BMJ open

Antiviral therapy for prevention of hepatocellular carcinoma and mortality in chronic hepatitis B: systematic review and meta-analysis

Maja Thiele,[1] Lise L Gluud,[2] Emilie K Dahl,[3] Aleksander Krag[1]

To cite: Thiele M, Gluud LL, Dahl EK, *et al*. Antiviral therapy for prevention of hepatocellular carcinoma and mortality in chronic hepatitis B: systematic review and meta-analysis. *BMJ Open* 2013;**3**:e003265. doi:10.1136/bmjopen-2013-003265

▸ Prepublication history and additional material for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2013-003265).

Received 21 May 2013
Revised 8 July 2013
Accepted 10 July 2013

For numbered affiliations see end of article.

Correspondence to
Dr Maja Thiele;
maja.thiele@rsyd.dk

ABSTRACT

Objectives: The effect of antiviral therapy on clinical outcomes in chronic hepatitis B virus (HBV) is not established. We aimed to assess the effects of interferon and/or nucleos(t)ide analogues versus placebo or no intervention on prevention of hepatocellular carcinoma (HCC) and mortality in chronic HBV.

Design: Random-effects pairwise meta-analysis of randomised trials and observational studies.

Setting: Electronic and manual searches were combined. Randomised controlled trials (RCTs) were included in the primary analyses. Observational studies were included in sensitivity analyses.

Primary and secondary outcome measures: The primary outcome measures were HCC incidence and mortality. The secondary outcome measure was HCC mortality.

Results: We included 8 RCTs, 8 prospective cohort studies and 19 case–control studies with a total of 3433 patients allocated to antiviral therapy and 4625 controls. The maximum duration of follow-up was 23 years. Randomised trials found no effect of antiviral therapy on HCC or mortality. Cohort studies found that antiviral therapy increased the risk of HCC (risk ratio 1.43; 95% CI 1.06 to 1.95), whereas case–control studies found a decreased risk of HCC in the intervention group (risk ratio 0.69; 95% CI 0.54 to 0.88). There was a clear difference between the results of RCTs and observational studies (test for subgroup differences, p<0.001). Antiviral therapy did not affect mortality in cohort studies, but reduced mortality in case–control studies (relative risk 0.71; 95% CI 0.54 to 0.93; test for subgroup differences, p=0.406).

Conclusions: The effect of antiviral therapy on clinical outcomes in HBV remains to be established. Although there was a positive effect in the sensitivity analyses, the strength of the evidence does not allow for extrapolation to clinical practice as research design plays an essential role in the overall assessment.

Trial registration number: Prospero number CRD42013003881.

ARTICLE SUMMARY

Article focus

- The effect of antiviral treatment for chronic hepatitis B has been assessed using surrogate markers.
- An evaluation of the effect on hepatocellular carcinoma and mortality is missing.

Key messages

- Research design plays an essential role on the hepatocellular carcinoma incidence estimates. As prospective cohorts and case–control series show opposing results, the reports from such trials should be interpreted with caution.
- Sensitivity analyses show a positive effect of treatment on mortality.

Strengths and limitations of this study

- A large number of observational studies were included that allowed for detailed sensitivity analyses with tests for subgroup differences.
- Only eight randomised controlled trials were included.
- The effect of modern nucleos(t)ides could not be assessed as newer trials do not include placebo-treated or untreated patients in the control groups.

INTRODUCTION

Worldwide, two billion people have been infected with hepatitis B virus (HBV). Chronic HBV may lead to hepatocellular carcinoma (HCC), cirrhosis and liver failure, and each year about 600 000 people die due to hepatitis.[1–3] Globally, HCC is the fifth most common cause of cancer deaths in men, and the sixth in women.[4–6] Vaccine programmes have decreased the incidence of HBV,[7 8] but mortality from HBV-related HCC and cirrhosis is increasing due to the high prevalence of chronically infected patients.[9 10] The aim of antiviral treatment is to prevent progression to these clinical outcome measures.[11–13] Recommended treatments include interferon and nucleos(t)ide analogues (NA).[14 15] A viral response may reduce the risk of HCC,[12] but the results of clinical studies and meta-analyses on antiviral

therapy are not consistent.[16–24] One meta-analysis[25] found that antiviral therapy decreased liver-related mortality, whereas a cohort series found decreased overall mortality in patients with a viral response to interferon.[26] On the other hand, randomised controlled trials (RCTs) have failed to show an effect on HCC or mortality.[27 28] We therefore conducted a systematic review of the evidence on antiviral treatment for prevention of HCC and mortality in patients with HBV.

METHODS

Scope

This systematic review evaluates the effects of antiviral therapy versus placebo or no intervention on prevention of HCC and mortality in patients with HBV. The review is based on a registered written protocol (Prospero number CRD42013003881) according to the methods specified in the Cochrane Handbook for Reviews on Interventions[29] and the MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies.[30] For a more detailed description of the methods, please see the MOOSE checklist.

Data sources

Eligible trials were identified through electronic and manual searches. Electronic searches were performed in MEDLINE (1966–2012), EMBASE (1928–2012) and Web of Science (1900–2012). Literature searches included keywords for HCC, chronic HBV and antiviral treatment. Manual searches included scanning of reference lists in relevant papers and conference proceedings and the International Clinical Trials Registry Platform.

Study selection

Our primary analyses included RCTs (primary analyses) on antiviral interventions (interferon and/or NA) versus placebo or no intervention for patients with HBV who had not previously received antiviral therapy (treatment naïve). Owing to the expected prognosis and the duration of follow-up necessary to evaluate intervention effects on clinical outcome measures in HBV, observational studies were included in sensitivity analyses. The primary outcome measures were HCC diagnosed using recommended criteria[31 32] and all-cause mortality. To avoid prevalent cases of HCC, the outcomes were assessed after at least 12 months of follow-up. Some studies did not perform screening ultrasonography and would therefore not detect small HCC present at inclusion. Hence, 12 months was chosen as a limit. The secondary outcome measure was HCC-related mortality.

Data extraction and quality assessment

Two authors extracted data independently. When data were not available in the published reports, additional information was retrieved through correspondence with the primary investigators.

The Cochrane Collaboration's Tool for Assessing Risk of Bias was used to evaluate bias control in RCTs. The assessment included the randomisation methods (allocation sequence generation and allocation concealment), blinding (of participants, personnel and investigators), completeness of outcome data, reporting of data and other biases.[33] All observational studies were classed as having a high risk of bias. Based on the MOOSE guidelines, the assessment of potential sources of bias within observational studies included documentation of how data were classified and coded (multiple raters, blinding and inter-rater reliability), assessment of confounding (comparability of cases and controls in studies where appropriate) and blinding of quality assessors, stratification or regression on possible predictors of study results.

Data synthesis and analysis

Statistics were performed using Stata V.12 (Statacorp, College Station, Texas, USA) and Trial Sequential Analysis (CTU, Copenhagen, Denmark). Meta-analyses were performed with results expressed as risk ratios, 95% CI and I^2 as a marker of heterogeneity. For meta-analyses showing a statistically significant effect, the number needed to treat was calculated based on the risk difference. Initial sensitivity analyses included repeating all meta-analyses using both random and fixed effect models. The results of these analyses were only reported if the conclusions differed. Regression analyses were performed to assess for publication bias and other small-study effects (Egger's test). Sequential analyses were performed for meta-analyses showing an intervention effect after adjusting for the risk of bias associated with cumulative testing.[34] The sequential analysis was performed using a random effects model, α (5%), power (80%) and the incidence rates and the intervention effects identified in the meta-analyses. Preplanned sensitivity analyses were performed with the inclusion of observational studies. These analyses were performed stratified by study design (RCT, prospective cohort or case–control study) and with fixed-effect inverse variance models that compared the results of subgroups. The result of the subgroup comparisons was expressed as p values (test for subgroup differences). Additional sensitivity analyses were performed to evaluate the influence of bias control (limiting the analysis to trials with adequate randomisation), the type of antiviral therapy (comparing interferon, NA or both) and the effect of HCC screening (comparing the results of trials with or without screening). Finally, subgroup analyses including only patients with cirrhosis were performed.

RESULTS

Literature searches and study inclusion

The electronic and manual searches identified 27 474 potentially relevant records (figure 1). After excluding duplicates and studies that did not fulfil our inclusion

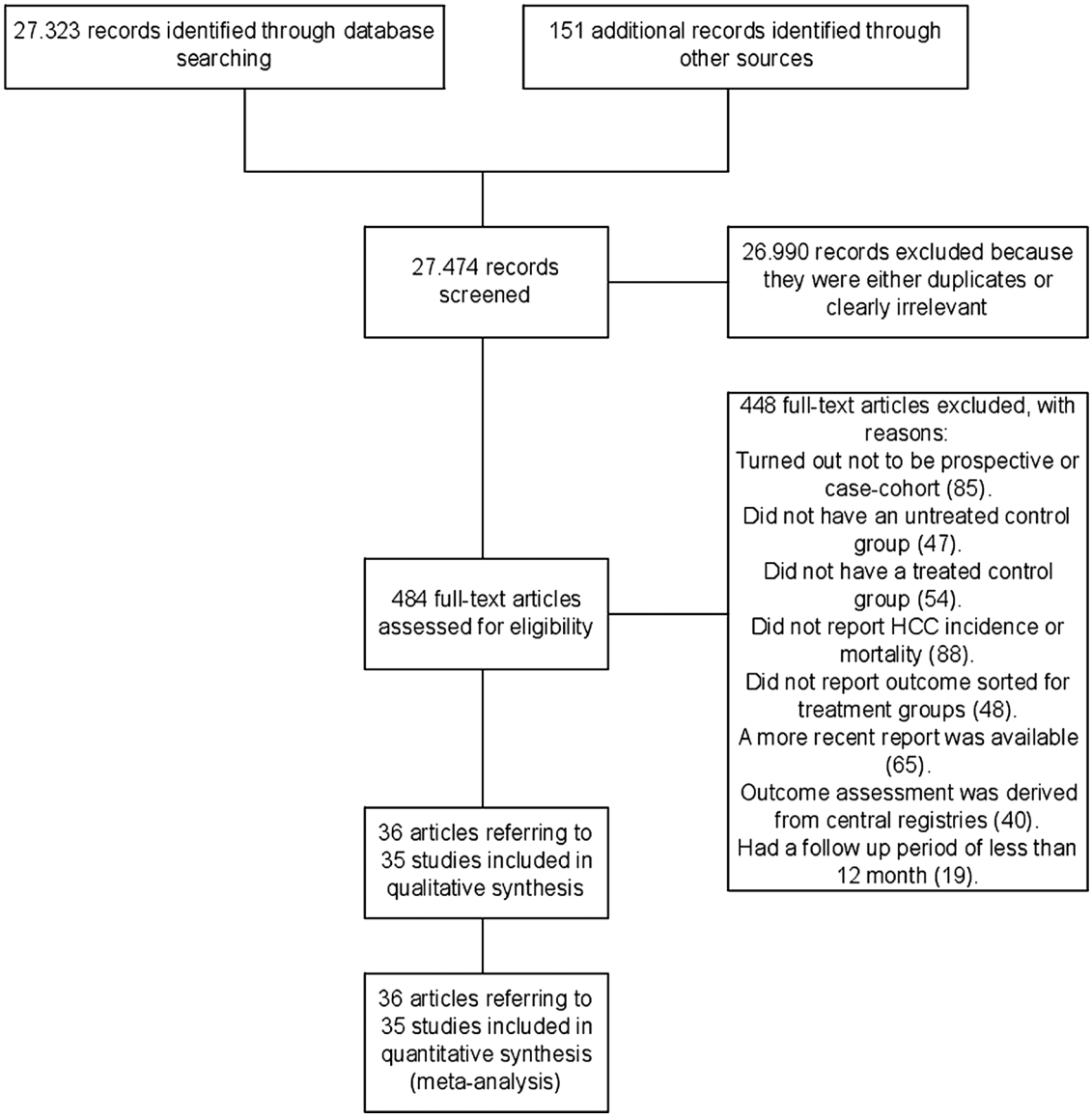

Figure 1 Flow diagram of the study.

criteria, 36 references referring to 8 RCTs, 8 prospective cohort studies and 19 case–control studies were included.[26–28 35–67]

Characteristics of the included RCTs and observational studies

The RCTs were conducted in Europe (n=4), Asia (n=2) and Africa (n=2). The duration of follow-up ranged from 1 to 11 years. One trial performed HCC screening. Six trials assessed interferon and two trials focused on NA (table 1). A total of 840 patients received antiviral therapy and 447 patients received placebo or no intervention. The proportion of men ranged from 70% to 100% and the mean age ranged from 33 to 44 years. The proportion of patients with cirrhosis at inclusion ranged from 0% to 66% (table 2). The proportion of patients with a virological response ranged from 7% to 58% in the treatment group and from 1% to 22% in controls. A biochemical response was achieved in 14–66% of patients in the treatment group and in 1–20% of controls. The randomisation methods were described as adequate in three trials (table 3).

The prospective cohorts and case–control studies were conducted in Europe (n=12), Asia (n=13), North America (n=1) and South America (n=1). The duration of follow-up ranged from 2 to 23 years. HCC screening was performed in all prospective cohort studies and in 13 of the case–control studies. In total, 18 studies assessed interferon, 7 assessed NA and 2 combined therapy with interferon and NA (table 1). A total of 2593 patients received antiviral therapy and 4178 patients received no intervention. The proportion of men ranged from 53% to 95% and the mean age ranged from 27 to 65 years. The proportion of patients with cirrhosis ranged from 0% to 100% (table 2). In the prospective cohorts, the proportion of patients with a virological response in the treatment and control groups was 23–69% and 0–23%, respectively. A biochemical

Table 1 Characteristics of trials

Study, year (reference)	Country of origin	Intervention (dose)	Number of patients	Follow-up (mean/ median year)	HCC screening (yes/no)	Outcomes reported
Randomised controlled trials						
Anderson *et al*, 1987[35]	England	IFN (2.5–7.5 MU/m^2/d)	I 14 C 16	I 1.0 C 1.0	No	Overall mortality
Chan *et al*, 2007[39]	China	Lamivudine (100 mg/d)	I 89 C 47	I 2.5 C 2.5	No	HCC incidence
Farci *et al*, 2004[43]	Italy	IFN (3–9 MU/×3w)	I 28 C 10	I 10.8 C 10.8	No	Overall mortality
Krogsgaard, 1998[28]	Europe	IFN (1.5–18 MU/×3w)	I 210 C 98	I 1.3 C 1.3	No	HCC incidence and mortality
Liaw *et al*, 2004[27]	Asia	Lamivudine (100 mg/d)	I 436 C 215	I 2.7 C 2.7	Yes	HCC incidence Overall mortality
Mazzella *et al*, 1999[53]	Italy	IFN (648 MU total)	I 33 C 31	I 7.2 C 6.6	No	HCC incidence and mortality
Robson *et al*, 1992[56]	South Africa	IFN (10 MU/×3w)	I 10 C 10	I 1.4 C 1.4	No	Overall and HCC mortality
Waked *et al*, 1990[62]	Egypt	IFN (5 MU/m^2/×3w–5 MU/m^2/d)	I 20 C 20	I 1.3 C 1.3	No	Overall and HCC mortality
Prospective cohorts						
Benvegnu *et al*, 1998[36]	Italy	IFN (5–10 MU/×3w)	I 13 C 24	I 6.0 C 6.0	Yes	HCC incidence Overall mortality
Brunetto *et al*, 2002[38]	Italy	IFN (9 MU/×3w)	I 103 C 61	I 6.0 C 6.0	Yes	Overall mortality
Chan *et al*, 2012[40] Wong *et al*, 2010[63]	China	Nucleos(t)ides IFN (NS)	I 158 C 1271	I 10.1 C 10.1	Yes	HCC incidence, overall and HCC mortality
Di Marco *et al*, 1999[42]	Italy	IFN (NS)	I 109 C 193	I 7.8 C 7.8	Yes	Overall mortality
Ma *et al*, 2008[49]	China	Nucleos(t)ides (NS)	I 41 C 176	I 2.9 C 2.9	Yes	Overall mortality
Mazzella *et al*, 1996[52]	Italy	IFN (10 MU/×3w)	I 34 C 28	I 4.1 C 4.0	Yes	HCC incidence
Papatheodoridis *et al*, 2001[55]	Greece	IFN (3 MU/×3w)	I 209 C 152	I 6.0 C 6.1	Yes	HCC incidence, overall and HCC mortality
Tong *et al*, 2006[59]	USA	IFN (NS)	I 22 C 378	I 7.0 C 7.0	Yes	HCC incidence, overall and HCC mortality
Case–control series						
Bolukbas *et al*, 2006[37]	Turkey	Lamivudine (100 mg/d)	I 23 C 15	I 1.5 C 2.0	Yes	Overall and HCC mortality
Das *et al*, 2010[41]	India	Lamivudine Adefovir (NS)	I 151 C 102	I 4.0 C 3.8	Yes	HCC incidence, overall and HCC mortality
Fattovich *et al*, 1997[44]	Europe	IFN (36 MU to >300 MU total)	I 40 C 50	I 6.2 C 6.2	No	HCC incidence, overall and HCC mortality

Continued

Table 1 Continued

Study, year (reference)	Country of origin	Intervention (dose)	Number of patients	Follow-up (mean/ median year)	HCC screening (yes/no)	Outcomes reported
IIHCSG, 1998[45]	Italy and Argentina	IFN (9 MU/w)	I 49 C 97	I 5.8 C 6.9	Yes	HCC incidence
Ikeda *et al*, 1998[46]	Japan	IFN (6 MU/×2w)	I 94 C 219	I 6.8 C 7.0	Yes	HCC incidence
Lin *et al*, 2001[47]	China	IFN (5 MU/×3w)	I 30 C 28	I 2.7 C 2.6	No	HCC incidence, overall and HCC mortality
Lin *et al*, 2007[48]	China	IFN (6–9 MU/m^2/×3w)	I 233 C 233	I 6.8 C 6.1	Yes	HCC incidence and mortality
Mahmood *et al*, 2005[50]	Japan	IFN (6 MU/d)	I 23 C 68	I 7.0 C 7.0	Yes	HCC incidence
Manolakopoulos *et al*, 2004[26]	Greece	Lamivudine (100 mg/d)	I 30 C 30	I 1.5 C 1.8	Yes	HCC incidence, overall and HCC mortality
Matsumoto *et al*, 2005[51]	Japan	Lamivudine (100 mg/d)	I 508 C 231	I 2.7 C 5.3	No	HCC incidence
Niederau *et al*, 1996[54]	Germany	IFN (2–5 MU/×3w)	I 103 C 53	I 4.2 C 3.2	No	Overall mortality
Romeo *et al*, 2009[57]	Italy	Lamivudine (NS) IFN (6–9 MU)	I 102 C 135	I 22.4 C 16.5	Yes	HCC incidence, overall and HCC mortality
Tangkijvanich *et al*, 2001[58]	Thailand	IFN (3–6 MU/×3w)	I 67 C 72	I 4.9 C 4.9	Yes	HCC incidence
Tong *et al*, 2009[60]	USA	Lamivudine (NS)	I 27 C 101	I 5.3 C 5.3	Yes	HCC incidence and mortality
Truong *et al*, 2005[61]	Japan	IFN (174–687 MU total)	I 27 C 35	I 7.0 C 6.2	Yes	HCC incidence and mortality
Yuen *et al*, 2001[64]	China	IFN (2.5–10 MU/m^2/ ×3w)	I 208 C 203	I 8.9 C 9.0	Yes	HCC incidence and mortality
Yuen *et al*, 2004[65]	China	IFN (NS)	I 6 C 86	I 10.5 C 10.5	No	HCC incidence
Yuen *et al*, 2007[66]	China	Lamivudine (100 mg/d)	I 142 C 124	I 7.5 C 9.0	Yes	HCC incidence
Zampino *et al*, 2009[67]	Italy	IFN (5 MU/m^2/×3w)	I 41 C 13	I 23 C 23	No	HCC incidence

/d, Daily; /×3w, thrice weekly; C, control; HCC, hepatocellular carcinoma; I, intervention; IFN, interferon; MU, million units; NS, not stated.

Table 2 Patient characteristics in included trials

Study, year (reference)	Median/mean age (years)	Proportion of men (%)	Proportion with cirrhosis (%)	Proportion with elevated ALT (%)	Proportion positive for HBeAg (%)	HBeAg seroconverters (n, %)
Randomised controlled trials						
Anderson *et al*, 1987[35]	I 36 C 35	100	20	77	100	I 2, 14 C 0, 0
Chan *et al*, 2007[39]	I 39 C 39	84	16	77	5	NS
Farci *et al*, 2004[43]	I 35 C 38	83	66	100	2	I NA C 1, 100
Krogsgaard, 1998[28]	I 36 C 36	81	19	100	100	NS
Liaw *et al*, 2004[27]	I 43 C 44	85	33	78	58	NS
Mazzella *et al*, 1999[53]	I 36 C 41	78	0	100	100	I 30, 91 C 19, 61
Robson *et al*, 1992[56]	I 33 C 31	70	NS	100	100	I 5, 50 C 1, 10
Waked *et al*, 1990[62]	I 35 C 35	78	40	100	100	I 13, 81 C 5, 33
Prospective cohorts						
Benvegnu *et al*, 1998[36]	I 57 C 60	65	100	NS	NS	NS
Brunetto *et al*, 2002[38]	I 40 C 40	80	38	NS	0	NA
Chan *et al*, 2012[40] Wong *et al*, 2010[63]	NS	67	32	87	NS	NS
Di Marco *et al*, 1999[42]	I 33 C 35	71	29	100	29	I 35, 32 C 29, 15
Ma *et al*, 2008[49]	I 54 C 54	72	100	NS	24	NS
Mazzella *et al*, 1996[52]	I 48 C 49	73	100	NS	NS	NS
Papatheodoridis *et al*, 2001[55]	I 47 C 49	83	31	100	0	NA
Tong *et al*, 2006[59]	I 48 C 48	71	35	NS	49	NS
Case–control series						
Bolukbas *et al*, 2006[37]	I 45 C 46	82	100	NS	0	NA
Das *et al*, 2010[41]	I 42 C 46	91	100	NS	45	I 12, 13 C 3, 10
Fattovich *et al*, 1997[44]	I 47 C 45	87	100	100	100	I 27, 68 C 30, 60

Continued

Table 2 Continued

Study, year (reference)	Median/mean age (years)	Proportion of men (%)	Proportion with cirrhosis (%)	Proportion with elevated ALT (%)	Proportion positive for HBeAg (%)	HBeAg seroconverters (n, %)
IIHCSG, 1998[45]	I 54 C 54	64	100	NS	NS	NS
Ikeda *et al*, 1998[46]	I 41 C 44	79	100	NS	52	NS
Lin *et al*, 2001[47]	I 39 C 41	95	10	100	0	NA
Lin *et al*, 2007[48]	I 32 C 31	94	9	NS	100	I 115, 49 C 86, 37
Mahmood *et al*, 2005[50]	I 49 C 49	69	100	NS	36	NS
Manolakopoulos *et al*, 2004[26]	I 65 C 63	80	100	100	0	NA
Matsumoto *et al*, 2005[51]	I 42 C 41	73	18	NS	55	NS
Niederau *et al*, 1996[54]	I 40 C 41	78	28	100	100	I 53, 51 C 7, 13
Romeo *et al*, 2009[57]	NS	77	35	NS	27	NS
Tangkijvanich *et al*, 2001[58]	I 37 C 40	72	20	NS	100	I 24, 36 C 7, 10
Tong *et al*, 2009[60]	I 46 C 46	86	100	14	53	NS
Truong *et al*, 2005[61]	I 33 C 37	53	2	100	60	I 9, 53 C 11, 55
Yuen *et al*, 2001[64]	I 27 C 28	64	NS	32	100	I 96, 46 C 93, 46
Yuen *et al*, 2004[65]	I 43 C 43	71	NS	NS	23	NS
Yuen *et al*, 2007[66]	I 34 C 33	74	0	48	100	NS
Zampino *et al*, 2009[67]	NS	67	0	NS	54	I 16, 62 C NS

ALT, alanine aminotransferase; C, Control; HBeAg, hepatitis B e antigen I, Intervention; NA, not applicable; NS, not stated;.

Table 3 Risk of bias summary

Study, year (reference)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Anderson *et al*, 1987[35]	?	?	+	+	?	?
Chan *et al*, 2007[39]	+	+	+	+	?	?
Farci *et al*, 2004[43]	+	+	+	+	?	?
Krogsgaard, 1998[28]	?	?	+	+	–	?
Liaw *et al*, 2004[27]	+	+	+	+	+	+
Mazzella *et al*, 1999[53]	?	?	+	+	+	?
Robson *et al*, 1992[56]	?	?	+	+	?	?
Waked *et al*, 1990[62]	?	?	+	+	?	?

+, Low risk of bias; –high risk of bias; ?, unknown risk of bias.

response was achieved for 23–69% of patients in the treatment groups and 31% in the control group (only reported in 1 study). In the case–control series, the proportion of patients with a virological response in the treatment and control groups ranged from 7% to 78% and 2% to 100%, respectively. A biochemical response in the two groups was 27–68% and 4–51%, respectively.

Prevention of HCC

HCC was diagnosed in 22 of 768 patients in the treatment group versus 19 of 391 controls (relative risk 0.58, 95% CI 0.32 to 1.07; I^2=0%). There was no evidence of small-study effects (Egger's test, p=0.269) and no difference between subgroups of trials assessing interferon or NA (test for subgroup differences, p=0.854). The overall result was confirmed in sensitivity analyses including RCTs with a low risk of bias and trials with HCC screening.

Sensitivity analyses including prospective cohort studies and case–control studies were performed. In the cohort studies, HCC was diagnosed in 51 of 436 patients in the treatment group and 174 of 1853 patients in the control group. In the case–control studies, the numbers were 99 of 1778 and 201 of 1827 patients, respectively. A meta-analysis that combined RCTs and observational studies found no effect of antiviral therapy on HCC (relative risk 0.88, 95% CI 0.73 to 1.05; I^2=63%). There was no evidence of small-study effects (Egger's test, p=0.730). Subgroup analyses showed a clear difference between the RCTs, prospective cohorts and case–control studies (test for subgroup differences, p<0.001; figure 2). The prospective cohort studies found that antiviral therapy increased the risk of HCC (relative risk 1.44, 95% CI 1.06 to 1.95), whereas the case–control studies found that antiviral therapy reduced the risk of HCC (relative risk 0.69, 95% CI 0.54 to 0.88). Owing to the high heterogeneity, a post hoc meta-regression analysis was performed. We evaluated the study and patient characteristics not accounted for in the sensitivity analyses, which may have influenced the result. No modifiers were found when adjusting for the following variables: proportion of men (coefficient, −0.074; p=0.08), mean age of treated patients at inclusion (coefficient, 0.020; p=0.94), mean age of untreated patients at inclusion (coefficient, 0.121; p=0.65), proportion with cirrhosis at inclusion (coefficient, −0.001; p=0.76) and region of trial (coefficient −0.394; p=0.55).

To further evaluate the influence of bias on the overall results, we performed additional subgroup analysis in which trials were stratified for HCC screening. The analysis found 8 trials that did not perform HCC screening (relative risk 0.40, 95% CI 0.26 to 0.63) and 18 trials that did perform HCC screening (relative risk 1.03, 95% CI 0.84 to 1.25). The results of subgroups were clearly different (test for subgroup differences, p<0.001).

Sensitivity analyses were performed to evaluate the risk of HCC among patients with cirrhosis. In the RCTs, 1 of 20 patients in the treatment group and 2 of 12 controls developed HCC (relative risk 0.75, 95% CI 0.10 to 5.77). In the prospective cohort studies, 32 of 184 vs 142 of 482 patients developed HCC, whereas the numbers were 63 of 680 vs 161 of 955, respectively, for case–control studies. Overall, antiviral therapy reduced the risk of HCC when including data from RCTs and observational studies (relative risk 0.74, 95% CI 0.57 to 0.96, I^2=0%, number needed to treat 28 patients; figure 3). The results of RCTs and observational studies were similar (test for subgroup differences, p=0.159). There was no evidence of small-study effects (Egger's test, p=0.890). In the trial sequential analysis, the monitoring and α-spending boundaries did not cross, suggesting that the result was not robust to adjustment for multiple testing.

Mortality

In the RCTs, there was no difference in mortality between the treatment and control groups (21 of 508 vs 9 of 271 patients, relative risk 1.24, 95% CI 0.58 to 2.66; I^2=0%). There was no evidence of small-study effects (Egger's test, p=0.783) and no difference between trials stratified by treatment (test for subgroup differences, p=0.668) and HCC screening (p=0.828). In the observational studies, the number of patients in the treatment and control groups who died was 51 of 655 vs 247 of 2231 for prospective cohort studies and 79 of 506 vs 92

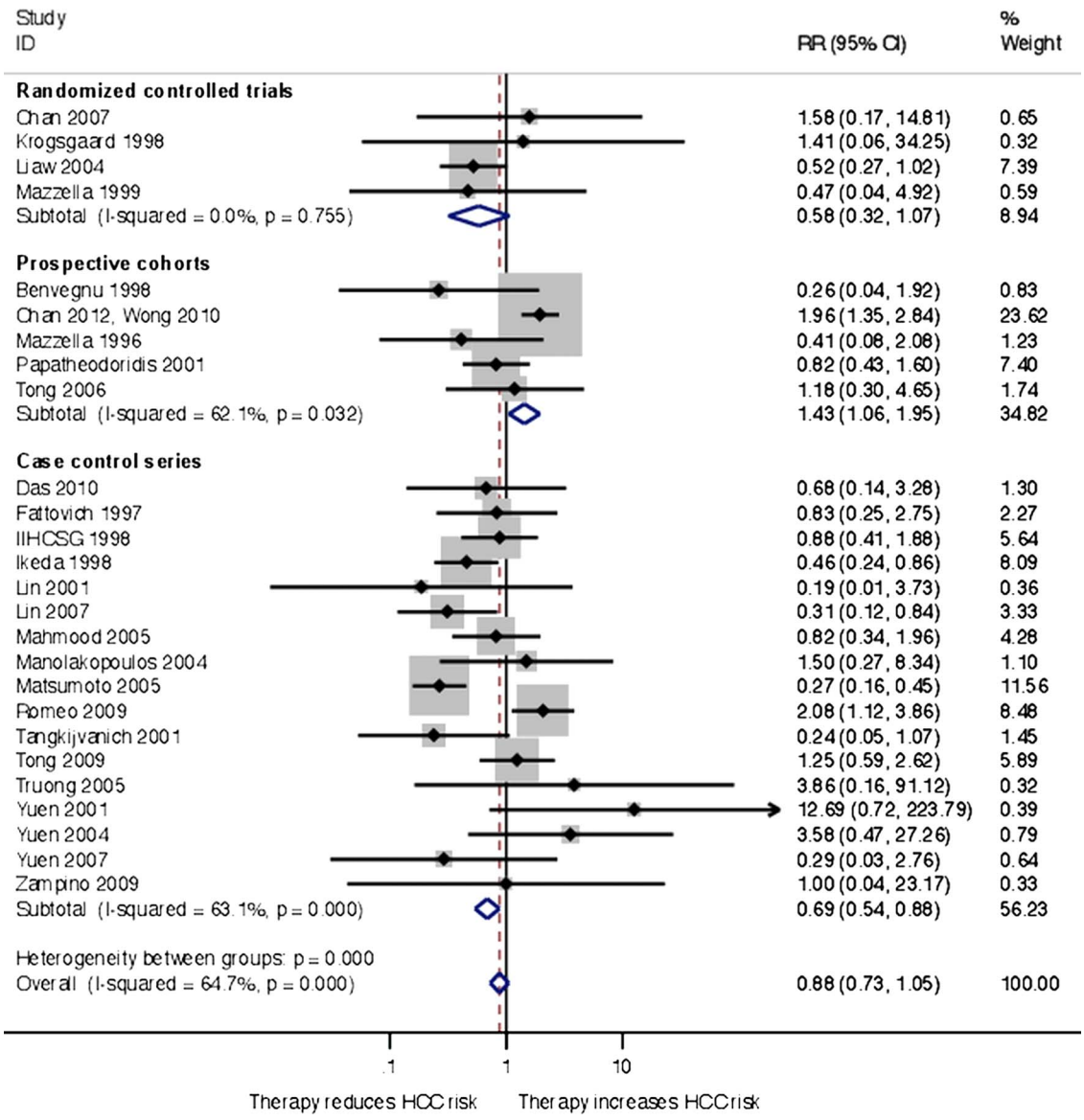

Figure 2 Random-effects inverse variance meta-analysis of antiviral therapy treatment effects on hepatocellular carcinoma in patients with chronic hepatitis B, subgroups according to trial design.

of 413 in the cohort studies. When combining RCTs and observational studies, random-effects meta-analysis showed that antiviral treatment decreased mortality (relative risk 0.76, 95% CI 0.62 to 0.95, I^2=14%, number needed to treat 77; Egger's test, p=0.487; figure 4). There was no difference between RCTs and observational studies (test for subgroup differences, p=0.406). In the trial sequential analysis, the monitoring boundary crossed the α-spending boundary in 2004, suggesting that the meta-analysis was robust to adjustments for multiple testing.

Only observational studies reported mortality in patients with cirrhosis. The number of patients who died in the intervention and control groups was 36 of 298 vs 141 of 499 (relative risk 0.61, 95% CI 0.44 to 0.86, I^2=9%; number needed to treat 16 patients). There were no small-study effects (Egger's test, p=0.533) and no differences between the prospective cohort and case–control studies (test for subgroup differences, p=0.292).

HCC-related mortality

Antiviral therapy had no effect on HCC-related mortality (3 of 282 vs 2 of 154, relative risk 0.50, 95% CI 0.10 to 2.44, I^2=0%; n=2 RCT). Including data from observational studies had little influence on the overall result (38 of 1233 vs 144 of 2632, relative risk 0.83, 95% CI 0.5 to 1.20, I^2=0%; Egger's test, p=0.248). There was no difference between subgroups of trials stratified by design (test for subgroup differences, p=0.481).

DISCUSSION

This systematic review found that the evidence of the effect of antiviral therapy on clinical outcomes in HBV is

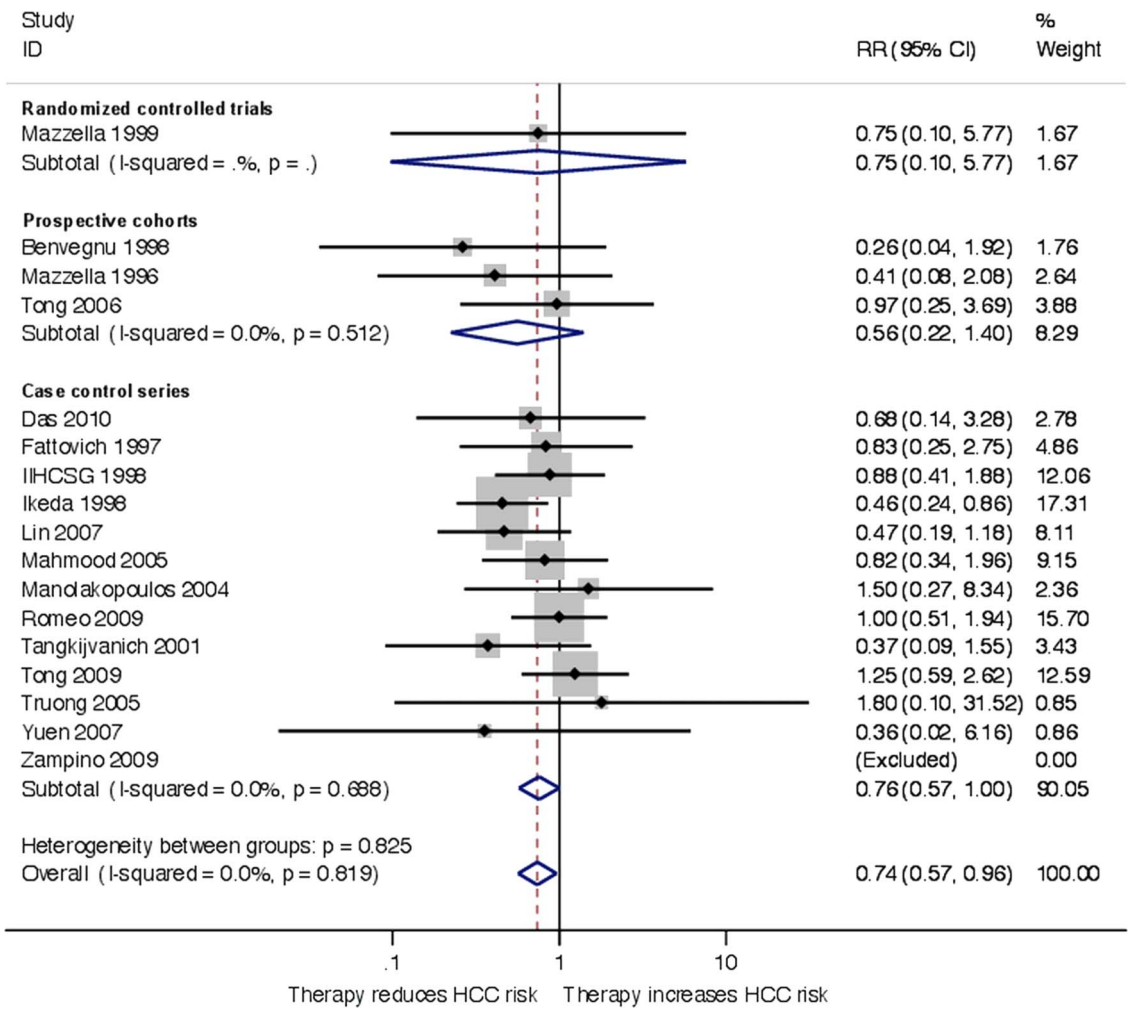

Figure 3 Random-effects inverse variance meta-analysis of antiviral therapy treatment effects on hepatocellular carcinoma in patients with chronic hepatitis B and cirrhosis, subgroups according to trial design.

weak. RCTs found no benefit of treatment on HCC, mortality or HCC-related mortality in HBV. The total number of patients and duration of follow-up may be too small to determine the clinical effects. The inclusion of observational studies did not strengthen the overall findings because there was clear evidence of bias suggesting that the study design was closely related to the estimated treatment effects. The prospective cohort studies found that antiviral therapy increased the risk of HCC and had no effect on mortality. Case–control studies found that antiviral therapy reduced HCC and mortality. These findings suggest that detection and ascertainment bias as well as confounding by indication had a considerable influence on the overall result, which may explain why previous meta-analyses have disagreed in their assessment of the benefit of antiviral therapy.[16–18 20 21 23 24] The importance of detection bias was underlined in the subgroup analysis of HCC screening. No intervention effect was found in trials that performed systematic HCC screening.

The main limitation of our review is the limited number of RCTs. Only one of the included trials had prevention of HCC as a primary outcome measure[27] and none were designed to evaluate the effect on mortality or HCC-related mortality. Tests to evaluate the robustness of the results (including Egger's test) were difficult to interpret.

The current recommendation to treat patients with HBV is primarily based on surrogate outcomes. At present, the evidence supporting the use of virological markers as surrogate outcomes is weak. The fact that some studies have found a correlation between a virological response and improved liver histology does not necessarily validate their use as surrogate outcomes. Previous evidence has shown that interventions supported by surrogate markers may in fact have no benefit or even harmful effects on clinical outcome measures.[68] Still, our findings are not sufficiently convincing and do not allow for changes in clinical practice.

Another limitation of the current review is our failure to extract data for analyses of treatment responders versus non-responders. However, only six cases of HCC were reportedly diagnosed in patients with biochemical or viral treatment response. This suggests that treatment response does not lead to elimination of the HCC risk,

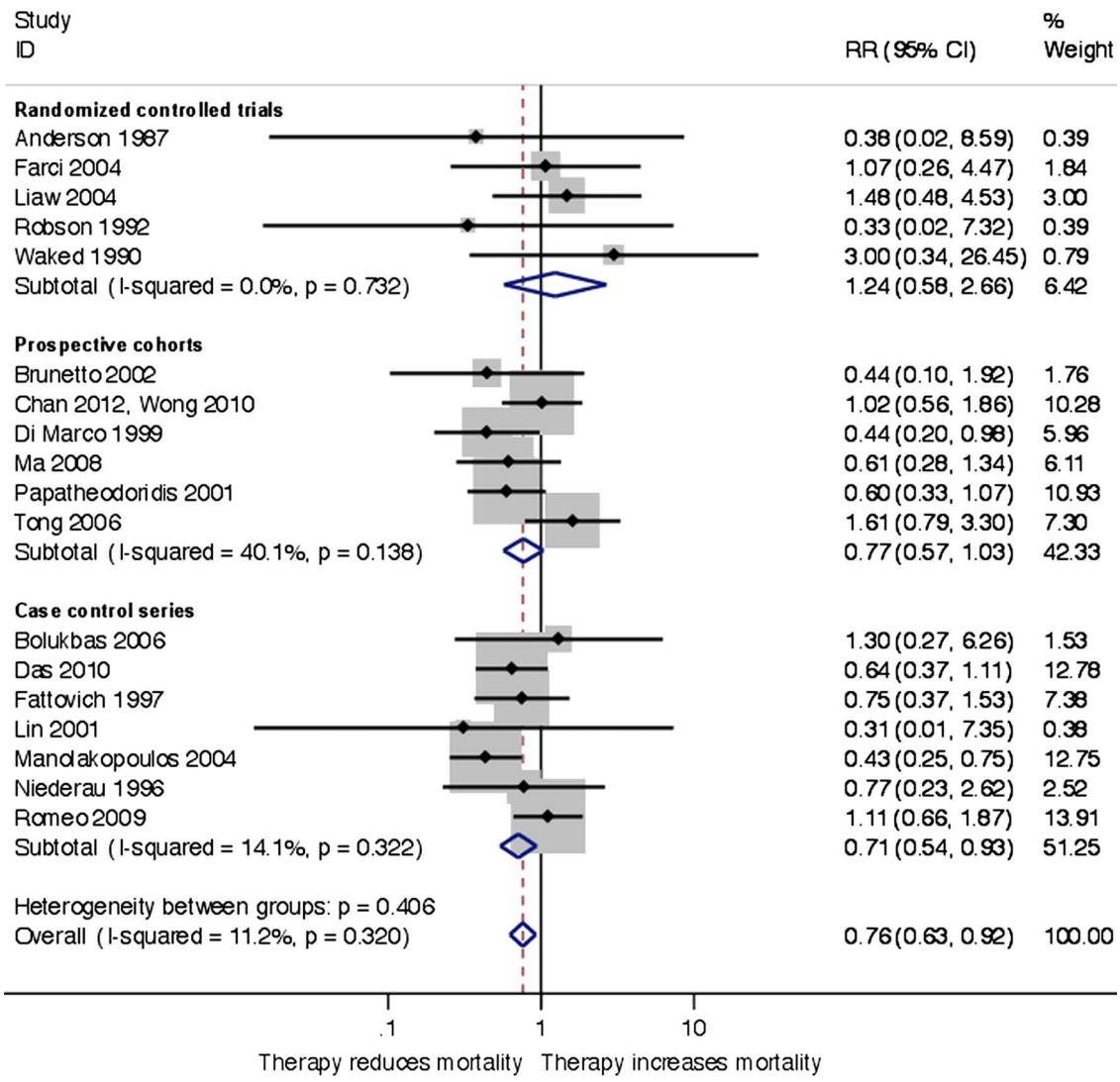

Figure 4 Random-effects inverse variance meta-analysis of antiviral therapy treatment effects on mortality in patients with chronic hepatitis B, subgroups according to trial design.

but probably decreases HCC incidence compared to non-responders or partial responders. This would be in line with previous findings.[19 25] The majority of included trials in the current review assessed first-generation NA and interferon, as reflected by the low response rates. It was, however, not within the scope of the review to investigate modern antiviral treatments, as we included untreated control groups. Newer treatments will most likely result in more patients achieving sustained suppression of HBV–DNA. It is therefore possible that the current review underestimates a potential treatment effect. It would also have been of interest had we been able to adjust for other common risk factors for HCC, such as non-alcoholic steatohepatitis, alcoholic liver disease and coinfection with hepatitis C virus (HCV), hepatitis D and HIV. Although data on these risk factors were extracted, there was not enough data to allow for statistical analyses.

There are several potential explanations for the discrepancies between RCTs and observational studies.[69] The fact that only prospective cohort studies found an increased risk of HCC among patients receiving antiviral therapy is in opposition to speculations that the treatment affected HCC development. The findings are more likely to reflect baseline differences in the viral load, genotype and degree of liver disease. The degree of monitoring in the treatment and control groups is also likely to differ and may lead to detection bias. The importance of detection bias is further supported by the subgroup differences observed according to HCC screening. The case–control studies are likely to have an even higher risk of bias, as confounding by indication and ascertainment bias is likely to exist in retrospective studies. Reporting bias should also be considered.[33]

The subgroup differences with regard to the type of intervention suggest a possible anticarcinogenic effect of interferon, as seen in HCV.[70] We also found a decrease in HCC incidence and overall mortality in sensitivity analyses of patients with cirrhosis. This could support the case for continued treatment of patients with cirrhosis.

We found a beneficial effect of interferon and/or NA on mortality in HBV when including RCTs and observational studies. The assessment of mortality is robust to bias.[71] Accordingly, our subgroup analysis showed no clear relation between the results and the study design. HCC mortality is more prone to bias. Whether antiviral treatment for HBV decreases mortality except from HCC is unknown.

In conclusion, antiviral treatment for HBV has no proven effect on the clinical outcomes, HCC and mortality. Bias has a paramount impact on the treatment effect estimates in observational studies and we recommend a critical approach to the conclusions drawn in such studies. Future trials on antiviral treatment for HBV should be designed to show an effect on clinical endpoints rather than surrogate markers.

Author affiliations
[1]Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark
[2]Department of Medicine, Copenhagen University Hospital of Gentofte, Hellerup, Denmark
[3]Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

Contributors MT, LLG and AK conceived the idea and design, and analysed and interpreted the data. MT and EKD collected and assembled the data. MT and LLG drafted the manuscript. LLG, EKD and AK revised the manuscript for important intellectual content. All authors discussed and approved the final version of the manuscript. MT is the guarantor.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The dataset is available from the corresponding author.

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