AP&T Alimentary Pharmacology and Therapeutics

Meta-analysis: the impact of oral anti-viral agents on the incidence of hepatocellular carcinoma in chronic hepatitis B

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Publication data
Submitted 3 February 2013
First decision 20 February 2013
Resubmitted 2 May 2013
Accepted 2 May 2013
Ev Pub Online 28 May 2013

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Mr M. Siddiqui.

SUMMARY

Background
Five oral nucleos(t)ide analogues are available to treat chronic hepatitis B (CHB). With the availability of newer agents, their efficacy on incidence of hepatocellular carcinoma (HCC) is not well described.

Aim
To determine the efficacy of oral anti-viral agents in reducing HCC risk in relationship with other known factors.

Methods
Published studies of at least 20 CHB patients treated with an oral anti-viral agent and followed for >2 years were analysed for incidence of HCC per 100 person years follow-up.

Results
Pooled homogeneous data from six studies showed lamivudine (LAM) treatment (n = 3306) to reduce HCC risk by 51% compared with no treatment (n = 3585) (3.3 vs. 9.7 per 100 person years, $P < 0.0001$). Pooled data from 49 studies (23 with LAM; 16 with adefovir; and 10 with entecavir, tenofovir or telbivudine) of 10 025 treated patients showed HCC incidence of 1.3 per 100 person years, independent of the agent used. Patient age >50 years and hepatitis B virus-DNA detectability at HCC diagnosis increased risk of HCC by twofold with a 10-fold higher risk among patients with cirrhosis compared with chronic hepatitis. Meta-regression showed patient age, study location (Eastern vs. Western) and type of study (randomised or not) contributed to heterogeneity.

Conclusions
Lamivudine treatment significantly reduces the incidence of HCC compared with no treatment. However, HCC still develops at a rate of 1.3 per 100 patient years in CHB patients receiving an oral anti-viral agent. This finding highlights the need for continued HCC surveillance, particularly in CHB patients with inadequate viral suppression, older age and cirrhosis.

Aliment Pharmacol Ther 2013; **38:** 98–106

doi:10.1111/apt.12344

INTRODUCTION

Worldwide chronic hepatitis B virus (HBV) infection is the most frequently identified cause of liver disease that predisposes patients to the development of hepatocellular carcinoma (HCC).[1, 2] Established risk factors for the development of HCC in untreated chronic HBV patients include subject age, male gender, the presence of cirrhosis, hepatitis B e antigen (HBeAg) + serostatus and higher levels of serum HBV-DNA.[2] In a large cohort of untreated Taiwanese patients with chronic HBV followed up for a mean of 11.4 years, high levels of HBV replication as manifest by high levels of HBV-DNA at enrolment and during follow-up were independent and strong predictors of developing HCC.[3] Over the past 20 years, five oral nucleos(t)ide analogues have been approved for the treatment of chronic HBV with improved short- and intermediate-term outcomes.[4, 5] The newer oral anti-viral agents, entecavir (ETV), tenofovir (TDF) and telbivudine (TBV) have been shown to be more potent suppressors of HBV replication compared with lamivudine (LAM) and adefovir (ADV) with a lower likelihood of leading to the emergence of drug-resistant HBV during prolonged therapy.[6] However, the impact of these newer agents on the incidence of HCC is not clear due to the limited number of treated patients and relatively short duration of follow-up. Since the last published review in this area, several studies employing the newer anti-viral agents (ETV, TDF and TBV) for prolonged periods of time in chronic HBV patients have been reported.[7–11] The aim of this systematic review was to determine the pooled effect of the individual oral anti-viral agents in reducing the incidence of HCC among chronic HBV patients. In addition, analyses were undertaken to identify the role of other clinical features on the risk of developing HCC in chronic HBV patients receiving an oral anti-viral agent.

METHODS

Study selection

Search strategy. Electronic databases (Medline, Cochrane reviews and EMBASE, ISI Web of science) from 1995 to 2013 were searched for publications including abstracts that were written in English. The initial search terms were hepatitis B, treatment and HCC. The search was later expanded using the MeSH terms lamivudine, adefovir, entecavir, tenofovir and telbivudine and boolean logic was used to combine the search terms. A manual search of the references from the identified manuscripts was also undertaken.

Study selection criteria. The following criteria were used to select the studies: (i) patient population – adult patients with chronic HBV (treatment naöve as well as treatment experienced); (ii) treatment regimen – single or combination oral nucleos(t)ide analogues; (iii) study design – retrospective or open-label prospective studies with or without a control group; and (iv) outcome – HCC at the last follow-up as determined by the American Association for the Study of Liver Diseases criteria.[4, 12, 13] Only studies with a total sample size of >20 and a median follow-up of at least 2 years were included. Studies that included HIV or HCV co-infected patients and/or liver transplant recipients were excluded.

Assessment of study quality. A study quality score was determined as reported earlier,[6] using the following binomial parameters: randomisation, blinding, control group or not, prospective or retrospective, defined inclusion criteria, defined intervention, defined outcome, similar baseline characteristics, intention-to-treat analysis and follow-up on drop outs or deaths. Each parameter was given a numerical score of 0 or 1 with an overall quality score ranging from 0 to 10. Studies with a quality score of <5 were rated as poor, while those ≥5 were rated as high.

Outcome measures

The primary outcome measure in this study was the incidence of HCC during follow-up

Data Collection

The following data fields were extracted from each of the included studies: (i) study characteristics (author and year of publication, country of origin, study design, sample size, study quality score); (ii) patient demographics (age, sex, ethnicity, per cent HBeAg positive, per cent cirrhosis, stage of cirrhosis [Child-Turcotte-Pugh (CTP) A vs. CTP B/C)]; (iii) inclusion and exclusion criteria; (iv) treatment details (i.e. anti-viral agent, treatment duration, lower limit of detection of HBV-DNA assay and median duration of follow-up); (v) response to treatment (HBV-DNA negative or positive due to non-response or virological breakthrough); and (vi) method of HCC detection (screening or symptomatic). The incidence of HCC was also determined in the following subgroups: anti-viral agent used, hemisphere (Western vs. Eastern), age (<50 vs. >50 years), HBeAg status (positive vs. negative), cirrhosis (yes vs. no), stage of cirrhosis (CTP A vs. CTP B/C), HBV-DNA status (detectable or undetectable) at HCC diagnosis or last follow-up visit

and method of detection of HCC (symptomatic vs. screening). If the outcome data were not clear from the manuscript, the corresponding authors were contacted for further information.

Data and Statistical Analyses

Data on HCC incidence were pooled and reported as per 100 person years of follow-up assuming a poisson distribution.[14] As the follow-up period was variable across studies, this variable was weighted for the sample size in each study that was pooled. Pooled effects with 95% confidence interval (CI) are reported for the uncontrolled data. Subgroups were considered significantly different if there 95% CI did not overlap. Odds ratios (OR) with 95% CI are reported for studies with a control group of untreated patients. Heterogeneity for both open and controlled data was assessed using the I^2 statistics of the pooled data. Publication bias was assessed through visual inspection of funnel plots and using the Egger's test. All P values < 0.05 were considered statistically significant.

If significant heterogeneity was noted in the pooled data, a meta-regression model was built to help identify which variables may have contributed to the heterogeneity. Data were pooled and analysed using the comprehensive meta-analysis software (Biostat, Engelwood, NJ, USA, http://www.meta-analysis.com/).

RESULTS

Baseline study characteristics

A total of 2562 studies were initially reviewed to select the 49 studies included in the current analysis (Figure 1). Two independent reviewers (AKS and SH) reviewed the study abstracts and/or manuscripts to identify the studies that met our inclusion and exclusion criteria. Studies substantially differed in regard to sample size, year of publication, study location (Western or Eastern hemisphere), type of study (randomised, prospective nonrandomised, retrospective), proportion of men, % with cirrhosis, oral anti-viral agent used, follow-up duration, method for detection of HCC and study quality score (Tables S1 and S2). Of the 49 studies included in this analysis, LAM was used in 23 studies [17 open-label studies including one randomised controlled trial (RCT) and six controlled studies including one double-blind placebo controlled RCT]; ADV was used in 16 studies (14 open-label studies of ADV alone or ADV+LAM combination and three RCT comparing ADV with ETV or ADV alone with ADV+LAM combination); ETV was used in six studies including a RCT comparing ETV with ADV; TBV was used in two studies including an RCT comparing LAM and TBV; and TDF was used in two open-label studies.

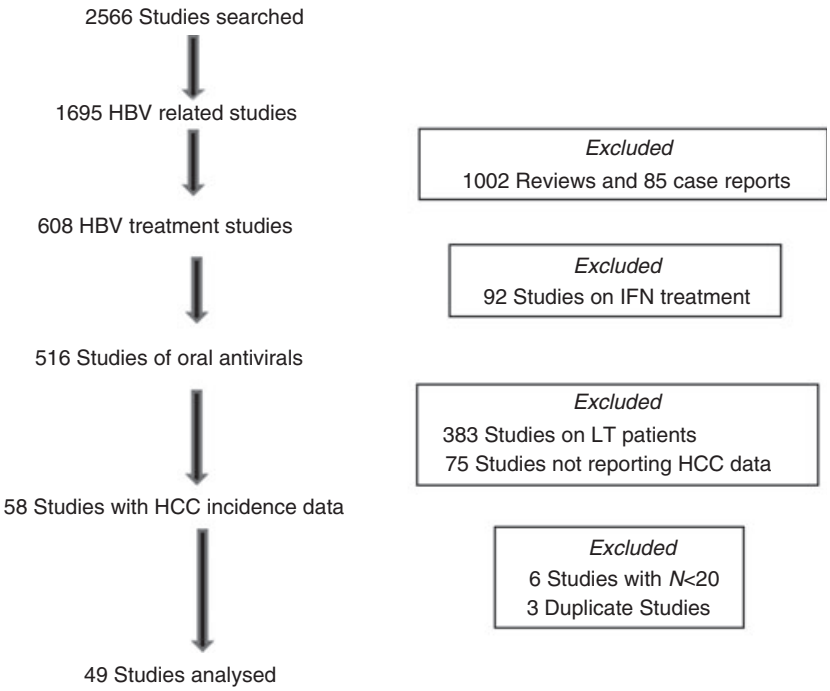

Figure 1 | Attrition diagram for selecting studies included in the current meta-analysis.

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Incidence of HCC: LAM vs. no therapy

The HCC rate was significantly lower among the LAM treated patients that were followed up for a median of 43 months in six controlled studies [113 of 3306 (3.4%) vs. 343 of 3571 (9.6%); $P < 0.0001$; OR (95% CI) of 0.48 (0.38–0.61)] (Figure 2). The pooled data from the six controlled studies using LAM were homogeneous (I^2 $P = 0.14$) without any evidence of publication bias (Egger's test $P = 0.16$). Results were similar irrespective of whether fixed effects or random effects model was used for this analysis. The addition of data from a controlled study of 472 ETV-treated patients and 1143 untreated controls also did not significantly alter the overall incidence of HCC with OR (95% CI) of 0.38 (0.23–0.64) (data not included in Figure 2).[15]

Incidence of HCC in chronic HBV patients treated with oral anti-viral agents

A total of 465 HCC cases were reported in the pooled analysis of the 10 025 chronic HBV patients treated with the various drugs: LAM ($n = 5946$); ADV ($n = 1929$); and other drugs including ETV ($n = 879$), TDF ($n = 657$), TBV ($n = 616$) and followed up for a median duration of 36 months. The pooled HCC incidence rate was 1.3 (95% Poisson confidence limits 1.1–1.6) per 100 person years of follow-up (Figure S1). Substantial heterogeneity was noted in the pooled data ($I^2 = 89.84$; $P < 0.0001$), which was further explored using meta-regression (see below).

Subgroup analyses. Anti-viral agent used: A total of 304 HCC were diagnosed among the 5946 LAM-treated patients treated for a median duration of 43 months (1.3 per 100 patient years). In addition, there were 95 HCC diagnosed among the 1929 ADV-treated patients treated for median duration of 35 months (1.5 per 100 patient years), and 66 HCC cases among the 2150 patients treated with TBV, ETV or TDF for median duration of 42 months years (1.3 per 100 patient years). The pooled HCC rate was similar irrespective of the oral anti-viral agent used with overlapping of the 95% Poisson confidence limits (Figure 3a). As a result, all 49 studies were pooled together when exploring other patient characteristics in relationship with developing HCC.

Patient age: The mean patient age was <50 years in 21 studies ($n = 6037$) and >50 years in 28 studies ($n = 3988$) (Table S3). The pooled HCC rate per 100 person years was more than twofold higher among studies with a mean patient age >50 years compared with studies with mean patient age of <50 years, which was statistically significantly different (Figure 3b).

Presence of cirrhosis: Data on the incidence of HCC were reported separately for patients with chronic HBV and no cirrhosis in 29 studies ($n = 6129$) and for patients with cirrhosis in 33 studies ($n = 3359$) (Table S3). The rate of HCC was 10-fold higher among patients with cirrhosis compared with chronic HBV patients without

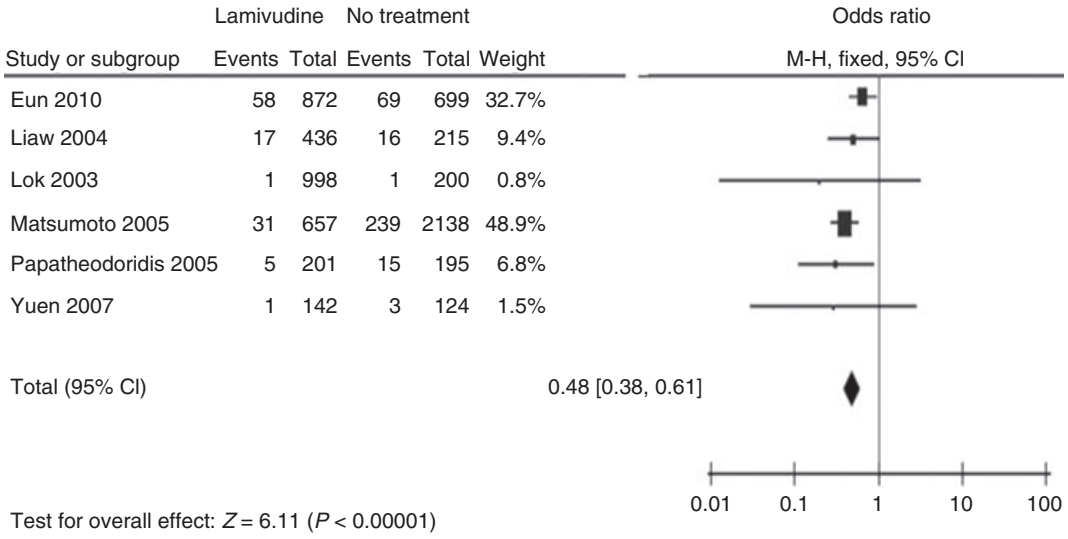

Figure 2 | Forrest plot comparing pooled incidence of hepatocellular carcinoma (HCC) among lamivudine (LAM)-treated and untreated patients with chronic hepatitis B virus. The incidence of HCC was significantly lower in the LAM-treated vs. untreated patients (3.3 vs. 9.7 per 100 person years, $P < 0.0001$).

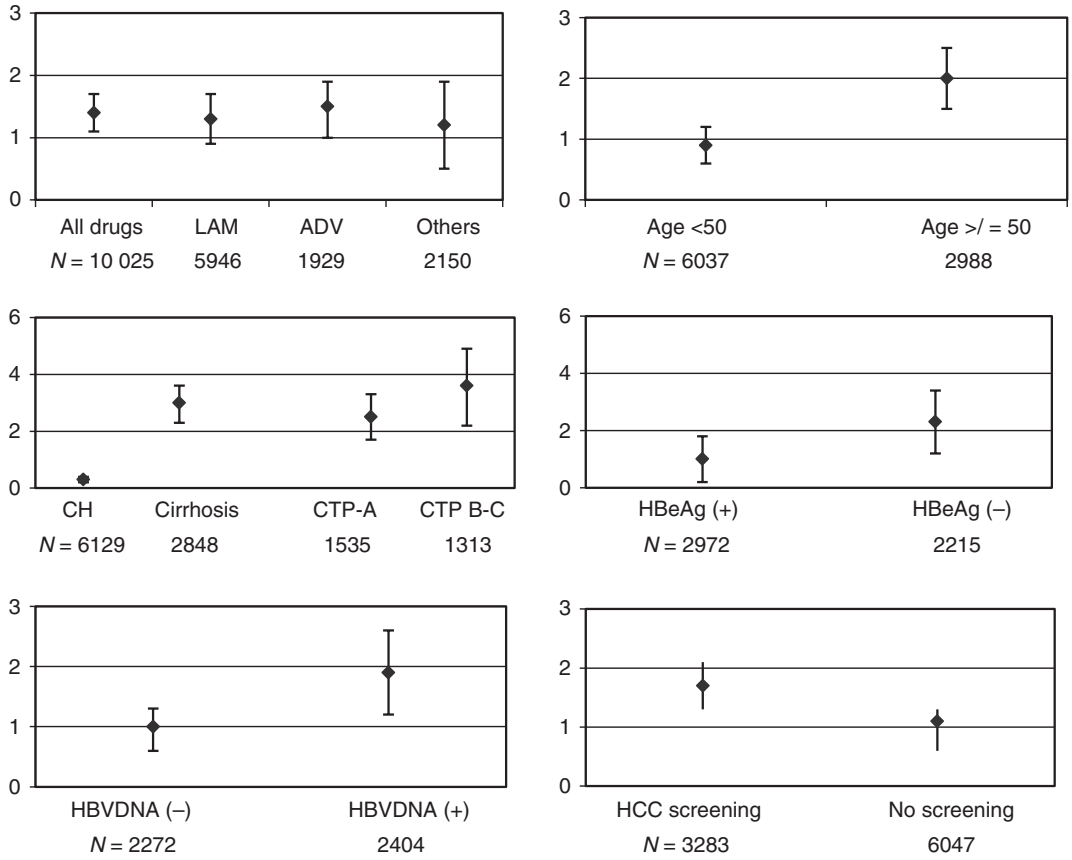

Figure 3 | Pooled data on the HCC rate per 100 person years follow-up for: (a) type of drug; (b) age at the start of treatment; (c) disease severity, (d) hepatitis B E antigen status; (e) HBV-DNA detectability at diagnosis; and (f) screening method for diagnosis of HCC. The incidence of HCC was not significantly different based on the anti-viral agent used and HBeAg status. However, age was significantly associated with HCC incidence [0.9 (0.6–1.2) vs. 2.0 (1.5–2.5)], HBV-DNA detectability at diagnosis [1 (0.6–1.2) vs. 1.9 (1.2–1.6)], method of HCC diagnosis: screening vs. no screening [1.7 (1.3–2.1) vs. 1.1 (0.6–1.3)] and stage of liver disease: chronic hepatitis vs. cirrhosis [0.3 (0.2–0.4) vs. 3 (2.3–3.6)]. Although the incidence of HCC was higher among the decompensated vs. compensated cirrhotics, this rate was not significantly different [3.6 (2.2–4.9) vs. 2.5 (1.7–3.3)]. Others includes entecavir, telbivudine and tenofovir. LAM, lamivudine; ADV, adefovir; CH, chronic hepatitis; CTP, Child-Turcotte-Pugh; HCC, hepatocellular carcinoma.

cirrhosis (3 vs. 0.3 per 100 person year follow-up) (Figure 3c). In addition, the pooled HCC rate was 2.5 per 100 person years follow-up among 20 studies (n = 1435) with CTP-A cirrhosis and 3.6 among 13 studies (n = 1238) with CTP- B or C cirrhosis (Table S3), but this difference was not significantly different (Figure 3c).

HBeAg status: The HCC incidence was reported separately for HBeAg-positive patients in seven studies (n = 2972) and for HBeAg-negative patients in nine studies (n = 2215) (Table S3). Although, HBeAg-negative patients developed HCC more frequently compared with HBeAg-positive ones (1 vs. 2.3 per 100 person years follow-up), the difference was not significant (Figure 3d).

HBV-DNA status*:* Data based on HBV-DNA status at the end of the study period or at the time of HCC diagnosis were reported separately among 20 studies (n = 2272) with undetectable HBV-DNA and 21 studies (n = 2404) with detectable HBV-DNA. The pooled HCC rate per 100 person years follow-up was nearly twofold higher (1.9 vs. 1 per 100 person years) among patients with detectable HBV-DNA compared with patients with undetectable HBV-DNA (Figure 3e).

Method of HCC detection: Hepatocellular carcinoma was detected using active cancer surveillance in 28 studies (n = 3755) and only when prompted by clinical symptoms in 19 studies (n = 6270) (Table S3). The

incidence of HCC per 100 person years of follow-up was 1.7 when the HCC was detected using the screening guidelines and 1.1 when HCC was detected on clinical indication (Figure 3f). Pooled data on most subgroup analyses were heterogeneous with significant publication bias (Table S3).

Meta-regression

Meta-regression models were built to assess the source of heterogeneity in the pooled data. Study location (Western vs. Eastern), age of the patient at enrolment (<50 vs. >50 years), type of study (randomised vs. nonrandomised), study quality and method of HCC detection (HCC screening or not) were individually assessed as contributors to study heterogeneity (Table S4). Meta-regression was performed with stepwise exclusion of the variable contributing the most heterogeneity with subsequent steps being performed on the remaining studies to recalculate an improved I^2 (indicating lower heterogeneity). In the first step, analysis of pooled data from 49 studies showed that patient age contributed the most to study heterogeneity ($P < 0.0001$, Table S4). In the second step, analysis of 28 studies with mean age of patient at enrolment >50 years was performed as this had lower I^2 compared with 21 studies with age of patient <50 years (69% vs. 90%; $P < 0.0001$). A repeat meta-regression model showed that the study location (Eastern vs. Western) contributed the most to the heterogeneity of these 28 pooled studies ($P = 0.0063$, Table S4). In the third step, analysis of 15 studies from the Western hemisphere with age >50 excluded study design variable ($P = 0.03$) leaving 12 studies with the most homogeneous data. The HCC rate on the pooled data from these 12 studies was 1.6 (1.0–2.2) per 100 person years follow-up. As in the original analysis, the anti-viral agent used did not impact the HCC rate per 100 person years follow-up: 1.6 (0.7–2.4) for LAM used in seven studies and 1.7 (0.7–2.6) for ADV used in the remaining five studies.

As all the studies did not report HCC incidence data stratified by the presence or absence of cirrhosis, HBeAg status and HBV-DNA status at diagnosis, these variables were not assessed in the overall meta-regression model. A separate meta-regression model in the 33 studies of cirrhotics showed patient age and study quality contributing the most to pooled heterogeneity. Pooled data from 11 studies with mean patient age of >50 years and poor study quality were homogeneous with an HCC rate per 100 person years follow-up of 2.4 (1.3–3.4) with no impact of anti-viral agent used: 2.4 (1.2–3.6) with LAM used in eight studies, 3.3 (2.5–9.2) with ADV in two studies and 2.7 (0.4–5.6) with ETV in one study. Similar analysis on 29 studies on chronic HBV patients without cirrhosis showed patient age and study design contributing to the heterogeneity. Pooled data from eight nonrandomised studies with mean patient age of 50 or more were homogeneous with an HCC rate per 100 person years of follow-up of 0.7 (0.5–1.0) without any impact of type of drug again: 0.7 (0.5–1.0) with LAM in four studies and 0.8 (0.3–1.8) with ADV in the four remaining studies. As the number of studies was limited based on HBeAg status and HBV-DNA detectability, meta-regression for these subgroups was not performed.

DISCUSSION

The current meta-analysis demonstrates several important points regarding the impact of anti-viral therapy on the incidence of HCC in chronic HBV patients. Firstly, LAM treatment for a median of 43 months reduces the incidence of HCC by more than 50% from 9.7% per year in untreated controls to 3.3% per year in LAM-treated chronic hepatitis B (CHB) patients. Our pooled data in 6877 (3306 treated) patients demonstrate a similar magnitude of benefit to that achieved in the pivotal RCT of LAM.[5] These findings further support recommendations regarding the need for indefinite therapy in chronic HBV patients with advanced histology to improve patient outcomes.[2]

Secondly, the overall incidence of HCC was 1.4% in the data pooled from over 10 000 patients treated with an oral anti-viral agent, but did not differ by the agent prescribed. Our inability to discern a difference among the various agents is similar to reports from individual centres.[16] Lastly, our data demonstrate that HCC occurs more frequently among chronic HBV patients receiving oral anti-viral therapy who are older, have cirrhosis and in those with persistently detectable HBV-DNA at the end of treatment or at the time of HCC diagnosis. These data confirm the importance of continuous suppression of HBV replication to improve patient outcomes. Lastly, contrary to prior studies of untreated chronic HBV patients, our data show that the incidence of HCC did not significantly differ by HBeAg status, and the presence of decompensation among the cirrhotic patients.

Prior retrospective studies by Fattovich *et al.* have shown the incidence of HCC among untreated Western chronic HBV patients to be proportional to the severity of underlying liver disease with rates of 0.04, 0.3, and 2.2 per 100 person years follow-up among asymptomatic carriers, CHB and compensated cirrhotics respectively.[17] Similar HCC rates have been reported among untreated

Asian patients with HCC rate of 0.5, 0.6 and 3.7 per 100 person years follow-up respectively.[18] In the current meta-analysis, the pooled HCC rate was lowest among chronic HBV patients without cirrhosis at only 0.3% per 100 person years, and 3% per 100 person years among cirrhotics, but did not differ in those with decompensated vs. compensated disease (3.6 vs. 2.5 per 100 person years). The low observed rate among the noncirrhotic patients is rather remarkable considering that all of these patients had chronic active hepatitis with active viral replication mandating the initiation of anti-viral treatment. We surmise that the noncirrhotic patients included in this analysis inevitably had more severe liver disease than the untreated chronic carriers reported in the literature. Nonetheless, these data demonstrate that even in the presence of anti-viral therapy, HCC may still develop albeit at a lower rate.

Cirrhosis is a known risk factor for development of HCC and is considered to be a premalignant condition.[2, 19] However, nearly 10–20% of chronic HBV patients with HCC do not have cirrhosis at the time of diagnosis.[20] In the current analysis, the incidence of HCC was nearly 10-fold higher in cirrhotics compared with patients without cirrhosis. Similar data have been reported from prospective natural history studies where the incidence of HCC was four to fivefold higher among untreated HBV cirrhotics compared with asymptomatic carriers.[21] Therefore, continued HCC surveillance is warranted in chronic HBV patients with advanced fibrosis who are started on anti-viral therapy.

In the current analysis, the pooled HCC rate was significantly higher among studies that used prospective surveillance for HCC compared with studies that relied upon clinical symptoms to prompt investigation. These data reiterate the recommendations of various professional societies regarding the importance of periodic surveillance to detect and diagnose HCC in an early and potentially treatable stage. Other risk factors for HCC development in the current analysis were increased age at enrolment and the inability to suppress HBV-DNA to undetectable levels. Patient age is known to be risk factor for many malignancies including HCC associated with chronic HBV and HCV.[22] This is likely due to a longer duration of infection with consequent prolonged pathogenic effect of the virus on the liver. Higher HBV-DNA level is also known to be a factor for the HCC development in untreated chronic HBV patients of Asian ethnicity.[3] Studies have shown an HCC rate of <1% with baseline HBV-DNA of 300–10 000 copies/mL and 13.5% with baseline HBV-DNA of $>10^6$ copies/mL during a mean follow-up of 11.4 years.[23] Although, we could not analyse the effect of baseline HBV-DNA due to inconsistent reporting of the data and use of varying assays, our data demonstrated a lower incidence of HCC among patients with undetectable HBV-DNA during treatment compared with patients with detectable HBV-DNA at the end of study or at the time of HCC detection (including patients with virological breakthrough). These data are similar to prospective studies showing lower HCC rate among patients with undetectable HBV-DNA treated with interferon.[2, 24, 25]

Hepatitis B e antigen status in this study did not significantly influence the incidence of HCC. Data from previous studies on the impact of HBeAg on the incidence of HCC have been conflicting. In the Eurohep study, HBeAg (+) status did not impact the incidence of HCC. However, other studies have reported higher HCC rate among HBeAg-positive patients.[26] The lack of correlation of HBeAg status with the HCC rate in this analysis could be due to the small number of studies reporting HCC incidence based on HBeAg status (seven for HBeAg positive and nine for HBeAg negative). In addition, it is possible that suppression of HBV replication may reduce the importance of this marker. Severity of disease and stage of cirrhosis also did not affect the HCC rate in our analysis. We speculated that decompensated patients may be dying from complications of cirrhosis such as ascites or variceal bleeding before the development of HCC. However, a prior meta-analysis on the safety and efficacy of the oral anti-viral agents in patients with decompensated cirrhosis showed a global improvement in patient survival in those treated with LAM vs. untreated controls.[6]

Limitations of this study include our inability to obtain patient level data to look at the individual predictive factors in a multivariate manner. In addition, there was substantial heterogeneity among the studies when pooled together. Our meta-regression suggests that the heterogeneity was, in part, due to age of the patient at enrolment, study design and study location (Eastern or Western hemisphere). Furthermore, it should be noted that the sensitivity of the HBV-DNA assays used in the pooled studies varied substantially between studies. Therefore, our confidence in the observation of persistently detectable HBV-DNA as a predictor of HCC development should be interpreted with caution. Lastly, the absence of an observed difference in the incidence of HCC stratified by the specific drug used may, in part, be due to pooling data for patients treated with ETV, TBV and TDF due to limited number of patients treated with respective drug.

As the newer oral anti-viral agents such as ETV and TDF are more potent and associated with a lower rate of drug resistance, we had anticipated to see a difference. However, the absence of a difference could also be confounded by differences in the proportion of patients with other environmental factors (alcohol use and smoking), viral factors (HBV genotype and baseline HBV-DNA level) and patient factors (age, disease severity). Of note, the studies with newer anti-viral agents included significantly younger patients, which may have reduced the observed rate of HCC. Finally, the limited duration of follow-up in the studies included in this analysis may have prevented us from detecting a difference with the newer anti-viral agents, which may prove more effective with less drug resistance after 5–10 years of continuous treatment.

In summary, our meta-analysis demonstrates that LAM therapy is associated with a 56% reduction in the incidence of HCC among chronic HBV patients compared with no treatment. In addition, among patients receiving an oral anti-viral agent, subject age, the presence of cirrhosis and method of HCC detection all significantly impact the incidence of HCC. Finally, although we did not observe a difference in the incidence of HCC based on the individual agent prescribed, additional prospective studies are needed that control for the confounders of subject age, gender, cirrhosis and HCC detection method to better estimate the risk of developing HCC among those receiving the newer anti-viral agents.

AUTHORSHIP

Guarantor of the article: Ashwani K. Singal.

Author contributions: Ashwani K. Singal contributed to the study inception and design, literature search, analysis and writing of the manuscript. Habeeb Salameh contributed to the literature search and writing of the manuscript. Young-Fang Kuo contributed to the statistical analysis. Robert J Fontana contributed to the study design, manuscript writing and study supervision. All authors approved the final version of the manuscript.

ACKNOWLEDGEMENT

Declaration of personal interests: Robert J. Fontana has served as a consultant for GlaxoSmithKline and Bristol Myers Squibb, and has received research funding from Bristol Myers Suibb and Gilead Sciences. Ashwani K. Singal is a consultant for Novartis pharmaceuticals.
Declaration of funding interests: None.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Forrest plot showing incidence of HCC per person year follow-up pooled from 49 studies of anti-viral agents in chronic HBV.

Table S1. Baseline characteristics of patients included in the 49 composite studies.

Table S2. Baseline characteristics of the treated chronic HBV patients.

Table S3. Subgroup analyses on HCC rate per 100 person years follow-up.

Table S4. Meta-regression of pooled studies with homogeneous data after excluding variables contributing to heterogeneity.

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