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REVIEW

Antiviral therapy in hepatitis B virus-infected with immune-tolerant: A meta-analysis

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Abstract To access the efficacy of antiviral therapy in patients of HBV-infected with immune-tolerant. We conducted a meta-analysis search of the Cochrane Library, PubMed, ClinicalTrials.gov, Web of science, and EMBASE on through August 2021. We combined the data by means of a random-effect DrSimonian-Laird model and calculated risk ratios (RRs) for the outcomes of hepatitis B surface antigen (HBsAg) loss, hepatitis B e antigen (HBeAg) seroconversion, HBV deoxyribonucleic acid (DNA) negative conversion rate, and the risk for hepatocellular carcinoma (HCC) and cirrhosis. An extensive literature search identified 328 relevant publications, and five were included in the study. Antiviral therapy was in favor of HBsAg loss (RR = 2.34, 95%CI 0.68–4.00, $p = 0.91$, $I^2 = 0.00\%$), HBV DNA negative conversion (RR = 2.08, 95%CI 0.10–4.05, $p = 0.07$, $I^2 = 58.24\%$) and reduce the risk for HCC (HR = 0.189, 95%CI 0.052–0.692, $p = 0.004$) and cirrhosis (HR = 0.347, 95%CI 0.095–1.270, $p = 0.036$), but not beneficial to HBeAg seroconversion (RR = 0.83, 95%CI −0.03 to 1.70, $p = 0.11$, $I^2 = 46.99\%$). Subgroup-analyzed by the research type was similar results of HBsAg loss, HBV DNA negative conversion, and HBeAg seroconversion.Patients in HBV-infected with immune-tolerant responded well to antiviral therapy. The evidence from this meta-analysis supports antiviral therapy for patients with HBV in the immune tolerance stage. Well-designed, multi-center, larger sample sizes, and excellent quality prospective studies are needed to confirm our conclusion.

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PALABRAS CLAVE
Infectados por el virus de la hepatitis B;
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Terapia antiviral

Terapia antiviral en infectados por el virus de la hepatitis B con inmunotolerantes: un metaanálisis

Resumen Para conocer la eficacia de la terapia antiviral en pacientes infectados con el virus de la hepatitis B (VHB) inmunotoler ante, se realizó una búsqueda de meta-análisis de la Cochrane Library, PubMed, ClinicalTrials.gov, Web of Science y EMBASE hasta agosto de 2021. Se combinaron los datos mediante un modelo DrSimonian-Laird y se calcularon los coeficientes de riesgo (RR) para los resultados de la pérdida del antígeno de superficie de la hepatitis B (HBsAg), la seroconversión del antígeno de superficie de la hepatitis B (HBeAg), la tasa de conversión negativa del ácido desoxirribonucleico (ADN) del VHB y el riesgo de carcinoma hepatocelular y de cirrosis. Una extensa búsqueda bibliográfica identificó 328 publicaciones relevantes, 5 de las cuales fueron incluidas en el estudio. El tratamiento antiviral favoreció la reducción de HBsAg (RR = 2,34; IC95%: 0,68−4,00; $p = 0,91$; $I^2 = 0,00\%$), la conversión negativa del ADN del VHB (RR = 2,08; IC95%: 0,10−4,05; $p = 0,07$; $I^2 = 58,24\%$) y redujo el riesgo de carcinoma hepatocelular (HR = 0,189, ic95% 0,052 a 0,692, p = 0,004) y de cirrosis (HR = 0,347; IC95%: 0,095−1,270; $p = 0,036$). Sin embargo, no fue beneficioso para la seroconversión a HBeAg (RR = 0,83; IC95%: −0,03−1,70; $p = 0,11$; $I^2 = 46,99\%$). El subgrupo analizado por el tipo de investigación mostró resultados similares de pérdida de HBsAg, conversión negativa del ADN del VHB y seroconversión del HBeAg. Los pacientes infectados con VHB inmunotolerantes respondieron bien a la terapia antiviral. La evidencia de este metaanálisis apoya el tratamiento antiviral para pacientes con VHB en estadio de inmunotolerancia. Se necesitan estudios prospectivos de excelente calidad para confirmar nuestra conclusión.

Background

Chronic hepatitis B (CHB), associating with a high risk of cirrhosis and cancer, is a life-threatening liver disease affecting 257 million people worldwide.[1] The natural history of chronic hepatitis B virus (HBV) infection is traditionally divided into four phases, namely, the immune tolerance phase (chronic HBV carrier status), and immune clearance, according to the patient's immune status and the impact of the interaction between the infected virus and the host on the liver.[2] The majority of chronic HBV infection was the immune tolerant phase. The concept of true immune tolerance has been under challenged.[3] In the 2017 EASL guidelines, HBV infection in the immune tolerance phase was characterized by high-replicative (hepatitis B e antigen (HBeAg) positivity, high HBV deoxyribonucleic acid (DNA) levels (>10^7 IU/mL)), and low-inflammatory (normal alanine aminotransferase (ALT), minimal inflammation detectable on liver biopsy).[2] Existing evidence shows that the lamivudine or interferon-α antiviral treatment of patients with immune tolerance is not effective.[4] However, persistently high HBV DNA levels are a risk factor for hepatocellular carcinoma (HCC) and are highly contagious.[5] Moreover, JY Park. etc. reported that among the 105 CHB patients with high viral load and persistently normal or slightly elevated serum ALT levels for at least 12 months, significant fibrosis (F2−F4 fibrosis) was observed in 63 patients (60.0%) and the actual significant histology was found in 65 patients (61.9%).[6] However, treatment guidelines do not recommend antiviral therapy for immune-tolerant CHB.[2] We conducted a meta-analysis to access the efficacy of antiviral therapy in patients of HBV infected with immune-tolerant.

Methods

This meta-analysis was performed according to the Cochrane Handbook for Systematic Reviews of Interventions and presented based on the Meta-Analysis guidelines.[7]

Data sources and searches

We identified studies that evaluated the efficacy of antiviral therapy in patients of hepatitis B virus-infected with immune-tolerant by searching Cochrane Library, PubMed, ClinicalTrials.gov, Web of science, and EMBASE databases from inception to August 2021, by using the following MeSH terms (''antiviral Agents'', ''interferons'', ''hepatitis B*'')and subject terms (''immune-tolerant*'', ''Tenofovir'', ''Tenofovir alafenamide fumarate tablets'', ''entecavir'', ''telbivudine'', ''Lamivudine'', ''Adefovir dipivoxil'', ''Interferons'', ''Interferon-alpha'', ''interferon-beta'', ''emtricitabine'', ''hepatitis B'', ''serum hepatitis'', ''hippie hepatitis'', ''injection hepatitis'', ''hepatitis type B''). Supplementary table* 1 shows the search strategy details.

Eligibility criteria

Types of studies

Available full-text articles in the English language for randomized controlled trials (RCT) or case-control studies were potentially eligible to be included.

Types of participants
Patients clinically diagnosed with HBV infected with immune-tolerant according to CHB guidelines.

Types of interventions
Studies of interest were patients who received antiviral therapy were compared with placebo or blank control.

Types of outcomes
Studies reporting one or more of the following outcome measures were eligible for inclusion: (1) hepatitis B surface antigen (HBsAg) loss, (2) HBeAg seroconversion, (3) the risk for HCC, (4) the risk for cirrhosis, and (5) HBV DNA negative conversion.

Data extraction

We independently recorded study characteristics as follows: (1) name of the first author, publication year, publication type, and country of origin; (2) study population, patient demographics and clinical characteristics, intervention condition, intervention period, and endpoint. All disagreements or discrepancies of data extraction were resolved by the third investigator (YSL). Where more than one paper for the same original data was found to have been published by the same investigators if possible consulted differences in the studies for researches.

Risk of bias assessment

Publication bias detection was not performed as less than 10 studies were included. The quality of RCT and case-control studies was evaluated using the Cochrane ROB and Newcastle-Ottawa scale, respectively. Review Manager 5.3 (Nordic Cochrane Centre) was used to present the results graphically.[8] This assessment was performed independently by two reviewers and in the event of disagreements regarding the assessment of studies, a third reviewer was consulted.

Data synthesis and analysis

HBsAg loss, HBeAg seroconversion, the risk for HCC, cirrhosis and HBV DNA negative conversion were calculated pooled relative risks (RRs) with 95% confidence intervals (CIs) with the random-effects DrSimonian-Laird model for pooling estimates for each analysis. The significance of the pooled effects was evaluated by a *Z*-test, and a *p* value of less than 0.1 was considered significant. The I^2 statistic was used to examine overall heterogeneity between studies, and values higher than 50% were defined to have high heterogeneity.[8] All statistical analyses were performed using STATA (version 16.0; StataCorp, USA).

Results

Characteristics of the included studies and quality assessment

The process for the selection of eligible studies is shown in Fig. 1. Three hundred twenty-eight records were identified. One hundred twenty-three records were removed duplicates by Endnote X7. After removing one hundred seventy-six records by scanned title and abstract, twenty nine full-text articles were assessed for eligibility. Through screening the abstracts and full-text of these potentially relevant articles, we excluded eight conference summaries and three of which were published in Chinese, thirteen articles lack of blank control group. Finally, five studies were included in this meta-analysis.

Characteristics of these studies are presented in Table 1. Three studies has assessed the quality by two researchers (YSL and JH) independently according to the NOS) of case-control study, another two studies were assessed according to the Cochrane ROB of RCT. Three case-control studies were identified as moderate quality ($5 \leq \text{NOS} \leq 7$). Both two RCT studies were high risk of sequence generation, high risk of allocation concealment, high risk of blinding, low risk of incomplete outcome data, low risk of selective outcome reporting, and low risk of other possible sources of bias. Hepatitis B virus-infected with immune-tolerant was clearly defined in all studies.

Antiviral therapy for HBV DNA negative conversion

There were 4 studies (213 patients) that evaluated the rate HBV DNA negative conversion of antiviral therapy. The aggregated data showed that antiviral therapy was significantly associated with a higher rate of HBV DNA negative conversion (RR = 2.08, 95%CI 0.10–4.05, $p = 0.07$, $I^2 = 58.24\%$) for immune-tolerant CHB. Subgroup-analyzed by research type, antiviral therapy was in favor of HBV DNA negative conversion in case-control studies (RR = 3.16, 95%CI 1.23–5.08, $p = 0.56$, $I^2 = 0.00\%$) rather than in RCT studies (RR = 0.89, 95%CI −3.23 to 5.01, $p = 0.02$, $I^2 = 81.84\%$) (Fig. 2). Sensitivity analysis was also utilized to explore the high heterogeneity. The outcome is presented in the Fig. 3. We seemed to be drawn from the Fig. 3 that study Mieli-Vergani[5] was influenced the summary statistic to the greatest extent. And the outcome had been verified by removing this study, the overall heterogeneity did materially change (RR = 3.00, 95%CI 1.64–4.36, $p = 0.82$, $I^2 = 0.00\%$) (Fig. 4).

Antiviral therapy for HBeAg seroconversion

Five studies (697 patients) reported that antiviral therapy was not beneficial for HBeAg seroconversion (RR = 0.83, 95%CI −0.03 to 1.70, $p = 0.11$, $I^2 = 46.99\%$) in immune-tolerant CHB. The heterogeneity was acceptable ($I^2 = 46.99\%$). Subgroup-analyzed by research type, both case-control studies (RR = 0.82, 95%CI −0.44 to 2.08, $p = 0.08$, $I^2 = 59.80\%$) and RCT studies (RR = 1.01, 95%CI −0.71 to 2.74, $p = 0.16$, $I^2 = 49.32\%$) showed that antiviral

Table 1 Characteristics of all trials included in the present meta-analysis.

Study	Country	Inclusion criteria	Exclusion criteria	Antiviral therapy group				Control group				
				Sample size	Age (year)	Female	ALT (U/L)	Sample size	Age (year)	Female	ALT (U/L)	Research type
R. Artan, 2005	Turkey	Positive for HBsAg and HBeAg, negative for anti-HBs and anti-HBe, HBV DNA >105 copies/mL, and ALT level < 45 U/L	The ''inactive HBsAg carriers'' were diagnosed and excluded with the characteristics below; HBeAg negative, anti-HBe positive, HBsAg positive for at least 6 months duration, serum HBV DNA <105 copy/mL (or <12 pg/mL), ALT maintained at normal levels. Immunodeficiency, cirrhosis, genetic liver diseases, metabolic diseases	17	10.6 ± 4.1	4	37.3 ± 6.36	6	9 ± 4	3	30.67 ± 7.78	Case–control study
U. Poddar, 2013	India	HBsAg positivity for 6 months or more, HBeAg positive, high viral load (HBV DNA >107 copies/mL), normal or near normal alanine amino transferase or ALT (<2 times ULN), and minimal or no histological changes on liver biopsy.	Children with neuropsychiatric illness, autoimmune disease, low platelet counts (<100 000), low total leukocyte count (<3000), age < 24 months, previous history of interferon or antiviral therapy, and co-infection with retrovirus or hepatitis C	28	5.92 ± 3.17	4	46.60 ± 17.79	34	7.82 ± 3.92	7	50.62 ± 17.25	case-control study

Table 1 (*Continued*)

Study	Country	Inclusion criteria	Exclusion criteria	Antiviral therapy group				Control group				
				Sample size	Age (year)	Female	ALT (U/L)	Sample size	Age (year)	Female	ALT (U/L)	Research type
Shishu Zhu, 2018	China	HBsAg positive> = 6 months, HBeAg positive, anti-HBe negative, HBV DNA>107 IU/mL, amino transferase (ALT)<60 U/L (1.5 times upper limit of normal (ULN, 40 U/L)) and no or minimal inflammation in liver histology	Previous antiviral treatment for HBV infection; coinfection with hepatitis A, C, D, E, Epstein–Barr virus, cytomegalovirus or human immunodeficiency virus; coexistence of any other liver diseases such as autoimmune hepatitis, drug-induced liver injury or Wilson's disease; liver transplantation; past or current hepatocellular carcinomas; evidence of thyroid disorders	46	7 ± 8	16	45 ± 10.5	23	8 ± 8	10	48 ± 31	RCT
Young Chang, 2017	Korea	HBeAg-positive CHB who had HBV DNA levels of >20 000 IU/mL and ALT levels of <40 IU/L.	NA	87	43.2 ± 13.0	41	30.6 ± 11.4	397	41.5 ± 12.5	202	26.8 ± 8.0	case-control study
Giorgina Mieli-Vergani, 2021	United Kingdom	HBsAg-positive, HBeAg-positive and had an HBV DNA titer >20000 IU/mL,normal ALT level at screening, and either no or minimal fibrosis on a liver biopsy performed within 2 years prior to baseline and stable normal ALT levels	Co-infected with hepatitis A, C, or D virus, human immunodeficiency virus, or if they had decompensated liver disease	26	11.9 ± 3.2	16	22.23 ± 10.07	33	10.9 ± 3.7	14	25.32 ± 13.11	RCT

RCT: randomized controlled trials; CHB: chronic hepatitis B; HBV: hepatitis B virus; HBeAg: hepatitis B e antigen; ALT: alanine aminotransferase; HBsAg: hepatitis B surface antigen; DNA: deoxyribonucleic acid; ULN: upper limit of normal.

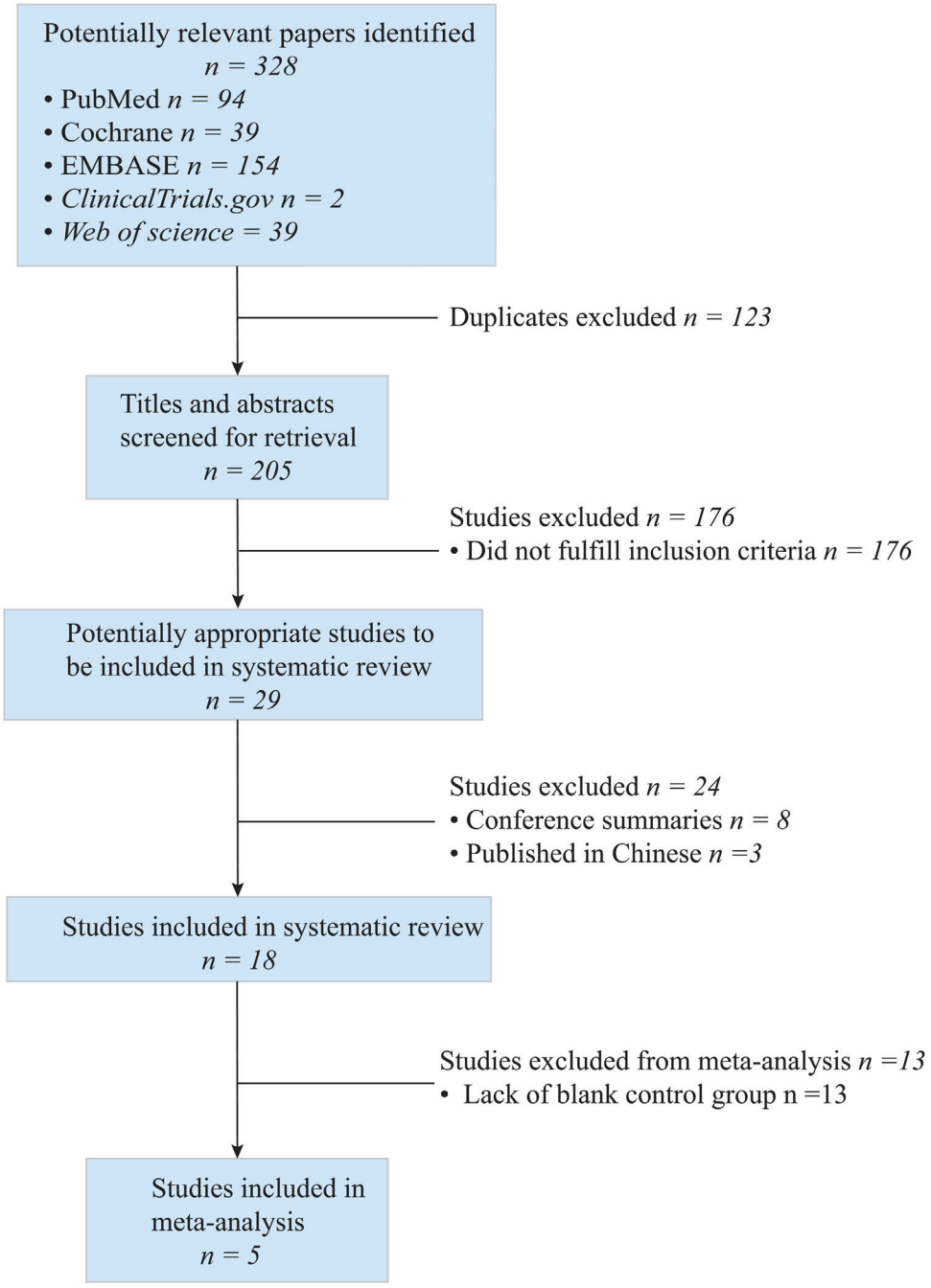

Figure 1 Diagram of the study selection process for the meta-analysis.

therapy has no significant effect on HBeAg seroconversion for immune-tolerant CHB (Fig. 5).

Antiviral therapy for HBsAg loss

Three studies (190 patients) pooled that antiviral therapy could increase the rate of HBsAg loss (RR = 2.34, 95%CI 0.68–4.00, $p = 0.91$, $I^2 = 0.00\%$) for immune-tolerant CHB. There was no evidence of heterogeneity ($I^2 = 0.0\%$). Subgroup-analyzed by research type, antiviral therapy was in favor of HBsAg loss in RCT studies (RR = 2.12, 95%CI 0.08–4.17, $p = 0.80$, $I^2 = 0.00\%$) rather than in case-control study (RR = 2.69, 95%CI −0.08 to 5.59) (Fig. 6).

Antiviral therapy for HCC and cirrhosis

Only one study reported that antiviral therapy reduces the risk of HCC (HR = 0.189, 95%CI 0.052–0.692, $p = 0.004$) and cirrhosis (HR = 0.347, 95%CI 0.095–1.270, $p = 0.036$) when after balancing the baseline characteristics by using inverse probability weighting in immune-tolerant CHB. As there was only one study, forest plot analysis was not performed.

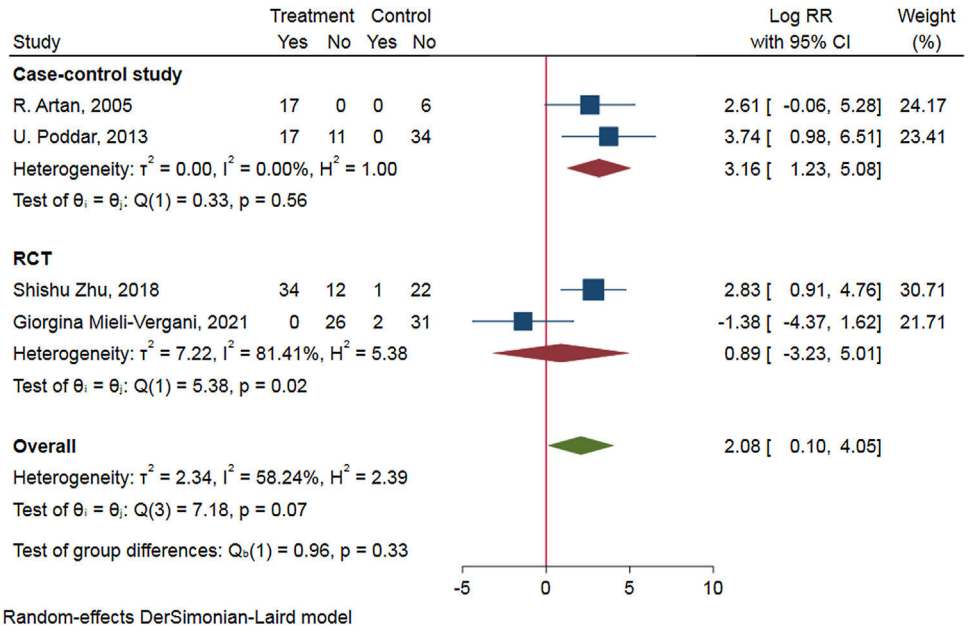

Figure 2 Forest plot of antiviral therapy for HBV DNA negative conversion.

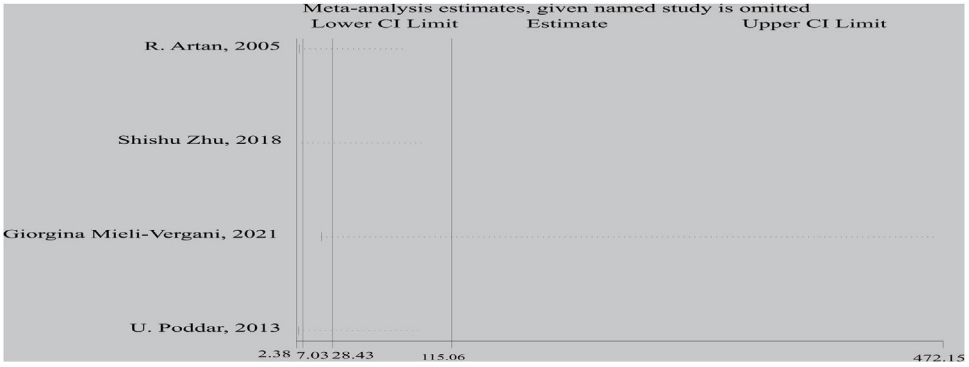

Figure 3 Plot of sensitivity analysis exploring the high heterogeneity.

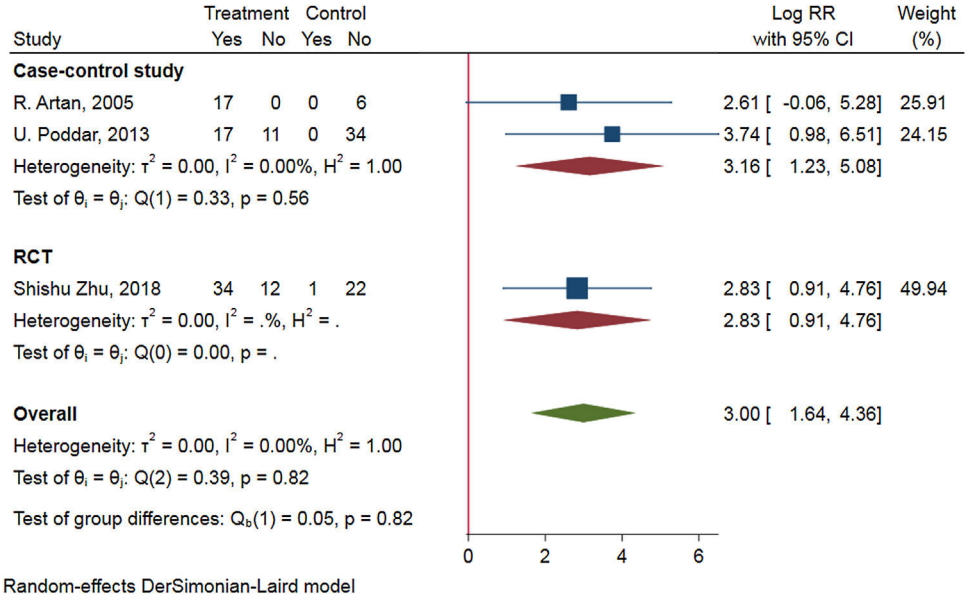

Figure 4 Forest plot of antiviral therapy for HBV DNA negative conversion after removing study Mieli-Vergani.[5]

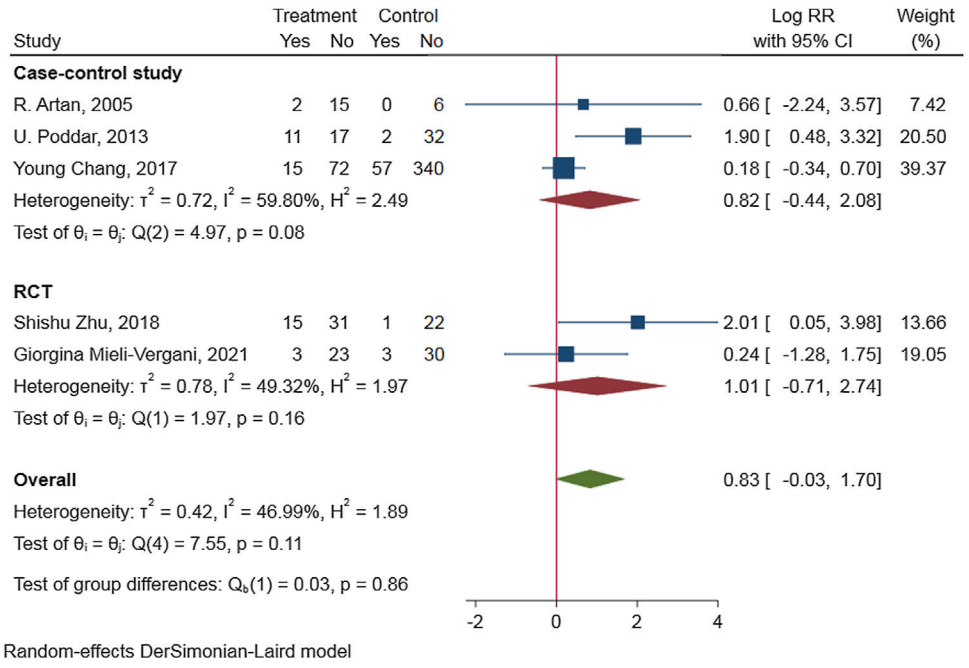

Figure 5 Forest plot of antiviral therapy for HBeAg seroconversion.

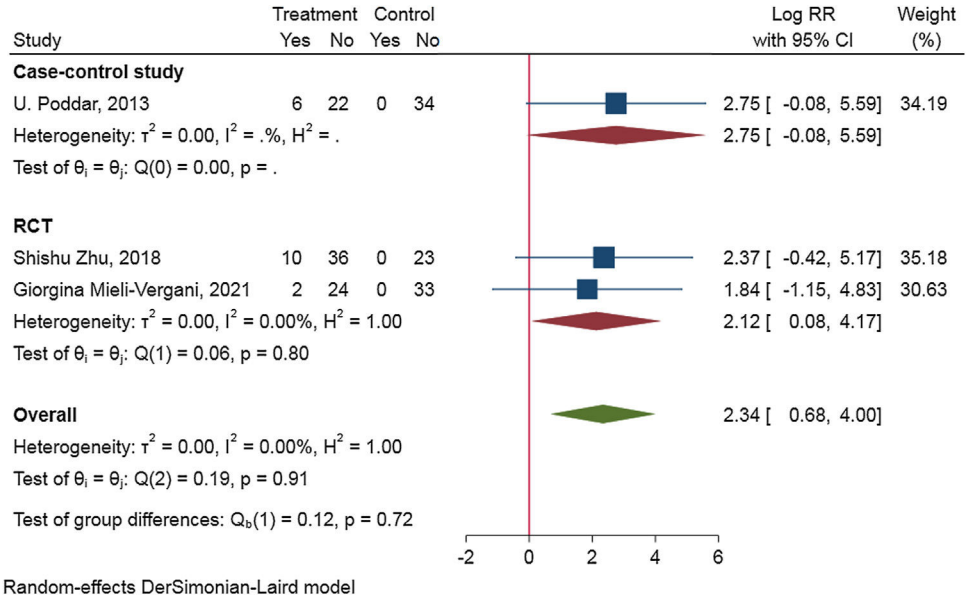

Figure 6 Forest plot of antiviral therapy for HBsAg loss.

Discussion

This meta-analysis of five studies indicated that antiviral therapy was significantly associated with a higher HBsAg loss rate, HBV DNA negative conversion rate, and lowered the risk for HCC and cirrhosis, but it was not beneficial to HBeAg seroconversion for immune-tolerant CHB.

In general, the previous treatment guidelines recommend against antiviral treatment for immune-tolerant CHB, except for having a family history of liver cancer or cirrhosis and being over 30 years old, perinatal or mother-to-child transmission.[2,9] Some studies have shown that antiviral therapy in the immune-tolerant CHB is difficult to achieve HBeAg seroconversion.[10] Furthermore, long-term treatment with NAs is expensive and involves high risks of adverse events and drug resistance.[4] The characteristics of this immune-clearance phase include together with a few special features at the molecular and immunological levels namely high level of HBV DNA integration and clonal hepatocyte expansion, possible proceeding hepatocarcinogenesis, preserved HBV specific T cell function at least until young adulthood, very low rate of spontaneous HBeAg loss and highly contagious due to the high levels of HBV DNA.[3,11–14] In our study, it was also confirmed again that antiviral therapy

during the immune tolerance phase could not increase the HBeAg seroconversion rate. However, disease progression is considerably slow prior to the immune-clearance phase. In addition, clinicopathological liver biopsy confirmed that approximately 27.8–40% immune-tolerant CHB patients who were HBeAg positive with persistently normal ALT levels had significant liver fibrosis and necroinflammation.[15,16] The rationale for considering treatment expansion to patients in the immune tolerant phase is further supported by a Korean study, which reported that untreated immune-clearance phase patients with CHB had higher risks of HCC and death/transplantation than treated immune-active phase patients.[17] Moreover, unnecessary deaths could be prevented through earlier antiviral intervention in select immune-clearance phase patients.[17] In our study, it was also confirmed that antiviral therapy during the immune tolerance phase could decrease the HCC and cirrhosis rate. Besides, one study in China included 144 inactive carriers who chose to receive Peg-IFNα +/− adefovir ($n = 94$) for up to 96 weeks or no treatment ($n = 40$) found that the treated group had significantly higher rates of HBV DNA undetectable and HBsAg clearance, 98% and 29.8%, 100% and 44.7%, at weeks 48 and weeks 96, respectively compared to 0.0% and 2.4% at both time points in the untreated control.[18] The same results are in our study that antiviral therapy was significantly associated with a higher rate HBsAg loss, HBV DNA negative conversion.

The present meta-analysis has several strengths. Firstly, we have discussed both short-term and long-term antiviral effects for hepatitis B virus-infected with immune-tolerant. Secondly, subgroup analysis was conducted to improve result reliability and reduce heterogeneity for each outcome. Furthermore, sensitivity analysis was also utilized to explore the high heterogeneity. And the outcome had been still verified that patients in hepatitis B virus-infected with immune-tolerant responded well to antiviral therapy by removing Mieli-Vergani[5] study, the overall heterogeneity did materially change.

Our meta-analysis has some limitations. First of all, Publication bias detection was not performed as less than 10 studies were included. Secondly, defining immune-tolerant phase is challenging, and whether a true immune-tolerant phase exists is debatable. The definition of the immune tolerance period in each study is different because trials included were published between 2005 and 2021. And then, the number of articles included was very low, which significantly reduced the reliability of the study. Finally according to the reference range of ALT 0–30 U/L for men and 0–19 U/L for women, the study population may include non-immune tolerance patients as four of the five studies included have ALT averages greater than 30 U/L.

Conclusions

Patients in HBV-infected with immune-tolerant responded well to antiviral therapy. The evidence from this meta-analysis supports antiviral therapy for patients with HBV in the immune tolerance stage. Well-designed, multi-center, larger sample sizes and excellent quality prospective studies are needed to confirm our conclusion.

Conflict of interest

All authors declare no conflict of interest.

Acknowledgements

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.gastrohep.2022.05.014.

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