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Efficacy of nucleoside analogues for hepatitis B virus-related liver failure: A network meta-analysis

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The purpose of this study was to compare the efficacy of nucleoside analogues (NAs) in the treatment of HBV-related liver failure. The data of patients with HBV-related liver failure treated with nucleoside analogues were used to conduct a network meta-analysis. A total of 1660 patients from 12 articles about the efficacy of lamivudine, entecavir, telbivudine and tenofovir for HBV-related liver failure treatment were recruited in the study. The highest two- and three-month survival rate was recorded for patients using tenofovir. The end-stage liver disease (MELD) score and mortality in patients undergoing tenofovir treatment were the lowest. Patients treated with telbivudine had the highest one-month survival rate. Patients receiving enticavir therapy showed the lowest HBV DNA level. Our results indicate that tenofovir may be the best therapy for the treatment of HBV-related liver failure compared to other nucleoside analogues (including lamivudine, entecavir and telbivudine) and non-NAs treatment.

Keywords: liver failure, hepatitis B virus, nucleoside analogue, tenofovir, network meta-analysis

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Hepatitis B virus (HBV) infection, the leading cause of liver failure, is a global health problem with more than 400 million people infected worldwide up to now (1). HBV-related liver diseases cause over 1 million deaths every year (2). Active HBV infection can be indicated by hepatitis B surface antigen and HBV DNA in serum (3). The pathogenesis of liver failure caused by HBV infection is as follows. HBV replication leads to a primary injury of liver cells and the host's immune cells such as cytotoxic T lymphocytes, and HBV replication causes a secondary lesion to the HBV-infected hepatocytes during viral clearance (4). Following this, patients may suffer from another two attacks of ischemic-hypoxic injury and endotoxemia (5).

There is no standard therapy for liver failure. Although liver transplantation is considered a life-saving treatment, its clinical use is hindered by the difficulty of finding suitable donors (6). Although an artificial and bioartificial liver support system is available for the treatment of liver failure, its efficacy and safety remain to be improved (7). In the past

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years, efficacy of nucleoside analogues, such as lamivudine, entecavir, telbivudine and tenofovir, for HBV-related liver failure has been reported. Nucleoside analogues are antiviral drugs that prevent the progression of liver failure by reducing HBV DNA replication through suppression of HBV-polymerase activity (8). There have been meta-analyses of the effects of nucleoside analogues for HBV-related liver failure treatment (9–11). Some of them compare the outcomes of two kinds of nucleoside analogues while the others analyze the efficacy of nucleoside analogue treatment in comparison with the non-nucleoside analogue (non-NA) treatment (10, 11). However, no conclusion on which nucleoside analogue is the most satisfactory drug for the treatment of HBV-related liver failure has not been reached yet. Therefore, a comprehensive comparison of lamivudine, entecavir, telbivudine and tenofovir efficacy for the HBV-related liver failure treatment is essential.

To identify the optimal therapy, a Bayesian network meta-analysis was conducted. Articles about the efficacy of lamivudine, entecavir, telbivudine and tenofovir for the HBV-related liver failure treatment were reviewed to evaluate the outcomes, including one-month to three-month survival rates, HBV DNA (log IU mL^{-1} indicates virological characteristics), model of the end-stage liver disease (MELD) score (consists of three objective parameters, TBIL, Cr and INR, which indicate the severity of the liver condition) and mortality.

DATA SOURCES

Literature search strategy

Network meta-analysis was performed following the guidelines of PRISMA-NMA (12). Relevant studies were obtained by searching electronic databases up to December 2016, including Pubmed and Embase. Keywords used for literature search were as follows: (hepatitis B or HBV) and (hepatic failure or liver failure or hepatargia) and (nucleoside analog* or nucleotide analog* or nucleoside analogue or lamivudine or LAM or entecavir or ETV or telbivudine or LdT or tenofovir disoproxil fumarate or TDF or adefovir). Language was restricted to English. In addition, the lists of retrieved articles were reviewed to identify additional literature.

Inclusion and exclusion criteria

Studies were included into this article if they met the following criteria: patients with HBV-related liver failure (P), treatment of HBV-related liver failure using a nucleoside analogue (I), studies including a comparison of several nucleoside analogues (C), outcomes including at least one of the following indicators: mortality, survival, HBV DNA or MELD score (O). Besides, repetitive publications, studies without sufficient original data for statistical analysis, studies with sample size less than five, reviews, reports, comments and letters were excluded.

Data extraction and quality assessment

Data extraction was performed by two investigators independently. Data extracted from each retrieved article were as follows: the first author's name, publication year, location, study period, study type, follow-up time, number of subjects, demographic data characteristics including gender, age, *etc*., and outcomes of indicators. Quality assessment of

randomized controlled trials (RCTs) was conducted using the Cochrane risk of bias tool recommended in the Cochrane handbook. Methodological quality of cohort studies was analyzed according to the Newcastle-Ottawa Scale (NOS, G. A. Wells *et al.*, University of Ottawa, Ontario, Canada). Any discrepancy during data extraction and quality assessment was solved through discussion with a third person.

STATISTICAL ANALYSIS

ADDIS software (1.16.5) (H. Hillege *et al.*, University of Groningen, Research Institute SOM - Systems, Organisations and Management, 2012) is a non-programming software used for prior assessment and implementation based on the Bayesian framework using the Markov chain Monte Carlo (MCMC) (13). The network meta-analysis was performed by ADDIS software. Parameter settings of ADDIS software were as follows: the number of chains: 4, tuning iterations: 20000, simulation iterations: 50000, thinning interval: 10, inference samples: 10000, variance scaling factor: 2.5, and odds risk (OR) with 95 % confidence interval (CI) or mean difference (MD) with 95 % CI were used to estimate the data. In this study, all models were random effect models. Node-splitting analysis was used to evaluate inconsistency. When p-value was > 0.05, a consistency model was used; otherwise, an inconsistency model was used. Convergences of models were estimated by the Brooks-Gelman-Rubin method *via* checking the potential scale reduction factor (PSRF) (14). The PSRF close to 1 indicates good convergence of the models and, in general, PSRF less than 1.2 is acceptable.

RESEARCH OUTCOMES

Characteristics of available studies

The flow chart of study selection and literature search is shown in Fig. 1. After comprehensive search of the Pubmed and Embase databases, a total of 821 studies were identified.

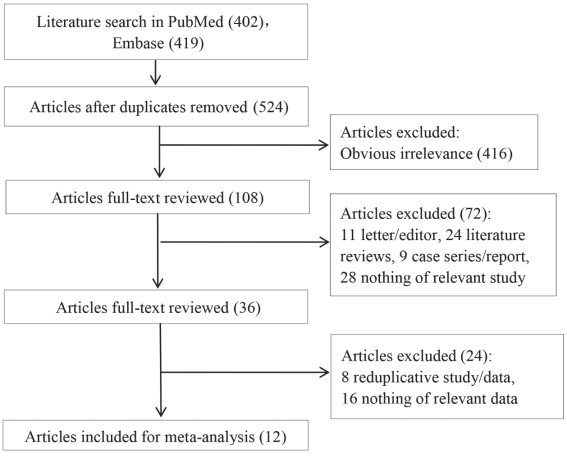

Fig. 1. Flow chart of study selection and literature search.

Table I. Characteristics of the trials

Author (ref.)	Publ. year	Study location	Study period	Study type	Follow-up	Group	N	Daily dose (mg)	Age Mean ± SD/ mean (min-max)	Male/ female	HBV DNA (mean ± SD, log10 IU mL^{-1})	MELD score	Outcome	NOS score
T. Y. Chen (20)	2012	China	2008.07-2010.06	Retrosp. cohort	3 months	Enticavir	42	0.5	39.02 ± 13.04	10/32	7.04 ± 1.58	26.69 ± 12.09	mortality survivalHBV DNA	9
						Lamivudine	30	100	42.3 ± 9.57	6/24	7.25 ± 0.89	28.53 ± 10.85		
						non-NAs	35	–	41.03 ± 11.95	7/28	5.73 ± 0.96	31.55 ± 14.01		
Y. L. Cui (21)	2010	China	2006.04-2008.12	Retrosp. cohort	3 months	Enticavir	33	0.5	38.39 ± 10.82	3/30	5.93 ± 1.52	24.04 ± 4.46	mortality survival HBV DNA	9
						Lamivudine	34	100	39.35 ± 10.61	3/31	5.91 ± 1.46	25.96 ± 6.37		
						non-NAs	37	–	41.03 ± 11.48	6/31	5.75 ± 1.34	24.16 ± 4.66		
T. Kanda (15)	2012	Japan	2003.03-2009.12	Retrosp. cohort	6 months	Lamivudine	24	100	37 (21–73)	18/6	7.24 ± 1.05	NA	HBV DNA	6
						Enticavir	10	0.5	39 (24–67)	9/1	7.56 ± 1.38	NA		
B. L. Lin (16)	2013	China	2007.08-2009.05	RCT	48 weeks	Enticavir	53	0.5	38 (32–49)	49/4	6.46 ± 1.54	26.2 ± 6.3	mortality survival HBV DNA, MELD score	–
						non-NAs	55	–	40 (34–47)	52/3	6.04 ± 1.36	26.4 ± 5.8		
W. Guo (23)	2012	China	2005.02-2010.03	Retrosp. cohort	3 weeks	Enticavir	124	0.5	42.24 ± 11.40	114/10	6.20 ± 1.60	20.24 ± 5.69	mortality survival MELD score	7
						non-NAs	124	–	42.31 ± 12.58	111/13	6.35 ± 1.31	21.70 ± 5.89		
J. S. Wang (26)	2014	China	2007-2011	Retrosp. cohort	4 weeks	Lamivudine	98	–	40 (16–70)	87/11	5.33 ± 1.74	20 ± 4.78	mortality survival HBV DNA MELD score	9
						Telbevudine	85	–	37 (17–72)	77/8	5.5 ± 1.65	19.82 ± 5.36		
						Enticavir	100	–	42 (18–72)	89/11	5.6 ± 1.9	19.39 ± 5.08		

J. Lai (24)	2013	China	2003.01-2011.12	Retrosp. cohort	3 months	Enticavir	24	0.5	46.0 ± 13.0	21/3	5.6 ± 1.2	36.0 ± 4.9	mortality MELD score	8
						Lamivudine	25	100	42.6 ± 12.5	23/2	5.6 ± 1.9	34.0 ± 3.6		
J. Lai (24)	2013	China	2003.01-2011.12	Retrosp. cohort	3 months	Enticavir	37	0.5	45.7 ± 12.4	34/3	6.4 ± 1.5	25.8 ± 2.0	mortality survival HBV DNA MELD score	
						Lamivudine	34	100	42.9 ± 9.7	31/3	5.6 ± 1.8	26.0 ± 2.4		
J. Lai (24)	2013	China	2003.01-2011.12	Retrosp. cohort	3 months	Enticavir	32	0.5	46.5 ± 8.2	27/5	5.6 ± 1.7	20.2 ± 1.9	mortality survival HBV DNA, MELD score	
						Lamivudine	30	100	42.0 ± 10.1	27/3	5.6 ± 1.9	19.5 ± 2.3		
W. L. Wang (18)	2013	China	2011.04-2012.01	Retrosp. cohort	8 weeks	Telbivudine	20	600	41.62 ± 11.38	17/3	5.68 ± 1.47	NA	mortality survival HBV DNA	9
						Lamivudine	18	100	42.43 ± 10.72	15/3	5.25 ± 1.94	NA		
Y. Zhang (25)	2014	China	2007.12-2011.07	Retrosp. cohort	60 days	Enticavir	65	0.5	42.8 ± 13.1	41/24	7.0 ± 1.4	27.2 ± 6.5	mortality survival HBV DNA MELD score	9
						Lamivudine	64	100	45.6 ± 11.4	36/18	7.2 ± 1.6	26.8 ± 6.3		
X. H. Yang (19)	2014	China	2008.01-2012.06.	Retrosp. cohort	24 weeks	Lamivudine	76	100	43.5 ± 12.90	59/17	6.56 ± 1.13	41.92 ± 3.47	mortality survival MELD score	8
						non-NAs	64	–	44.23 ± 12.80	54/10	7.58 ± 8.76	42.49 ± 3.62		
H. Garg (22)	2011	India	2007.10-2009.01	RCT	3 months	Tenofovir	14	300	47.5 ± 16-62	10/4	NA	28.7 ± 8.6	mortality survival MELD score	–
						non-NAs	13	–	45 ± 16-67	10/3	NA	28.0 ± 9.5		
L. J. Sun (17)	2009	China	2001.01-2008.12	Retrosp. cohort	3 months	Lamivudine	76	100	44.5 ± 3.6	60/16	NA	25.1 ± 4.8	mortality survival	6
						non-NAs	76	–	45.2 ± 3.7	60/16	NA	24.9 ± 4.2		
L. J. Sun (17)	2009	China	2001.01-2008.12	Retrosp. cohort	3 months	Lamivudine	54	100	44.1 ± 3.8	44/10	NA	37.5 ± 3.6	mortality survival	
						non-NAs	54	–	44.4 ± 3.7	44/10	NA	37.0 ± 3.9		

MELD – model for end-stage liver disease, NA – not applicable, non-NAs – non-nucleoside analogues, RCT – randomized controlled trial.

Table II. Node-splitting analyses of outcomes in patients undergoing different treatments [log OR (95 % CI)]

Name	Direct effect	Indirect effect	Overall	*p*-value
A: One-month survival rate				
Enticavir, lamivudine	–0.59 (–2.24, 1.03)	2.46 (–0.82, 6.04)	–0.14 (–1.92, 1.59)	0.08
Enticavir, non-NAs	–0.65 (–2.13, 0.90)	–3.72 (–7.38, –0.58)	–1.12 (–2.88, 0.58)	0.07
Lamivudine, non-NAs	–1.41 (–3.96, 1.11)	–0.16 (–3.35, 3.15)	–0.95 (–2.95, 0.98)	0.48
B: Two-month survival rate				
Enticavir, Lamivudine	–0.28 (–1.53, 0.97)	0.01 (–2.09, 1.99)	–0.20 (–1.30, 0.89)	0.77
Enticavir, non-NAs	–0.35 (–1.83, 1.04)	–1.52 (–3.63, 0.73)	–0.68 (–1.93, 0.59)	0.31
Enticavir, telbivudine	–0.20 (–2.15, 1.91)	1.02 (–1.66, 3.84)	–0.08 (–1.53, 1.53)	0.43
Lamivudine, non-NAs	–0.67 (–2.17, 0.92)	–0.09 (–2.51, 2.52)	–0.48 (–1.69, 0.79)	0.62
C: Three-month survival rate				
Enticavir, lamivudine	0.19 (–0.30, 0.64)	0.53 (–0.31, 1.43)	0.24 (–0.17, 0.69)	0.44
Enticavir, non-NAs	–0.65 (–1.23, –0.09)	–1.03 (–1.83, –0.31)	–0.76 (–1.26, –0.27)	0.37
Lamivudine, non-NAs	–1.06 (–1.59, –0.57)	–0.57 (–1.68, 0.57)	–1.00 (–1.48, –0.59)	0.41
D: HBV DNA				
Lamivudine, non-NAs	1.13 (–0.40, 2.48)	5.81 (3.69, 7.90)	2.29 (–0.04, 4.54)	0.01
E: MELD score				
Enticavir, lamivudine	0.18 (–2.63, 2.94)	3.42 (–3.40, 10.32)	0.70 (–1.82, 3.39)	0.29
Enticavir, non-NAs	5.20 (1.09, 9.12)	1.95 (–3.93, 7.89)	4.08 (0.77, 7.52)	0.28
Lamivudine, non-NAs	1.73 (–3.83, 7.23)	5.05 (0.13, 9.53)	3.37 (–0.23, 7.07)	0.28
F: Mortality				
Enticavir, lamivudine	0.03 (–0.71, 0.78)	–0.89 (–2.23, 0.44)	–0.23 (–0.93, 0.51)	0.21
Enticavir, non-NAs	0.22 (–0.60, 1.07)	1.69 (0.50, 3.02)	0.63 (–0.16, 1.47)	0.04
Enticavir, telbivudine	0.04 (–1.82, 1.90)	–1.39 (–3.94, 1.04)	–0.33 (–1.76, 1.06)	0.33
Lamivudine, non-NAs	1.25 (0.53, 1.99)	–0.42 (–1.69, 0.71)	0.86 (0.08, 1.67)	0.01

CI – confidence interval, non-NAs – non-nucleoside analogues, OR – odds risk

After a series of selections and searches, 12 articles were included in our meta-analysis (15–26). The total number of hepatic failure patients was 1660, among which 563 patients were treated with lamivudine, 520 patients were treated with enticavir, 105 patients were treated with telbivudine, 14 patients were treated with tenofovir and 458 patients were treated with non-nucleoside analogues (non-NAs). The main characteristics of eligible studies are given in Table I. Quality assessment revealed that the quality of each study was high: NOS scores of the cohort study ranged from 6 to 9 and most of the categories were of low risk in the RCT study.

Network meta-analyses of survival rates

One-month survival rate, two-month survival rate and three-month survival rate were analyzed using ADDIS software. Inconsistency was estimated by the node-splitting analysis; $p > 0.05$ indicated consistency (Table II). The PSRFs ranged from 1.00 to 1.02, suggesting that convergence of the models was complete, the effects of iteration were very good and the results were stable. Therefore, consistency models were chosen. As shown in Table III and Fig. 2a, the one-month survival rate in the telbivudine group patients was

Table III. Network meta-analyzes of outcomes in patients undergoing different treatments

A: One-month survival rate		OR (95 % CI)		
Enticavir	0.87 (0.15, 4.90)	0.79 (0.01, 43.92)	0.33 (0.06, 1.78)	1.09 (0.05, 22.52)
1.15 (0.20, 6.82)	Lamivudine	0.94 (0.01, 56.66)	0.39 (0.05, 2.68)	1.25 (0.07, 27.34)
1.27 (0.02, 74.57)	1.07 (0.02, 68.35)	Tenofovir	0.42 (0.01, 15.52)	1.38 (0.01, 204.33)
3.05 (0.56, 17.77)	2.59 (0.37, 19.16)	2.36 (0.06, 93.61)	non-NAs	3.32 (0.13, 99.93)
0.92 (0.04, 18.52)	0.80 (0.04, 14.68)	0.72 (0.00, 102.99)	0.30 (0.01, 7.68)	Telbivudine
B: Two-month survival rate		OR (95 % CI)		
Enticavir	0.81 (0.27, 2.43)	6.18 (0.35, 163.02)	0.51 (0.15, 1.81)	0.92 (0.22, 4.63)
1.23 (0.41, 3.68)	Lamivudine	7.77 (0.43, 188.47)	0.62 (0.18, 2.19)	1.13 (0.30, 5.41)
0.16 (0.01, 2.83)	0.13 (0.01, 2.32)	Tenofovir	0.08 (0.00, 1.14)	0.15 (0.00, 3.88)
1.97 (0.55, 6.89)	1.61 (0.46, 5.41)	12.37 (0.88, 248.54)	non-NAs	1.84 (0.32, 11.98)
1.09 (0.22, 4.64)	0.89 (0.18, 3.29)	6.73 (0.26, 202.01)	0.54 (0.08, 3.08)	Telbivudine
C: Three-month survival rate		OR (95 % CI)		
Enticavir	1.27 (0.84, 2.00)	3.94 (0.57, 33.21)	0.47 (0.28, 0.77)	0.93 (0.42, 2.02)
0.79 (0.50, 1.19)	Lamivudine	3.09 (0.46, 25.94)	0.37 (0.23, 0.55)	0.72 (0.34, 1.58)
0.25 (0.03, 1.75)	0.32 (0.04, 2.18)	Tenofovir	0.12 (0.01, 0.76)	0.24 (0.03, 1.97)
2.15 (1.31, 3.52)	2.72 (1.81, 4.39)	8.30 (1.31, 69.38)	non-NAs	1.98 (0.87, 4.71)
1.07 (0.50, 2.36)	1.38 (0.63, 2.98)	4.18 (0.51, 39.41)	0.51 (0.21, 1.15)	Telbivudine
D: HBV DNA		MD (95 % CI)		
Enticavir	0.33 (–1.25, 1.91)	2.66 (0.16, 5.19)	0.25 (–4.08, 4.73)	
–0.33 (–1.91, 1.25)	Lamivudine	2.21 (–0.81, 5.20)	–0.05 (–4.18, 4.05)	
–2.66 (–5.19, –0.16)	–2.21 (–5.20, 0.81)	non-NAs	–2.29 (–7.35, 2.87)	
–0.25 (–4.73, 4.08)	0.05 (–4.05, 4.18)	2.29 (–2.87, 7.35)	Telbivudine	
E: MELD score		MD (95 % CI)		
Enticavir	0.70 (–1.82, 3.39)	–3.79 (–10.08, 2.80)	4.08 (0.77, 7.52)	–1.16 (–6.07, 4.02)
–0.70 (–3.39, 1.82)	Lamivudine	–4.47 (–10.93, 2.25)	3.37 (–0.23, 7.07)	–1.91 (–6.83, 3.17)
3.79 (–2.80, 10.08)	4.47 (–2.25, 10.93)	Tenofovir	7.85 (2.20, 13.27)	2.59 (–5.61, 10.48)
–4.08 (–7.52, –0.77)	–3.37 (–7.07, 0.23)	–7.85 (–13.27, –2.20)	non-NAs	–5.24 (–11.11, 0.66)
1.16 (–4.02, 6.07)	1.91 (–3.17, 6.83)	–2.59 (–10.48, 5.61)	5.24 (–0.66, 11.11)	Telbivudine
	F: Mortality		OR (95 % CI)	
Enticavir	0.91 (0.47, 1.72)	0.39 (0.02, 5.02)	1.46 (0.69, 3.38)	0.95 (0.24, 3.29)
1.10 (0.58, 2.13)	Lamivudine	0.43 (0.03, 5.17)	3.91 (1.45, 10.50)	0.59 (0.09, 3.07)
2.54 (0.20, 46.38)	2.34 (0.19, 38.96)	Tenofovir	9.14 (0.88, 133.01)	1.34 (0.06, 36.58)
0.69 (0.30, 1.44)	0.26 (0.10, 0.69)	0.11 (0.01, 1.13)	non-NAs	0.15 (0.02, 1.06)
1.05 (0.30, 4.17)	1.69 (0.33, 10.60)	0.75 (0.03, 15.74)	6.70 (0.94, 56.52)	Telbivudine

CI – confidence interval, MELD – model for end-stage liver disease, non-NAs – non-nucleoside analogues, OR – odds risk

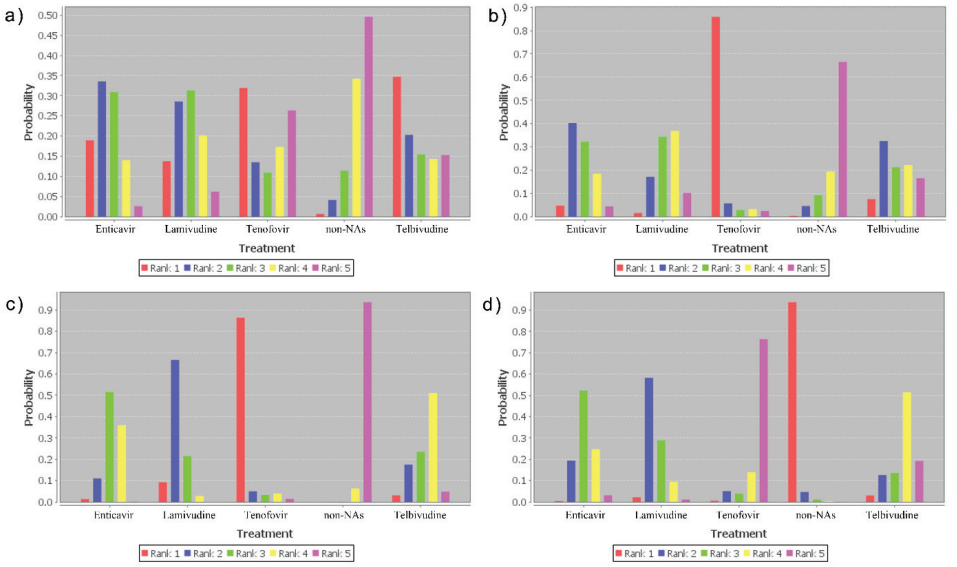

Fig. 2. Rank probability of different treatments: a) one-month survival rate, b) two-month survival rate, c) three-month survival rate, d) model for end-stage liver disease (MELD) score. Rank 1 is the best, indicating the highest treatment effect, and rank 5 is the worst, indicating the lowest treatment effect.

the highest, but there was no significant difference compared to the enticavir group (OR: 1.09; 95 % CI: 0.05–22.52), lamivudine group (OR: 1.25; 95 % CI: 0.07–27.34), tenofovir group (OR: 1.38; 95 % CI: 0.01–204.33) and non-NAs group (OR: 1.32; 95 % CI: 0.13–99.93). The two-month survival rate (Table III and Fig. 2b) of the tenofovir group was the highest, but the differences were not significant compared to the enticavir group (OR: 6.18; 95 % CI: 0.35–163.02), lamivudine group (OR: 7.77; 95 % CI: 0.43–188.47), telbivudine group (OR: 6.73; 95 % CI: 0.26–202.01) and non-NAs group (OR: 12.37; 95 % CI: 0.88–248.54). Further, the three-month survival rate (Table III and Fig. 2c) of the tenofovir group was the highest and the difference was significant compared to the non-NAs group (OR: 8.30; 95 % CI: 1.31–69.38). However, the differences compared with the other nucleoside analogues, including the enticavir group (OR: 3.94; 95 % CI: 0.57–33.21), lamivudine group (OR: 3.09; 95 % CI: 0.46–25.94) and telbivudine group (OR: 4.18; 95 % CI: 0.51–39.41) were not significant.

Network meta-analysis of HBV DNA

The $p < 0.05$ suggested that there was significant inconsistency (Table II). The PSRFs ranged from 1.00 to 1.03, indicating that model convergences were complete. Hence, an inconsistency model was used. Our results from Table III show that the concentration of HBV DNA in the enticavir group was the lowest and there was a significant difference compared to the non-NAs group (MD = –2.66, 95 % CI: –5.19 to –0.16), but there were no significant differences between the enticavir group and the other two nucleoside analogue groups, including the lamivudine group (MD: –0.33; 95 % CI: –1.91 to 1.25) and telbivudine group (MD: –0.25; 95 % CI: –4.73 to 4.08).

Network meta-analysis of MELD score

Inconsistency assessment for the MELD score revealed that all *p*-values were greater than 0.05 (Table II) and PSRFs ranged from 1.00 to 1.02. Hence, a consistency model was chosen. As shown in Table III and Fig. 2d, the tenofovir group had the lowest MELD score. There was also a significant difference between the tenofovir group and the non-NAs group (MD: –7.85, 95 % CI: –13.27 to –2.20) while the differences between the tenofovir group and the other nucleoside analogues groups, including enticavir group (MD: –3.79; 95 % CI: –10.08 to 2.80), lamivudine group (MD: –4.47; 95 % CI: –10.93 to 2.25) and telbivudine group (MD: –2.59; 95 % CI: –10.48 to 5.61), were not significant.

Network meta-analysis of mortality

p-Values between the lamivudine group and the non-NAs group and between the enticavir group and the non-NAs group were found to be less than 0.05 (Table II), indicating that the inconsistency was significant. The PSRFs ranged from 1.00 to 1.03 and, as a result, an inconsistency model was used. Mortality of the tenofovir group was found to be the lowest (Table III). However, there were no significant differences compared to the enticavir group (OR: 0.39; 95 % CI: 0.02–5.02), lamivudine group (OR: 0.43; 95 % CI: 0.03–5.17), telbivudine group (OR: 0.75; 95 % CI: 0.03–15.74) and non-NAs group (OR: 0.11; 95 % CI: 0.01–1.13).

DISCUSSION AND LIMITATIONS

It is reported that the three-month survival rate of ACLF patients receiving tenofovir treatment was significantly higher than that of the placebo group, and the MELD score and HBV DNA level were significantly reduced in the tenofovir group compared to the placebo group (22). In addition, tenofovir inhibited the viral DNA replication of lamivudine-resistant HBV in patients infected with HBV or patients co-infected with HBV and HIV (27). Besides, Ceylan *et al*. (28) reported that the virological response was better in chronic HBV infected patients treated with tenofovir than in patients treated with entecavir, while the side effects were not significantly different between the two nucleoside analogues. Furthermore, Lee *et al*. (29) revealed that in patients infected with lamivudine-resistant HBV, tenofovir monotherapy was as effective as the combination of tenofovir with lamivudine or telbivudine. It is also reported that treatments with both tenofovir and telbivudine were effective and the safety of the two nucleoside analogues was acceptable, but the estimated glomerular filtration rate (eGFR) was deteriorated in the tenofovir group while the telbivudine group showed improvement in eGFR (30). In addition, tenofovir had superior antiviral efficacy in patients with chronic hepatitis B compared to adefovir, another nucleoside analogue with a similar safety profile (31). Also, tenofovir was reported to have successfully rescued a hepatic decompensation patient infected with an adefovir resistant HBV mutant (32). The results of these studies demonstrate that the effects of tenofovir for treating HBV infection are better than or as good as other nucleoside analogues, including lamivudine, entecavir, telbivudine, tenofovir and adefovir, while their safety is acceptable. In line with previous studies, our present study showed that tenofovir treatment had the highest two-month and three-month survival rates, indicating that the patients treated

with tenofovir had a higher short-term survival rate compared to patients treated with other nucleoside analogues despite the differences not being significant. Besides, patients treated with tenofovir showed the lowest MELD score and mortality, suggesting that patients might have a better prognosis after being treated with tenofovir. Such results indicated that tenofovir was more effective than other nucleoside analogues and non-NAs in the treatment of patients with HBV-related liver failure.

To the best of our knowledge, this study was the first network meta-analysis comparing the efficacy of four nucleoside analogues, including lamivudine, entecavir, telbivudine and tenofovir, and non-NAs treatment, for the treatment of HBV-related liver failure. Major limitations of our study were as follows. First, due to incomplete data, no subgroup analysis was conducted. Second, not all drugs formed an closed loop and the number of included studies was limited, which might have resulted in exaggerated efficacy. Third, this study was unable to include all nucleoside analogues such as adefovir because of the lack of suitable studies. Fourth, out of 12 included studies, ten were conducted in China, and the other 2 studies were also from Asian countries, which might be associated with race and treatments. Hence, further tracking of related studies is needed. Fifth, only 2 RCT studies were included in the present study, the majority of studies were cohort studies, the level of evidence of which was not as good as RCT. Further studies could not be performed because of fewer RCT studies.

CONCLUSIONS

In the present study, to compare the therapeutic effect of four nucleoside analogues, we conducted a network meta-analysis based on the Bayesian framework. Our results showed that the tenofovir treatment had the highest two-month and three-month survival rates, the lowest MELD score and mortality. In conclusion, to compare the efficacy of NAs in the treatment of HBV-related liver failure, our results suggested that tenofovir might be better therapy for the treatment of HBV-related liver failure than other nucleoside analogues and non-NAs. The results of our meta-analysis may be useful as a guide for the clinical treatment of HBV-related liver failure.

Acronyms. – CI – confidence interval, eGFR – estimated glomerular filtration rate, HBV – hepatitis B virus, HIV – immunodeficiency virus, MCMC – Markov chain Monte Carlo, MD – mean difference, MELD – model for end-stage liver disease, NOS -–Newcastle-Ottawa scale (NOS), non-NAs – non-nucleoside analogues, OR – odds risk, PSFR – potential scale reduction factor, RCT – randomized controlled trial

REFERENCES

1. Y. Zhijian, L. Hui, Y. Weiming, L. Zhanzhou, C. Zhong, Z. Jinxin, W. Hongyan, D. Xiangbin, Y. Weizhi, L. Duoyun, L. Xiaojun and D. Qiwen, Role of the aspartate transaminase and platelet ratio index in assessing hepatic fibrosis and liver inflammation in adolescent patients with HBeAg-positive chronic hepatitis B, *Gastroenterol. Res. Pract.* **2015** (2015) Article ID 906026 (6 pages); https://doi.org/10.1155/2015/906026
2. Q. Zhou and H. Tang, The progress of antiviral therapy in patients with HBV-related liver failure, *Hepatogastroenterology* **60** (2013) 1877–1880.

3. S. Locarnini, Molecular virology of hepatitis B virus, *Semin. Liver Dis.* **24** (Suppl 1) (2004) 3–10.
4. Y. F. Liaw, Hepatitis B virus replication and liver disease progression: the impact of antiviral therapy, *Antivir. Ther.* **11** (2006) 669–679.
5. Y. N. Ye and Z. L. Gao, Three attacks in the development of HBV-related liver failure, *Infect. Dis. Inf.* **22** (2009) 276–279; https://doi.org/10.3969/j.issn.1007-8134.2009.05.006
6. S. Uemoto, Y. Inomata, T. H. Egawa, S. Fujita, T. Kiuchi, M. Hayashi, M. Yasutomi, H. Yamabe and K. Tanaka, Living donor liver transplantation for fulminant hepatic failure, *Transplant. Proc.* **42** (2010) 990–993; https://doi.org/10.18926/AMO/55435
7. J. Gu, X. Shi, H. Ren, Q. Xu and J. Wang, Systematic review: extracorporeal bio-artificial liver-support system for liver failure, *Hepatol. Int.* **6** (2012) 670–683; https://doi.org/10.1007/s12072-012-9352-9
8. M. K. Jain, L. Comanor, C. White, P. Kipnis, C. Elkin, K. Leung, A. Ocampo, N. Attar, P. Keiser and W. M. Lee, Treatment of hepatitis B with lamivudine and tenofovir in HIV/HBV-coinfected patients: factors associated with response, *J. Viral Hepatitis* **14** (2007) 176–182; https://doi.org/10.1111/j.1365-2893.2006.00797.x
9. Y. W. Kim, J. H. Kwon, E. Chung, S. W. Lee, J.-y. Lee, J. W. Jang, K. W. Chung and S. W. Nam, Short term virologic efficacies of telbivudine versus entecavir against hepatitis B-related hepatocellular carcinoma, *Gastroenterol. Res. Pract.* **2015** (2015) Article ID 181065 (7 pages); https://doi.org/10.1155/2015/181065
10. J. F. Zhang, Y. Guo, C. X. Chen, H. Y. Song, J. Dong, X. Chen, Z. L. Chen and B. Liu, A study on the treatment effect of telbivudine on hepatitis B patients with acute on chronic liver failure, *Mil. Med. J. Southeast China* (2016); https://doi.org/10.3760/cma.j.issn.1007-3418.2015.01.006
11. S. S. Ma, Effect of enticavir on survival of patients with HBV-related liver failure: A meta-analysis, *Shi Jie Hua Ren Xiao Hua Za Zhi* (*World Chin. J. Digestol.*) **21** (2013) 2594–2600.
12. B. Hutton, G. Salanti, D. M. Caldwell, A. Chaimani, C. H. Schmid, C. Cameron, J. P. A. Ioannidis, S. Straus, K. Thorlund, J. P. Jansen, C. Mulrow, F. Catalá-López, P. C. Gøtzsche, K. Dickersin, I. Boutron, D. G. Altman and D. Moher, The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations, *Ann. Intern. Med.* **162** (2015) 777–784; https://doi.org/10.7326/m14-2385
13. C. P. Robert and G. Casella, *Monte Carlo Statistical Methods*, 2nd ed., Springer, New York, 2004.
14. S. P. Brooks and A. Gelman, General methods for monitoring convergence of iterative simulations, *J. Comput. Graph. Stat.* **7** (1998) 434–455.
15. T. Kanda, M. Shinozaki, H. Kamezaki, S. Wu, S. Nakamoto, M. Arai, K. Fujiwara, N. Goto, F. Imazeki and O. Yokosuka, Efficacy of lamivudine or entecavir on acute exacerbation of chronic hepatitis B, *Int. J. Med. Sci.* **9** (2012) 27–32.
16. B. Lin, C. Q. Pan, D. Xie, J. Xie, S. Xie, X. Zhang, B. Wu, C. Lin and Z. Gao, Entecavir improves the outcome of acute-on-chronic liver failure due to the acute exacerbation of chronic hepatitis B, *Hepatol. Int.* **7** (2013) 460–467; https://doi.org/10.1007/s12072-012-9415-y
17. L. J. Sun, J. W. Yu, Y. H. Zhao, P. Kang and S. C. Li, Influential factors of prognosis in lamivudine treatment for patients with acute-on-chronic hepatitis B liver failure, *J. Gastroenterol. Hepatol.* **25** (2010) 583–590; https://doi.org/10.1111/j.1440-1746.2009.06089.x
18. L. Wang, H. Chen, C. Fan and Z. Gong, Efficacy and safety of telbivudine therapy in liver failure patients with chronic hepatitis B virus infection, *J. Med. Virol.* **85** (2013) 1907–1912; https://doi.org/10.1002/jmv.23689
19. Y. Xianghui, X. Lang, Z. Yan, Z. Li, S. Xiaofeng and R. Hong, Prediction of prognosis to lamivudine in patients with spontaneous reactivation of hepatitis B virus-related acute-on-chronic liver failure: Using virologic response at week 4, *Eur. J. Intern. Med.* **25** (2014) 860–864; https://doi.org/10.1016/j.ejim.2014.10.007

20. T. Chen, Y. He, X. Liu, Z. Yan, K. Wang, H. Liu, S. Zhang and Y. Zhao, Nucleoside analogues improve the short-term and long-term prognosis of patients with hepatitis B virus-related acute-on-chronic liver failure, *Clin. Exp. Med*. **12** (2012) 159–164; https://doi.org/10.1007/s10238-011-0160-7
21. Y. L. Cui, Y. Fang, Y. B. Wang, X. Q. Song, L. Li, X. Z. Lei, M. H. Zheng, T. Hong and F. Ping, Nucleoside analogue can improve the long-term prognosis of patients with hepatitis B virus infection-associated acute or chronic liver failure, *Dig. Dis. Sci*. **55** (2010) 2373–2380; https://doi.org/10.1007/s10620-010-1257-7
22. H. Garg, S. K. Sarin, M. Kumar, V. Garg, B. C. Sharma and A. Kumar, Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure, *Hepatology* **53** (2011) 774–780; https://doi.org/10.1002/hep.24109
23. K. Ma, W. Guo, M. Han, G. Chen, T. Chen, Z. Wu, D. Yang, J. Huang, Y. Huang, X. Zhao, J. Song, J. Qi and Q. Ning, Entecavir treatment prevents disease progression in HBV related acute-on-chronic liver failure: Establishment of a novel logistical regression model, The International Liver Congress™ 201 – 46th annual meeting of the European Association for the Study of the Liver, Berlin, March 30 to April 3, 2011, Poster 742, *J. Hepatol*. **54** (Suppl. 1) (2011) S298; https://doi.org/10.1016/S0168-8278(11)60744-7
24. J. Lai, Y. Yan, L. Mai, Y. B. Zheng, W. Q. Gan and W. M. Ke, Short-term entecavir versus lamivudine therapy for HBeAg-negative patients with acute-on-chronic hepatitis B liver failure, *Hepatob. Pancreat. Dis. Int.* **12** (2013) 154–159.
25. Y. Zhang, X. Y. Hu, S. Zhong, F. Yang, T. Y. Zhou, G. Chen, Y. Y. Wang and J. X. Luo, Entecavir vs lamivudine therapy for naïve patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure, *World J. Gastroenterol*. **20** (2014) 4745–4752; https://doi.org/10.3748/wjg.v20.i16.4745
26. J. Wang, K. Ma, M. Han, W. Guo, J. Huang, D. Yang, X. Zhao, J. Song, D. Tian and J. Qi, Nucleoside analogs prevent disease progression in HBV-related acute-on-chronic liver failure: validation of the TPPM model, *Hepatol. Int.* **8** (2014) 64–71; https://doi.org/10.1007/s12072-013-9485-5
27. J. Wang, J. Liu, C. Qi, T. Yan, F. Cao, L. Jin, Y. He, Y. Yang, S. Zhang, T. Chen and Y. Zhao, Efficacy of tenofovir disoproxil fumarate to prevent vertical transmission in mothers with lamivudine-resistant HBV, *Antivir. Ther.* **20** (2015) 681–687; https://doi.org/10.3851/IMP2981
28. B. Ceylan, C. Yardimci, M. Fincanci, G. Eren, U. Tozalgan, C. Muderrisoglu and Y. Akkoyunlu, Comparison of tenofovir and entecavir in patients with chronic HBV infection, *Eur. Rev. Med. Pharmacol. Sci*. **17** (2013) 2467–2473.
29. Y. B. Lee, E. U. Jung, B. H. Kim, J. H. Lee, H. Cho, H. Ahn, W. M. Choi, Y. Y. Cho, M. Lee and J. J. Yoo, Tenofovir monotherapy versus tenofovir plus lamivudine or telbivudine combination therapy in treatment of lamivudine-resistant chronic hepatitis B, *Antimicrob. Agents Ch*. **59** (2014) 972–978; https://doi.org/10.1128/AAC.04454-14
30. Z. Krastev, D. Petrova, I. Kotzev, M. K. Celen, M. Mendelson, R. Chandra, P. Pandey and K. Hamed, Telbivudine *vs* tenofovir in hepatitis B e antigen-negative chronic hepatitis B patients: OPTIMA roadmap study, *World J. Hepatol*. **8** (2016) 1402–1413; https://doi.org/ 10.4254/wjh.v8.i32.1402
31. P. Marcellin, Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B, *New Engl. J. Med*. **359** (2009) 2442–2455; https://doi.org/10.1056/NEJMoa0802878
32. V. Ratziu, V. Thibault, Y. Benhamou and T. Poynard, Successful rescue therapy with tenofovir in a patient with hepatic decompensation andesistant HBV mutant, *Comp. Hepatol*. **5** (2006) 1–4; https://doi.org/10.1186/1476-5926-5-1