



Upgrade Combination Response Is Limited by Prolonged Nucleos(t)ide Analogue Therapy in HBeAg-positive Chronic Hepatitis B: A Real-life Study

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Abstract

Background and Aims: Few previous studies have reported on a combination response (hepatitis B virus (HBV) DNA undetected, alanine aminotransferase normalization and hepatitis B e antigen (HBeAg) seroconversion) following nucleos(t)ide analogue (NAs) long-term therapy in patients with chronic hepatitis B (CHB). This study aimed to investigate the combination response on long-term NAs therapy in patients with HBeAg-positive CHB and to determine whether prolonged therapy is beneficial for combination response, particularly in optimal patients (baseline alanine aminotransferase level ≥ 5 upper limit of normal and HBV DNA level $< 10^9$ copies/mL). **Methods:** In total, 280 HBeAg-positive CHB patients were enrolled in this study. Among them, 190 were treated with entecavir and 90 were treated with telbivudine. **Results:** The cumulative rates of combination response in the total number of patients were 8.6% at 1 year, 13.2% at 2 years, 19.1% at 3 years, 24.2% at 4 years and 26.0% at 5 years. In optimal patients, the cumulative rate of combination response was significantly higher than that in the non-optimal patients at 3 years ($p = 0.043$); the trend of the cumulative rate was not strong at the later time. Interestingly, in optimal patients, combination response mainly occurred in the first 3 years. Multivariate analysis identified HBeAg/anti-HBe seroconversion at 1 year as the only factor for combination response in optimal patients (hazard ratio: 16.321; $p = 0.000$). During the 3 years, the proportion with aspartate aminotransferase to platelet ratio index ≤ 0.5 increased from 15.6% at baseline to 71.3% at year 3. **Conclusions:** Upgrading the rate of combination response is limited by prolonging the treatment duration of NAs from 3 years to 5 years in HBeAg-positive CHB patients; a new switch treatment strategy modification should be considered, particularly in optimal patients.

Keywords: Chronic hepatitis B; Combination response; Nucleos(t)ide analogue; Long-term therapy.

Abbreviations: ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; CHB, chronic hepatitis B; ETV, entecavir; HBe, hepatitis B e; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LDT, telbivudine; NA, nucleos(t)ide analogue; qPCR, real-time polymerase chain reaction; RCT, randomized controlled trial; ULN, upper limit of normal; VR, virological response.

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Introduction

Worldwide, an estimated 240 million people are chronically infected with hepatitis B virus (HBV)¹ and have an increased risk of developing cirrhosis and hepatocellular carcinoma (HCC). In China, 22.9% of patients with liver disease have been found to have chronic HBV.^{2,3}

The goal of therapy for CHB is to prevent further development of the disease and progression to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC and death. The current main drugs for the clinical treatment of CHB are interferon and nucleos(t)ide analogues (NAs).⁴ In the course of antiviral treatment, studies usually evaluate the efficacy of drugs by virological response and chemical remission. The combination of virological and chemical responses collectively represent a significant marker by which to assess the efficacy of antiviral drugs.

The European Association for the Study of the Liver, Asian Pacific Association for the Study of the Liver, and American Association for the Study of Liver Disease guidelines for treatment recommendations of CHB advocate that a satisfactory endpoint is a sustained off-therapy virological response with sustained anti-hepatitis B e (HBe) seroconversion in HBe antigen (HBeAg)-positive patients.^{5–7} Furthermore, Chinese clinical guidelines recommend a satisfactory endpoint of a sustained off-therapy virological response with sustained anti-HBe seroconversion and alanine aminotransferase (ALT) normality in HBeAg-positive patients.⁸ Therefore, patients may be allowed to stop antiviral therapy if they have achieved a sustained combination of virological and chemical responses.

The previous studies have usually assessed the efficacy of NA treatment for CHB by achievement of undetectable HBV DNA, HBeAg seroconversion and ALT normality, respectively. Although some investigations have assessed the efficacy of interferon using the combined response,^{9,10} reports of combination responses are not prevalent in the literature, and the characteristics of the combination response remain unknown. Thus, estimates of satisfactory endpoints have not been reliable.

On this basis, the present real-life cohort study aimed to investigate the combination response to long-term NA therapy

in HBeAg-positive CHB patients and to identify the characteristics of the combination response.

Methods

Patients

The cohort study patients were recruited from 329 HBeAg-positive patients who were followed up between August 2004 and February 2014 at the Department of Infectious Diseases of the Second Affiliated Hospital of Chongqing Medical University (China). This study was a part of the Follow-up and Outcome of Clinical Hepatitis B: A Long-term Study (Focal study). Key inclusion criteria were: (a) ages of ≥ 16 and ≤ 70 years; (b) detection of hepatitis B surface antigen, HBeAg and HBV DNA ($\geq 10^5$ copies/mL) for more than 6 months; (c) ALT ≥ 2 times the upper limit of the normal (ULN) range or cirrhosis and obvious liver fibrosis detected via non-invasive markers and imaging technique tests in patients with ALT < 2 ULN. Patients who had infection with hepatitis C virus, hepatitis D virus or human immunodeficiency virus, or had undergone treatment with other antiviral drugs within 6 months were excluded. Moreover, no patients included in the study had used bifendate or bicyclol during their treatment course. The patient treatments were administered according to the Chinese guidelines for preventing and treating chronic hepatitis B.

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University. Written informed consent was obtained from each patient participant.

Study design

Eligible patients had been treated with entecavir (ETV) and telbivudine (LDT) monotherapy. Patients could receive adefovir if they had a suboptimal response and exhibited viral breakthrough. All patients underwent clinical examinations, liver function tests and HBV DNA analyses every 3–6 months. All patients included in the analysis participated in at least 48 weeks of follow-up and completed the therapy duration. Patients who did not have data regarding their HBV DNA or HBeAg levels or who had discontinued treatment because of the combination of other antiviral drugs before 48 weeks were excluded from further analysis.

In the patients who made up the study cohort, the time points of who received another antiviral drug or the switch therapy strategy because of a suboptimal response or viral breakthrough were regarded as the last follow-up endpoint. Finally, according to the baseline HBV DNA and ALT levels, the remaining 280 patients were divided into an optimal patient group and a non-optimal patient group for analysis.

Assay methodology

Serum hepatitis B surface antigen and anti-hepatitis B surface protein, HBeAg and anti-HBe, were tested by using aAxSYM-microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL, USA). HBV DNA levels were measured by a real-time polymerase chain reaction (qPCR) assay using the COBAS TaqMan HBV quantitative test (Roche Molecular Systems, Inc., Branchburg, NJ, USA). Serum aspartate aminotransferase (AST) and ALT were measured by an auto-analyzer

(Roche Analytics; Roche Professional Diagnostics, Penzberg, Germany). The ULN of ALT was defined as 40 IU/L.

Liver cirrhosis was diagnosed by imaging, such as ultrasonography and or computed tomography/magnetic resonance image scanning. The aspartate aminotransferase to platelet ratio index (APRI) values were calculated using the following formula:

$$APRI = \frac{ALT \text{ level}/(ULN)}{\text{platelet counts} \left(\frac{10^9}{L} \right)} \times 100$$

An APRI index of ≤ 0.5 signified the absence of significant fibrosis. APRI index of ≤ 1.0 signified the absence of cirrhosis. APRI of > 1.5 signified the presence of significant fibrosis. APRI of > 2 signified the presence of cirrhosis. APRI scores between 1.0 and 1.5 signified the progressive stages of fibrosis.^{11,12}

Evaluation of treatment efficacy and definitions

The primary endpoint was the cumulative probability of the combination response, which was defined as the collective HBeAg/anti-HBe seroconversion, HBV DNA < 1000 copies/mL, and ALT normalization for the duration of treatment. The secondary endpoints included the cumulative probability of HBeAg/anti-HBe seroconversion, the cumulative probability of the biochemical response, the cumulative probability of the virological response and changing APRI results. Optimal patients were defined as patients with a baseline ALT level of ≥ 5 ULN and HBV DNA level of $< 9 \log_{10}$ copies/MI.^{13–16} Other patients were considered non-optimal patients.

Statistical analysis

All statistical analyses were performed by the SPSS v.22 software (SPSS, Inc., Chicago, IL, USA). Continuous variables were summarized by the mean, median, minimum and maximum values. Binary variables were summarized by counts and percentages. Baseline characteristics were compared by χ^2 tests (for dichotomous variables) and the 2-sample *t*-test with unequal variances (for quantitative variables). Kaplan-Meier estimators were used to present the cumulative incidence of the combination response, HBeAg/Anti-HBe seroconversion, ALT normality and undetectable HBV-DNA, and differences were determined using the log-rank test. A two-sided *P*-value of < 0.05 was considered significant for all statistical tests.

Results

Patient characteristics

We identified 329 HBeAg-positive patients treated with ETV and LDT monotherapy. Thirty-nine patients were excluded due to missing data regarding HBV DNA and HBeAg for the follow-up duration, and 10 patients were excluded because of switch to another treatment protocol before 48 weeks. Hence, in total, 280 patients were included, consisting of 51 patients who were optimal and 229 who were non-optimal.

We followed 280, 252, 176, 127 and 87 patients for 48, 96, 144, 192 and 240 weeks, respectively (Fig. 1). Only one non-optimal patient progressed to HCC. The baseline characteristics of the patients were compared by optimal/non-optimal

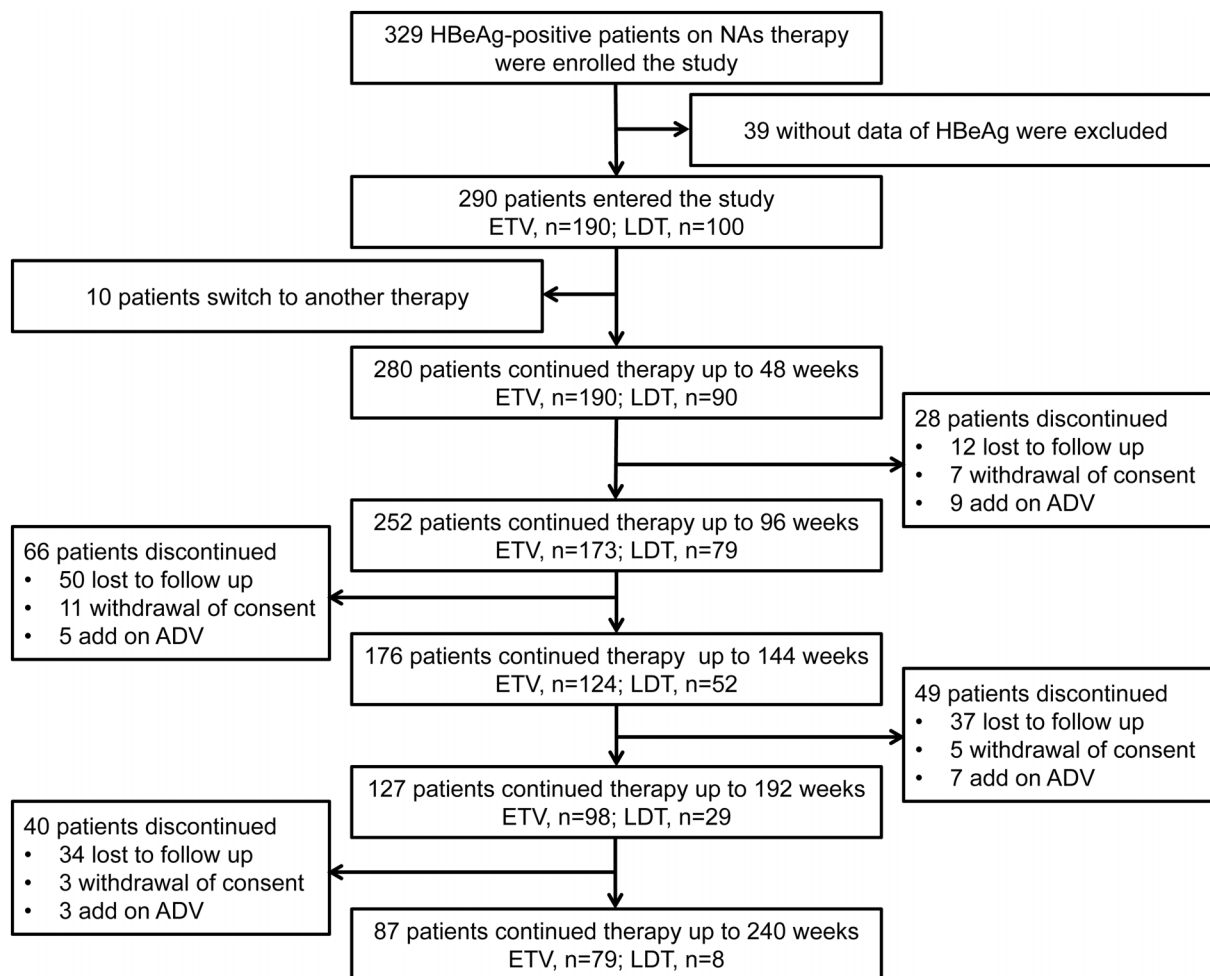


Fig. 1. Flowchart showing the enrollment and exits of patients during the course of treatment. Abbreviations: ADV, adefovir; ETV, entecavir; HBeAg, hepatitis B e antigen; LDT, telbivudine; NAs, nucleos(t)ide analogues.

grouping (Table 1). The patients in the optimal group had a higher level of serum HBV DNA ($p = 0.012$) and ALT ($p = 0.000$) than did the non-optimal group, whereas there were no significant differences in their sex, age or presence of cirrhosis.

Combination response rates were low among the total patients following long-term NA therapy

A Kaplan-Meier plot was used to analyze the cumulative rates of combination response, and the differences were calculated by the log-rank test. The cumulative rates of combination response in the total patients were 8.6% at 48 weeks, 13.2% at 96 weeks, 19.1% at 144 weeks, 24.2% at 192 weeks and 26.0% at 240 weeks. The rates were lower than the cumulative rates of HBeAg/anti-HBe seroconversion, ALT normality and undetectable HBV DNA (Fig. 2).

The combination response rates of patients between LDT and ETV treatment were evaluated. The combination response rates of the LDT-treated patients were higher than those of the ETV-treated patients. The cumulative rates of combination response were 15.6% versus 5.3% at 48 weeks, 30.2% versus 13.8% at 144 weeks, and 32.6% versus 22.1% at 240 weeks, respectively.

Combination response occurred mainly during the first 3 years

In optimal patients, the 144-week cumulative rate of combination response was significantly higher than that in the non-optimal patients ($p = 0.042$), and the trend of the cumulative rate was not strong at the later time (Fig. 3). The cumulative rates of combination response in the optimal and non-optimal groups were 27.4% versus 17.6% at 144 weeks and 27.4% versus 25.4% at 240 weeks, respectively. Interestingly, in optimal patients, the combination response mainly occurred during the first 3 years (Fig. 4). The cumulative rates of combination response increased 8.6% from year 1 to year 2 and 3.1% from year 2 to year 3. The growth trend of the combination response clearly descended, with no incremental after 3 years.

Impact factors associated with the combination response in optimal patients

In optimal patients, the combination response mainly occurred during the first 3 years; that is, prolonged therapy duration of NAs from 3 years to 5 years could not achieve a combination response for optimal patients with HBeAg-positive CHB

Table 1. Patients characteristics

Variable	Total patients, n = 280	Entire cohort		P
		Optimal group, n = 51	Non-optimal group, n = 229	
Male, n (%)	216 (77.1)	39 (76.5)	177 (68.5)	0.899
Cirrhosis, n (%)	69 (24.6)	13 (25.5)	56 (24.5)	0.877
Age in years	31.88 ± 8.57	31.88 ± 8.57	30.36 ± 7.99	0.226
HBV-DNA levels, as log ₁₀ copies/mL	8.81 ± 1.30	7.67 ± 0.98	8.17 ± 1.34	0.012
ALT, as U/L	108 (2–841)	258 (201–841)	95 (2–586)	0.000
Drug, n (%)				0.594
Telbivudine	90 (32.1)	18 (35.3)	72 (31.4)	
Entecavir	190 (67.9)	33 (64.7)	157 (68.6)	

patients. The multivariate analysis demonstrated that HBeAg/anti-HBe seroconversion at 1 year was the only determining factor for the combination response (hazard ratio: 16.321; $p = 0.000$) (Table 2). Similarly, the same trend was evident for HBeAg/anti-HBe seroconversion.

Hepatic fibrosis obviously improved after long-term NA treatment

In total, 160 patients had available complete dates of APRI from baseline to year 3 of follow-up. After 3 years of NA

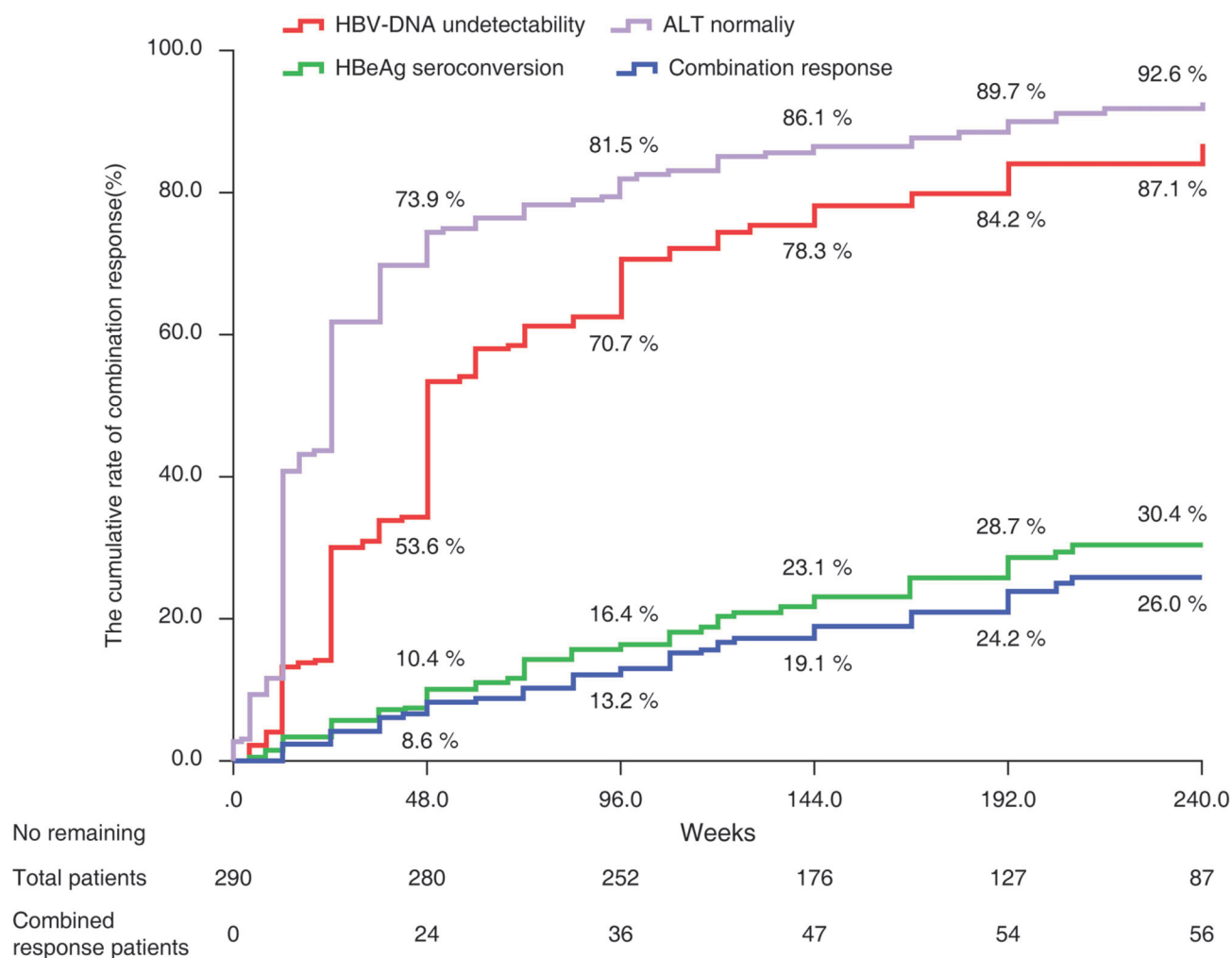


Fig. 2. Effects of LDT and ETV on the combination response. The cumulative combination response rates were estimated by the Kaplan–Meier method. Abbreviations: ETV, entecavir; LDT, telbivudine.

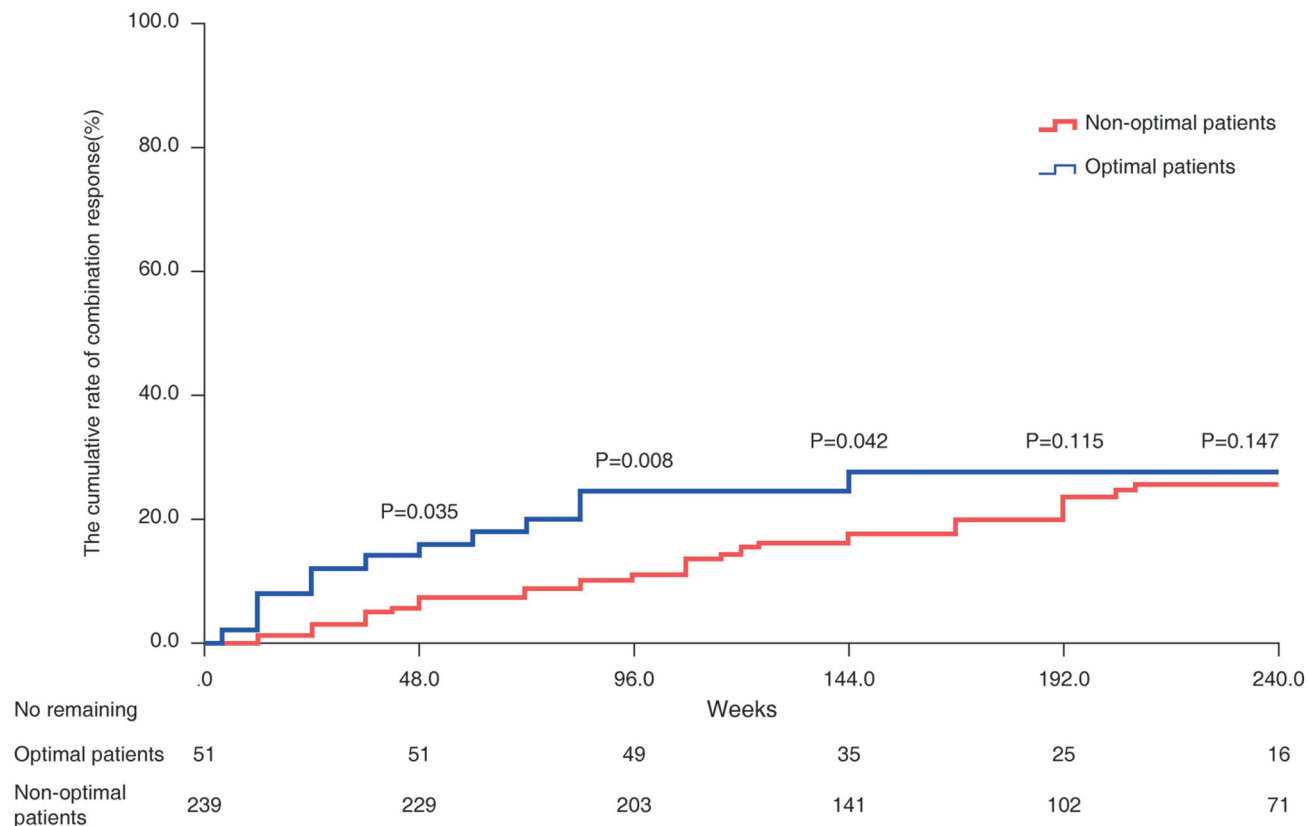


Fig. 3. Combination response in patient subgroups, stratified by baseline ALT and HBV DNA levels. Cumulative combination response rates were estimated by the Kaplan-Meier method, and the differences were supported by the log-rank test. Abbreviation: ALT, alanine transaminase.

treatment duration, the proportions of patients with APRI were changed (Fig. 5). The proportions with APRI of ≤ 0.5 increased from 15.6% (25/160) at baseline to 71.3% (114/160) at year 3, and APRI of >1.5 decreased from 43.8% (70/160) at baseline to 1.9% (3/160) at year 3.

Discussion

Our study has shown that with up to 5 years of ETV and LDT monotherapy, the cumulative rate of combination response

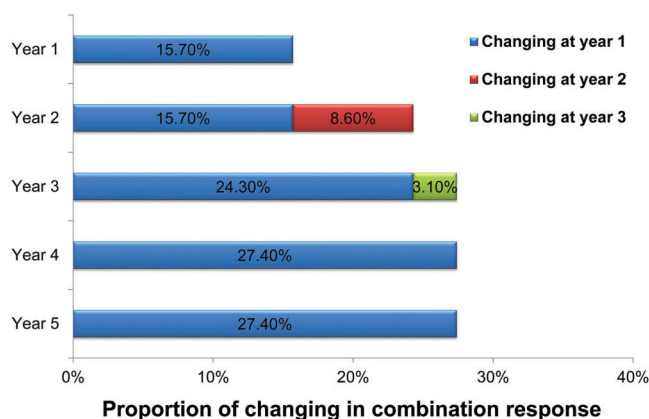


Fig. 4. Combination response occurred mainly during the first 3 years in optimal patients.

was only 26.0%. The rate was lower than the cumulative rates of HBeAg/anti-HBe seroconversion, undetectable HBV DNA and ALT normality, respectively, in previous clinical trials. One previous clinical study indicated that the 240-week cumulative rates of HBeAg/anti-HBe seroconversion upon treatment with ETV and LDT were 36% and 53%, respectively.¹³ Another study showed that the HBeAg/anti-HBe seroconversion rate was 36.7% with 5-year ETV treatment in HBeAg-positive CHB.¹⁷ In an ETV 7-year treatment study, HBeAg/anti-HBe seroconversion rates at years 3 and 7 were 26.7% and 37.5%, respectively.¹⁸ Additionally, many investigations have shown that ETV and LDT have a higher rate of HBeAg/anti-HBe seroconversion in patients with HBeAg-positive CHB.¹⁹⁻²⁴ Therefore, in an analysis of the efficacy of long-term antiviral drug therapy, the combination response showed no strong trend with the virological response or chemical remission.

Similarly, in optimal patients, combination response rates were low, and the combination response and HBeAg/anti-HBe seroconversion mainly occurred during the first 3 years; prolonged therapy after 3 years is limited for the combination response and HBeAg/anti-HBe seroconversion. The same result was reported in a head-to head study.¹³ In other words, new switch-treatment strategies are necessary to pursue a greater combination response after 3 years of NA treatment in optimal patients with baseline HBV DNA levels $<9 \log_{10}$ copies/mL and ALT ≥ 5 ULN. This finding is clinically significant and may be used to guide treatment decisions and avoid unnecessary treatment of optimal patients. In addition,

Table 2. Univariate and multivariate analyses for factors associated with combination response in optimal patients on NA therapy

Variable	Value of patients		Univariate	Multivariate
	With combination response, <i>n</i> = 13	Without combination response, <i>n</i> = 38	<i>P</i>	HR (95%CI) <i>P</i>
Male, <i>n</i> (%)	8 (61.5)	31 (81.6)	0.127	
Age in years	33.54 ± 10.74	31.32 ± 7.77	0.301	0.720
HBV DNA, as log ₁₀ copies/mL	7.57 ± 1.19	7.70 ± 0.92	0.628	0.620
ALT, as U/L	270 (207–841)	250 (201–477)	0.103	0.148
VR* at yr 1, <i>n</i> (%)	7 (53.8)	21 (55.3)	0.938	0.723
HBeAg seroconversion at yr 1, <i>n</i> (%)	8 (61.5)	2 (5.3)	0.000	16.321 (4.472–59.563) 0.000

* undetectable HBV DNA (HBV DNA <1.0 × 10³ copies/mL) by sensitive PCR assay at year 1.

Abbreviations: ALT, alanine aminotransaminase; HBeAg, hepatitis B e antigen; HR, hazard ratio.

further studies with a larger sample size are needed to confirm the conclusion.

In optimal patients, the cumulative rate of HBeAg/anti-HBe seroconversion was significantly higher than that of non-optimal patients, which indicates that baseline HBV DNA <9 log₁₀ copies/mL and ALT ≥5 ULN may contribute to the higher rate of HBeAg seroconversion. This finding confirms previously reported relationships between HBeAg seroconversion and baseline HBV DNA and ALT levels. It also agrees with previous reports of baseline ALT >5 ULN as a positive predictor for HBeAg seroconversion,^{13,14} and serum HBV DNA <9 log₁₀ copies/mL as a strong predictor for better virological outcomes.^{13–17}

The present study showed that HBeAg/anti-HBe seroconversion at 1 year was the only determining factor of combination response in optimal patients, which demonstrated that the sooner HBeAg/anti-HBe seroconversion occurs, the easier the combination response will be in optimal patients who have HBeAg-positive CHB during NA treatment.

After 3 years of LDT and ETV treatment, the proportion with APRI ≤0.5 increased from 15.6% at baseline to 71.3% at year 3, and APRI >1.5 decreased from 43.8% at baseline to 1.9% at year 3. APRI, as a marker of hepatic fibrosis, was significantly improved. In other words, the hepatic fibrosis

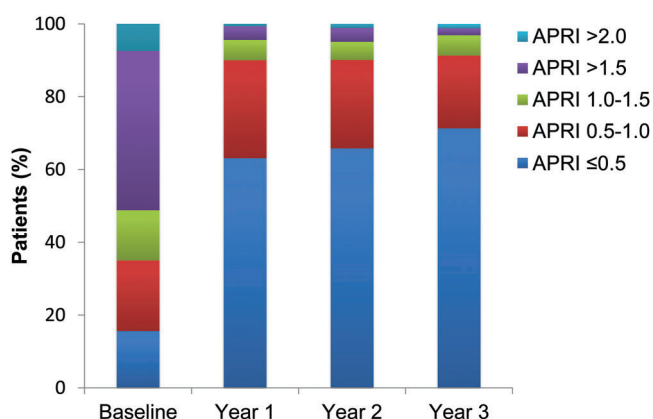


Fig. 5. Changing results of APRI over the 3-year therapy course. Abbreviation: APRI, aspartate aminotransaminase to platelet ratio index.

had obviously improved after the 3-year NA treatment, and this finding was similar to those of previous studies.^{23,25–27}

The present study had limitations. First, it was not a randomized controlled trial in design, and it was conducted only with Chinese patients. Second, the optimal sample size was small and comprised of young individuals. Therefore, the conclusions should be confirmed by further studies from multicenter and randomized cohorts.

In conclusion, prolonged therapy after 3 years is limited for the combination response to 5-year NA treatment in optimal patients with HBeAg-positive CHB. Consequently, new switch-treatment strategies are required.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Contributed to the study design, data collection and analysis, as well as performing the research and drafting the manuscript (QW), statistical analysis (HL), data collection (DD), study design and revision of the manuscript (MP, HR), responsible for the entire study design, data analysis and manuscript revision (PH). All authors have approved the final version of the manuscript.

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