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Original Article

Comparison of Peg-INF plus TDF versus TDF Monotherapy in Indeterminate-phase Chronic Hepatitis B Patients with High HBsAg levels, HBeAg-negative status, and Normal ALT Levels

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Abstract

Background and Aims: Chronic hepatitis B patients with baseline hepatitis B surface antigen (HBsAg) <1500 IU/mL are considered as the favorable population for achieving functional cure. This trial aimed to explore a treatment strategy to help the unfavorable population characterized by high HBsAg levels (>3000 IU/mL), hepatitis B e antigen-negative status, and normal alanine transaminase levels in the indeterminate phase (HBeIP), transition to the favorable group. ***Methods:*** In this investigator-initiated, open-label clinical trial, we randomly assigned participants aged 18 to 60 years with HBeIP characteristics to receive either tenofovir disoproxil fumarate (TDF) monotherapy (monotherapy group) or pegylated interferon alfa-2b (Peg-IFNα-2b) plus TDF (combination group). The primary endpoints were the HBsAg loss rate and the proportion of participants with HBsAg <1,500 IU/mL through week 96. ***Results:*** From May 2021 to November 2023, we enrolled 263 participants, with 131 randomly assigned to the combination group and 132 to the monotherapy group. In the primary analysis, none of the 132 participants (0%) in the monotherapy group achieved HBsAg loss, compared with 10 of 131 (7.6%) in the combination group (P = 0.001). Through week 96, 48.9% (64/131) of participants in the combination group achieved HBsAg <1,500 IU/mL, and a reduction in HBsAg level greater than 1 $\log_{10}$ IU/mL between baseline and week 24 was an independent predictor of this endpoint (Odds Ratio = 16.957, 95% Confidence Interval: 3.002–95.797, P = 0.001). In contrast, only two participants (1.5%) in the monotherapy group achieved HBsAg <1,500 IU/mL. ***Conclusions:*** Compared with TDF monotherapy, combination therapy with Peg-IFNα-2b and TDF significantly improved both HBsAg <1,500 IU/mL and HBsAg loss rates in HBeIP patients.

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Introduction

Emerging data indicate that 28%–55% of patients with chronic hepatitis B (CHB) do not meet the conventional criteria for any established phase in the natural history of the disease and are therefore classified as being in the indeterminate phase.[1–3] Previous studies[4–7] have reported on the severity of liver injury and hepatic fibrosis, as well as the risks of cirrhosis and hepatocellular carcinoma (HCC), in CHB patients in the indeterminate phase.

Wang *et al*. conducted a retrospective study of 197 hepatitis B e antigen (HBeAg)-negative patients in the indeterminate phase who underwent liver biopsy and found that nearly 70% of them had significant histological changes despite persistently normal alanine aminotransferase (ALT) levels.[5] A large multinational study showed that participants in the indeterminate phase have a 14-fold higher risk of HCC compared with inactive hepatitis B surface antigen (HBsAg) carriers.[8] Furthermore, Huang *et al*. compared HCC incidence between 405 treated and 450 untreated patients in the indeterminate phase, and the results showed that antiviral therapy can reduce HCC risk by up to 70% in this population.[6] Additionally, Tseng *et al*. reported that serum hepatitis B core-related antigen is a useful biomarker and can stratify HCC risk in HBeAg-negative patients in the indeterminate phase.[9] As demonstrated by the above studies, patients in the indeterminate phase are exposed to a significantly elevated risk of end-stage liver disease–related events. However, current national and international clinical guidelines for CHB do not recommend antiviral therapy for this population,[10,11] citing limited evidence on the relative benefits or harms of the therapy.

Based on the expert consensus on the treatment for functional cure of CHB in China, patients with a baseline HBsAg level < 3,000 IU/mL may be considered for combination regimens involving nucleos(t)ide analogues (NUCs) and pegylated interferon (Peg-IFN).[12,13] Moreover, baseline HBsAg <1,500 IU/mL, HBeAg-negative status, and undetect-

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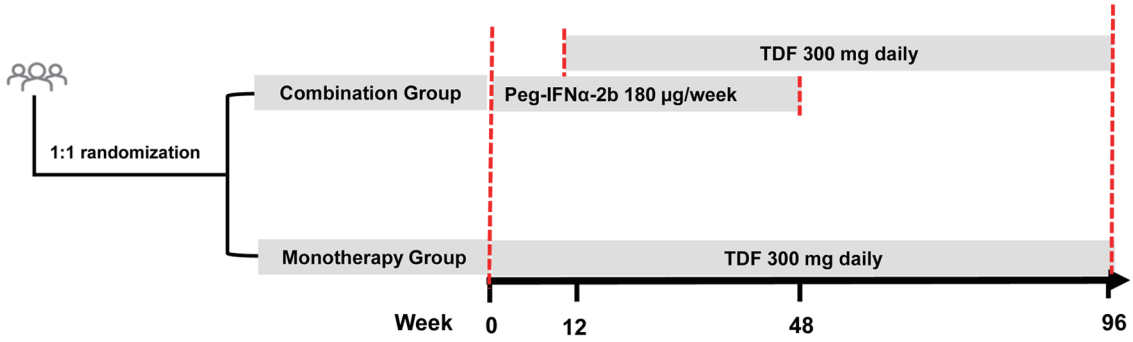


Fig. 1. Trial design. Patients in the combination group received Peg-IFNα-2b 180 μg/week for 48 weeks, with the addition of TDF (300 mg/day) at the end of week 12 through week 96. Patients in the monotherapy group received TDF for 96 weeks. Peg-IFNα-2b, pegylated interferon alfa-2b; TDF, tenofovir disoproxil fumarate.

able hepatitis B virus (HBV) DNA in patients receiving NUC therapy are recognized as the definitions of the favorable population—individuals with a higher likelihood of achieving functional cure of CHB.[13] An ongoing real-world trial of the Everest project in China has achieved a functional cure rate exceeding 30% in the NUC-experienced favorable population at week 48 after additional Peg-IFN therapy.[14]

However, apart from the favorable population, there is an unfavorable group who also shows a strong willingness to pursue functional cure of CHB, despite the challenges involved. Therefore, we designed a clinical trial to explore an effective therapeutic regimen for CHB patients with high baseline HBsAg levels (>3,000 IU/mL), HBeAg-negative status, and normal ALT in the indeterminate phase (HBeIP), comparing the efficacy and safety of two strategies: combination therapy with Peg-IFNα-2b and tenofovir disoproxil fumarate (TDF) versus TDF monotherapy.

Methods

Study design

This was a single-center, investigator-initiated, open-label, randomized controlled trial (ChiCTR2100046859).

After written informed consent was obtained, patients were randomly assigned in a 1:1 ratio to the combination group or the monotherapy group. Random group assignment can be implemented in spreadsheet software by generating uniform random numbers using the RAND() function and subsequently sorting the dataset based on these values. Patients in the combination group received 180 μg of Peg-IFNα-2b weekly for 48 weeks, with 300 mg/day of TDF added at week 12 and continued until week 96. Patients in the monotherapy group received 300 mg/day of TDF for 96 weeks.

All patients were assessed every 12 weeks and followed up to week 96 (Fig. 1). The trial was approved by the research ethics committee of the First People's Hospital of Yunnan Province (ethics approval number: KHLL2021-KY052) and was conducted in accordance with the Declaration of Helsinki.

Patients

Patients aged 18–60 years with HBeIP characteristics and HBV infection who had not received antiviral therapy within the preceding six months were enrolled from the Department of Infectious Disease and Hepatic Disease at the First People's Hospital of Yunnan Province, China, between May 2021 and November 2023. The inclusion criteria were HBsAg positivity for at least six months; quantitative HBsAg >3,000 IU/mL; HBeAg negativity; ALT levels <40 U/L; and liver stiffness measurement <9.4 kPa.

Key exclusion criteria included a history of cirrhosis or malignancy; any other medical conditions that could be exacerbated by Peg-IFNα-2b or TDF therapy; baseline neutrophil count $<2.0 \times 10^9$/L or platelet count $<100 \times 10^9$/L; co-infection with human immunodeficiency virus or other hepatitis viruses; other chronic liver diseases; severe alcohol use disorder; and pregnancy or lactation.

Endpoints

The primary efficacy endpoints were HBsAg loss and the proportion of patients achieving HBsAg <1,500 IU/mL through week 96. Secondary endpoints included the virological response rate, defined as serum HBV DNA <10 IU/mL, and the decline in HBsAg levels from baseline to week 96. All adverse events (AEs) were recorded and graded at each scheduled clinical visit.

Sample size

In patients who received TDF monotherapy, the rate of HBsAg loss was 1% up to week 96.[15] Due to potential synergistic effects, the rate of HBsAg loss with Peg-IFNα-2b plus TDF in the combination group was estimated to be 10%. Using PASS statistical software (Version 15.0, NCSS, Kaysville, UT, USA), we calculated that a total of 200 participants would be required to achieve 80% power at a two-sided significance level of 0.05 for detecting a difference in HBsAg loss rates between the two groups after 96 weeks of treatment. Accounting for an approximate 10% dropout rate and maintaining a 1:1 randomization ratio, 110 participants were needed in each group.

Statistical analysis

Two analysis populations were defined for post hoc analyses: the intention-to-treat (ITT) analysis set and the per-protocol (PP) analysis set. The ITT population included all eligible patients. The PP population excluded patients who discontinued treatment or switched treatment. The primary analyses were conducted according to the ITT principle.

Continuous variables are presented as median (interquartile range). Categorical variables are presented as frequency and percentage. Group comparisons were conducted using the independent-samples *t*-test or Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Logistic regression was used to identify independent predictors of achieving HBsAg <1,500 IU/mL up to week 96 in the combination group. All statistical analyses were conducted using two-sided hypothesis tests with a significance level of $\alpha = 0.05$, using SPSS version 26.0.

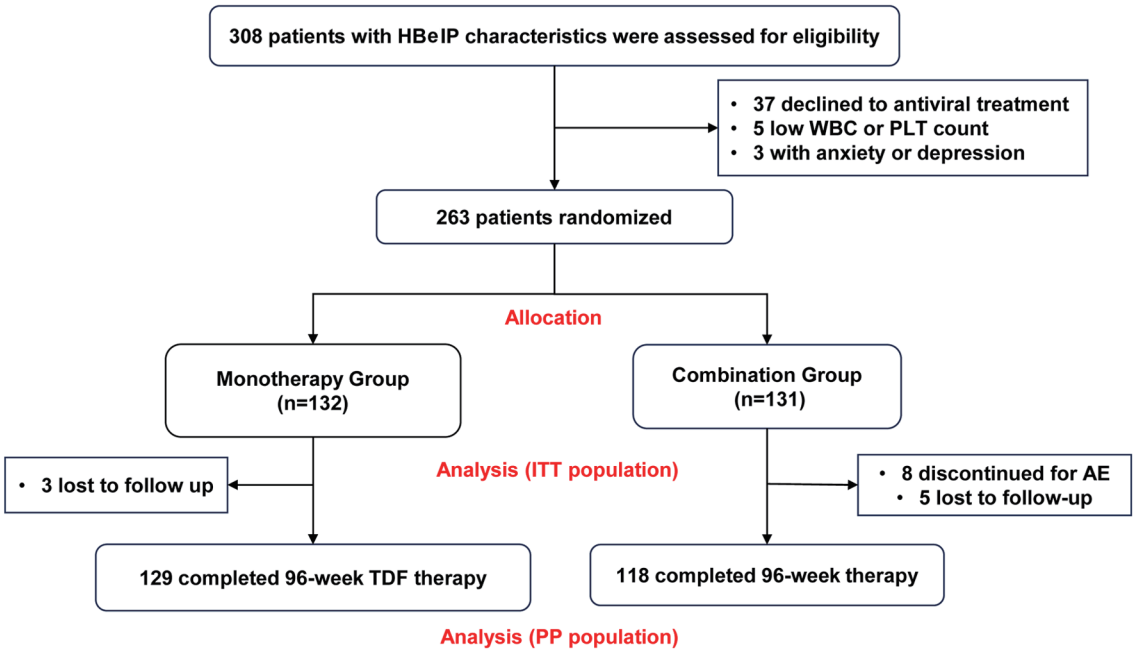


Fig. 2. Patient disposition. AE, adverse event; ITT, intention-to-treat; WBC, white blood cell; PLT, platelet; PP, per-protocol; HBeIP, HBeAg-positive immune-tolerant phase, hepatitis B e antigen-negative status, and normal alanine transaminase levels in the indeterminate phase.

Results

Study cohort

A total of 308 patients were screened for eligibility; of them, 37 declined participation, primarily due to concerns about the duration of treatment, and 8 were excluded for other pre-specified reasons. Consequently, 263 patients underwent randomization, of whom 131 were assigned to the combination group and 132 to the monotherapy group. In the combination group, 5 patients were lost to follow-up, 8 discontinued treatment due to AEs potentially associated with Peg-IFNα-2b, and 118 completed the full 96-week treatment regimen. In the monotherapy group, 3 patients were lost to follow-up, and 129 completed the scheduled 96-week treatment (Fig. 2).

Patient characteristics

Baseline variables and demographics are presented in Table 1, and no significant differences in patient characteristics were observed between the two groups. In the combination group, the median age was 34 years (interquartile range: 28–41), 68.7% of participants were over 30 years of age, 59.5% were female, and 64.9% had HBV DNA levels <2,000 IU/mL. In addition, the median HBsAg levels in the combination and monotherapy groups were 6,461.5 IU/mL and 6,562.6 IU/mL, respectively.

Efficacy

In the ITT analysis, HBsAg loss was observed in 10 of 131 participants in the combination group through week 96, compared with 0 of 132 in the monotherapy group (P = 0.001). Figure 3 depicts the longitudinal trajectories of HBsAg levels in the 10 patients who achieved HBsAg loss, plotted at pre-specified key visit time points.

The HBsAg loss rate increased from 4.6% at week 48 to 7.6% at week 96 in the combination group, which likely reflects the post-treatment effect of Peg-IFNα-2b following discontinuation after one year of therapy. In addition, the proportion of patients with HBsAg <1,500 IU/mL increased from 45.8% at week 48 to 48.9% at week 96 in the combination group, compared with only 2 of 132 (1.5%) through week 96 in the monotherapy group (P < 0.001) (Fig. 4).

The virological response was achieved in 126 participants (96.2%) in the combination group and 120 (90.9%) in the monotherapy group through week 96, with no significant difference between the groups. Additionally, median serum HBsAg levels at each key visit (weeks 0, 24, 48, and 96) for patients in the combination and monotherapy groups are shown in Figure 5. In the combination group, HBsAg levels decreased significantly from 6,462 IU/mL at baseline to 1,796 IU/mL at week 48 and further to 1,678 IU/mL at week 96 (P < 0.001), whereas no significant change in median HBsAg levels was observed from baseline to week 96 in the monotherapy group (P = 0.361).

Baseline and on-treatment factors predictive of achieving HBsAg <1,500 IU/mL by week 96 in the combination group based on PP analysis

In the combination therapy group, 118 patients completed the scheduled treatment regimen, and 61 achieved HBsAg <1,500 IU/mL through week 96.

Univariate and multivariate logistic regression analyses were performed to identify predictive factors for achieving HBsAg <1,500 IU/mL through week 96. Baseline factors included sex, age, and body mass index. On-treatment factors included ALT levels at weeks 12 and 24, and HBsAg decline from baseline to weeks 12 and 24. The results showed that a reduction >1 $\log_{10}$ IU/mL in HBsAg from baseline to week 24 (Odds Ratio = 16.957, 95% Confidence Interval: 3.002–95.797, P = 0.001) was an independent predictor of treatment response (Table 2).

Safety

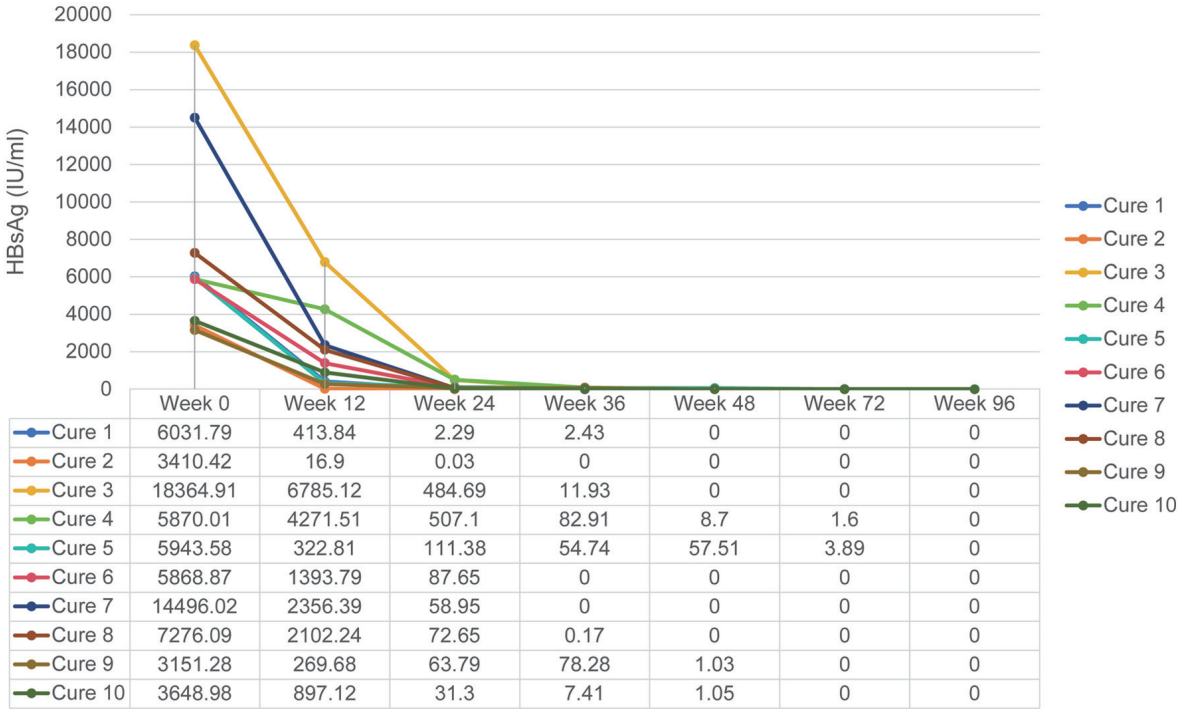
A higher incidence of AEs was observed in the combination

Table 1. Baseline characteristics of enrolled patients in the ITT population

Characteristics	Combination group (n = 131)	Monotherapy group (n = 132)	*P*
Female, n (%)	78 (59.5%)	77 (58.3%)	0.900
Age (years)	34 (28, 41)	36 (29, 44)	0.057
<30 (%)	41 (31.3%)	36 (27.3%)	
≥30 (%)	90 (68.7%)	96 (72.7%)	
BMI (kg/m^2)	22.6 (20.0, 24.9)	22.4 (21.0, 24.2)	0.617
Mode of transmission			0.802
Vertical	52 (39.7%)	55 (41.7%)	
Others	79 (60.3%)	77 (58.3%)	
Family history of cirrhosis	20 (15.3%)	21 (15.9%)	1.000
Family history of HCC	18 (13.7%)	20 (15.2%)	0.861
HBsAg (IU/mL)	6,461.5 (4,137.0, 1,2519.7)	6,562.6 (4,536.8, 9,814.9)	0.953
HBV DNA (IU/mL)			0.701
<2,000	85 (64.9%)	82 (62.1%)	
≥2,000	46 (35.1%)	50 (37.9%)	
ALT (U/L)	22 (16, 28)	23 (17, 31)	0.326
FIB-4*	0.88 (0.61, 1.24)	0.92 (0.67, 1.18)	0.824
APRI&	0.24 (0.19, 0.30)	0.25 (0.21, 0.31)	0.144
FibroScan value	6.8 (6.1, 7.4)	7.0 (6.1, 7.8)	0.240

*FIB-4 = age × AST [U/L]/(platelet count [10^9/L] × $\sqrt{\text{ALT}}$ [U/L]; &APRI = (AST [U/L] /upper limit of normal AST [U/L] × 100/platelet count (10^9/L); ITT, intention-to-treat; BMI, body mass index; HCC, hepatocellular carcinoma; ALT, alanine aminotransferase. AST, aspartate aminotransferase.

group compared with the monotherapy group. Within the combination group, 8 participants discontinued Peg-IFNα-2b due to hyperthyroidism, and 17 temporarily reduced the dose from 180 μg/week to 135 μg/week: 8 due to neutrophil counts <0.75 × 10^9/L, 5 due to ALT elevations exceeding ten times the upper limit of normal, 3 due to platelet counts <50 × 10^9/L, and 1 due to a positive antinuclear antibody test at a dilution of 1:1,000. Furthermore, one 33-year-old male



	Week 0	Week 12	Week 24	Week 36	Week 48	Week 72	Week 96
Cure 1	6031.79	413.84	2.29	2.43	0	0	0
Cure 2	3410.42	16.9	0.03	0	0	0	0
Cure 3	18364.91	6785.12	484.69	11.93	0	0	0
Cure 4	5870.01	4271.51	507.1	82.91	8.7	1.6	0
Cure 5	5943.58	322.81	111.38	54.74	57.51	3.89	0
Cure 6	5868.87	1393.79	87.65	0	0	0	0
Cure 7	14496.02	2356.39	58.95	0	0	0	0
Cure 8	7276.09	2102.24	72.65	0.17	0	0	0
Cure 9	3151.28	269.68	63.79	78.28	1.03	0	0
Cure 10	3648.98	897.12	31.3	7.41	1.05	0	0

Fig. 3. Median levels of HBsAg at each visit time point for patients who achieved HBsAg loss. HBsAg, hepatitis B surface antigen.

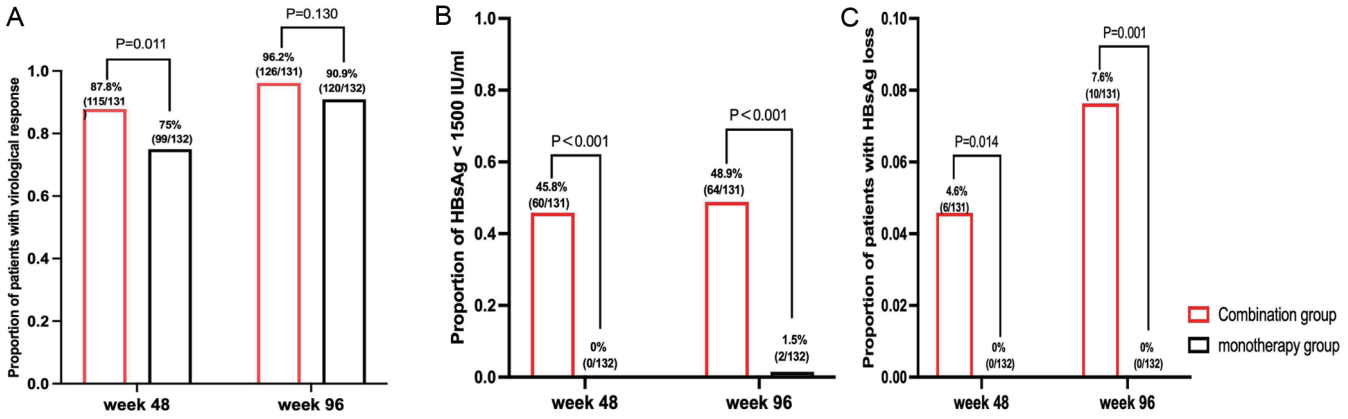


Fig. 4. Proportions of patients with treatment responses. Comparison of virological response rates, the proportion of patients with HBsAg <1,500 IU/mL, and HBsAg loss rates between the combination therapy and monotherapy groups at weeks 48 and 96 based on ITT analysis. (A) Virological response rates. (B) Proportion of patients with HBsAg <1,500 IU/mL. (C) HBsAg loss rates. ITT, intention-to-treat; HBsAg, hepatitis B surface antigen.

participant developed a large hepatic hemangioma at week 48 and underwent embolization therapy. The most frequently reported AEs were fever (69.5% [91/131]), followed by elevated ALT levels (66.4% [87/131]) and mild decreases in neutrophil and platelet counts (51.9% [68/131] and 39.7% [52/131], respectively). Other AEs included fatigue, elevated aspartate transaminase, alopecia, decreased appetite, hypophosphatemia, myalgia, rash, and insomnia. Above all AEs were assessed as potentially related to Peg-IFN treatment.

In the monotherapy group, 5 (3.8%) patients experienced ALT elevations, and 2 (1.5%) developed hypophosphatemia. Additionally, a 29-year-old male participant was diagnosed with HCC at week 72 and underwent surgical resection (Table 3).

Discussion

Our team previously conducted the first meta-analysis to summarize the incidence of HCC and HBsAg loss in CHB patients in the indeterminate phase, and the results showed a high incidence of HCC and a low rate of spontaneous HBsAg loss in this population, particularly among HBeAg-negative individuals and Asian populations.[16] This meta-analysis suggested that antiviral therapy may improve the long-term prognosis of the indeterminate phase population. However, few studies have explored the functional cure rate of CHB patients in the indeterminate phase.

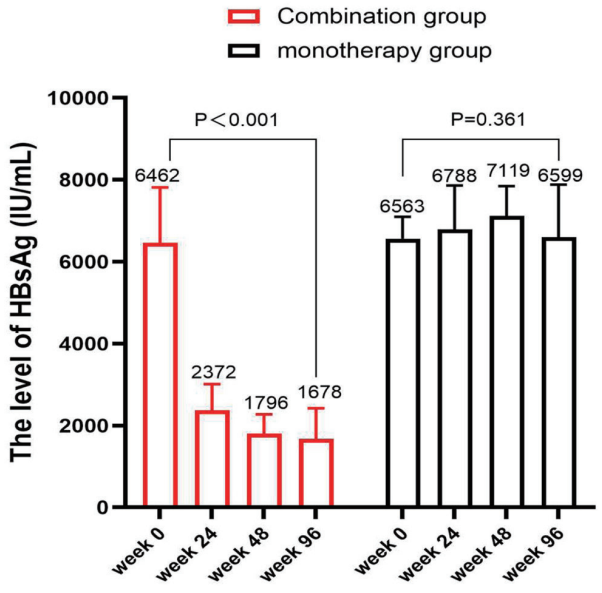


Fig. 5. Median levels of HBsAg at each visit time point for patients in the two groups by ITT analysis. ITT, intention-to-treat; HBsAg, hepatitis B surface antigen.

Functional cure is an ideal endpoint under current medical conditions for CHB patients. As evidenced by previous studies, an increased likelihood of functional cure is significantly associated with younger age, female sex, genotype A or B, HBeAg-negative status, and lower baseline HBsAg levels.[17–23] Based on previous trials, treatment-naïve inactive HBsAg carriers who received combination therapy with Peg-IFN and NUCs for 96 weeks achieved an HBsAg clearance rate of 44.7%,[24] and a multicenter randomized controlled trial reported approximately a 10% HBsAg loss rate with the addition of 48 weeks of Peg-IFN in treatment-experienced HBeAg-negative CHB patients.[25] Here, we found that combination therapy with Peg-IFN and TDF resulted in a 7.6% HBsAg loss rate in HBeIP patients, significantly higher than that of TDF monotherapy (0%).

HBeIP patients with high HBsAg levels and normal ALT represent a noninflammatory state. We designed a sequential treatment strategy involving 12 weeks of Peg-IFN monotherapy to induce partial activation of HBV-specific immune responses and establish relatively sustained immune modulation, followed by combination therapy with TDF to further enhance the immune response, thereby promoting greater HBsAg decline and subsequent HBsAg clearance.[26] Therefore, we adopted a "step-by-step" strategy: the first step involves reducing serum HBsAg levels to below 1,500 IU/mL, followed by achieving HBsAg clearance in this population. As a result, up to 48.9% of HBeIP patients from the unfavorable group for functional cure successfully transitioned to the favorable group after receiving one year of combination therapy with Peg-IFNα-2b and TDF. In contrast, only two patients in the monotherapy group achieved HBsAg levels below 1,500 IU/mL, and none achieved HBsAg loss. In addition, in the combination group, HBsAg levels decreased significantly from 6,462 IU/mL at baseline to 1,678 IU/mL at week 96 (P < 0.001). In contrast, in the TDF monotherapy group, the median HBsAg level increased from 6,563 IU/mL at baseline to 6,599 IU/mL at week 96, suggesting that short-term NUC

Table 2. Baseline and on-treatment variables associated with HBsAg <1,500 IU/mL through week 96 in the combination therapy group (PP analysis)

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Baseline						
Sex						
Male	Ref.					
Female	0.889	0.428–1.846	0.752	0.846	0.341–2.098	0.719
Age (years)						
<30	Ref.					
≥30	1.859	0.840–4.116	0.126	1.776	0.687–4.589	0.236
BMI (kg/m^2)						
<18.5	Ref.					
18.5 - 24	0.764	0.180–3.237	0.714	0.888	0.150–5.262	0.896
>24	0.845	0.392–1.824	0.669	1.021	0.400–2.608	0.965
On-treatment						
ALT week 12 (U/L)						
<2 ULN	Ref.					
≥2 ULN	2.114	1.010–4.422	0.047	1.152	0.459–2.886	0.763
ALT week 24 (U/L)						
<2 ULN	Ref.					
≥2 ULN	2.713	1.177–6.250	0.019	1.832	0.668–5.024	0.240
HBsAg change from baseline to week 12 (IU/mL)						
<0.5 $\log_{10}$	Ref.					
≥0.5 $\log_{10}$	5.551	2.255–13.661	<0.001	0.779	0.182–3.341	0.737
HBsAg change from baseline to week 24 (IU/mL)						
<1.0 $\log_{10}$	Ref.					
≥1.0 $\log_{10}$	16.312	4.597–57.886	<0.001	16.957	3.002–95.797	0.001

PP, per-protocol; OR, odds ratio; CI, confidence interval; BMI, body mass index; ALT, alanine aminotransferase; Ref., reference; HBsAg, hepatitis B surface antigen.

monotherapy in CHB patients with HBeIP characteristics results in minimal HBsAg decline or loss.

Furthermore, we performed univariate and multivariate logistic regression analyses to identify predictors of achieving HBsAg <1,500 IU/mL through week 96 in the combination group. The results showed that a decline in HBsAg level of more than 1 $\log_{10}$ IU/mL from baseline to week 24 was a strong predictor of treatment response, consistent with findings from previous trials.[27,28]

This study has several limitations. First, it was an open-label, single-center trial, which may render the findings susceptible to selection bias and confounding. Second, HBV genotyping was not performed due to low baseline HBV DNA levels in 63.5% (167/263) of patients, although genotypes B and C are predominant in China.[29] Third, no Peg-IFN monotherapy group was included for comparison. Fourth, AEs associated with Peg-IFN therapy remain a major barrier to its clinical adoption; not all patients offered Peg-IFN therapy may choose to receive it, even if it could provide clinical benefit. Fifth, to reduce the risk of end-stage liver disease–related events, we recommended that all participants receive long-term antiviral treatment, leading to the unavailability of data on treatment discontinuation. Because TDF was continued uniformly across the cohort, the study design inherently restricts the ability to isolate and attribute clinically meaningful endpoints—such as HBsAg loss or sustained off-treatment remission—to the Peg-IFN add-on, thereby constraining interpretation of its incremental therapeutic benefit.

Conclusions

This is the first randomized controlled trial to compare the efficacy and safety of Peg-IFNα-2b combined with TDF versus TDF monotherapy in HBeIP patients. This study demonstrates that combination therapy with Peg-IFN plus TDF achieves a higher rate of HBsAg loss and greater HBsAg decline compared with TDF monotherapy, which may enable more HBeIP patients from the unfavorable population to successfully transition into the favorable population for achieving functional cure.

Acknowledgments

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Table 3. Adverse events in the combination group and monotherapy group (ITT population)

Groups/Adverse events	N (%)
Combination group (n = 131)	
Discontinuation	
Hyperthyroidism	8 (6.1%)
Dose modification	
Neutrophil count <0.75 × 10^9/L	8 (6.1%)
ALT flare	5 (3.8%)
Platelet count <50 × 10^9/L	3 (2.3%)
Antinuclear antibody positivity at 1:1,000	1 (0.8%)
Others	
Fever	91 (69.5%)
Elevated ALT	87 (66.4%)
Decreased neutrophil count	68 (51.9%)
Decreased platelet count	52 (39.7%)
Fatigue	37 (28.2%)
Elevated AST	26 (19.8%)
Alopecia	21 (16.0%)
Decreased appetite	12 (9.2%)
Myalgia	10 (7.6%)
Hypophosphatemia	4 (3.1%)
Rash	4 (3.1%)
Insomnia	3 (2.3%)
Large hepatic hemangioma	1 (0.8%)
Monotherapy group (n = 132)	
Elevated ALT	5 (3.8%)
Hypophosphatemia	2 (1.5%)
hepatocellular carcinoma	1 (0.8%)

ITT, intention-to-treat; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase

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Conflict of interest

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

Author contributions

Study concept and design (JG, ML, WY), data collection (ML, LlZ, YZ, BB, JL, LZ, LH, YW), analysis and interpretation of data (ML, BB, LZ), statistical analysis (ML, AX), drafting of the manuscript (ML, AX), and critical revision of the manuscript for important intellectual content (JG, WY). All authors have approved the final version and publication of the manuscript.

Ethical statement

The trial was approved by the research ethics committee of the First People's Hospital of Yunnan Province (ethics approval number: KHLL2021-KY052) and was conducted in accordance with the Declaration of Helsinki (as revised in 2024). Written informed consent was obtained from all patients. Trial registration number: ChiCTR2100046859.

Data sharing statement

Individual participant data reported in this publication will be available, after de-identification, to researchers who provide an ethically approved research proposal from the corresponding authors, upon reasonable request.

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