducted. Most of them have been retrospective with matched historical controls and all of them showed that lamivudine reduced statistically the risk for disease

progression to cirrhosis and for development of HCC[57-60]. However, different methods of HBV-DNA assay with different limits in its detection were used in these studies, many patients had YMDD mutations and in some studies there was no match with untreated controls for HBV-DNA levels, HBeAg positivity, and duration of follow-up or age. These limitations could have possibly resulted in downgrading of the differences between the treated and control patients[57-60].

During the last eight years, one meta-analysis[61] and one systematic review[62] were published dealing with the crucial debate of whether nucleos(t)ide analogs and mainly lamivudine treatment of chronic hepatitis B significantly reduces the risk of HCC both in cirrhotic and in non-cirrhotic patients[61,62].

The meta-analysis included 5 studies[56-60] with 1267 patients treated mostly with LAM and compared them with 1022 untreated ones[61]. Overall, with the use of LAM the incidence of HCC was reduced by 78% (2.5% *vs* 11.7%, RR = 0.22, $P < 0.001$). The risk of HCC was significantly reduced in cirrhotics (3.9% *vs* 22.4%, RR = 0.17, $P = 0.020$), non-cirrhotics (1.8% *vs* 8%, RR = 0.21, $P < 0.001$), both in patients who developed drug resistance (3.3% *vs* 6.4%, RR = 0.52, $P = 0.04$) or not: $P = 0.008$ and in HBeAg (+) (1.7% *vs* 7.9%, $P < 0.001$) patients while in HBeAg (-) patients the difference was not statistically significant (3% *vs* 10%, $P = 0.06$).

The systematic review included 21 studies with 3881 patients treated mainly with lamivudine [and/or adefovir (ADV)] and 534 untreated ones[62]. Of the studied patients, 33% were cirrhotics and 49% were HBeAg (+), while sixteen studies included treatment-naïve patients and five included patients with lamivudine resistance. Three studies followed-up both treated and untreated patients[56-58] and their analysis showed that treated patients had a significantly lower risk for HCC (2.8% *vs* 6.4%, $P = 0.003$) than untreated ones, while this benefit remained the same whether being in virological remission (2.5% *vs* 6.4%, $P = 0.015$) or not (2.8% *vs* 6.4%, $P = 0.016$). Patients under remission had a lower risk for HCC compared to those with breakthrough or without response to treatment (2.3% *vs* 7.5%, $P < 0.001$). Moreover, if remission was accomplished with the initial treatment, then the risk for HCC was lower compared to the risk in patients who accomplished remission under rescue therapy with ADV (2.3% *vs* 5.9%, $P = 0.003$). As expected, treatment naïve patients with cirrhosis had higher HCC incidence than non-cirrhotic ones (10.8% *vs* 0.5%, $P < 0.001$), while the risk for HCC was higher in older ($\geqslant$ 50 years old) (6% *vs* 2.8%, $P < 0.001$) and HBeAg (-) patients (5.5% *vs* 0.5%, $P < 0.001$) than in younger (< 50 years old) and HBeAg (+) ones, respectively. In patients with lamivudine resistance, those with cirrhosis had a higher risk for HCC compared to non-cirrhotic ones (17.6% *vs* 0%, $P < 0.001$). Rescue treatment with ADV in patients who developed biochemical breakthrough did not appear to reduce the risk for HCC compared to patients who remained untreated without remission (8.8% *vs*

5.6%, $P = 0.466$).

Therefore, lamivudine treatment with/or without rescue treatment with ADV seems to reduce but not eliminate the risk for HCC. However, a more recent study[63] revealed that even on-treatment virological remission achieved in cirrhotic patients may not lead to reduction of the incidence of HCC, while another study showed significant reduction in the risk for HCC with on-treatment response[64]. Nevertheless, it must be taken into account that most studies of lamivudine treatment with/without rescue treatment with ADV conducted in the past suffer from several drawbacks: (1) Usually they are non-randomized trials without pretreatment stratification for age, gender, severity of disease and other HCC predictors; (2) Surrogate endpoints of response, such as HBeAg seroconversion or biochemical responses have been applied and not hard endpoints, such as reversal of cirrhosis or prevention from HCC; (3) Because of their design they were completed while serum HBV-DNA was still detectable in many cases; (4) Probably the length of the follow-up was too short to detect a change in the risk for HCC; and (5) HBV resistance to NAs a factor linked with increased risk for HCC was most frequently encountered in the treatment with lamivudine.

Following lamivudine and ADV, many steps forward were made in the therapy of chronic hepatitis B with the newer NAs ETV and TDF of high potency and high barrier to HBV resistance and several studies have accumulated on the effect of long-term NA therapy in the prevention of development of HCC in the course of chronic HBV infection.

ETV, telbivudine, TDF

There are 3 third generation anti-HBV NAs approved for the treatment of CHB: ETV approved in 2005, telbivudine (LdT) approved in 2007 and TDF approved in 2008. All 3 are highly potent anti-HBV compounds but the barrier of resistance of LdT is low and thus for the time being only therapies with ETV and TDF are considered as first line ones. Since ETV has been licensed and used longer than TDF, especially in Asian countries, there is more information regarding the potential benefit of the former than of the latter in CHB as well as on its comparison to lamivudine. Most studies with these compounds have been conducted in Asiatic populations but significant evidence has now accumulated regarding TDF and ETV also in Western countries.

In a retrospective study from Japan the outcome of 316 patients under ETV treatment was compared to that of an equal number of historical untreated controls and of 182 patients under LAM treatment without rescue therapy upon development of HBV resistance[65]. The cohort of ETV treated patients had a 63% reduction of HCC incidence compared to untreated ones (cumulative HCC incidence at 5 years 3.7% *vs* 13.7%, $P < 0.001$), which was most obvious in cirrhotic patients (7% *vs* 39%, $P < 0.001$), but not in non-cirrhotic ones (2.5% *vs* 3.6%, $P = 0.44$). Moreover, reduction in the incidence of

HCC under ETV treatment was greater than in the non-rescued LAM group of cirrhotic patients (7% *vs* 22%, *P* = 0.043), but again not in the non-cirrhotics (2.5% *vs* 4.9%, *P* > 0.05). Nevertheless, the advantage of ETV over lamivudine could not be proved in two other studies, one again from Japan and the other from Greece as well as in a recent meta-analysis[66-68].

In the Asian study, 129 naïve patients (22% cirrhotics) under ETV therapy were prospectively followed (median F-UP: 4.25 years) and compared with 127 patients (27% cirrhotics) under LAM treatment[66]. The cumulative 5-year risk for HCC was 12.4 in both groups, yet patients under LAM therapy who developed resistance (60/127, 47%) had statistically higher HCC risk compared to those without resistance (*P* = 0.035).

Similar to the aforementioned results are those of a multicenter Greek study, published three years later, in which 321 HBeAg (-) patients (86% naïve-14% treatment experienced, 25% cirrhotics) under ETV treatment were followed (median F-UP: 30 mo) and were compared with a known cohort of 818 patients under LAM treatment rescued with ADV upon development of HBV resistance (26% cirrhotics)[67]. In this study, only a trend towards lower 5-year cumulative HCC incidence in the ETV-group was shown compared to the LAM-group (4.8% *vs* 5.6%, *P* = 0.096), while in multivariate analysis, HCC development was statistically associated with older age, male gender and presence of cirrhosis but not with the type of initial treatment.

In a most recent study from Asia, 5374 patients either under LAM or ETV treatment (3374 and 2000 patients with median treatment duration 6.1 and 2.6 years respectively from 1999 until 2011) were retrospectively analyzed (median F-UP for the LAM and ETV treated patients: 3.1 and 8.7 years respectively)[69]. Importantly, ETV-treated cirrhotic patients had statistically lower relative risk for death or liver transplantation compared to LAM-treated ones. However, no difference was found between the two groups regarding the risk for development of HCC.

Conflicting is the information derived from a large retrospective nationwide cohort study conducted in Taiwan with 21595 patients treated for at least 90 d with LAM, ETV or LdT[70]. The results were compared with those of 21595 controls treated with only an hepatoprotective agent. Treated patients had a significantly lower 7-year incidence of HCC compared to controls (7.32% *vs* 22.7%, *P* < 0.001) and the difference was more obvious in young patients without cirrhosis as well as in those without diabetes mellitus.

Moreover, in a roll-over study of registration trials of TDF in HBeAg (+) and HBeAg (-) patients, using the REACH-B scoring system for HCC development, a 55% reduction in HCC risk was shown among 641 patients who completed 6 years of treatment and in cirrhotic patients after the 5th year of treatment, while no difference could be detected in the non-cirrhotic ones[71].

Yet, while a statistical significant difference in the risk for development of HCC between treated and untreated patients has been clearly documented in many Asiatic studies, this has not been the case with studies in Caucasian population, in which the difference in the risk for HCC between treated and untreated patients has been only marginal[63,67,72-74].

Thus, in agreement with the results of the Greek studies[63,67], an Italian one of long-term treatment with ETV showed an annual development of HCC of 0.8% in non-cirrhotic patients and of 2.6% in the cirrhotic ones. These rates are not statistically different from those in untreated historical controls[16,72].

Moreover, similar are the results in European multicenter studies published this year. A total of 744 patients from 11 European centers were included in the first of the studies (42% Caucasian, 29% Asian, 77% naïve, 22% cirrhotic)[73]. They were all treated with ETV and after a median follow-up of 167 wk, 14 patients developed HCC with 64% of them being cirrhotics. The 5-year cumulative HCC incidence was 2.1% for non-cirrhotic patients and 10.9% for cirrhotic ones (*P* < 0.001), with HCC incidence being higher in older patients and those with lower baseline platelet counts.

In another large European multicenter, retrospective cohort study 1666 CHB patients [85% HBeAg (-), 67% with CHB, 29% cirrhotics and 3% with decompensated cirrhosis], from 7 centers treated with ETV or TDF were followed-up for a median period of 39 mo[74]. HCC developed in 71 (4.3%) of the 1666 patients with an incidence rate of 1.37 new HCC cases per 100 patients per year. The cumulative probability of HCC was 1.3% at the 1st year, 3.4% at the 3rd year and 8.7% at the 5th year after the onset of treatment. Again these findings are not different from those on the risk of HCC development among published untreated or lamivudine treated cohorts of patients[16,56,60,62]. Virological remission was achieved in 92% of the patients and it was not found to be significantly associated with the probability of HCC development. In the multivariate analysis, the factors positively associated with development of HCC were age, severity of liver disease and platelet count at the start of treatment[74]. The summary of the mentioned studies and meta-analyses is outlined in Table 1.

Furthermore, the last two studies evaluated the recently developed scoring systems (GAG-HCC, CU-HCC and REACH-B scores) in population of Caucasian patients[73,74]. These scores, based on characteristics of the virus and of the patients, were validated and used to predict HCC development in treated Asian patients[75-78], Table 2. In both studies, the predictability of these scoring systems was poor to modest for the overall Caucasian population of patients, showing that a considerable proportion of individuals, particularly Caucasians, who will develop HCC, cannot be identified by these scoring systems. Hence, their clinical utility especially in Caucasians remains debatable.

The topic of the risk for development of HCC in chronic hepatitis B patients and its possible reduction by antiviral treatment has been widely covered in the

Table 1 Summary of studies and meta-analyses evaluating the effect of antiviral therapy on the incidence of hepatocellular carcinoma in chronic hepatitis B patients

Ref.	Total no. of patients, trx/untrx	Type of study	NUC used	F-up (median) trx/untrx	Cumulative incidence of HCC % trx/% untrx	RR or SIR (95%CI)	P value
Liaw et al[56]	436/215	RCT; prospective	LAM vs placebo	2.7 yr	3.9/7.4	RR: 0.49	0.047
Yuen et al[57]	142/104	Prospective	LAM	8.2 yr	0.7/2.4	RR: 0.20 (CI: 0.03-2.76)	0.005
Matsumoto et al[58]	657/2138	Retrospective	LAM vs placebo	2.7/5.3 yr	1.1/13.3	RR: 0.08 (CI: 0.03-0.22)	< 0.001
Eun et al[59]	872/699	Retrospective	LAM vs placebo	5.1 ± 2.7/6.1 ± 4.3 yr	Annual incidence: 0.95 (VR with LAM)/4.1 (controls)/2.18 (R)	RR: 0.14 (0.006-0.34)	0.005 (CIR), 0.123 (non-CIR)
Papatheodoridis et al[60]	201/195	Retrospective	LAM, LAM + ADV	3.8 ± 1.4 yr	2.48/7.7	RR: 0.32 (0.12-0.87)	0.01
Papatheodoridis et al[63]	818	Retrospective	LAM, ADV (add-on), switch to ADV or ETV upon R	4.7 yr	6% (2.5%/yr)	RR: 1 (VR) RR: 2.04 (0.49-8.3) (no VR)	0.322
Kurokawa et al[64]	293	Retrospective	LAM		3 (CHB)/30 (CIR)	HCC reduction by 63% with ETV	
Hosaka et al[65]	316 (ETV)/316 (untrx)/182 (LAM)	Retrospective	LAM, ETV	67.6 ± 27.4 mo / 5.4 yr	ETV/untrx 3.7/13.7	HR: 0.37 (0.15-0.91)	< 0.001
Kobashi et al[66]	ETV/LAM 129/127	Prospective	ETV, LAM	4.25 yr	12.4		No difference ETV vs LAM
Papatheodoridis et al[67]	ETV/LAM 321/818	Retrospective	ETV, LAM	30 mo	ETV/LAM 4.8/5.6		0.096
Lim et al[69]	LAM/ETV 3374/2000	Retrospective	LAM, ETV	LAM: 3.1 yr / ETV: 8.7 yr	137/2000 (6.85)/ 234/3374 (6.9)	ETV/LAM HR: 1.01 (CI: 0.8-1.24)	0.95
Wu et al[70]	21595/21595	Retrospective	LAM, ETV, LdT vs controls	7 yr	7.32/22.7	CI: 6.77-7.87/22.1-23.3	< 0.001
Kim et al[71]	641	Prospective roll-over	TDF	5.52 yr	56% reduction in CIR after the 5th year	SIR:0.55 (0.32-0.94) at 5.52 yr	
Lampertico et al[72]	418	Retrospective/prospective	ETV	58 mo	4 (CHB)/13/(CIR)		
Arends et al[73]	744	Prospective	ETV	167 wk	Cumulative (5-yr) 2.1 (non-CIR)/10.9 (CIR)		CIR/non-CIR < 0.001
Papatheodoridis et al[74]	1666	Retrospective	ETV, TDF	39 mo	1.3(1st year), 3.4 (3d year), 8.7 (5th year)		No difference from untrx published cohorts
Sung et al[61]	5 studies 1267/1022	Meta-analysis	LAM			RR: 0.22 (0.10-0.50) HBeAg (-): RR: 0.25 (0.06-1.06)	< 0.001 NS
Papatheodoridis et al[62]	21 studies 3881/534	Systematic review	LAM		2.8/6.4	LAM vs untrx	0.003
Singal et al[68]	49 studies 10025/3571	Meta-analysis	LAM, ADV, ETV, LdT, TDF		Pooled HCC incidence rate: 1.3 (1.1-1.6)/100 person-years	RR: 0.48 (0.38-0.61)	< 0.001 No difference between NA

Trx: Treated; Untrx: Untreated; RR: Relative risk; SIR: Standardized incidence ratio; LAM: Lamivudine; VR: Virological remission; R: Resistance; CIR: Cirrhosis; ADV: Adefovir; CHB: Chronic hepatitis B; ETV: Entecavir; HR: Hazard ratio; LdT: Telbivudine; TDF: Tenofovir; NS: Non-significant; HCC: Hepatocellular carcinoma; NA: Nucleoside analogues; RCT: Randomized controlled trial.

Table 2 Risk scoring system for hepatocellular carcinoma in chronic hepatitis B

CU-HCC score[76]		GAG-HCC score[75]		REACH-B score[77]	
Variable	Points	Variable	Points	Variable	Points
Age		Age		Age	
> 50 yr	3	Per year	1	Per 5 years over 30	1
Albumin		Gender		Gender	
< 3.5 g/dL	20	Male	16	Male	2
Bilirubin		BCP mutations		ALT (IU/L)	
> 1.1 mg/dL	1.5	Present	19	15-44	1
Cirrhosis		Cirrhosis		≥ 45	2
Presence	15	Presence	30	HBeAg (+)	2
HBV-DNA		HBV-DNA		HBV-DNA	
4-6 log10	1	Per log10	3	< 4log10	0
> 6 log10	4			4 - < 5log10	3
				5 - < 6log10	5
				≥ 6log10	4
Risk category		Risk category		Risk category	
Low	< 5	Low	< 101	A 17 point risk scale	
Intermediate	5-20	High	≥ 101		
High	> 20				

CU-HCC: Chinese University-Hepatocellular Carcinoma Score; GAG-HCC: Guide with Age, Gender, HBV-DNA, Core Promoter Mutations and Cirrhosis; REACH-B: Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B; BCP: Basic core promoter; ALT: Alanine transaminase.

last AASLD meeting of 2014 in Boston with several oral presentations and posters[79-88]. From an overall analysis of these studies it can be deduced that antiviral therapy is associated with reduction of the risk for development of HCC. However, the risk still remains high, particularly in males of older age and in patients with cirrhosis. Therefore continuous surveillance is imperative in all CHB patients regardless of the outcome of anti-HBV therapy even if HBsAg has been cleared and anti-HBs have developed. Irrespective of virological remission induced by antiviral treatment, CHB patients and especially those with the highest risk - men > 50 and cirrhotics - should continue to be surveilled, according to the existing recommendations[45]. Moreover, CHB patients whether with or without cirrhosis, who experience HBsAg loss with or without seroconversion to anti-HBs, continue to remain at risk for HCC and therefore, their surveillance should also be continued[89,90].

Moreover, loss of HBsAg at the age ≥ 50 years was found to be an independent predictor of development of HCC.

CONCLUSION

In view of the above pooled data from studies of more than ten years, it is reasonable to conclude that treatment of chronic hepatitis B with oral antiviral agents, especially the first line ones ETV and TDF, definitely prolongs survival and changes the natural history of the disease, with significant reduction of the incidence of cirrhosis, decompensation of cirrhosis, and end-stage liver disease leading to death or liver transplantation[52,53,69,91,92]. Yet, the potential benefits of antiviral treatment in the reduction of the risk for development of HCC have not been very impressive. A

reduction but not elimination in its incidence has been documented even in patients who achieved loss of HBsAg. This has an impact also in the waiting lists of liver transplantation. Thus, in the United States patients enlisted for transplantation for complications of CHB, a 42% relative reduction of end-stage liver disease and a concomitant 72% relative increase of HCC are recorded. To a significant extent, these changes have been secondary to antiviral treatment[93]. Furthermore, in Europe the percentage of HBV cirrhotics transplanted for consequences of viral hepatitis has been reduced from 24% to 16% of the total[92].

The self-contradictory finding that antiviral treatment in CHB can prevent clinical decompensation while it does not seem to affect considerably the development of HCC, is due on the one hand to the prolongation of survival without clinical consequences of hepatic decompensation, and on the other hand to the ongoing extended exposure of the patients to the harmful effects of integrated HBV sequences.

Hopefully, in the years to come, new anti-HBV therapies may manage to timely and completely eradicate HBV from the host genome and therefore may also manage to eliminate the risk for development of HCC in CHB[94].

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