

Supplementary data

Recurrence risk factors for chronic hepatitis B virus-infected patients who achieve functional cure with pegylated interferon- α -2b-based therapy: a multicenter pilot study

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Table S1. Comparison of baseline characteristics between sustained responder and recurrence in CHB patients receiving PEG-IFN- α -2b add-on NAs therapy ($n=70$)

Characteristic	Sustained responder group	Recurrence group	<i>P</i> value
Patients enrolled, <i>n</i>	62	8	
Male gender, <i>n</i> (%)	32 (51.61%)	5 (62.50%)	0.561
Age (years)	40.24 $\pm$ 9.49	41.13 $\pm$ 14.55	0.817
HBV DNA undetectable (<50 IU/ml), <i>n</i> (%)	47 (75.81%)	5 (62.40%)	0.418
HBV DNA detectable (>50 IU/ml), <i>n</i> (%)	15 (24.19%)	3 (37.60%)	
HBsAg (IU/ml)	50.23(7.26, 249.3)	90.21(23.71, 1841)	0.272
HBsAg <10 IU/ml, <i>n</i> (%)	18 (29.03%)	1 (12.50%)	0.405
HBsAg 10~100 IU/ml, <i>n</i> (%)	21 (33.87%)	3 (37.50%)	
HBsAg 100~1000IU/ml, <i>n</i> (%)	20 (32.25%)	2 (25.00%)	
HBsAg >1000 IU/ml, <i>n</i> (%)	3 (4.85%)	2 (25.00%)	
HBeAg positive, <i>n</i> (%)	5 (8.06%)	0 (0.00%)	
Blood routine test			
White blood cells ($\times 10^9$ /L)	5.03 $\pm$ 1.18	5.00 $\pm$ 0.93	0.937
Neutrophils ($\times 10^9$ /L)	3.01 $\pm$ 0.82	2.83 $\pm$ 0.73	0.572
Platelets ($\times 10^9$ /L)	199.1 $\pm$ 59.31	215.3 $\pm$ 68.83	0.480
Red blood cells ($\times 10^{12}$ /L)	4.89 $\pm$ 0.62	4.70 $\pm$ 0.39	0.393
Hemoglobin (g/L)	147.8 $\pm$ 20.03	147.8 $\pm$ 13.06	0.999
Liver function			
ALT (U/L)	22.50 (15.75, 30.00)	30.00 (18.00, 37.50)	0.237
AST (U/L)	22.00 (18.75, 26.00)	23.00 (18.50, 26.00)	0.919
T-BIL (μ mol/L)	17.25 (11.18, 22.48)	15.15 (7.98, 19.05)	0.310
Total protein (g/L)	73.12 $\pm$ 9.31	72.08 $\pm$ 7.77	0.761
Albumin (g/L)	49.22 $\pm$ 3.16	46.83 $\pm$ 3.82	0.053
Globulin (g/L)	24.97 $\pm$ 3.38	25.35 $\pm$ 4.08	0.772

CHB: chronic hepatitis B; HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; HBeAg: hepatitis B e antigen; ALT: alanine aminotransferase; AST: aspartate aminotransferase; T-BIL: total bilirubin

Table S2. Comparison of baseline characteristics between sustained responder and recurrence in IHC receiving PEG-IFN- α -2b monotherapy
(*n*=31)

Characteristic	Sustained responder group	Recurrence group	<i>P</i> value
Patients enrolled, <i>n</i>	23	8	
Male gender, <i>n</i> (%)	15 (55.29%)	5 (62.50%)	0.890
Age (years)	39.17 $\pm$ 7.20	38.50 $\pm$ 6.09	0.815
HBV DNA undetectable (<50 IU/ml), <i>n</i> (%)	19 (82.61%)	8 (100%)	0.206
HBV DNA detectable (>50 IU/ml), <i>n</i> (%)	4 (17.39%)	0 (0.00%)	
HBsAg (IU/ml)	18.15 (2.29, 181.6)	12.79 (0.99, 120.4)	0.685
HBsAg <10 IU/ml, <i>n</i> (%)	10 (43.48%)	4 (50.00%)	
HBsAg 10~100 IU/ml, <i>n</i> (%)	6 (26.09%)	2 (25.00%)	
HBsAg 100~1000IU/ml, <i>n</i> (%)	5 (21.74%)	2 (25.00%)	
HBsAg >1000 IU/ml, <i>n</i> (%)	2 (8.69%)	0 (0.00%)	
Blood routine test			
White blood cells ($\times 10^9$ /L)	5.83 $\pm$ 1.67	6.00 $\pm$ 1.93	0.819
Neutrophils ($\times 10^9$ /L)	3.48 $\pm$ 1.20	3.52 $\pm$ 1.64	0.932
Platelets ($\times 10^9$ /L)	211.0 $\pm$ 40.94	226.1 $\pm$ 75.42	0.481
Red blood cells ($\times 10^{12}$ /L)	5.01 $\pm$ 0.44	5.04 $\pm$ 0.46	0.877
Hemoglobin (g/L)	153.9 $\pm$ 17.90	141.5 $\pm$ 23.95	0.133
Liver function			
ALT (U/L)	21.00 (14.00, 32.00)	22.00 (15.00, 25.00)	0.941
AST (U/L)	20.00 (18.00, 26.00)	19.00 (18.00, 21.00)	0.268
T-BIL (μ mol/L)	11.10 (7.60, 21.00)	11.60 (10.20, 14.50)	0.980
Total protein (g/L)	74.96 $\pm$ 4.82	73.27 $\pm$ 5.83	0.471
Albumin (g/L)	48.71 $\pm$ 3.37	47.98 $\pm$ 4.68	0.670
Globulin (g/L)	26.57 $\pm$ 2.79	25.62 $\pm$ 1.79	0.437

IHC: inactive hepatitis B virus carrier; HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; HBeAg: hepatitis B e antigen; ALT: alanine aminotransferase; AST: aspartate aminotransferase; T-BIL: total bilirubin

Table S3. Comparison of characteristics at therapy cessation between sustained responder and recurrence in CHB patients receiving PEG-IFN- α -2b add-on NAs therapy ($n=70$)

Characteristic	Sustained responder group	Recurrence group	<i>P</i> value
Patients enrolled, <i>n</i>	62	8	
Total PEG-IFN- α -2b injection (weeks)	48.00 (27.25, 60.00)	54.50 (23.50, 78.75)	0.370
Treatment time (weeks)	24.00 (13.75, 41.25)	37.50 (15.75, 69.25)	0.211
Received consolidative therapy, <i>n</i> (%)	49 (79.03%)	4 (50.00%)	0.072
Consolidation time (weeks)	12.00 (4.00, 24.00)	6.00 (0.00, 21.00)	0.211
Anti-HBs positive, <i>n</i> (%)	43 (69.35%)	1 (12.50%)	0.002
Anti-HBs titer (mIU/ml)	52.45 (0.00, 272.9)	0.00 (0.00, 0.00)	0.006
Blood routine test			
White blood cells ($\times 10^9/L$)	2.84 (2.30, 3.42)	2.95 (2.58, 3.66)	0.441
Neutrophils ($\times 10^9/L$)	1.50 (1.14, 1.78)	1.45 (1.14, 2.13)	0.939
Platelets ($\times 10^9/L$)	110.3 $\pm$ 36.11	149.5 $\pm$ 45.60	0.007
Red blood cells ($\times 10^{12}/L$)	4.27 $\pm$ 0.60	4.02 $\pm$ 0.70	0.275
Hemoglobin (g/L)	129.4 $\pm$ 19.82	128.8 $\pm$ 17.51	0.935
Liver function			
ALT (U/L)	46.00 (31.50, 75.50)	42.00 (25.75, 94.25)	0.822
AST (U/L)	46.00 (30.50, 71.25)	40.00 (35.25, 112.8)	1.000
T-BIL ($\mu\text{mol/L}$)	13.50 (10.45, 16.60)	12.65 (9.85, 21.00)	0.810
Total protein (g/L)	72.18 $\pm$ 4.09	73.74 $\pm$ 2.54	0.329
Albumin (g/L)	45.82 $\pm$ 3.29	44.64 $\pm$ 2.62	0.365
Globulin (g/L)	26.28 $\pm$ 4.10	29.10 $\pm$ 3.13	0.084

CHB: chronic hepatitis B; PEG-IFN- α -2b: pegylated interferon- α -2b; Anti-HBs: hepatitis B surface antibody; ALT: alanine aminotransferase; AST: aspartate aminotransferase; T-BIL: total bilirubin

Table S4. Comparison of characteristics at therapy cessation between sustained responder and recurrence in IHC receiving PEG-IFN- α -2b monotherapy ($n=31$)

Characteristic	Sustained responder group	Recurrence group	<i>P</i> value
Patients enrolled, <i>n</i>	23	8	
Total PEG-IFN- α -2b injection (weeks)	30.00 (16.00, 55.00)	28.50 (21.00, 41.00)	0.769
Treatment time (weeks)	23.00 (12.00, 36.00)	24.00 (14.00, 30.25)	1.000
Received consolidative therapy, <i>n</i> (%)	14 (60.87%)	6 (75.00%)	0.472
Consolidation time (weeks)	4.00 (0.00, 20.00)	6.00 (1.00, 8.00)	0.889
Anti-HBs positive, <i>n</i> (%)	12 (52.17%)	3 (37.50%)	0.474
Anti-HBs titer (mIU/ml)	8.60 (0.00, 21.30)	0.00 (0.00, 141.8)	1.000
Blood routine test			
White blood cells ($\times 10^9/L$)	3.11 (2.30, 3.49)	3.75 (2.98, 3.97)	0.321
Neutrophils ($\times 10^9/L$)	1.37 (1.18, 2.38)	1.85 (1.11, 2.35)	0.604
Platelets ($\times 10^9/L$)	102.0 (88.00, 142.0)	140.0 (87.25, 231.5)	0.343
Red blood cells ($\times 10^{12}/L$)	4.43 $\pm$ 0.55	4.50 $\pm$ 0.58	0.783
Hemoglobin (g/L)	135.4 $\pm$ 14.75	129.4 $\pm$ 28.71	0.445
Liver function			
ALT (U/L)	45.00 (26.00, 60.00)	54.50 (24.00, 96.50)	0.769
AST (U/L)	42.00 (23.00, 63.00)	44.00 (26.00, 82.00)	0.701
T-BIL ($\mu\text{mol/L}$)	14.30 (10.80, 19.30)	11.30 (8.98, 16.58)	0.343
Total protein (g/L)	72.04 $\pm$ 3.38	74.43 $\pm$ 3.47	0.100
Albumin (g/L)	45.93 $\pm$ 3.22	46.26 $\pm$ 4.57	0.823
Globulin (g/L)	26.20 $\pm$ 2.48	28.13 $\pm$ 2.84	0.081

IHC: inactive hepatitis B virus carrier; PEG-IFN- α -2b: pegylated interferon- α -2b; Anti-HBs: hepatitis B surface antibody; ALT: alanine aminotransferase; AST: aspartate aminotransferase; T-BIL: total bilirubin

Table S5. Comparison of characteristics at followed-up between sustained responder and recurrence in CHB patients receiving PEG-IFN- α -2b add-on NAs therapy ($n=70$)

Characteristic	Sustained responder group	Recurrence group	<i>P</i> value
Patients enrolled, <i>n</i>	62	8	
Followed-up time (weeks)	72.00 (48.00, 96.00)	48.00 (48.00, 57.00)	0.011
HBsAg level (IU/ml)	<0.05	0.44 (0.10, 2.11)	-
Anti-HBs positive, <i>n</i> (%)	40 (64.52%)	3 (37.50%)	0.140
Anti-HBs titer (mIU/ml)	49.70 (0.00, 435.0)	0.00 (0.00, 35.80)	0.041
Blood routine test			
White blood cells ($\times 10^9/L$)	3.56 (2.61, 4.72)	4.42 (3.60, 5.04)	0.109
Neutrophils ($\times 10^9/L$)	2.01 (1.24, 2.72)	2.35 (2.18, 2.56)	0.202
Platelets ($\times 10^9/L$)	150.5 $\pm$ 63.16	186.4 $\pm$ 42.72	0.153
Red blood cells ($\times 10^{12}/L$)	4.45 $\pm$ 0.74	4.61 $\pm$ 0.74	0.591
Hemoglobin (g/L)	135.5 $\pm$ 23.69	146.4 $\pm$ 21.55	0.256
Liver function			
ALT (U/L)	23.00 (16.00, 38.00)	26.00 (18.00, 48.00)	0.801
AST (U/L)	25.00 (20.00, 39.25)	19.00 (19.00, 33.00)	0.168
T-BIL ($\mu\text{mol/L}$)	14.05 (11.63, 17.50)	18.90 (12.80, 23.40)	0.169
Total protein (g/L)	74.02 $\pm$ 4.90	74.30 $\pm$ 5.83	0.892
Albumin (g/L)	46.27 $\pm$ 3.50	44.87 $\pm$ 2.23	0.310
Globulin (g/L)	27.69 $\pm$ 4.23	29.57 $\pm$ 4.72	0.283

CHB: chronic hepatitis B; PEG-IFN- α -2b: pegylated interferon- α -2b; HBsAg: hepatitis B surface antigen; Anti-HBs: hepatitis B surface antibody; ALT: alanine aminotransferase; AST: aspartate aminotransferase; T-BIL: total bilirubin

Table S6. Comparison of characteristics at followed-up between sustained responder and recurrence in IHC receiving PEG-IFN- α -2b monotherapy ($n=31$)

Characteristic	Sustained responder group	Recurrence group	<i>P</i> value
Patients enrolled, <i>n</i>	23	8	
Followed-up time (weeks)	64.00 (48.00, 108.0)	73.00 (48.00, 132.0)	0.762
HBsAg level (IU/ml)	<0.05	0.63 (0.24, 4.60)	-
Anti-HBs positive, <i>n</i> (%)	10 (43.48%)	2 (25.00%)	0.355
Anti-HBs titer (mIU/ml)	0.00 (0.00, 38.20)	0.00 (0.00, 24.75)	0.341
Blood routine test			
White blood cells ($\times 10^9$ /L)	3.28 (2.46, 4.67)	5.19 (4.07, 7.12)	0.031
Neutrophils ($\times 10^9$ /L)	1.85 (1.22, 2.65)	3.01 (2.36, 4.46)	0.038
Platelets ($\times 10^9$ /L)	163.5 $\pm$ 63.27	203.6 $\pm$ 60.15	0.193
Red blood cells ($\times 10^{12}$ /L)	4.51 $\pm$ 0.59	5.12 $\pm$ 0.43	0.028
Hemoglobin (g/L)	136.8 $\pm$ 17.20	149.1 $\pm$ 21.08	0.181
Liver function			
ALT (U/L)	23.00 (19.50, 47.00)	21.50 (15.50, 27.25)	0.333
AST (U/L)	35.00 (23.50, 44.00)	20.50 (15.00, 33.50)	0.174
T-BIL (μ mol/L)	12.60 (8.95, 15.85)	12.95 (9.00, 16.00)	1.000
Total protein (g/L)	72.67 $\pm$ 2.92	72.30 $\pm$ 3.27	0.808
Albumin (g/L)	45.45 $\pm$ 3.69	46.27 $\pm$ 2.38	0.627
Globulin (g/L)	27.64 $\pm$ 3.76	26.70 $\pm$ 2.42	0.586

IHC: inactive hepatitis B virus carrier; PEG-IFN- α -2b: pegylated interferon- α -2b; HBsAg: hepatitis B surface antigen; Anti-HBs: hepatitis B surface antibody; ALT: alanine aminotransferase; AST: aspartate aminotransferase; T-BIL: total bilirubin

Table S7. Logistic regression analysis of factors influencing recurrence at therapy cessation in CHB patients receiving PEG-IFN- α -2b add-on NAs therapy ($n=70$)

Characteristics	Univariate model		Multivariate model	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Male gender	1.562 (0.343-7.112)	0.564		
Age	1.009 (0.937-1.087)	0.814		
Baseline HBsAg level	1.031 (0.885-1.093)	0.612		
Treatment time	1.022 (0.997-1.049)	0.087		
Consolidation time	0.956 (0.890-1.026)	0.213		
Anti-HBs positive	0.063 (0.007-0.549)	0.012	0.064 (0.007-0.612)	0.017
PEG-IFN- α -2b add-on ETV therapy	1.000			
PEG-IFN- α -2b add-on TDF therapy	2.036 (0.404-10.261)	0.389		
PEG-IFN- α -2b add-on TAF therapy	1.900 (0.176-20.559)	0.597		
PEG-IFN- α -2b add-on TMF therapy	<0.001	0.999		
Blood routine test				
White blood cells	1.127 (0.523-2.432)	0.760		
Neutrophils	0.895 (0.305-2.630)	0.840		
Platelets	1.028 (1.006-1.050)	0.012	1.027 (1.003-1/052)	0.027
Red blood cells	0.480 (0.132-1.751)	0.266		
Hemoglobin	0.998 (0.961-1.038)	0.934		
Liver function				
ALT	1.007 (0.996-1.019)	0.227		
AST	1.003 (0.988-1.018)	0.705		
T-BIL	1.029 (0.925-1.144)	0.598		
Total protein	1.105 (0.910-1.342)	0.313		
Albumin	0.883 (0.683-1.141)	0.341		
Globulin	1.175 (0.983-1.404)	0.077		

CHB: chronic hepatitis B; PEG-IFN- α -2b: pegylated interferon- α -2b; OR: odds ratio; 95% CI: 95% confidence interval; HBsAg: hepatitis B surface antigen; anti-HBs: hepatitis B surface antibody; ETV: entecavir; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide; TMF:

tenofovir amibufenamide; ALT: alanine aminotransferase; AST: aspartate aminotransferase; T-BIL: total bilirubin

Table S8. Logistic regression analysis of factors influencing recurrence at therapy cessation in IHC receiving PEG-IFN- α -2b monotherapy
(*n*=31)

Characteristics	Univariate model		Multivariate model	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Male gender	0.889 (0.168-4.716)	0.890		
Age	0.985 (0.873-1.111)	0.807		
Baseline HBsAg level	1.003 (0.998-1.017)	0.683		
Treatment time	0.988 (0.942-1.036)	0.624		
Consolidation time	0.971 (0.895-1.054)	0.485		
Anti-HBs positive	0.550 (0.106-2.860)	0.477		
Blood routine test				
White blood cells	0.956 (0.616-1.484)	0.840		
Neutrophils	0.893 (0.523-1.526)	0.679		
Platelets	1.194 (1.007-1.218)	0.033	1.030 (1.002-1.059)	0.039
Red blood cells	1.246 (0.277-5.603)	0.775		
Hemoglobin	0.884 (0.743-0.998)	0.043	0.085 (0.739-0.990)	0.036
Liver function				
ALT	1.001 (0.984-1.017)	0.968		
AST	1.007 (0.982-1.019)	0.969		
T-BIL	0.952 (0.828-1.094)	0.491		
Total protein	1.235 (0.956-1.595)	0.106	3.391 (1.117-10.292)	0.031
Albumin	1.029 (0.813-1.303)	0.813		
Globulin	1.331 (0.956-1.853)	0.090		

IHC: inactive hepatitis B virus carrier; PEG-IFN- α -2b: pegylated interferon- α -2b; OR: odds ratio; 95% CI: 95% confidence interval; HBsAg: hepatitis B surface antigen; anti-HBs: hepatitis B surface antibody; ALT: alanine aminotransferase; AST: aspartate aminotransferase; T-BIL: total bilirubin

Table S9. Logistic regression analysis of factors influencing recurrence at followed-up in CHB patients receiving PEG-IFN- α -2b add-on NAs therapy ($n=70$)

Characteristics	Univariate model		Multivariate model	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Male gender	1.526 (0.342-7.112)	0.564		
Age	1.003 (0.937-1.087)	0.814		
Baseline HBsAg level	1.091 (0.258-2.716)	0.612		
Treatment time	1.022 (0.997-1.049)	0.087		
Consolidation time	0.956 (0.890-1.026)	0.213		
Anti-HBs positive	0.705 (0.661-0.896)	0.037	0.033 (0.002-0.568)	0.019
PEG-IFN- α -2b add-on ETV therapy	1.000			
PEG-IFN- α -2b add-on TDF therapy	0.214 (0.062-0.746)	0.015		
PEG-IFN- α -2b add-on TAF therapy	0.200 (0.023-1.712)	0.142		
PEG-IFN- α -2b add-on TMF therapy	<0.001	0.999		
Blood routine test				
White blood cells	1.413 (0.846-2.360)	0.187		
Neutrophils	1.797 (0.738-4.375)	0.197		
Platelets	1.009 (0.996-1.022)	0.161		
Red blood cells	1.368 (0.445-4.202)	0.584		
Hemoglobin	1.022 (0.984-1.062)	0.254		
Liver function				
ALT	0.996 (0.970-1.022)	0.735		
AST	0.966 (0.895-1.042)	0.372		
T-BIL	1.085 (0.957-1.201)	0.173	1.270 (1.004-1.606)	0.046
Total protein	1.012 (0.861-1.189)	0.889		
Albumin	0.887 (0.705-1.117)	0.307		
Globulin	1.092 (0.928-1.285)	0.288		

CHB: chronic hepatitis B; PEG-IFN- α -2b: pegylated interferon- α -2b; OR: odds ratio; 95% CI: 95% confidence interval; HBsAg: hepatitis B surface antigen; anti-HBs: hepatitis B surface antibody; ETV: entecavir; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide; TMF:

tenofovir amibufenamide; ALT: alanine aminotransferase; AST: aspartate aminotransferase; T-BIL: total bilirubin

Table S10. Logistic regression analysis of factors influencing recurrence at followed-up in IHC receiving PEG-IFN- α -2b monotherapy ($n=31$)

Characteristics	Univariate model		Multivariate model	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Male gender	0.889 (0.168-4.716)	0.890		
Age	0.985 (0.873-1.111)	0.807		
Baseline HBsAg level	0.998 (0.837-1.079)	0.683		
Treatment time	0.988 (0.942-1.036)	0.624		
Consolidation time	0.971 (0.895-1.054)	0.485		
Anti-HBs positive	0.433 (0.263-0.722)	0.036	0.100 (0.010-0.975)	0.048
Blood routine test				
White blood cells	1.747 (0.919-3.321)	0.089		
Neutrophils	2.030 (0.832-4.954)	0.012		
Platelets	1.011 (0.995-1.028)	0.190		
Red blood cells	12.001 (0.923-56.001)	0.058		
Hemoglobin	1.041 (0.982-1.103)	0.179		
Liver function				
ALT	0.944 (0.856-1.041)	0.246		
AST	0.941 (0.861-1.027)	0.173		
T-BIL	0.961 (0.737-1.254)	0.771		
Total protein	0.956 (0.680-1.343)	0.794		
Albumin	1.087 (0.793-1.489)	0.606		
Globulin	0.904 (0.639-1.279)	0.568		

IHC: inactive hepatitis B virus carrier; PEG-IFN- α -2b: pegylated interferon- α -2b; OR: odds ratio; 95% CI: 95% confidence interval; HBsAg: hepatitis B surface antigen; anti-HBs: hepatitis B surface antibody; ALT: alanine aminotransferase; AST: aspartate aminotransferase; T-BIL: total bilirubin