The Efficacy and Safety of Nucleos(t)ide Analogues in Patients with Spontaneous Acute Exacerbation of Chronic Hepatitis B: A Systematic Review and Meta-Analysis

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Abstract

Background: Spontaneous acute exacerbation (AE) of chronic hepatitis B (CHB) is often detrimental but sometimes leads to sustained immune control and disease remission. The efficacy and safety of nucleos(t)ide analogues (NAs) in patients with spontaneous AE of CHB remains unclear.

Methods: We performed a systematic review and meta-analysis of NAs in patients with spontaneous AE of CHB. We calculated pooled effects of NAs in these patients of each study and conducted quantitative meta-analysis, displaying results using Forest plots.

Results: 15 studies were included and substantial heterogeneity was noted in the inclusion/exclusion criteria and controls. Pooled data showed no benefit of lamivudine (LAM) vs. untreated controls for transplant-free survival in patients with spontaneous AE of CHB (OR = 0.98 (95% CI, 0.50–1.92; P = 0.956)), hepatic decompensation (OR = 0.94 (95% CI, 0.47–1.88; P = 0.862)) and liver failure owing to AE (OR = 2.30 (95% CI, 0.35–15.37; P = 0.387)) at 3 months. Entecavir achieved even higher short-term mortality than LAM. NAs led to rates of ALT normalization, undetectable HBV DNA, HBeAg loss, HBeAg seroconversion and drug resistance at 1 year in 88%, 61%, 46%, 35% and 5%. Pooled data also showed benefit favoring LAM vs. untreated controls for ALT normalization (OR = 1.98 (95% CI, 1.03–3.80; P = 0.039)) and undetectable HBV DNA (OR = 38.50 (95% CI, 7.68–192.99; P < 0.001)) at 3 months. All NAs were relatively safe and well tolerated.

Conclusion: NAs had no obvious impact on short-term survival in patients with AE of CHB, despite of possible better antiviral responses. We suggest additional studies to evaluate the efficacy of other NAs and early introduction of immunosuppressant in combination with NAs. We highlight developing prognostic models to identify predictors of mortality and disease progression for AE of CHB.

Citation: Yu W, Zhao C, Shen C, Wang Y, Lu H, et al. (2013) The Efficacy and Safety of Nucleos(t)ide Analogues in Patients with Spontaneous Acute Exacerbation of Chronic Hepatitis B: A Systematic Review and Meta-Analysis. PLoS ONE 8(6): e65952. doi:10.1371/journal.pone.0065952

Editor: James Fung, The University of Hong Kong, Hong Kong

Received January 24, 2013; Accepted May 1, 2013; Published June 11, 2013

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Funding: The authors have no support or funding to report.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Chronic hepatitis B virus (HBV) infection is a major global public health problem. It is estimated that approximately over 350 million people worldwide have been chronically infected with HBV [1]. The infection can result in a variable spectrum of liver disease, ranging from an inactive carrier state, through persistent chronic hepatitis B (CHB), and eventually to end stage liver diseases including decompensated cirrhosis and hepatocellular carcinoma (HCC) [2]. In a small number of patients, acute exacerbation (AE) or acute flare of CHB, which is defined as an abrupt elevation of serum alanine aminotransferase (ALT) levels to greater than five times the upper limit of normal (ULN) occurs spontaneously [3]. Severe acute exacerbation (SAE) presented with high ALT levels accompanied by jaundice can also be seen in approximately 15%–37% of CHB patients in 4 years [4]. These exacerbations may progress to acute on chronic liver failure with high potential mortality [5]. To date, no specific therapy is established for this critical scenario from chronic hepatitis to fulminate hepatic failure owing to AE. The underlying pathogenesis is likely related to excessive host immune responses against HBV-infected hepatocytes. And the goals of treatment are to (1), prevent the short-term development or deterioration of hepatic decompensation and (2), improve HBV clearance and achieve better long-term virological and serological responses.

Nucleos(t)ide analogues (NAs), having rapid and direct role in suppression of HBV, which hopefully can calm down the immune activity and buy time for the hepatitis to settle, might be the treatment of choice. Although majority of the studies have demonstrated no benefits of NAs therapy on either improvement of short-term survival or protection against rapid progression of
the disease to liver failure [6,7]. In a small preliminary study in Japan, 3 patients with SAE had developed hepatic encephalopathy (HE) and severe coagulopathy responded to lamivudine (LAM) and survived dramatically [8]. Another study from Taiwan suggested that LAM treatment had definite survival benefit among patients with low baseline serum bilirubin level (<20 mg/dL) [6]. It is also noted that good virological and biochemical responses have been achieved in the patients with AE of CHB who received NAs therapies [9,10,11]. It was estimated that patients with a pre-therapy ALT level over 5 × ULN appeared to have a rate of hepatitis B e antigen (HBeAg) seroconversion as high as 64% after 1 year of LAM therapy [12]. If the patients with SAE of CHB received a longer LAM treatment, an even higher HBeAg seroconversion rate of 70% could be obtained [13]. On the contrary, other studies indicated that LAM treatment, compared with untreated group, did not increase the rate of sustained remission among patients with AE of CHB [14]. The NAs therapies might also result in high rates of virological breakthrough and drug resistance during or after therapies [13,15,16]. Since the current studies are largely limited by small sample sizes, lack of contemporary controls, short durations of follow-up, and discrep-
tant inclusion criteria, it is still controversial whether the patients with AE of CHB may achieve better clinical outcomes and antiviral responses if NAs therapies were given.

In the present study, we aim to investigate the efficacy and safety of NAs in the treatment of patients with AE of CHB by performing a systematic review and meta-analysis.

**Methods**

**Search Strategy**

Studies of the English/Chinese-language were identified by an electronic search using MEDLINE, EMBASE, ISI Web of Knowledge, English Medical Current Contents (EMCC), China National Knowledge Infrastructure (CNKI), WANFANG Database, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. A manual search of abstracts of international liver meetings (from 2006 to 2012) and reference lists of retrieved articles and qualitative topic reviews was also performed. The following key words were searched (on December 12th, 2012) with appropriate modification of the PubMed search strategy for other databases:

- (hepatitis b virus infection OR chronic hepatitis b virus infection OR chronic hepatitis b) OR “Hepatitis b”[Mesh] AND (acute flare OR acute flares OR acute exacerbation OR acute exacerbations OR severe acute exacerbation OR severe acute exacerbations) AND (therapy OR therapies OR treatment OR treatments) OR (nucleoside analogues OR nucleotide analogues OR oral agents) OR “lamivudine”[Mesh] OR “adefovir”[Mesh] OR “entecavir”[Mesh] OR “tenofovir”[Mesh] OR “telbivudine”[Mesh]) AND (mortality OR mortalities OR fatality OR fatalities OR prognoses OR prognosis OR prognostic OR death OR deaths OR died OR survival OR survivor OR survivors OR survived OR alive OR HBeAg loss OR HBeAg seroclearance OR HBeAg seroconversion) OR “Mortality”[Mesh] OR “Prognosis”[Mesh] OR “Survival”[Mesh] OR “Survivors”[Mesh] OR “Death”[Mesh] OR “HBeAg”[Mesh]).

The literature retrieval, trial selection and data extraction were operated independently by two researchers, reaching to consensus by conferring with each other when discrepancies appeared. In addition, the citations in retrieved publications were also searched manually.

**Inclusion and Exclusion Criteria**

The inclusion criteria were included as following: (1) study population: adult CHB patients with spontaneous AE presented with elevation of serum ALT levels to greater than 5 × ULN, studies in patients with SAE of CHB defined as elevation of ALT levels accompanied by jaundice and/or coagulopathy were also included; (2) treatment regimen: oral NAs monotherapy or in combination; (3) study design: any design including retrospective or open-label prospective studies with or without a control group.

The following exclusion criteria were used: (1) non-adult study population, liver transplantation recipients or pregnancy; (2) AE occurring in patients receiving chemotherapy, immunosuppressive therapy or anti-HBV therapy; (3) interferon, traditional Chinese medicine, stem cells or corticoids treatments; (4) co-infection with hepatitis A, C, D, E virus, Epstein-Barr virus, cytomegalovirus or human immunodeficiency virus (HIV); (5) other concomitant liver diseases such as autoimmune hepatitis, alcoholic liver disease, drug-induced liver injury or Wilson’s disease.

**Assessment of Study Quality**

A quality score for each study was determined using several binomial parameters (Table S1). Parameters were chosen based on their relevance to the analysis of observational studies. Each parameter was given a numerical score of 0 or 1 with an overall quality score ranging from 0 to 10. Studies with a quality score of <5 were rated as poor while those ≥5 were rated as high quality studies.

**Efficacy Measures and Definitions**

Efficacy measures were categorized as: (1) total liver transplant (LT)-free survival rate defined as proportion of patients with AE of CHB surviving without LT; (2) LT-free survival rate of patients with hepatic decompensation and liver failure owing to AE defined as proportion of patients experienced hepatic decompensation or developed liver failure at baseline or during therapy due to clinical deterioration surviving without LT; (3) worsening of liver disease rate defined as proportion of patients developed liver disease worsening manifested by occurrence of hepatic decompensation and liver failure; (4) biochemical, virological and serological: proportion of patients with ALT normalization, undetectable HBV DNA, HBeAg loss and HBeAg seroconversion. The following measures were used for evaluating safety for each drug: (1) proportion of patients with drug related serious adverse events; (2) proportion of patients with confirmed drug resistant HBV determined using direct sequencing or line probe assay.

**Data Collection and Analysis**

Data were extracted for: (1) study characteristics (author and year of publication, area of origin, study design, sample size, study quality); (2) patient demographics (age, gender, percentage of HBeAg positivity, percentage of liver cirrhosis, distribution of HBV genotypes); (3) inclusion and exclusion criteria; (4) treatment details (antiviral agent used, dose of drug, duration of treatment and duration of follow-up); and (5) study outcomes of the treatment. Quantitative meta-analysis was conducted using Comprehensive Meta-Analysis (V2.0; Biostat, Englewood Cliffs, New Jersey, USA). Pooled effects with 95% confidence interval (CI) were reported for the uncontrolled data while odds ratios (OR) with 95% CI were reported for studies with untreated control groups. A P value of less than 0.05 was considered to indicate a statistically significant difference. Heterogeneity was assessed for each analysis using Cochrane’s Q test. A P value less than 0.10 indicated heterogeneity. Meta-analysis was performed
using random-effect methods, despite the absence of significant heterogeneity. The potential risk of publication bias was examined using the Egger’s test. Publication bias was indicated if the P value was less than 0.05.

Results

Characteristics of the Included Studies

15 studies involving a total of 1181 patients fulfilled the criteria for this systematic review and meta-analysis (Figure 1 and Table 1). Most of these studies (14/15) were related to LAM. Of the 14 studies evaluating LAM, 6 were open-label studies, 4 compared LAM to untreated or historical controls, 2 compared LAM in CHB patients between with or without AE, and 2 compared LAM to entecavir (ETV) as historical controls [6,7,8,10,11,13,14,15,16,17,18,19,20,21]. Both of the 2 studies evaluating ETV had a historical control group of LAM [10,21]. Telbivudine (LDT) was evaluated in one prospective study as compared to a control group without AE [9].

Baseline characteristics of the patients enrolled in the studies were shown in Table 1. The sample size ranged from 10 to 253 treated patients among these studies. All of the studies were conducted in the Southeast Asian region. There was great variability among these studies regarding inclusion criteria (e.g. ALT levels at entry, percentage of HBeAg positivity, distribution of HBV genotypes), exclusion criteria (co-infection with HCV, HDV and/or HIV, HCC, acute liver failure), and definition of hepatic decompensation (Table 1). Furthermore, the selection of controls was variable among the controlled studies. Nonetheless, the majority of these studies were of good quality with a total quality score ≥5 (Table S1).

Efficacy Analysis

Total LT-free survival rate. Analysis of the pooled open-label data did not show beneficial effects for LAM regarding the total LT-free survival rate in patients with AE of CHB. LAM was associated with a total LT-free survival rate of 97% at 3 months, followed by a decline to 93% at 1 year. Moreover, total LT-free survival rate with LAM was not significantly higher compared to untreated controls at 3 months (Table 2 and Figure 2).

In one retrospective study comparing LAM (n = 24) and ETV (n = 10) in patients with 500 IU/L or higher ALT, ETV was not superior to LAM for LT-free survival at 1 year. All patients in both groups survived, despite one LAM-treated patient had HE at baseline [21].

LT-free survival rate in patients with hepatic decompensation and liver failure owing to AE. Hepatic decompensation owing to AE was defined as significant liver function abnormality as indicated by raised serum bilirubin and prolonged prothrombin time or occurrence of complications such as ascites during the exacerbation period [22]. Liver failure owing
| Year Ref. | Area      | No. of subjects | No. and type of controls | No. of liver cirrhosis | No. of HBeAg+ | Genotype A—B—C—B+C | Duration treatment (months) |
|----------|-----------|-----------------|--------------------------|-----------------------|---------------|---------------------|-----------------------------|
| 2001[8]* | Japan     | 10              | NA                       | 0                     | 4             | 8                   | NA                          | 15                          |
| 2001[9]+ | Taiwan    | 31              | NA                       | 0                     | 5±ULN         | 0                   | NA                          | 15                          |
| 2002[10] | Hong Kong | 28              | 18 historical controls   | 6±ULN                 | 0±ULN         | 16                  | NA                          | 1–34                       |
| 2003[11]*| Taiwan    | 60              | 31 historical controls   | 0±ULN                 | 19            | 23                  | NA                          | 1.5 (1–12)                 |
| 2005[12]| Japan     | 25              | 25 historical controls   | 0±ULN                 | 4±ULN         | 21                  | NA                          | 2.23±0.0                   |
| 2006[13]**| Taiwan    | 75              | NA                       | 0±ULN                 | 19±ULN        | 75                  | 0.39±0.5                    | 18                          |
| 2006[14] | Hong Kong | 32              | NA                       | 0±ULN                 | 7±ULN         | 0±23±9±0           | 33                          | 33±1±0                     |
| 2008[15]**| Taiwan    | 45              | 31 non AE                | 0±ULN                 | 10±ULN        | 45                  | 1±30±8±2                   | 34                          |
| 2009[16]**| Taiwan    | 253             | NA                       | 0±ULN                 | 9±ULN         | 253                 | 3±7±31±*                   | 12–18                     |
| 2009[17] | Taiwan    | 102             | 52 untreated controls    | 0±ULN                 | 5±ULN         | 102                 | 0±4±45±11                  | 18                          |
| 2010[18]**| Taiwan    | 146             | HBeAg+, naive, Age 18+   | 5±ULN                 | 7±ULN         | 102                 | 0±10±4±3±0                 | 19.1                       |
| Year Ref. | Area       | No. of subjects | No. and type of controls | Key inclusion criteria | Key exclusion criteria | No. and definition of hepatic decompensation | No. of liver cirrhosis | No. of HBeAg+ | Genotype | Duration treatment (months) |
|----------|------------|-----------------|--------------------------|------------------------|------------------------|---------------------------------------------|-----------------------|--------------|----------|-----------------------------|
| 2011[10] | Hong Kong  | 117             | 36 ETV                   | TB: >45 μmol/L, naive  | HAV, HCV, HEV co-infections, HCC, HE, biliary obstruction | NA                           | 10 >ULN     | 25          | 55       | NA                          | 12            |
| 2012[21]| Japan     | 24              | 10 ETV                   | HBV DNA: >4.5 log IU/mL, naive | HAV, HCV, HDV, HEV, HIV coinfections, HCC | NA                           | 10 >ULN     | 2           | 18       | NA                          | 12            |

**Studies using ETV**

| Year Ref. | Area       | No. of subjects | No. and type of controls | Key inclusion criteria | Key exclusion criteria | No. and definition of hepatic decompensation | No. of liver cirrhosis | No. of HBeAg+ | Genotype | Duration treatment (months) |
|----------|------------|-----------------|--------------------------|------------------------|------------------------|---------------------------------------------|-----------------------|--------------|----------|-----------------------------|
| 2011[10] | Hong Kong  | 36              | 117 LAM historical TB: >45 μmol/L, naive | HAV, HCV, HEV co-infections, HCC, HE, biliary obstruction | NA | 10 >ULN | 5 | 13 | NA | 12 |
| 2012[21]| Japan     | 10              | 24 LAM historical HBV DNA: >4.5 log IU/mL, naive | HAV, HCV, HDV, HEV, HIV coinfections, HCC | NA | 10 >ULN | 0 | 4 | NA | 12 |

**Studies using LDT**

| Year Ref. | Area       | No. of subjects | No. of non AE | HBV DNA: >5 log copies/mL, naive | HCV, HDV, HEV co-infections, HCC, LC, ALD | No. and definition of hepatic decompensation | No. of liver cirrhosis | No. of HBeAg+ | Genotype | Duration treatment (months) |
|----------|------------|-----------------|---------------|---------------------------------|---------------------------------------------|---------------------------------------------|-----------------------|--------------|----------|-----------------------------|
| 2010[9]  | China      | 40              | 40 non AE     | HBV DNA: >5 log copies/mL, naive | HCV, HDV, HEV co-infections, HCC, LC, ALD | NA | 10-20 >ULN | 0 | 40 | NA | 12 |

AIH, autoimmune hepatitis; ALD, alcoholic liver disease; ALT, alanine aminotransferase; DM, diabetes mellitus; ETV, entecavir; HAV, hepatitis A virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HE, hepatic encephalopathy; HEV, hepatitis E virus; HIV, Human immunodeficiency virus; LAM, lamivudine; LDT, telbivudine; NA, not available; NAs, nucleos(t)ide analogues; PT, prothrombin time; TB, serum total bilirubin; ULN, upper limit of normal.

1. Of 10 enrolled, 6 patients with dose of LAM 300 mg/day, 4 had undergone interferon or corticosteroid treatment for liver disease.
2. Patients had comorbid illnesses in both groups.
3. Dose of LAM 150 mg/day; otherwise the doses of drugs were as follows: LAM 100 mg/day, ETV 0.5 mg/day, LDT 600 mg/day.
4. IgM anti-HBc seronegative patients were recruited as control group.
5. Patients without AE were recruited as control group, and subset data on 45 patients with AE were abstracted.
6. 15 patients with SAE were treated with LAM 300 mg/day for only a short term at the start of therapy.
7. 38.3% and 4.8% of patients had exposed to LAM and had definitely LAM resistance before enrolment, 104 were examined for HBV genotypes.
8. Detection limit for HBV DNA was 100 copies/ml for calculation.

DOI: 10.1371/journal.pone.0065952.t001
to AE was manifested by occurrence of HE and/or PTA<40% in this study. In the patients with hepatic decompensation, LAM was found to be associated with LT-free survival rate of 85% and 83% at 3 months and 1 year, respectively. Among the patients diagnosed as liver failure, the use of LAM was associated with survival rate as low as 35% and 34% at 3 months and 1 year, respectively. Moreover, no beneficial effect of LAM on the LT-free survival rate was observed in the patients with hepatic decompensation compared to untreated controls at 3 months (Table 2 and Figure 3).

In one retrospective study comparing LAM (n = 117) and ETV (n = 36) in patients with ALT and serum bilirubin increased beyond 10×ULN and 3×ULN, respectively, although ETV and LAM were similar in achieving mortality rate between one month and one year (8% vs. 3%, P = 0.14), ETV achieved an even higher mortality within the first month compared to LAM historical controls (11% vs. 2%, P = 0.028). If only considering liver related mortality, ETV was also likely to exhibit a significantly higher incidence compared to LAM (17% vs. 3%, P = 0.014) [10].

Worsening of Liver Disease

Progression to hepatic decompensation from AE of CHB. In a single study of 154 patients with ALT levels greater than 5×ULN without jaundice or coagulopathy, comparing with untreated controls (n = 52), LAM (n = 102) showed no beneficial effects regarding the protection from progressing to hepatic decompensation. 3 (3%) LAM patients, but none of untreated controls, progressed to hepatic decompensation at 1.5 years [14].

Development of liver failure in patients with hepatic decompensation. Analysis of the pooled open-label data did not show beneficial effect for LAM regarding the proportion of liver failure development in patients with hepatic decompensation. 23 out of 123 LAM patients (19%, 95% CI, 12%–26%) with hepatic decompensation developed liver failure during the first month. Moreover, LAM was not effective in reducing the incidence of liver failure in patients with hepatic decompensation at 3 months compared to untreated controls with OR of 0.82 (95% CI, 0.39–1.70, P = 0.59) (Table 2).

Worsening of liver disease was also indicated by occurrence of other complications such as variceal bleeding and hepatorenal syndrome. Although one study comparing ETV (n = 36) and LAM (n = 117) showed that the proportion of patients developing variceal bleeding, spontaneous bacterial peritonitis, and hepatorenal syndrome were similar with these two agents, occurrence of HE and ascites were even more common in ETV-treated patients (17% vs. 3%, P = 0.012; 11% vs. 2%, P = 0.028, respectively) [10].

Table 2. Pooled effect of four LAM studies with an untreated control group in AE of CHB.

| Study name          | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value | Odds ratio and 95% CI |
|---------------------|------------|-------------|-------------|---------|---------|----------------------|
| Chan HL 2002        | 1.410      | 0.358       | 5.553       | 0.492   | 0.623   | 0.981 (0.501–1.918)   |
| Chien RN 2003       | 0.614      | 0.242       | 1.558       | -1.027  | 0.304   |                      |
| Tsubota A 2005      | 1.833      | 0.387       | 6.867       | 0.764   | 0.445   |                      |
| Sheu MJ 2009        | 0.981      | 0.502       | 1.918       | -0.055  | 0.956   |                      |

LT-free survival in patients with AE of CHB 4 215 182 126 107 0.981 (0.501–1.918) 0.956 2.100 0.551 0.187

LT-free survival in patients with hepatic decompensation 3 116 83 74 55 0.941 (0.472–1.876) 0.862 1.851 0.396 0.031

LT-free survival in patients with liver failure 2 15 4 12 2 2.308 (0.347–15.368) 0.387 0.015 0.903 NA

Rate of progression to hepatic decompensation 4 215 24 126 17 0.892 (0.438–1.817) 0.752 1.003 0.800 0.460

Rate of development of liver failure 3 113 21 74 17 0.818 (0.393–1.703) 0.592 0.078 0.962 0.089

ALT normalization 2 85 58 67 33 1.983 (1.034–3.802) 0.039 14.818 <0.001 NA

Undetectable HBV DNA 1 25 22 25 4 38.500 (7.681–192.985) <0.001 NA NA NA

HBeAg loss 1 21 11 18 9 1.100 (0.312–3.877) 0.882 NA 0.700 NA

LT, liver transplantation; OR, odds ratio.

Efficacy and Safety Evaluation of NAs Therapy

PLOS ONE | www.plosone.org 6 June 2013 | Volume 8 | Issue 6 | e65952

Table 2. Pooled effect of four LAM studies with an untreated control group in AE of CHB.
Biochemical, virological and serological responses. Analysis of the pooled data showed beneficial effects for NAs in regard to the proportion of patients with ALT normalization, undetectable HBV DNA, HBeAg loss and HBeAg seroconversion (Table 3). The use of LAM was associated with rates of ALT normalization, undetectable HBV DNA, HBeAg loss and HBeAg seroconversion at 3 months as Table 3. Pooled effect from open-label studies on efficacy and safety outcomes.

| Study name          | Odds ratio Lower limit | Odds ratio Upper limit | Z-Value | p-Value |
|---------------------|------------------------|------------------------|---------|---------|
| Chan HL 2002        | 1.410                  | 0.358                  | 5.553   | 0.492   | 0.623  |
| Chien RN 2003       | 0.614                  | 0.242                  | 1.558   | -1.027  | 0.304  |
| Tsubota A 2005      | 1.833                  | 0.387                  | 8.674   | 0.764   | 0.445  |
|                     | 0.941                  | 0.472                  | 1.876   | -0.174  | 0.862  |

Figure 3. Meta-analysis of LT-free survival in patients with hepatic decompensation. At 3 months, 71% of the 116 LAM-treated patients with hepatic decompensation survived without liver transplantation as compared to 74% of the 74 untreated controls with odds ratio of 0.94 (95% CI, 0.472–1.876, P = 0.862).

doi:10.1371/journal.pone.0065952.g003

doi:10.1371/journal.pone.0065952.t003

Table 3. Pooled effect from open-label studies on efficacy and safety outcomes.

| Study name          | ALT normalization (%) | Undetectable HBV DNA (%) | HBeAg loss (%) | HBeAg seroconversion (%) | Drug resistance (%) |
|---------------------|-----------------------|--------------------------|----------------|--------------------------|---------------------|
| Studies using LAM (3 months) | 3 288 | 77(60–88) | 0.001 | 3 144 | 34(21–51) | 0.062 |
| Studies using all NAs (1 year) | 6 591 | 88(79–93) | <0.001 | 5 338 | 61(43–76) | 0.051 |
| Studies using LAM (1 year) | 4 527 | 89(78–95) | <0.001 | 3 274 | 41(35–47) | 0.005 |
| Studies using ETV (1 year) | 1 24 | 98(75–100) | 0.006 | 1 24 | 71(50–85) | 0.048 |
| Studies using LDT (1 year) | 1 40 | 75(60–86) | 0.003 | 1 40 | 73(57–84) | 0.006 |
| Studies using LAM (2 years) | 3 343 | 70(42–89) | 0.161 | 3 343 | 48(29–68) | 0.864 |
| Studies using LAM (3 years) | 1 7 | 57(23–86) | 0.706 | 1 7 | 57(23–86) | 0.706 |
| Studies using all NAs (1 year) | 7 528 | 46(42–51) | 0.098 | 9 550 | 35(27–44) | 0.002 |
| Studies using LAM (1 year) | 5 477 | 46(42–51) | 0.092 | 6 495 | 34(24–46) | 0.009 |
| Studies using ETV (1 year) | 1 11 | 64(34–86) | 0.372 | 2 15 | 41(19–71) | 0.479 |
| Studies using LDT (1 year) | 1 40 | 45(31–60) | 0.528 | 1 40 | 38(24–53) | 0.118 |
| Studies using LAM (2 years) | 3 343 | 49(39–59) | 0.852 | 3 347 | 35(29–41) | <0.001 |
| Studies using LAM (3 years) | 1 7 | 43(14–78) | 0.706 | 1 7 | 14(2–58) | 0.097 |
| Studies using all NAs (1 year) | 5 325 | 52(12–11) | <0.001 | |
| Studies using LAM (1 year) | 4 285 | 9(6–13) | <0.001 | |
| Studies using ETV (1 year) | 2 0 | 0 | NA | |
| Studies using LDT (1 year) | 1 40 | 3(4–16) | <0.001 | |
| Studies using LAM (2 years) | 3 82 | 16(6–38) | 0.005 | |
| Studies using LAM (3 years) | 2 52 | 26(17–38) | <0.001 | |
null
term (less than 1 year) observation, and was likely related to presumed duration of AE.

Additionally, the high mortality rate despite NAs treatment could be partially related to the delayed commencement, when the livers of these patients had already undergone massive or submassive hepatic necrosis, as the main determinants for recovery are the rapid cessation of ongoing necro-inflammation and liver regeneration. Thus further researches about the prognostic factors that could sensitively mirror the severity of hepatic impairment and possibility of recovery might be warranted. Many prognostic markers, such as serum bilirubin, HBV DNA, platelet (PLT) and PT were researched closely to find the risk of progression. During AE of HBeAg-positive CHB, serum HBV DNA cut-off value of $1.55 \times 10^5$ copies/mL can predict decompensation and be used to identify patients in need of immediate antiviral therapy [29]. Serum bilirubin ($>5$ mg/dl) was identified as a significant determinant of progression to liver failure and prothrombin activity ($<45\%$) as a determinant of liver related death [30]. Low PLT ($\leq 143 \times 10^9/L$) and high serum bilirubin ($>172 \text{ mmol/L}$) was also reported to be the only independent factors of mortality [17]. Platelet count ($<100 \times 10^9$/L) was linked to rapid progression to hepatic failure [7]. The cut-off values for bilirubin predictive of mortality were also reported as 10 mg/dL by Chan et al. [21] and 20 mg/dL by Chien et al. [6]. However, in all studies, the level of serum ALT had no prognostic value.

Higher ALT reflects a more robust immune clearance of HBV both in the setting of natural course and during therapy [1]. Our pooled analysis of uncontrolled studies showed numerically much better biochemical and virological responses among CHB patients with AE than that without AE [31]. Especially in meta-analysis, LAM led to much more undetectable HBV DNA with OR of 38.5 at 3 months. Previous trials had also reported an association between high baseline ALT levels and increased HBeAg seroconversion rates. However, it was reported that post treatment relapses were common. High rate of SAE among the relapers (18–50%) posed great risk to patients upon treatment cessation [13,15,16,23]. In addition, once initiated, life long therapy might be necessary. According to Asian-Pacific consensus statement on the management of CHB, it is reasonable to delay treatment for an observation period of 3 months, if there is no concern about hepatic decompensation in patients with elevation of ALT to more than $5 \times \text{ULN}$ [22]. Thus, it might be rational to carefully start to treat these patients without evidence of development or deterioration of hepatic decompensation. And early introduction of immunosuppressive therapy in combination with NAs might offer an alternative for treating patients with hepatic decompensation due to AE. In addition, prognostic models to identify the predictive parameters for disease progression and mortality that can assist management decision might be warranted.

Drug related serious adverse event is another important consideration when treating patients with AE of CHB. Drug safety is a particular consideration in patients with hepatic decompensation and impending liver failure who had potential impaired drug metabolism and renal function. In our results, elevation of CK was seen in about 10% of LDT-treated patients, but did not result in medication cessation or dose adjustments. Serious adverse events such as renal insufficiency, mitochondrial toxicity and lactic acidosis were not reported in either LAM or ETV patients. Drug resistance was also much less common in LAM-treated and LDT-treated patients than previous reports [15,18,32,33]. It may, in part, relate to the more severe inflammatory process and the subsequent more rapid viral loads and HBeAg titer decrease in AE. On the other hand, patients receiving ETV did not need to change their medication, which echoed with previous study [34].

Several limitations regarding our systematic review require comment. Firstly, the inclusion criteria, patients number and study design varied greatly among the studies included. The heterogeneity in patient populations leads to a lower level of confidence in the accuracy of the pooled estimates. However, all the study patients had characteristics of AE and we were able to extract the majority parameters of most studies. Secondly, there were only two studies of ETV and one of LDT, and the difference of parameters between them limited our ability to make recommendations regarding these agents. In addition, the definition of hepatic decompensation was variable, however, it manifests impending liver failure. Lastly, we were unable to conduct analysis to reveal the association between the distribution of HBV genotypes and the clinical outcomes.

In summary, our results indicated that NAs therapy had no benefit with respect to LT-free survival rate and prevention of disease deterioration of patients with AE of CHB, despite of better biochemical and virological responses. Thus, it might be rational to carefully start to treat these patients without evidence of development or deterioration of hepatic decompensation. And early introduction of immunosuppressive therapy in combination with NAs might offer an alternative for treating patients with hepatic decompensation due to AE. In addition, prognostic models to identify the predictive parameters for disease progression and mortality that can assist management decision might be warranted.

Supporting Information

### Table S1 Quality scores of the studies included in this systematic review.

(DOC)

### Author Contributions

Conceived and designed the experiments: CZ. Performed the experiments: WY CS YW HL JF. Analyzed the data: WY CS YW HL JF. Wrote the paper: WY.

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