Meta-Analysis

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A comparative network meta-analysis of standard of care treatments in treatment-naïve chronic hepatitis B patients

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Objective: Published network meta-analyses of chronic hepatitis B (CHB) treatments are either out-of-date or excluded key treatments. Therefore, we aimed to comprehensively update the efficacy evidence for the following end points: Hepatitis B surface antigen (HBsAg) loss, hepatitis B early antigen (HBeAg) seroconversion and hepatitis B virus DNA (HBV DNA) suppression. **Materials & methods:** Approved treatments in CHB and their combinations were evaluated. A systematic literature review was conducted to identify all randomized controlled trials in treatment-naïve CHB patients. Included studies reported at least one of the end points of interest. A frequentist probability network meta-analysis was performed for each end point. The choice of fixed effect or random-effect model was based on the I-square statistic, a measure of variation in study outcomes between studies. The analyses were performed separately for HBeAg-positive and HBeAg-negative patients. For the primary analyses, end points measured 48 ± 4 weeks after treatment initiation were considered. **Results:** A total of 47 randomized controlled trials (13,826 patients), covering 23 unique treatment regimens, were included: a total of 29 reported HBsAg loss, 36 reported HBeAg seroconversion and 37 reported HBV DNA suppression. For both HBsAg loss and HBeAg seroconversion, pegylated interferon-based regimens were the most effective strategy in both HBeAg-positive and HBeAg-negative patients. On the other hand, for HBV DNA suppression, nucleosides-based regimens were the most effective strategy in both HBeAg-positive and HBeAg-negative patients. **Conclusion:** Our findings confirm available evidence around the comparative efficacy of available CHB treatments. Therefore, they can be used to update relevant cost–effectiveness analyses and clinical guidelines.

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Keywords: comparative effectiveness research • gastroenterology/hepatology • infectious diseases • meta-analysis • systematic review

It is estimated that the hepatitis B virus (HBV) severely threatens the lives of an estimated 292 million people worldwide [1]. In 2015, complications related to the disease (including cirrhosis and liver cancer) were responsible for approximately 887,000 deaths globally [2]. Further, the global burden of disease study found that viral hepatitis was the seventh leading cause of death in 2013 worldwide [3].

The current standard of care (SoC) for chronic hepatitis B (CHB) aims to keep viral replication under control and reduce the risk of liver damage and any other further complications, in order to improve long-term survival. There are currently two main treatment options for CHB: treatment with a nucleoside analog (NUC; e.g., adefovir, entecavir, lamivudine, telbivudine, tenofovir and tenofovir alafenamide) or treatment with pegylated interferon [4].

Future Medicine

The WHO recommends the use of oral antiviral agents with a particular preference for tenofovir, tenofovir alafenamide or entecavir since these are regarded to be the most potent, rarely lead to drug resistance (relative to antivirals that have lower barriers to resistance, e.g., lamivudine, telbivudine or adefovir) and have relatively few side effects [5]. Despite the NUCs' efficacy in reducing viral load, nucleosides usually need to be administered for long periods of time or lifetime, in order to keep the virus under control. When treatment with NUCs is discontinued, the viral load usually increases again. Hence, the need for chronic treatment, resulting in an increased risk of treatment-related complications [6].

Pegylated interferon may be considered as a treatment option for patients with a well-functioning liver [7]. Its use in more severe patients (i.e., with decompensated cirrhosis) is not recommended due to life-threatening infections [8]. It is usually administered by a weekly injection for finite periods of time (usually 48 weeks [9]) and can be an effective alternative, however, its side effects often make it an unfavorable choice among many patients. Either discontinuation of therapy or suboptimal exposure to treatments can also result in a rebound of the viral load which can lead to disease progression and an increased risk of viral transmission [2].

There have been three NMAs previously published with a similar scope as this study that have addressed the efficacy of CHB treatments. In an NMA performed by NICE, two efficacy end points were assessed: hepatitis B early antigen (HBeAg) seroconversion and hepatitis B virus DNA (HBV DNA) suppression [10]. The included studies were published between 1998 and 2010 and no analyses were conducted on the hepatitis B surface antigen (HBsAg) end point. Results from this NMA were further incorporated into a cost–effectiveness analysis for the treatment of patients with HBeAg-positive and HBeAg-negative CHB [10]. The second NMA was conducted by Govan and colleagues [11]. In this NMA, among others, three efficacy end points were assessed: HBsAg loss, HBeAg seroconversion and HBV DNA suppression [10]. They included studies published before 2012. At that time, a connected network for HBsAg loss in HBeAg-negative patients was not possible. In the third study published by Wong *et al.* in 2017, PEG IFN treatment was excluded from the quantitave analysis. We feel PEG IFN is a key treatment that should have been included in the analysis [12]. Further, they included studies published before June 2017. In summary, the most recent NMAs of CHB treatments are either out-of-date or excluded key treatments.

In this paper, we aimed to comprehensively update the efficacy evidence by means of an NMA for the following end points: HBsAg loss, HBeAg seroconversion and HBV DNA suppression.

Materials & methods

Literature search

A systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement to identify relevant studies [13]. The search syntaxes can be found in Supplementary Tables 1 & 2. In August 2019, two bibliographic databases (PubMed and Embase) were searched to identify relevant randomized controlled trials (RCTs) for treatments for CHB.

To be consistent with previously published NMAs, RCTs with NUCs and/or pegylated interferons as an intervention in NUC naïve patients were included. The following list of approved treatments was considered: adefovir, entecavir, lamivudine, pegylated interferon, telbivudine, tenofovir and tenofovir alafenamide. Not all treatments that were included are considered first choices in published guidelines. However, they may still reinforce the robustness of the network, as well as be SoC in different countries. Any combinations (indicated with +), optimizations (indicated with +/-) or sequential (indicated with ->) strategies of these treatments were also considered. All these treatment strategies will be referred to as SoC in this study. In case of sequential and optimization treatment regimens, the second treatment must have been indicated before the 48 weeks mark. The following definition for NUC-naïvety was adopted: >80% of patients were required not to have received any NUC treatment within 6 months of the start of the study. Further, a patient population, or a subgroup analysis, was required to contain at least 90% HBeAg-positive patients or at least 90% HBeAg-negative patients. This should ensure that results from these analyses are externally valid to the population of interest. Pediatric patient populations, patient populations with lamivudine resistance and immunotolerant patients (high viral load, low/normal alanine aminotransferase [ALT] levels) were excluded. We restricted the NMA to publications in English, and we did not impose any limitations on the publication date.

Quality assessment of individual studies

Retrieved RCT quality was assessed using the Cochrane risk of bias tool [14]. This tool consists of six domains: selection (both sequence generations and allocation concealment, performance (the blinding of patients and

personnel), detection (the blinding of outcome assessment), attrition (the completeness of outcome assessment), reporting (selective reporting) and other risks of bias. Scores are reported alongside descriptive statistics and were not used to include/exclude studies, nor conduct any sensitivity analyses.

Outcomes

We assessed the following end points: HBsAg loss, HBeAg seroconversion and HBV DNA suppression (<300 copies/ml). The end points are binary, and the results will be presented using the risk difference (RD) and are based on frequentist statistics. CIs will be given as part of the results. The primary analyses are also conducted with risk ratios (RR) and odds ratios (OR) as effect measures.

Functional cure (i.e., HBsAg seroclearance) is regarded as an optimal end point for patients with CHB, indicating viral suppression and a sustained reduction in viral and other disease markers, even after treatment cessation [6,15,16]. We included studies showing HBsAg loss, not restricting the analysis only to patients reaching functional cure (sustained HBsAg loss). Thus, the results of this NMA may be conservatively inflating the efficacy of current SoC (some of the patients that had lost HBsAg might have relapsed later). Alternatively, patients might achieve HBsAg loss after the 48 weeks mark.

HBeAg seroconversion is defined as the loss of HBeAg and the presence of anti-HBe antibody HBeAg [17]. It is associated with remission of the activity of CHB and in case of sustained HBeAg seroconversion, cessation of antiviral therapy might be considered [10]. HBV DNA suppression is defined in this study as achieving HBV DNA <300 copies/ml at the end of 48 weeks (+/- 4 weeks) of antiviral treatment. Long-term HBV DNA suppression might decrease disease progression and associated complications, such as liver cirrhosis and hepatocellular carcinoma [10]. Due to heterogeneity in the threshold used for HBV DNA suppression, a model was used to estimate the number of patients meeting the threshold of 300 copies/ml from other thresholds. This model was developed and validated using trial data [18]. The threshold of 300 copies/ml was chosen as the majority of the included RCTs reported their outcomes by means of this threshold.

Statistical analysis

Following Cochrane guidelines, a fixed-effect model or random-effect model is chosen based on the level of between-study heterogeneity. The I-square test is used as a measure for quantifying the level of inconsistency. It describes the variability in effect estimates as a result of heterogeneity rather than as a result of chance/sampling [14]. The I-square statistic's interpretation is rather tentative, however, in the case of an I-square larger than 50%, a random-effects model is indicated and in case of an I-square smaller than 50%, a fixed-effects model is indicated [14]. For the ranking of treatment regarding efficacy, the p-score is used. The p-score measured the mean extent of certainty that a treatment is better than the competing treatments [19]. The statistical program R and the packages 'meta' and 'netmeta' are used for all analyses.

Sensitivity analyses

Sensitivity analyses are conducted for all end points. In the sensitivity analyses for HBsAg loss, studies that measured the HBsAg loss rate at a different time point than 48 weeks (+/- 4) were included, in addition to the RCTs included in the base case for both the HBeAg-positive and HBeAg-negative patient populations. The same sensitivity analyses were conducted for the end points HBeAg seroconversion and HBV DNA suppression. For the end points, HBV DNA suppression, an additional sensitivity analysis was conducted regarding the HBV DNA suppression threshold. As described in the methods above, an algorithm to estimate the number of patients meeting the threshold of 300 copies/ml from other thresholds was used in the base case for the end point HBV DNA suppression. Therefore, a sensitivity analysis was also conducted for the HBV DNA suppression rates without the algorithm applied and the results will be reported in the Supplementary data.

Results

Study selection & characteristics

After the removal of duplicates, there were 1834 studies to be screened based on title and abstract. The PRISMA statement that shows the reasons for excluding articles can be found in Supplementary Figure 1. Baseline characteristics of included studies are presented in Supplementary Table 3. In total, 46 publications for 23 unique treatment regimens (including combination, sequential and optimization regimens) were included in the NMA. Table 1 shows all included studies, and the number of events that occurred in the included number of patients per

Table 1. Characteristics of included studies for the end points hepatitis B surface antigen, hepatitis B early antigen seroconversion and hepatitis B virus DNA suppression – base case and sensitivity analyses.

Study (year)	Treatment arms	Outcome (n of events/sample size)					Ref.
		HBeAg-positive			HBeAg-negative		
		HBsAg loss	HBeAg SC	HBV DNA†	HBsAg loss	HBV DNA†	
Hou *et al.* (2008)	Telbivudine	0/147	35/138	67/147	0/20	17/20	[19]
	Lamivudine	0/143	25/138	38/143	0/20	17/10	
Sung *et al.* (2008)	Lamivudine	-	9/54	24 (23)/56†	-	-	[20]
	Lamivudine + adefovir	-	5/52	22 (21)/54†	-	-	
Chan *et al.* (2007)	Telbivudine	0/44	12/44	26/44	-	-	[21]
	Adefovir	0/46	8/44	18/44	-	-	
	Adefovir (24 weeks) ->telbivudine	0/46	11/46	25/46	-	-	
Ren *et al.* (2007)	Lamivudine	-	4/21	8/21	-	-	[22]
	Entecavir	-	3/21	12/21	-	-	
Kaymakoglu *et al.* (2007)	Pegylated interferon	-	-	-	-	12 (12)/19†	[23]
	Pegylated interferon + lamivudine	-	-	-	-	23 (23)/29†	
Lau *et al.* (2005)	Pegylated interferon	8/271	72/271	63 (68)/271†	-	-	[15]
	Pegylated interferon + lamivudine	8/271	64/271	181 (186)/271†	-	-	
	Lamivudine	0/272	55/272	63 (68)/272†	-	-	
Chan *et al.* (2005)	Pegylated interferon + lamivudine	1/50‡	25/50‡	-	-	-	[24]
	Lamivudine	0/50‡	14/50‡	-	-	-	
Tassopoulus *et al.* (1999)	Placebo	-	-	-	0/60	-	[25]
	Lamivudine	-	-	-	1/65	-	
Dienstag *et al.* (1999)	Lamivudine	1/66	11/63	-	-	-	[26]
	Placebo	0/71	4/69	-	-	-	
Lai *et al.* (2006)	Entecavir	-	-	-	1/325	293/325	[27]
	Lamivudine	-	-	-	1/313	225/313	
Janssen *et al.* (2005)	Pegylated interferon + lamivudine	9/130	33/130	141 (43)/130†	-	-	[28]
	Pegylated interferon	7/136	30/136	11 (13)/136†	-	-	
Chang *et al.* (2006)	Entecavir	6/354	74/354	236/354	-	-	[29]
	Lamivudine	4/355	64/355	129/355	-	-	
Hadziyannis *et al.* (2003)	Adefovir	-	-	-	-	61 (63)/123	[30]
	Placebo	-	-	-	-	0 (0)/61	
Marcellin *et al.* (2004)	Pegylated interferon	-	-		7/177‡	110 (112)/177†	[31]
	Pegylated interferon + lamivudine	-	-	179	5/179‡	153 (156)/179†	
	Lamivudine			181	0/181‡	130 (133)/181†	
Marcellin *et al.* (2008)	Tenofovir	5/158	32/153	131 (134)/176†	0/250	229 (233)/250†	[32]
	Adefovir	0/82	14/80	10.5 (12)/90†	0/125	77 (79)/125†	
Lok *et al.* (2012)	Entecavir	4/126	28/126	77 (77)/126†	0/56	51 (51)/56†	[33]
	Entecavir + tenofovir	2/138	25/138	103 (103)/138†	0/59	24 (24)/55†	
Yao *et al.* (2008)	Entecavir	0/225‡	33/225	116/225	0/33‡	31/33	[34]
	Lamivudine	0/221‡	39/221	83/221	0/40‡	29/40	
Lai *et al.* (2007)	Telbivudine	-	103/458	275/680		195/222	[35]
	Lamivudine	-	100/463	185/687		159/224	
Papadopoulos *et al.* (2009)	Pegylated interferon + lamivudine	-	-	-	-	73 (73)/88†	[36]
	Pegylated interferon	-	-	-	-	24 (24)/35†	
Leung *et al.* (2009)	Entecavir	-	5/33	19/33	-	-	[37]
	Adefovir	-	7/32	6/32	-	-	
Jun *et al.* (2018)	Pegylated interferon	-	12/66‡	6 (19)/81†,‡	-	-	[38]

†The number of HBV DNA suppression events given is after applying the HBV DNA transformation formula, the number of events as in the article is given between parentheses. Therefore, the number of events after the transformation algorithm (the number of events as given in the article)/sample size.
‡Only included in the sensitivity analyses.
+: Indicates a combination treatment; ->: Indicated a sequential treatment; +/-: Indicates an optimization treatment.
HBeAg: Hepatitis B early antigen; HBsAg: Hepatitis B surface antigen; HBV DNA: Hepatitis B virus DNA; SC: Seroconversion.

Table 1. Characteristics of included studies for the end points hepatitis B surface antigen, hepatitis B early antigen seroconversion and hepatitis B virus DNA suppression – base case and sensitivity analyses (cont.).

Study (year)	Treatment arms	Outcome (n of events/sample size)					Ref.
		HBeAg-positive			HBeAg-negative		
		HBsAg loss	HBeAg SC	HBV DNA†	HBsAg loss	HBV DNA†	
	Entecavir (12 weeks) ->pegylated (starting at week 5) interferon	-	12/66‡	6 (19)/81†,‡	-	-	
Luo *et al.* (2017)	Telbivudine	0/91‡	31/91	63 (74)/91†	-	-	[39]
	Entecavir	0/93‡	10/93	61 (73)/93†	-	-	
Lee *et al.* (2017)	Entecavir	-	6-	-	-	52/56‡	[40]
	Lamivudine	-	-	-	-	43/64‡	
Xu *et al.* (2017)	Pegylated interferon	-	4/28	-	-	-	[41]
	Pegylated interferon + entecavir	-	8/33	-	-	-	
	Pegylated interferon + adefovir		7/33	-		-	
De Niet *et al.* (2017)	Pegylated interferon + adefovir	-	-	-	1/46	-	[42]
	Pegylated interferon + tenofovir	-	-	-	3/45	-	
	Placebo	-	-	-	0/43	-	
Buti *et al.* (2016)	Tenofovir alafenamide	-	-	-	0/281	268/285	[43]
	Tenofovir	-	-	-	0/138	130/140	
Chan *et al.* (2016)	Tenofovir alafenamide	4/581	58/565	391 (371)/581†	-	-	[44]
	Tenofovir	1/292	23/285	205 (195)/292†	-	-	
Koike *et al.* (2018)	Entecavir	-	2/27	12 (10)/28†	-	28 (27)/28†	[45]
	Tenofovir	-	4/43	30 (28)/51†	-	59 (56)/58†	
Krastev *et al.* (2016)	Telbivudine	-	-	-	0/113	104/113	[46]
	Tenofovir	-	-	-	0/117	111/117	
Zhang *et al.* (2016)	Pegylated interferon	2/32	9/32	12 (13)/32†	-	-	[47]
	Pegylated interferon + adefovir	11/97	33/97	70 (73)/97†	-	-	
Sriprayoon *et al.* (2017)	Entecavir	1/95‡	26/95‡	-	1/105‡	-	[48]
	Tenofovir	1/92‡	31/92‡	-	2/108‡	-	
Marcellin *et al.* (2016)	Tenofovir + pegylated interferon (24 weeks)	7/108	25/108	-	4/78	-	[49]
	Tenofovir + pegylated interferon (16 weeks) ->tenofovir (32 weeks)	3/105	20/105	-	1/79	-	
	Tenofovir	0/109	9/109	-	0/76	-	
	Pegylated interferon	4/106	13/106	-	1/79	-	
Liang *et al.* (2015)	Lamivudine + adefovir	1/120‡	20/120‡	64/120	-	-	[50]
	Lamivudine ->adefovir or lamivudine	1/120‡	17/120‡	58/120	-	-	
	Lamivudine	1/118‡	20/118‡	41/118	-	-	
Hou *et al.* (2015)	Tenofovir	0/103‡	16/103	77 (79)/103†	0/154	146 (149)/152†	[51]
	Adefovir	0/99‡	9/99	16 (18)/99†	0/153	106 (109)/153†	
Wen *et al.* (2014)	Adefovir	-	83/252	148 (178)/252†	-	-	[52]
	Placebo	-	6/274	0 (12)/274†	-	-	
Xie *et al.* (2014)	Pegylated interferon	3/72‡	14/72	33 (38)/72†	-	-	[53]
	Pegylated interferon (48 weeks) + entecavir (24 weeks)	5/73‡	13/73	48 (52)/73†	-	-	
	Entecavir (24 weeks) ->pegylated interferon (48 weeks, starting at week 21)	2/73‡	15/73	30 (35)/73†		-	
Liu *et al.* (2014)	Pegylated interferon + adefovir	-	11/30	21 (23)/30†	-	-	[54]
	Pegylated interferon	-	8/31	7 (9)/31†	-	-	

†The number of HBV DNA suppression events given is after applying the HBV DNA transformation formula, the number of events as in the article is given between parentheses. Therefore, the number of events after the transformation algorithm (the number of events as given in the article)/sample size.
‡Only included in the sensitivity analyses.
+: Indicates a combination treatment; ->: Indicated a sequential treatment; +/-: Indicates an optimization treatment.
HBeAg: Hepatitis B early antigen; HBsAg: Hepatitis B surface antigen; HBV DNA: Hepatitis B virus DNA; SC: Seroconversion.

Table 1. Characteristics of included studies for the end points hepatitis B surface antigen, hepatitis B early antigen seroconversion and hepatitis B virus DNA suppression – base case and sensitivity analyses (cont.).

Study (year)	Treatment arms	Outcome (n of events/sample size)					Ref.
		HBeAg-positive			HBeAg-negative		
		HBsAg loss	HBeAg SC	HBV DNA†	HBsAg loss	HBV DNA†	
Li *et al.* (2014)	Telbivudine	-	4/24	24 (21)/24†	-	-	[55]
	Lamivudine	-	2/28	28 (25)/28†	-	-	
Tseng *et al.* (2014)	Entecavir	0/7	2/7	-	0/15	-	[56]
	Placebo	0/10	0/10	-	0/11	-	
Sun *et al.* (2014)	Telbivudine +/- adefovir	0/300	43/300	196/300	-	-	[57]
	Telbivudine	1/299	52/299	170/299	-	-	
Jia *et al.* (2014)	Telbivudine	0/147	37/147	67/147	0/20	18/20	[58]
	Lamivudine	0/143	26/143	38/143	0/22	15/22	
Cao *et al.* (2013)	Pegylated interferon + lamivudine	-	12/24	23 (24)/24†	-	-	[59]
	Pegylated interferon + adefovir	-	10/23	22 (23)/23†	-	-	
Wang *et al.* (2013)	Adefovir	-	18/64‡	-	-	55 (53)/100†	[60]
	Lamivudine	-	11/59‡	-	-	71 (69)/102†	
He *et al.* (2012)	Lamivudine	-	8/50	39/50	-	-	[60,61]
	Adefovir	-	9/50	14/50	-	-	
	Lamivudine + adefovir	-	21/50	50/50	-	-	
Zhang *et al.* (2017)	Tenofovir	-	5/60	-	-	-	[62]
	Entecavir	-	4/56	-	-	-	
Marcellin *et al.* (2003)	Placebo	-	9/161	0 (0)/167†	-	-	[63]
	Adefovir	-	20/171	33 (36)/171†	-	-	
Lai *et al.* (2005)	Lamivudine	0/19‡	-	-	-	-	[64]
	Telbivudine	0/22‡	-	-	-	-	
	Lamivudine + telbivudine	0/21‡	-	-	-	-	

†The number of HBV DNA suppression events given is after applying the HBV DNA transformation formula, the number of events as in the article is given between parentheses. Therefore, the number of events after the transformation algorithm (the number of events as given in the article)/sample size.
‡Only included in the sensitivity analyses.
+: Indicates a combination treatment; ->: Indicated a sequential treatment; +/-: Indicates an optimization treatment.
HBeAg: Hepatitis B early antigen; HBsAg: Hepatitis B surface antigen; HBV DNA: Hepatitis B virus DNA; SC: Seroconversion.

end point, separately for HBeAg-positive and HBeAg-negative patients.

Quality assessment of individual studies

All studies are assessed using the Cochrane risk of bias tool and results per individual study are presented in Supplementary Table 4. All included studies were randomized, 79% of studies reported appropriate randomization sequence generation methods and 47% of the studies were double-blinded. Further, the majority of the studies were considered to be free of selective reporting and free of other biases.

Results: HBsAg loss

A total of 16 unique studies [17,20,22,27,29,30,33,34,45,48,50,57,58,65,66] were included in the base case network for HBsAg loss in HBeAg-positive patients, measured at 48 weeks (+/- 4 weeks). In these 16 studies, there were a total of 5303 patients, of which 81 patients experienced HBsAg loss. The sensitivity analysis for HBeAg-positive patients included six [25,35,40,49,51,54] additional studies to the base case unique studies with a total of 6423 patients, of which 97 patients experienced HBsAg loss. The base case analysis and sensitivity analysis for HBeAg-negative patients included 11 and 15 studies, respectively (in total, 20 out of 3175 and 34 out of 4110 patients obtained HBsAg loss, respectively). The networks of evidence, baseline characteristics and characteristics of the included studies can be found in Supplementary Table 1 & Supplementary Figure 5, for both the base case and sensitivity analyses.

Figure 2 shows a forest plot of the RD of all treatment included in the network, compared with placebo. The I-square was 0% for all networks of evidence for the end point HBsAg loss, and therefore the fixed effect

Table 2. Ranking of treatments for the networks for A. hepatitis B surface antigen loss, B. hepatitis B early antigen seroconversion and C. hepatitis B virus DNA suppression.

Rank	HBeAg-positive network – base case		HBeAg-positive network – sensitivity analyses		HBeAg-negative network – base case		HBeAg-negative network – sensitivity analyses	
	Treatment	Best	Treatment	Best	Treatment	Best	Treatment	Best
A. HBsAg loss								
1.	TDF + PEGIFN	0.917	TDF + PEGIFN	0.910	TDF + PEGIFN	0.843	TDF + PEGIFN	0.899
2.	PEGIFN + ADV	0.886	PEGIFN + ADV	0.877	PEGIFN + TDF	0.770	PEGIFN + TDF	0.882
3.	PEGIFN + LAM	0.801	PEGIFN + ETV	0.837	TDF + PEGIFN->TDF	0.565	PEGIFN	0.722
4.	PEGIFN	0.787	PEGIFN + LAM	0.782	PEGIFN	0.565	TDF + PEGIFN->TDF	0.646
5.	TDF + PEGIFN->TDF	0.714	PEGIFN	0.778	PEGIFN + ADV	0.549	PEGIFN + ADV	0.632
6.	ETV	0.500	TDF + PEGIFN->TDF	0.720	ETV + TDF	0.416	PEGIFN + LAM	0.627
7.	TAF	0.443	ETV->PEGIFN	0.552	LAM	0.414	Placebo	0.420
8.	LdT + LAM	0.418	TAF	0.462	ETV	0.412	TDF	0.403
9.	LAM	0.398	ETV	0.418	Placebo	0.411	ADV	0.403
10.	LdT	0.394	LdT + LAM	0.413	LdT	0.391	TAF	0.402
11.	TDF	0.365	LdT	0.393	TAF	0.389	LdT	0.384
12.	ADV->LdT	0.341	LAM	0.391	ADV	0.388	ETV + TDF	0.232
13.	LdT+/-ADV	0.310	LAM+/-ADV	0.387			ETV	0.177
14.	ETV + TDF	0.254	LAM + ADV	0.387			LAM	0.172
15.	ADV	0.248	TDF	0.384				
16.	Placebo	0.225	ADV->LdT	0.345				
17.			LdT+/-ADV	0.306				
18.			ADV	0.255				
19.			Placebo	0.216				
20.			ETV + TDF	0.189				
B. HBeAg seroconversion								
1.	PEGIFN + TDF	0.848	PEGIFN + TDF	0.879				
2.	PEGIFN ->TDF	0.745	PEGIFN ->TDF	0.784				
3.	PEGIFN + ADV	0.698	PEGIFN + ADV	0.755				
4.	LdT	0.685	PEGIFN + LAM	0.694				
5.	LAM + ADV	0.652	LdT	0.659				
6.	ETV ->PEGIFN	0.638	PEGIFN + ETV	0.649				
7.	PEGIFN + ETV	0.613	ETV ->PEGIFN	0.647				
8.	PEGIFN + LAM	0.574	PEGIFN	0.585				
9.	LdT +/- ADV	0.549	LdT +/- ADV	0.523				
10.	PEGIFN	0.521	LAM + ADV	0.514				
11.	ADV ->LdT	0.502	TAF	0.510				
12.	TAF	0.484	ADV ->LdT	0.506				
13.	TDF	0.390	TDF	0.421				
14.	LAM	0.352	LAM + ADV	0.338				
15.	ADV	0.283	ADV	0.313				
16.	ETV	0.245	LAM	0.298				
17.	ETV + TDF	0.208	ETV	0.221				
18.	Placebo	0.013	ETV + TDF	0.190				
19.			Placebo	0.013				
C. HBV DNA suppression								
1.	ETV + TDF	0.816	ETV + TDF	0.830	ETV + TDF	0.978	ETV + TDF	0.985
2.	TDF	0.811	TDF	0.823	TAF	0.780	ETV	0.775
3.	PEGIFN + ADV	0.776	PEGIFN + ADV	0.759	ETV	0.743	TAF	0.768
4.	TAF	0.739	TAF	0.748	TDF	0.700	TDF	0.688

+: Indicates a combination treatment; ->; indicated a sequential treatment; +/-; Indicates an optimization treatment.
ADV: Adefovir; ETV: Entecavir; HBeAg: Hepatitis B early antigen; HBsAg: Hepatitis B surface antigen; LAM: Lamivudine; LdT: Telbivudine; PEG IFN: Pegylated interferon; TAF: Tenofovir alafenamide; TDF: Tenofovir.

Table 2. Ranking of treatments for the networks for A. hepatitis B surface antigen loss, B. hepatitis B early antigen seroconversion and C. hepatitis B virus DNA suppression (cont.).

Rank	HBeAg-positive network – base case		HBeAg-positive network – sensitivity analyses		HBeAg-negative network – base case		HBeAg-negative network – sensitivity analyses	
	Treatment	Best	Treatment	Best	Treatment	Best	Treatment	Best
5.	PEGIFN + LAM	0.698	PEGIFN + LAM	0.718	LdT	0.603	LdT	0.593
6.	LdT +/- ADV	0.670	LdT +/- ADV	0.677	PEGIFN + LAM	0.530	PEGIFN + LAM	0.525
7.	LAM + ADV	0.630	LAM + ADV	0.636	LAM	0.329	LAM	0.329
8.	ETV	0.598	ETV	0.598	PEGIFN	0.187	PEGIFN	0.187
9.	LdT	0.551	LdT	0.547	ADV	0.151	ADV	0.151
10.	PEGIFN + ETV	0.516	LAM +/- ADV	0.547	Placebo	0.000	Placebo	0.000
11.	LdT + LAM	0.475	PEGIFN + ETV	0.514				
12.	ADV ->LdT	0.323	LdT + LAM	0.467				
13.	LAM	0.322	ADV ->LdT	0.309				
14.	PEGIFN	0.245	LAM	0.308				
15.	ETV ->PEGIFN	0.231	PEGIFN	0.220				
16.	ADV	0.100	ETV ->PEGIFN	0.212				
17.	Placebo	0.002	ADV	0.087				
18.		0.816	Placebo	0.001				

+: Indicates a combination treatment; ->; indicated a sequential treatment; +/-; Indicates an optimization treatment.
ADV: Adefovir; ETV: Entecavir; HBeAg: Hepatitis B early antigen; HBsAg: Hepatitis B surface antigen; LAM: Lamivudine; LdT: Telbivudine; PEG IFN: Pegylated interferon; TAF: Tenofovir alafenamide; TDF: Tenofovir.

model is indicated. The random-effects outcomes can be found in Supplementary Figure 6. In the base case analysis for HBeAg-positive, we see that there is one treatment that is statistically significantly better than placebo treatment (Figure 2A): a combination treatment of pegylated interferon and tenofovir (RD = 0.08 [CI: 0.01–0.15]). The sensitivity analysis (Figure 2B) for HBeAg-positive patients indicates that pegylated interferon + tenofovir (RD = 0.08 [CI: 0.01–0.14] is statistically significant better than placebo treatment, based on the CI).

In the base case for HBeAg-negative patients (Figure 2C), no treatment was statistically significantly better than placebo and in the sensitivity analysis for HBeAg-negative patients Figure 2D, one treatment was statistically significantly better than placebo (pegylated interferon + tenofovir [RD = 0.06 (CI: 0.01–0.11)]).

Ranking by means of the p-score can found in Table 2A. It shows that pegylated IFN-based treatments are ranked highest regarding HBsAg loss in HBeAg-positive patients and HBeAg-negative patients in the base cases and sensitivity analyses. The primary analyses were also conducted with RR and OR as effect measures. This did not change the results of the ranking of the treatments. The results of these analyses are presented in Supplementary Figure 7.

HBeAg seroconversion

A total of 31 [17,20–23,27,29,30,33–36,38–40,42,45,46,48–50,52–59,66] unique studies were included in the base case for the end point HBeAg seroconversion. For the base case, there were a total of 8910 patients, of which 1641 patients experienced HBeAg seroconversion. The sensitivity analysis included five more studies [25,39,49,51,61] than the base case, and 1828 out of 9759 included patients who experienced HBeAg seroconversion. The networks of evidence, baseline characteristics and characteristics of the included studies can be found in Supplementary Figures 8 & 9. Figure 1 shows a forest plot of the RD of all treatment included in the network, compared with placebo. The I-square is 60% in the base case and 61% in the sensitivity analysis, therefore, a random-effects model is used. In the base case, all treatments were statistically better than placebo treatment, except entecavir + tenofovir (RD = 0.12 [CI: -0.10–0.33]). In the sensitivity analysis, only two treatments were not statistically better than placebo (entecavir + tenofovir [RD = 0.11 [CI = -0.09–0.31] and lamivudine +/- adefovir [RD = 0.17 [CI = -0.01–0.35]). Ranking by means of the p-score can be found in Table 2B. For both the base case and sensitivity analysis, it is apparent that combination and sequential treatment of pegylated interferon and NUCs are ranked highest, followed by telbivudine. The primary analysis was also conducted with RR and OR as effect measures. This did not change the results of the ranking of the treatments. The results of these analyses are presented in Supplementary Figure 10.

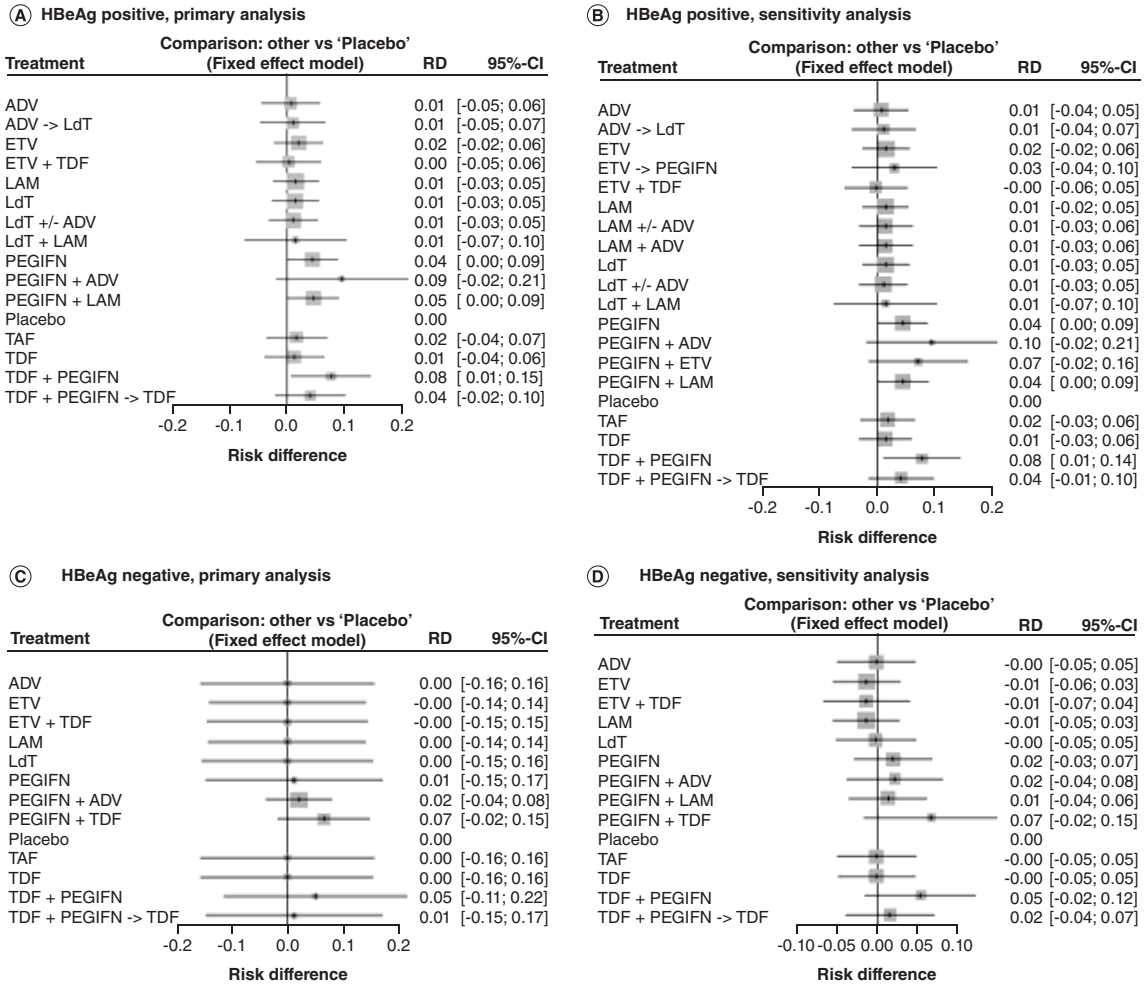

Figure 1. Forest plots; pairwise comparison of treatments for HBsAg loss. In nucleoside analogue naïve patients in HBeAg-positive patients – **(A)** base case, **(B)** sensitivity analysis and in HBeAg-negative patients **(C)** base case and **(D)** sensitivity analyses.
ADV: Adefovir; ETV: Entecavir; HBeAg: Hepatitis B early antigen; HBsAg: Hepatitis B surface antigen; LAM: Lamivudine; LdT: Telbivudine; PEG IFN: Pegylated interferon; RD: Risk difference; TAF: Tenofovir alafenamide.

HBV DNA suppression

A total of 27 unique studies [17,20–23,29,30,33–36,38,40,45,46,48,51–56,58,60,62–64,66] were included in the base case and two more [39,60] in the sensitivity analysis NMA for HBV DNA suppression in HBeAg-positive patients. For HBeAg-negative patients, 15 [20,24,28,31–37,46,47,52,59,61,66] RCTs were included in the base case network. One more was included in the sensitivity analysis [41]. A total of 4347 out of 8652 included HBeAg-positive patients experienced HBV DNA suppression in the base case and 4626 out of 9520 in the sensitivity analysis, and 3310 out of 4205 out of included HBeAg-negative patients and 3405/4325 of HBeAg-negative patients experienced HBV DNA suppression for the base case and sensitivity analysis, respectively.

Figure 3 shows forest plots of the RD of all treatment included in the network, compared with placebo. The I-squares for the base case and sensitivity analysis for HBeAg-positive patients are respectively, 89.5 and 87.3%, so, a random-effect model is indicated. For HBeAg-negative patients, the I-squares are for both the base case and sensitivity analysis 0%. Thus, a fixed-effect model is indicated. In the base case, all treatments were statistically better than placebo treatment, except for entecavir ->pegylated interferon (RD = 0.54 [CI: -0.01–1.10]). In the sensitivity analysis, all treatments are significantly better than the placebo. Ranking by means of the p-score can found in Table 2C. For the base cases and sensitivity analyses in both the HBeAg- positive and-negative patient populations, entecavir + tenofovir is ranked highest for viral suppression. For HBeAg-positive patients,

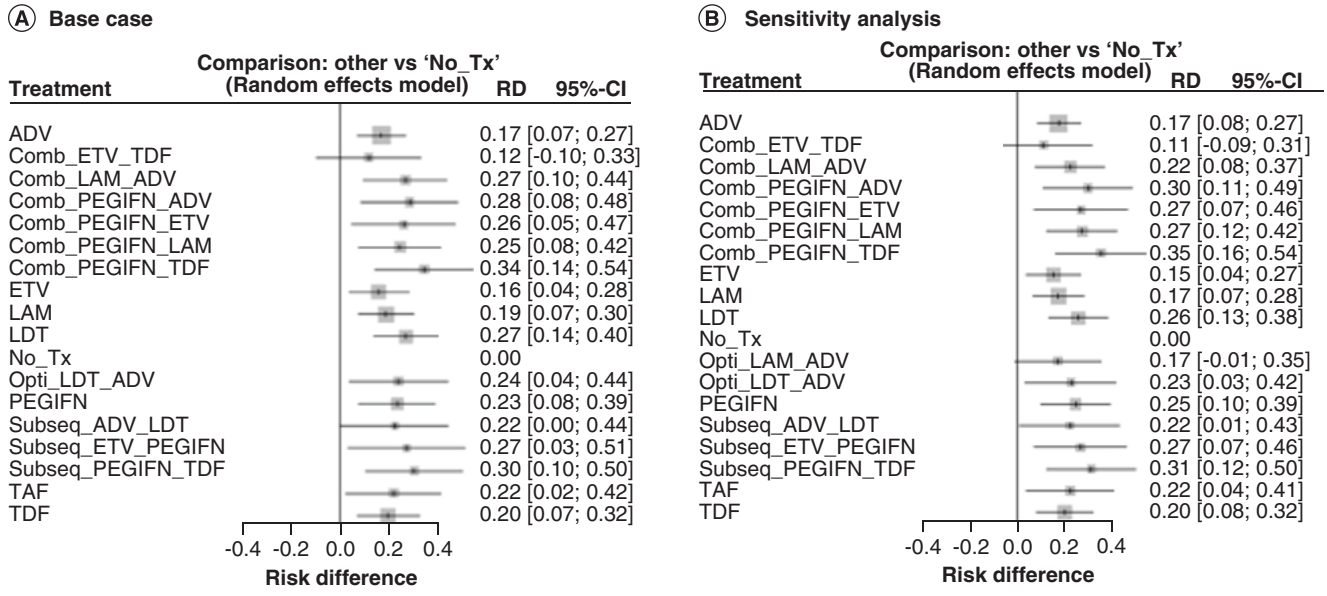

Figure 2. Forest plots; pairwise comparison of treatments for HBeAg seroconversion. In nucleoside analogue naïve patients in HBeAg-positive patients – **(A)** base case and **(B)** sensitivity analysis.
+: Indicates a combination treatment; ->: Indicated a sequential treatment; +/-: Indicates an optimization treatment.
ADV: Adefovir; ETV: Eentecavir; HBeAg: Hepatitis B early antigen; LAM: Lamivudine; LdT: Telbivudine; PEG IFN: Pegylated interferon; RD: Risk difference; TAF: Tenofovir alafenamide; TDF: Tenofovir.

this is followed by tenofovir, pegylated interferon + adefovir and for HBeAg-negative patients, this is followed by tenofovir alafenamide, entecavir and tenofovir. No large differences are observed in the sensitivity analyses. The primary analyses were also conducted with RR and OR as effect measures. Doing this did not change the results of the ranking of the treatments. The results of these analyses are presented in Supplementary Figure 13.

Discussion

Our findings substantiate and confirm available evidence around the comparative efficacy of available CHB treatments. For the HBsAg loss networks, it can be concluded that pegylated interferon-based treatment regimens of pegylated interferons in combinations with nucleoside analogs are the most effective regarding HBsAg loss in both HBeAg-positive and HBeAg-negative patient populations. Considering monotherapy treatment regimens, pegylated interferon ranks best in all networks for HBsAg loss. For HBeAg-positive patients, pegylated interferon is followed by entecavir and tenofovir alafenamide and for HBeAg-negative patients, it is followed by lamivudine and entecavir (base cases). For the HBeAg seroconversion networks, combination treatments of pegylated interferons and nucleoside analogs are ranked the highest. For both HBeAg- positive and-negative patients, the highest-ranked treatment was a combination of entecavir and tenofovir. The highest-ranked monotherapy for HBeAg seroconversion is telbivudine (base case). Nucleoside analog-based treatments appear to be the most effective in all networks for viral suppression. The most effective monotherapy regarding viral suppression is tenofovir for HBeAg-positive patients and tenofovir alafenamide for HBeAg-negative patients (base cases). None of the sensitivity analyses (i.e., networks that included studies that measured end points at a later point of time than 48 weeks) inherently changed the ranking of treatments, in any of the end points.

Our results are consistent with different guidelines: viral suppression is universally high with NUCs, pegylated interferons are most effective regarding HBeAg levels and pegylated interferons are more effective on HBsAg loss levels than NUCs, albeit low. These guidelines include European Association for the Study of the Liver [13], American Association for the Study of Liver Diseases [15] and the Asian Pacific Association for the Study of the Liver (APASL) [67]. The analyses in this paper might include outdated treatment regimens. However, these treatments might be SoC in different countries and might help to close and increase the robustness of the network of evidence.

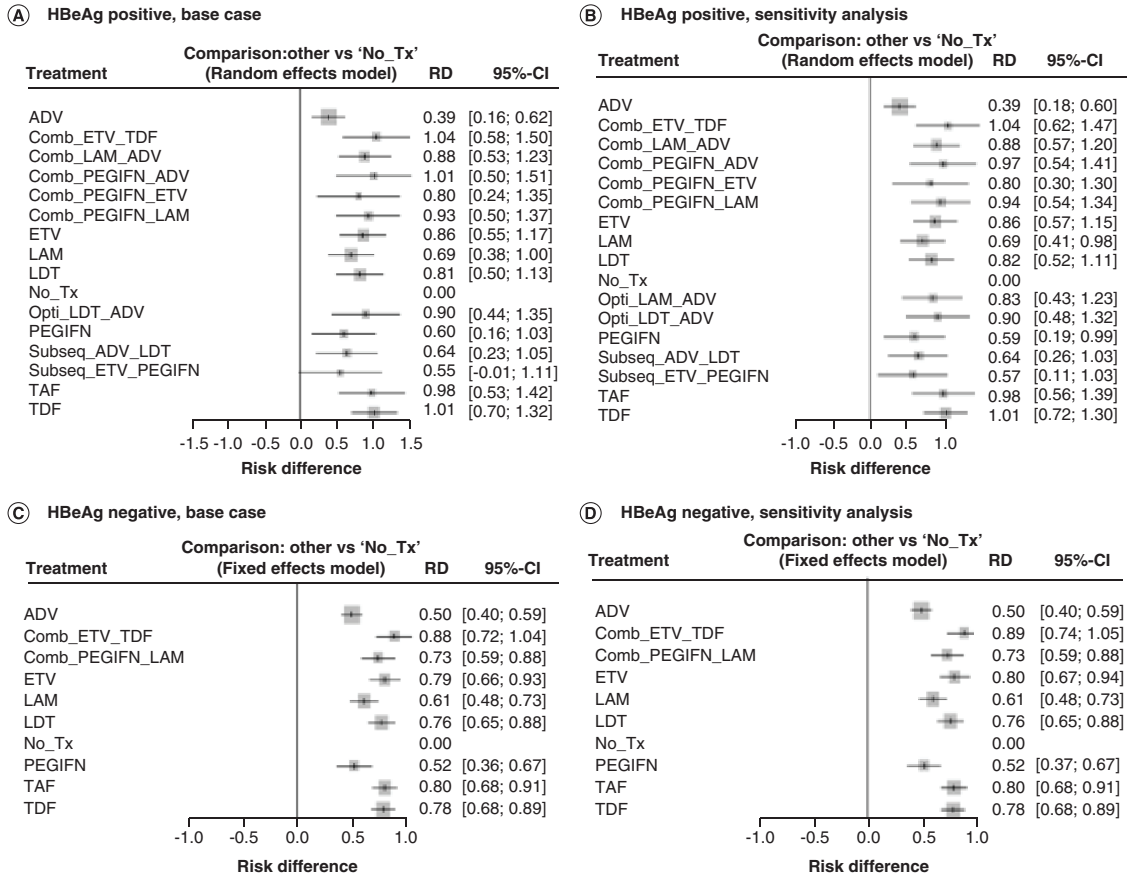

Figure 3. Forest plots; pairwise comparison of treatments for HBV DNA suppression. In HBeAg-positive patients – **(A)** base case, **(B)** sensitivity analysis and in HBeAg-negative patients **(C)** base case and **(D)** sensitivity analyses.
HBeAg: Hepatitis B early antigen; HBV DNA: Hepatitis B virus DNA; RD: Risk difference.

Furthermore, our results are consistent with the NMA conducted by NICE [10], Govan *et al.* [11] and Wong *et al.* [12]. As of today, our NMA is the most up-to-date systematic synthesis of the available evidence. However, there are discrepancies between NICE's NMA and the efficacy inputs of the economic model. The efficacy inputs to the model shows that pegylated interferons are more efficacious in terms of viral suppression rather than tenofovir or entecavir [10]. This in turn may have led to recommendations that are not consistent with the available evidence. Therefore, there is a need to update the economic model with the updated efficacy evidence.

Sustained HBsAg loss might be over or under-estimated because most studies only report HBsAg loss at 48 weeks, not restricting the analysis to patients reaching functional cure. This does not necessarily indicate that HBsAg loss is sustained after treatment discontinuation [68]. However, several RCTs that were included in the networks for HBsAg loss at 48 weeks (+/- 4 weeks) also reported the HBsAg loss rate at a later time point after treatment discontinuation, which is indicative of sustained HBsAg loss. No large differences in the HBsAg loss rate after 48 weeks [+/- 4 weeks]) and at the end of follow-up (e.g., 6 months after treatment discontinuation [29], or 12 months after treatment discontinuation [54]) are noted. This is indicative that the HBsAg loss rate is highly similar to the sustained HBsAg loss rate.

This study has some limitations. We included studies written in the English language and, therefore, excluded for instance, relevant studies in the Chinese language. This might be a limitation, given a high prevalence of CHB in China [69]. Different SoC might be in place in different countries, which might not be accurately captured in studies published in English. This study is aimed at NUC naïve patients, and therefore, it does not capture the current state of Soc in treatment and/or NUC experienced patients. Future NMAs should include treatment-experienced patients. Future updates should attempt to include evidence in other languages and extend this to other relevant

subpopulations in CHB. HBsAg loss or functional cure is rarely achieved with current SoC. Novel agents with higher efficacy compared with SoC are needed.

Conclusion

This NMA substantiates and confirms the findings of previously published NMAs. For both HBsAg loss and HBeAg seroconversion, pegylated interferon in combination tenofovir was the most effective strategy in both HBeAg-positive and HBeAg-negative patients. On the other hand, for HBV DNA suppression, tenofovir in combination with entecavir was the most effective strategy in both HBeAg-positive and HBeAg-negative patients.

Summary points

- The global burden of disease study found that viral hepatitis was the seventh leading cause of death in 2013 worldwide.
- Published network meta-analyses (NMAs) of chronic hepatitis B treatments are either out-of-date or excluded key treatments.
- In this paper, we aimed to comprehensively update the efficacy evidence by means of an NMA for the following end points: hepatitis B surface antigen (HBsAg) loss, hepatitis B early antigen seroconversion and hepatitis B virus DNA suppression.
- To be consistent with previously published NMAs, randomized controlled trials with nucleoside analogues (NUCs) and/or pegylated interferons as an intervention in NUC naïve patients were included by means of a systematic literature review.
- In total, 46 publications for 23 unique treatment regimens (including combination, sequential and optimization regimens) were included in the NMA.
- Our findings substantiate and confirm available evidence around the comparative efficacy of available chronic hepatitis B treatments.
- Our results are consistent with different guidelines: viral suppression is universally high with NUCs, pegylated interferons are most effective regarding hepatitis B early antigen levels and that pegylated interferons are more effective on HBsAg loss levels than NUCs, albeit low.
- HBsAg loss or functional cure is rarely achieved with current standard of care. Novel agents with higher efficacy compared with SoC are needed.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2020-0068

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U Sbarigia is an employee of Janssen Pharmaceutica NV Belgium and holds stocks at Johnson & Johnson. P Wigfield, M Hashim and T Vincken are employees at Ingress-health (a research consultancy specializing in health economics and real-world evidence). B Heeg is a partner at Ingress-health. M Postma reports grants and personal fees from various pharmaceutical industries, all outside the submitted work. M Postma holds stocks in Ingress Health and Pharmacoeconomics Advice Groningen (PAG Ltd) and is advisor to Asc Academics, all pharmacoeconomic consultancy companies. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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