HBeAg-Negative Chronic Hepatitis B 使用 Pegasys 治療經驗之分享

消化系內科
賴學洲

CHINA MEDICAL UNIVERSITY

長效型干擾素治療慢性B型肝炎E抗原陰性病患

PEGYLATED INTERFERON α-2A THERAPY FOR HBEAG-NEGATIVE CHRONIC HEPATITIS B

賴學洲　彭成元 蘇文邦 莊伯恒 高榮達

中國醫藥大學附設醫院
內科部消化系

Background and Aims
目的及背景

- 長效型干擾素在治療慢性B型肝炎e抗原陰性病患，已證實為有效的治療方法。

  (Patrick Marcellin, et al. N engl J Med 2004;351:1206-17)
  (Piratvisuth T, et al. hepatol Int 2008;2:102-10)
  (Patrick Marcellin, et al. Gastroentrology 2009)

- 在台灣治療的效果尚未釐清。
- 探討慢性 B型肝炎e抗原陰性患者，接受48週長效型干擾素治療及追蹤24週的療效評估。

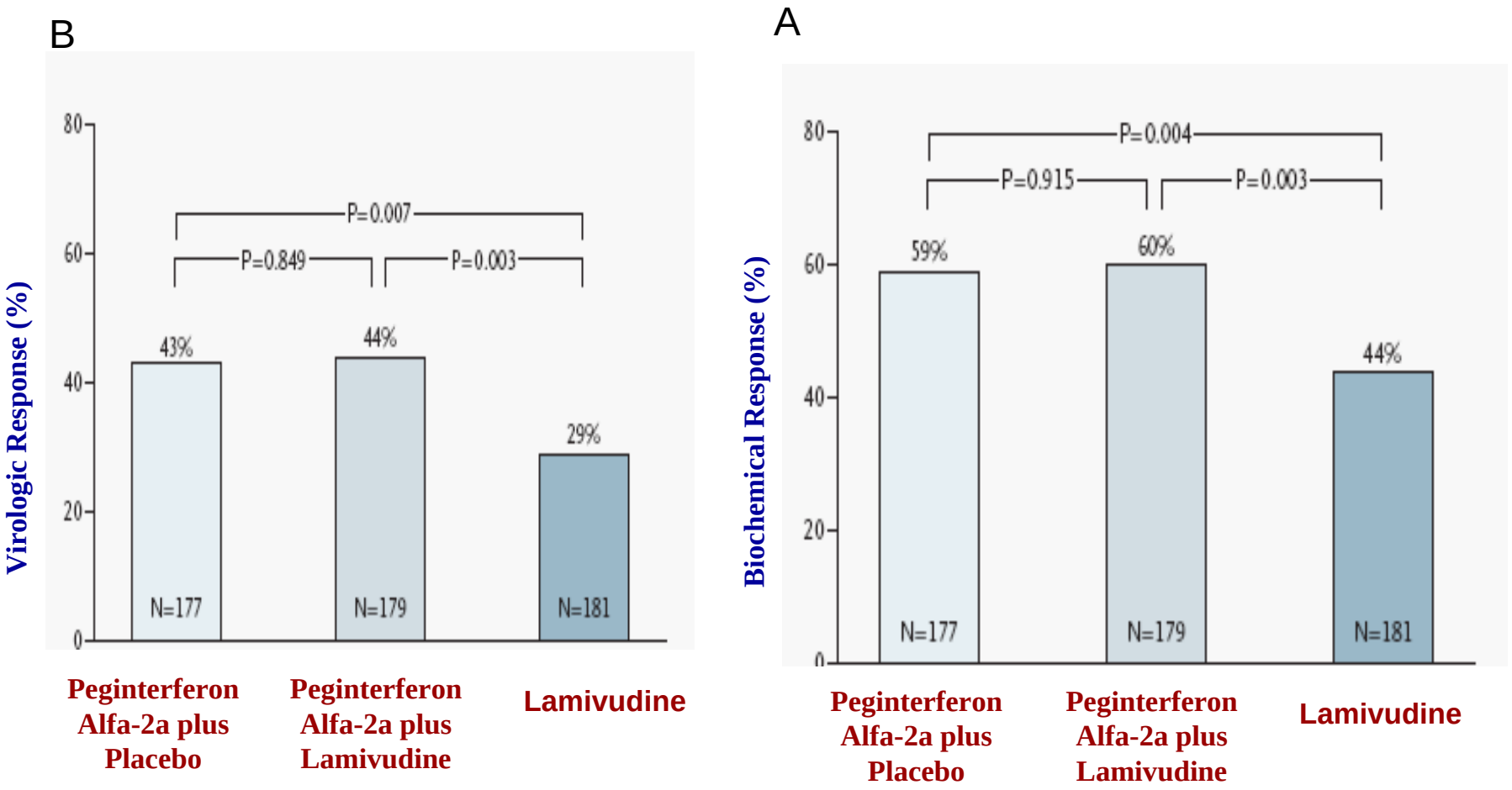


Figure 1. Rates of Biochemical Response (Panel A) and Virologic Response (Panel B) after 24 Weeks of Follow-up.

(Patrick Marcellin, et al. N engl J Med 2004;351:1206-17)

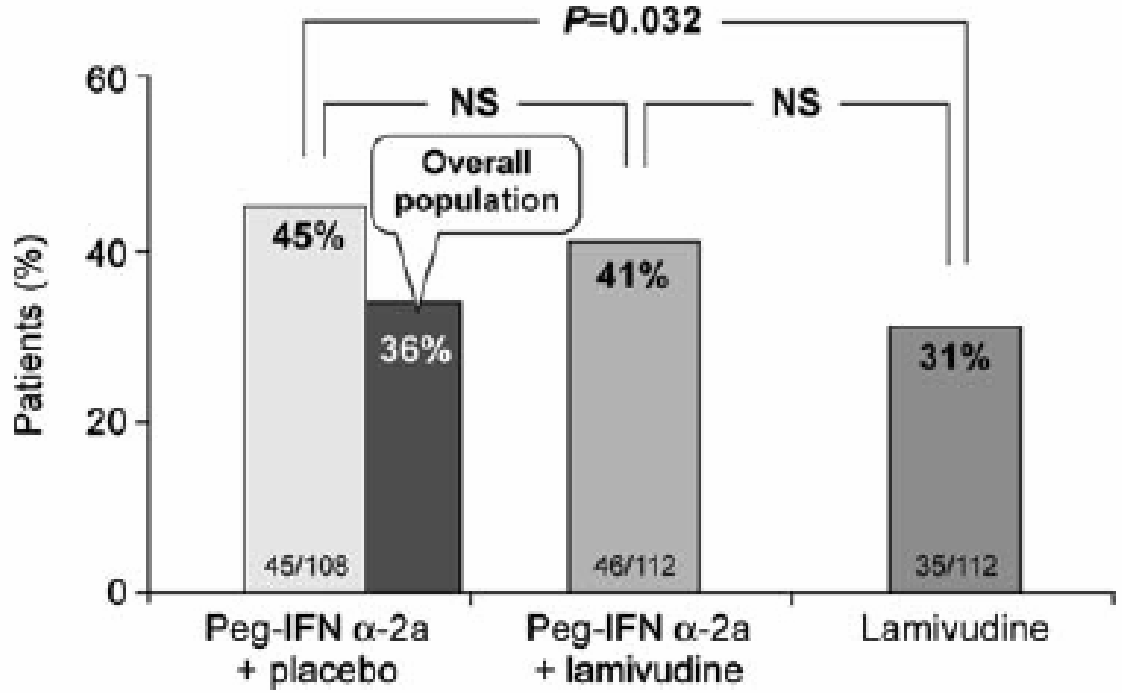


Fig. 5 Asian patients with HBeAg-negative CHB: Combined response at 24 weeks posttreatment (intention-to-treat population). A significantly higher percentage of patients administered peginterferon alfa-2a experienced a combined response of ALT normalization and HBV DNA <20,000 copies/ml than did patients given lamivudine

(Piratvisuth T, et al. hepatol Int 2008;2:102-10)

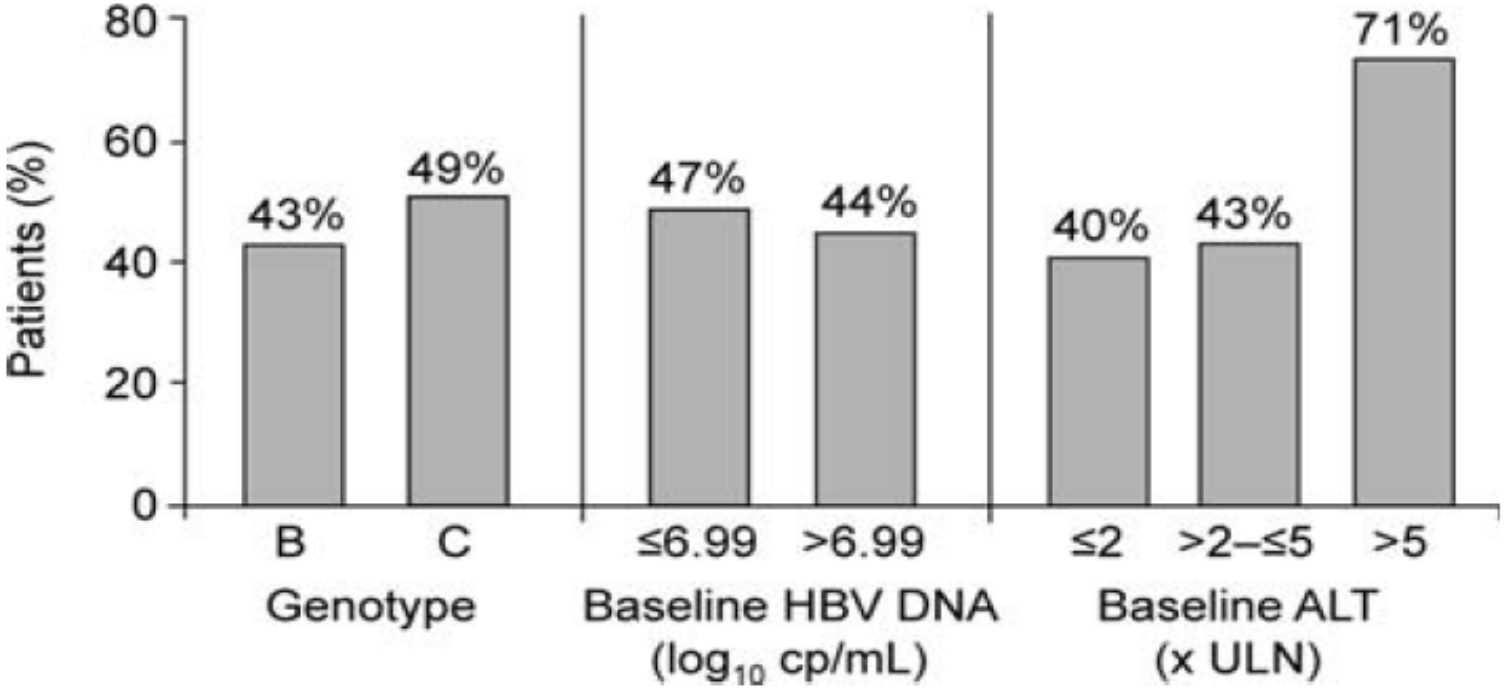


Fig. 6 Asian patients with HBeAg-negative CHB: Effect of viral and host factors on combined response (intention-to-treat population) to peginterferon alfa-2a (Peg-IFN-α-2a) monotherapy. The combined response (ALT normalization and HBV DNA <20,000 copies/ml) rate at 24 weeks posttreatment with Peg-IFN-α-2a was slightly higher for genotype C than genotype B. Baseline HBV DNA levels had no influence on combined response. However, the combined response was markedly higher in patients with baseline ALT >5 × ULN than lower levels of baseline ALT

(Piratvisuth T, et al. hepatol Int 2008;2:102-10)

Table 1. Characteristics of patients in the initial study* and in the long-term follow-up study

	Peginteferon alfa 2a		Peginteferon alfa 2a + Lamivudine		Lamivudine	
	Initial study	LT study	Initial study	LT study	Initial study	LT study
	n=177	N=116	n=179	N=114	n=181	n=85
Age (yr; mean / median)	40 / 41	40 / 41	41 / 40	40 / 39	40 / 40	39 / 39
Gender (female / male) in %	15 / 85	16 / 84	18 / 82	18 / 82	14 / 86	13 / 87
Race						
Caucasian	37%	25%	36%	30%	38%	32%
Oriental	61%	73%	63%	71%	62%	68%
Other	2%	2%	1%	0%	0%	0%
Weight (kg, mean)	71.0	69.8	69.7	68.7	70.6	72.0
HBV Genotype A	6%	6%	6%	7%	4%	6%
B	24%	28%	23%	29%	27%	33%
C	36%	43%	39%	40%	32%	34%
D	31%	20%	30%	21%	35%	26%
Other (E, H, B/C, D/G)	3%	3%	3 %	3%	2%	1%
HBV DNA at before treatment start (log10 cp/mL) mean/ median / range	7.1 7.0 2.3–12.0	7.1 7.0 2.3–12.0	7.3 7.2 2.7–12.0	7.2 7.0 3.1–12.0	7.2 7.0 2.8–12.0	6.9 6.8 3.5–12.0
ALT before treatment start (IU/L) mean/ median / range	94.4 61.5 10.2–508	86.5 60.4 10.2–454	90.8 64.2 11.3–514	88.2 63.1 16.5–514	105.7 71.6 9.8–1051	85.1 87.2 18.0–643
Presence of bridging fibrosis or cirrhosis before treatment start n/ (%)	54 (31%)	33 (28%)	40 (22%)	22 (20%)	53 (29%)	16 (19%)
Use of lamivudine / NAs prior study treatment n/ (%)	7 (4%)	5 (4%)	15 (8%)	9 (8%)	9 (5%)	3 (4%)

(Patrick Marcellin, et al. Gastroentrology 2009)

Table 2. Patient disposition and overview of response at end of treatment, 6 months post treatment and 1, 2 and 3 years post treatment

Response Parameter	Initial study (48 weeks of treatment and 24 weeks of follow up)					
	PegIFNα-2a (n=177)		PegIFNα-2a + lamivudine (n=179)		Lamivudine (n=181)	
	n	%	n	%	n	%
End of treatment						
ALT<1 x ULN	67	38	87	49	132	73
HBV DNA≤20,000 cp/mL	144	81	164	92	154	85
HBV DNA ≤400 cp/mL	112	63	156	87	113	73
6-months post treatment						
ALT<1 x ULN	105	59	107	60	80	44
HBV DNA≤20,000 cp/mL	76	43	79	44	53	29
HBV DNA ≤400 cp/mL	34	19	35	20	12	7
HBsAg loss	7	5	5	3	0	0

	Entered long term follow-up study								
	n	% Follow up study population (n=116)	% Initial study population (n=177)	n	% Follow up study population (n=114)	% Initial study population (n=179)	n	% Follow-up study population (n=85)	% Initial study population (n=181)
1 year post-treatment									
ALT<1 x ULN	58	50	33	51	45	28	28	33	15
HBV DNA≤10,000 cp/mL	35	30	20	35	31	20	17	20	9
HBV DNA ≤400 cp/mL	17	15	10	14	12	8	6	7	3
HBsAg loss	4	3	2	5	4*	3	0	0	0
2 years post-treatment									
ALT<1 x ULN	37	32	21	32	28*	18	17	20	9
HBV DNA≤10,000 cp/mL	32	28	18	24	21	13	10	12	6
HBV DNA ≤400 cp/mL	18	16	10	13	11	7	3	4	2
HBsAg loss	7	6	4	6	5*	3	0	0	0
3 years post-treatment									
ALT<1 x ULN	36	31*	20 **	35	31*	20**	15	18	8
HBV DNA≤10,000 cp/mL	32	28#	18##	28	25#	16##	13	15	7
HBV DNA ≤400 cp/mL	21	18±	12±±	15	13±	8±±	5	6	3
HBsAg loss	9	8¶	5¶¶	9	8¶	5¶¶	0	0	0

(Patrick Marcellin, et al. Gastroenterology 2009)

Materials and Methods
方法

- 自民國九十三年十一月至九十八年三月間，在中國醫藥大學附設醫院共收治50位慢性B型肝炎e抗原陰性患者進入本研究(男性40位、女性10位、平均年齡44±12)。病患接受長效型干擾素每週一次皮下注射共治療48週，結束後追蹤24週。在治療前偵測病人血清中的病毒量、病毒基因型、肝生檢及肝功能檢查，並於治療第12週、24週、48週及72週分別偵測病人血清中的病毒量。
- HBV DNA 以 COBAS AMPLICOR HBV MONITOR (Roche) 檢測。
- HBV genotype 以 Mizokami 之 RFLP method 檢測。
- 合併反應(combined response) 的定義為治療結束後第六月血清中ALT值正常且HBV DNA$\leqq 10^4$ copies/ ml。

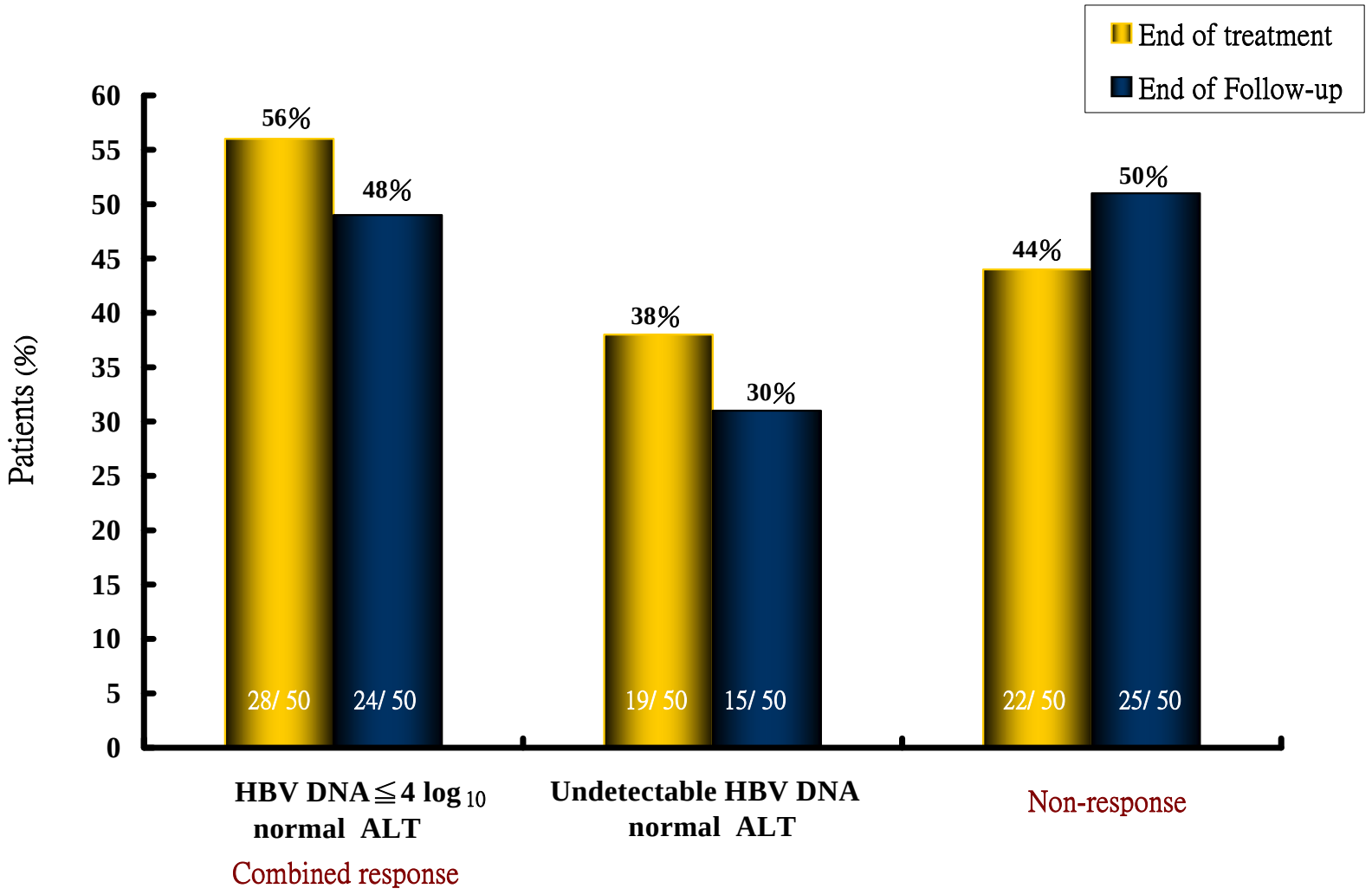
Results

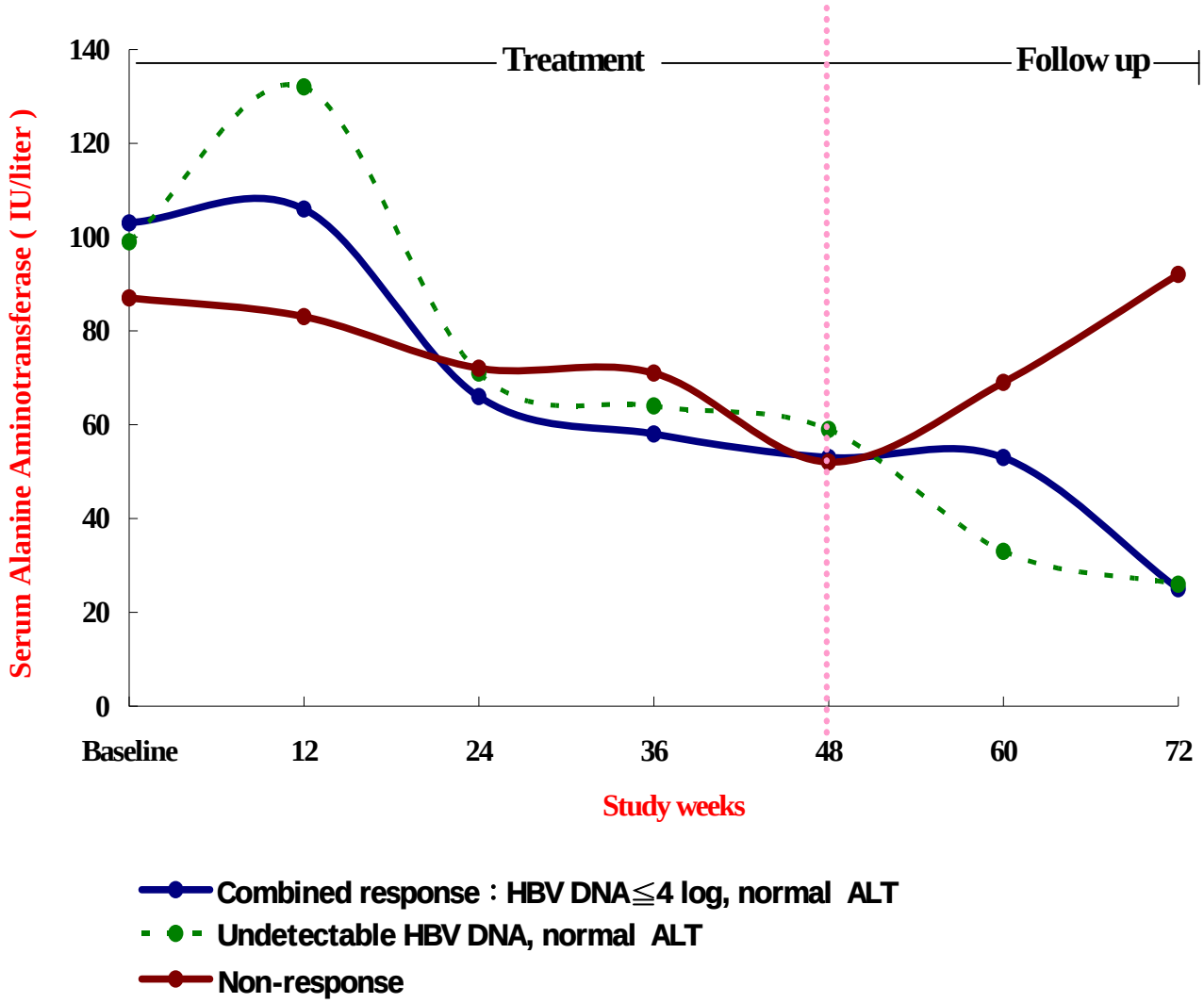
結果

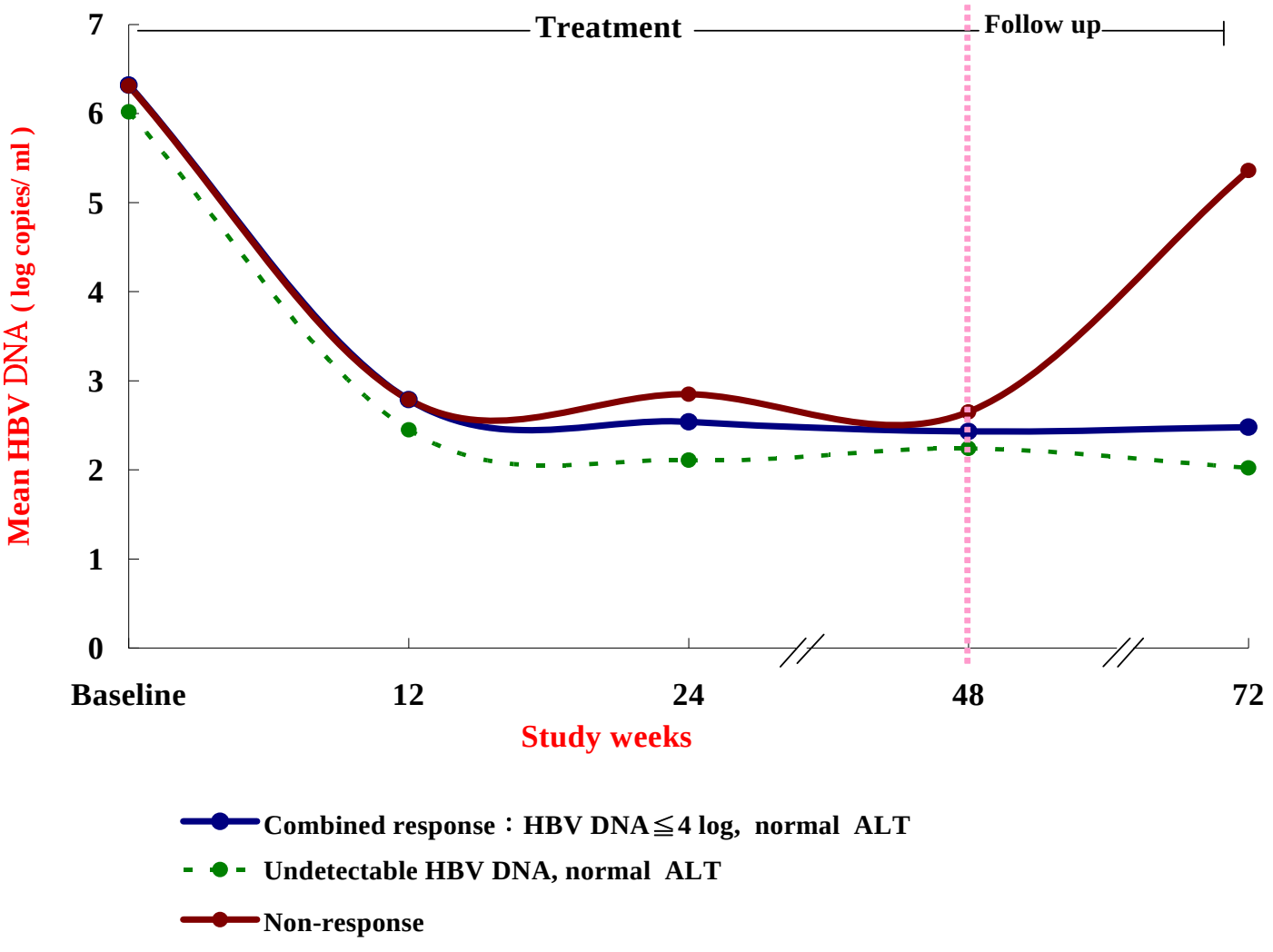
Table 1. Baseline and Demographic Characteristics of the Patients

No. of patients	**50**
Age, years	
Mean ± SD	**44 ± 12**
Range	**22 ~ 67**
Gender, male:female	**40:10:00**
Serum ALT, IU/L	
Mean ± SD	**97.6 ± 63.35**
Range	**21 ~ 284**
Serum AFP, ng/ml	
Mean ± SD	**11.89 ± 22**
Range	**1.52 ~ 133**
HBeAg negative, n(%)	**50 (100)**
Anti-HBe positive, n(%)	**49 (98)**
Anti-HCV positive, n(%)	**0 (0)**
Baseline HBV DNA (log_{10} copies/ml)	
Mean ± SD	**6.28 ± 1.97**
Range	**2.49 ~ 10.16**
HBV genotype, B: C	**40:10:00**
METAVIR score	
Fibrosis 1/ 2/ 3/ 4	**9/ 24/ 13/ 3 ND*1**
Inflammatory Activity 1/ 2/ 3	**24/ 18/ 7 ND*1**

ND*: no data available


End of treatment
End of Follow-up
Patients (%)
60
55
50
45
40
35
30
25
20
15
10
5
0
56%
48%
38%
30%
44%
50%
28/ 50
24/ 50
19/ 50
15/ 50
22/ 50
25/ 50
HBV DNA≦4 log10
normal ALT
Undetectable HBV DNA
normal ALT
Non-response
Combined response


Treatment
Follow up
Serum Alanine Aminotransferase (IU/liter)
140
120
100
80
60
40
20
0
Baseline
12
24
36
48
60
72
Study weeks
Combined response：HBV DNA≦4 log, normal ALT
Undetectable HBV DNA, normal ALT
Non-response


Treatment
Follow up
Mean HBV DNA (log copies/ ml)
7
6
5
4
3
2
1
0
Baseline
12
24
48
72
Study weeks
Combined response：HBV DNA≦4 log, normal ALT
Undetectable HBV DNA, normal ALT
Non-response

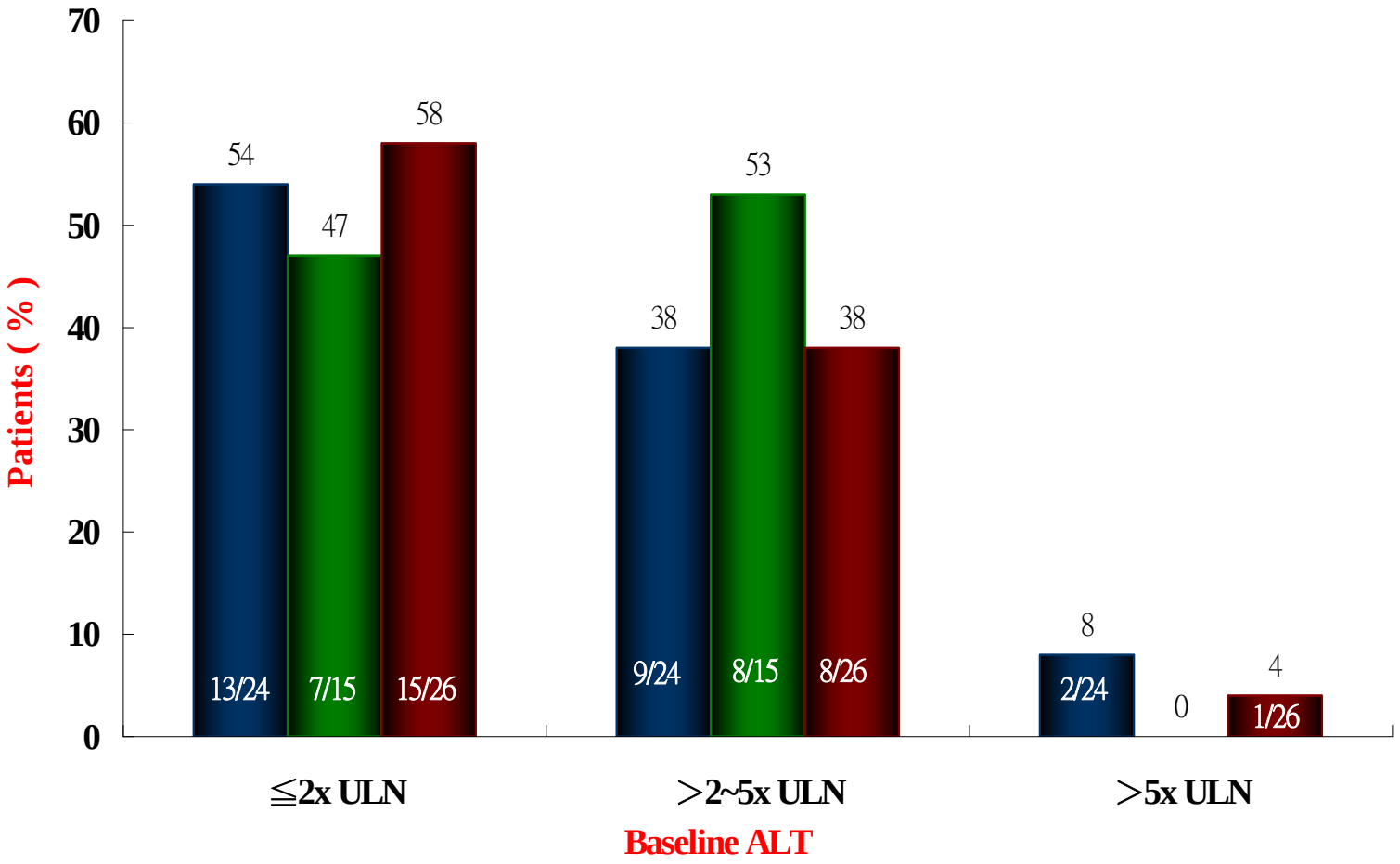

70
60
50
40
30
20
10
0
Patients (%)
54
47
58
38
53
38
8
0
4
13/24
7/15
15/26
9/24
8/15
8/26
2/24
1/26
≦2x ULN
＞2~5x ULN
＞5x ULN
Baseline ALT
Combined response：HBV DNA≦4 log, normal ALT
Undetectable HBV DNA, normal ALT
Non-response

Table 2. Pre-treatment and on-treatment characteristics in patients with combined response or non-combined response

Characteristic	combined response* n = 24 (48%)	non-combined response n = 26 (52%)	P vaue
Age (years)	46.46 ± 12.49 (49.0)	42.31± 11.33 (42.0)	0.331
Gender			0.7278
Male	83%	77%	
Female	17%	23%	
Body weight (kg)	67.82± 9.38 (68.85)	69.78± 14.19 (69.0)	0.87
BMI (kg/m^2)	23.9± 2.93 (24.2)	24.64± 3.38 (24.15)	0.736
METAVIR score			
Stage of fibrosis	2.21 ± 0.83 (2.0)	2.2 ± 0.82 (2.0)	0.872
1~2	15 (62%)	18 (69%)	
3~ 4	9 (38%)	7 (31%)	
Inflammatory activity	1.79 ± 0.83 (2.0)	1.52 ± 0.59 (1.0)	0.302
0~1	11 (46%)	13 (50%)	
2~3	13 (54%)	12 (46%)	
Baseline ALT	103.25 ± 68.85 (79.0)	92.38 ± 58.7 (74.5)	0.021
＞5xULN	8%	4%	
＞2~5xULN	38%	38%	
≦ 2xULN	54%	58%	
Peak ALT level weeks 0~48 (IU/L)	185.29 ± 125.37 (176.0)	192.12 ± 144.44 (151.5)	0.931

Table 2. Pre-treatment and on-treatment characteristics in patients with combined response or non-combined response

Characteristic	combined response* n = 24 (48%)	non-combined response n = 26 (52%)	P vaue
Baseline HBV DNA (log_{10} copies/ml)	6.32 ± 2.27 (6.96)	6.31 ± 1.43 (6.16)	0.63
HBV DNA at week 12 (log_{10} copies/ml)	2.79 ± 1.25(2.0)	2.79 ± 1.19 (2.0)	1.00
＜ 312 copies/ml	54%	58%	
＞312~10000 copies/ml	25%	27%	
HBV DNA at week 24 (log_{10} copies/ml)	2.54 ± 1.12(2.0)	2.85 ± 1.52 (2.0)	0.421
＜ 312 copies/ml	71%	65%	
＞312~10000 copies/ml	17%	12%	
HBV DNA at end of treatment (log_{10} copies/ml)	2.43 ± 0.97 (2.0)	2.65 ±1.06 (2.33)	0.076
＜ 312 copies/ml	79%	48%	
＞312~10000 copies/ml	13%	31%	
HBV genotype			0.294
B	21 (88%)	19 (73%)	
C	3 (12%)	7 (27%)	

*Combined response： both ALT normlisation and an HBV DNA level of < 10_4 copies/ ml

[a] Data are presented by mean ± standard deviation (median) by Wilcoxon Sign Rank test

[b] Data are presented by number (percent) analyzed between combined response and non-combined response group by Fisher's Exact test

Table 3. Logistic regression analysis on pre-treatment factors and sustained combined respons

Pre-treament factor	Comparison	Odds ratio (95%CI)	pValue
Age	＜50 vs ≧50	0.113 (0.01~1.249)	0.0753
Sex	female vs male	1.732 (0.108~27.783)	0.6981
BMI	1 kg/ m^2 decrease	1.318 (0.94~1.847)	0.109
Baseline HBV DNA	1 $\log_{10}$ unit (copies/ ml) decrease	1.689 (0.748~3.812)	0.207
Genotype	B vs C	0.251 (0.011~5.546)	0.3811

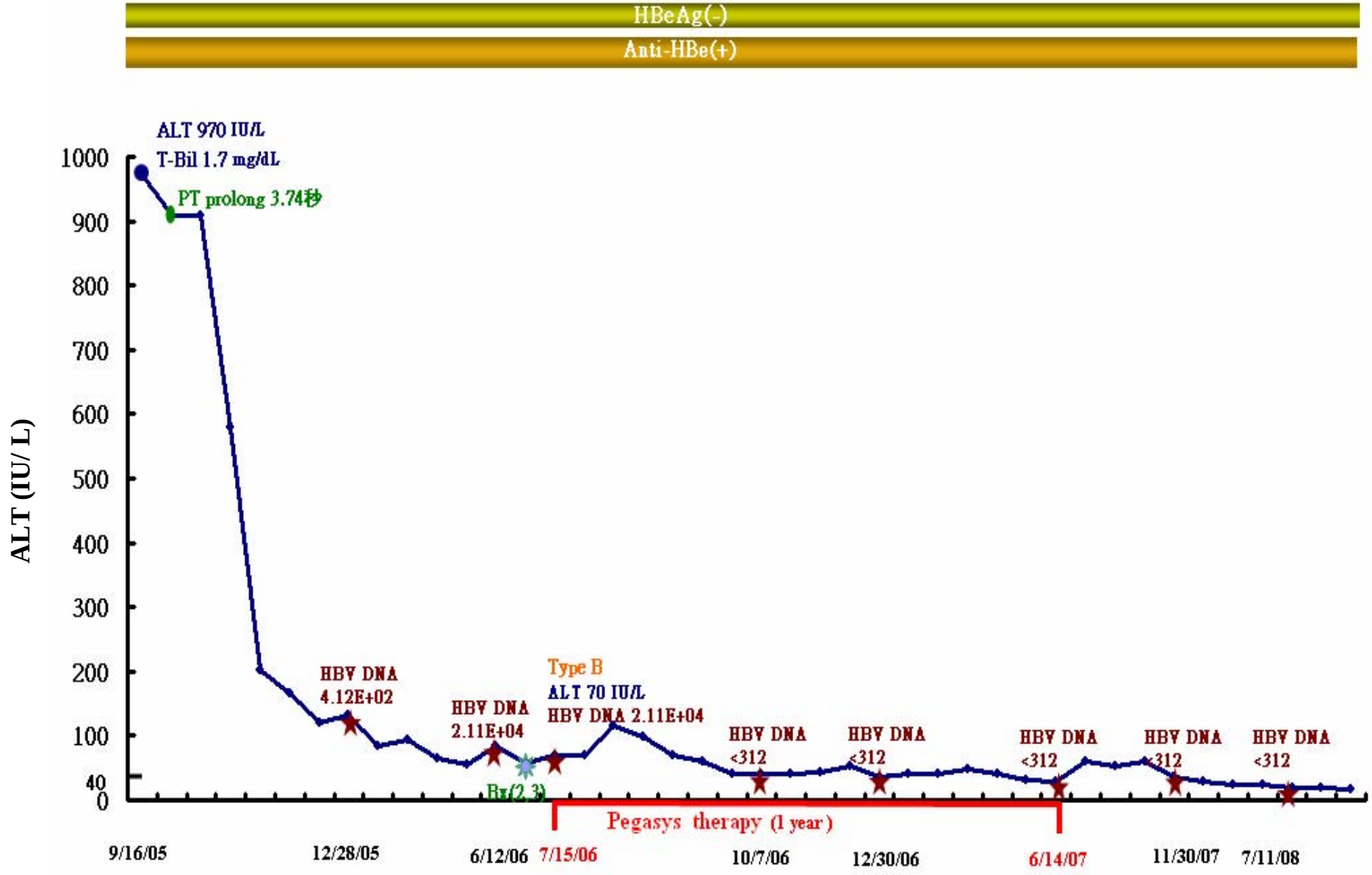
multivariate logistic regression

Discussion

- 本研究顯示長效型干擾素治療台灣慢性B型肝炎e抗原陰性患者，產生合併反應者為48%，正常ALT合併undetectable HBV DNA為30%，證實此為有效治療方法。
- 治療起始ALT高者，有較佳的合併反應。
- 研究結果比文獻報告佳，可能是HBV DNA 較低及Genotype B 較多。
- 本研究並沒有觀察到延遲性的合併反應，對於長效型干擾素治療後的效果，更長時間的觀察與追蹤是必需的。

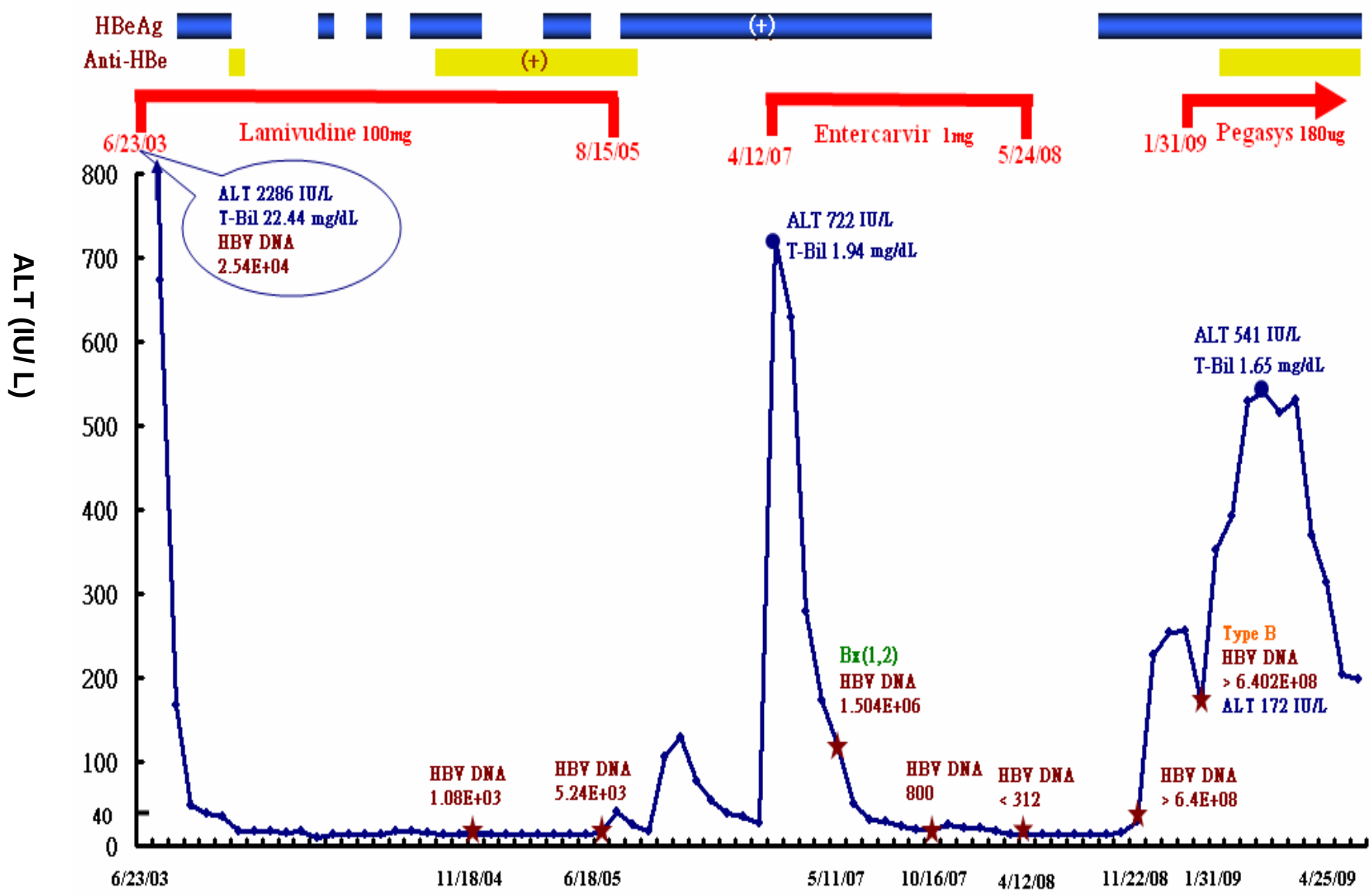
Case Presentation

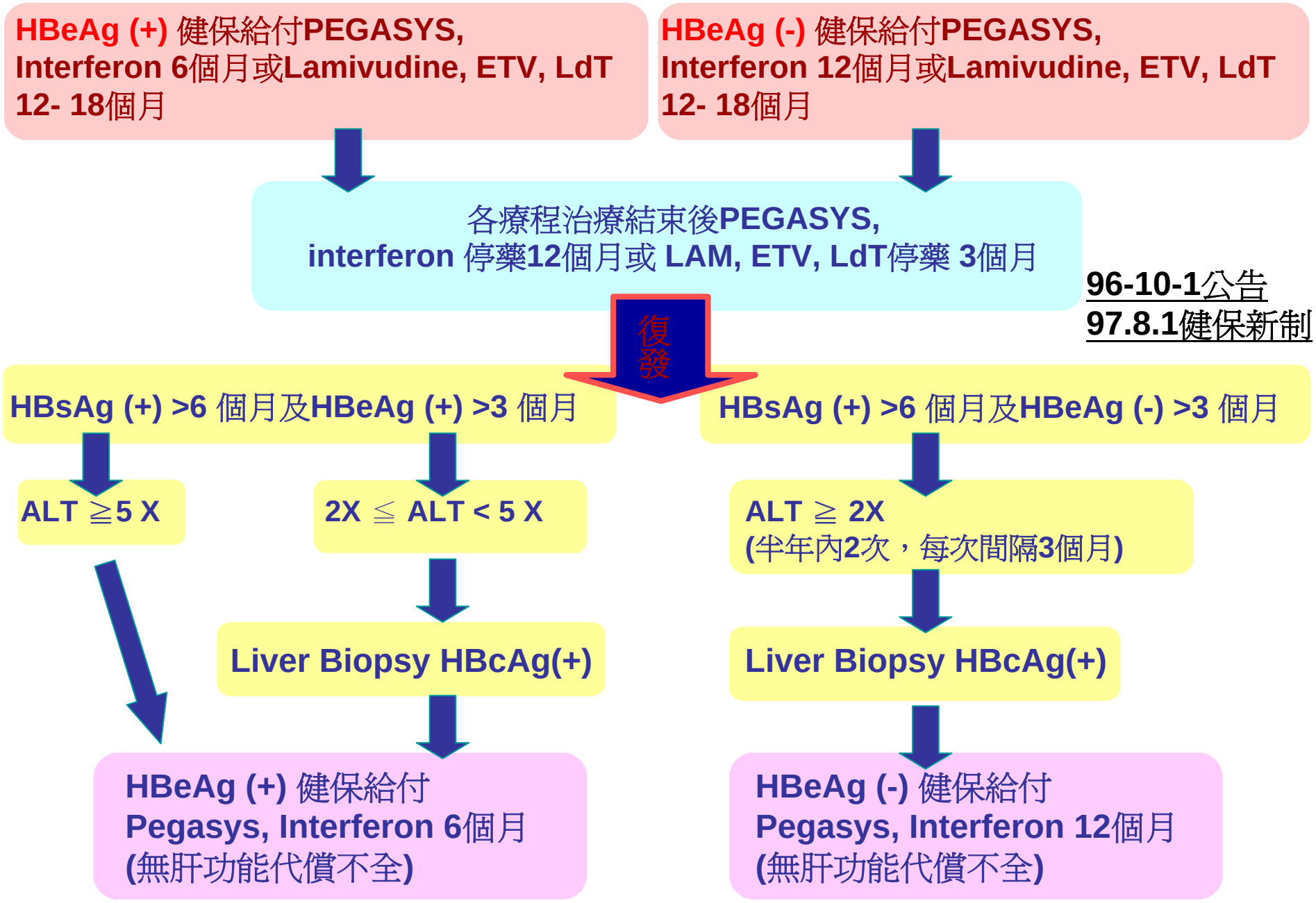
- 31 years old female
- Hepatitis B carrier, HBeAg positive (previous)
- Chronic hepatitis B with acute exacerbation


HBeAg(-)
Anti-HBe(+)
ALT 970 IU/L
T-Bil 1.7 mg/dL
PT prolong 3.74秒
ALT (IU/ L)
1000
900
800
700
600
500
400
300
200
100
40
0
HBV DNA
4.12E+02
HBV DNA
2.11E+04
Bx(2.3)
Type B
ALT 70 IU/L
HBV DNA 2.11E+04
HBV DNA
<312
HBV DNA
<312
HBV DNA
<312
HBV DNA
<312
HBV DNA
<312
Pegasys therapy (1 year)
9/16/05
12/28/05
6/12/06
7/15/06
10/7/06
12/30/06
6/14/07
11/30/07
7/11/08

Case Presensation

- 31 years old male
- Hepatitis B carrier. HBeAg-positive
- Chronic hepatitis B with acute exacerbation


HBeAg
(+)
Anti-HBe
(+)
6/23/03
Lamivudine 100mg
8/15/05
4/12/07
Entercarvir 1mg
5/24/08
1/31/09
Pegasys 180ug
ALT (IU/L)
800
700
600
500
400
300
200
100
40
0
ALT 2286 IU/L
T-Bil 22.44 mg/dL
HBV DNA
2.54E+04
ALT 722 IU/L
T-Bil 1.94 mg/dL
ALT 541 IU/L
T-Bil 1.65 mg/dL
Bx(1,2)
HBV DNA
1.504E+06
Type B
HBV DNA
> 6.402E+08
ALT 172 IU/L
HBV DNA
1.08E+03
HBV DNA
5.24E+03
HBV DNA
800
HBV DNA
< 312
HBV DNA
> 6.4E+08
6/23/03
11/18/04
6/18/05
5/11/07
10/16/07
4/12/08
11/22/08
1/31/09
4/25/09


HBeAg (+) 健保給付PEGASYS, Interferon 6個月或Lamivudine, ETV, LdT 12- 18個月
HBeAg (-) 健保給付PEGASYS, Interferon 12個月或Lamivudine, ETV, LdT 12- 18個月
各療程治療結束後PEGASYS, interferon 停藥12個月或 LAM, ETV, LdT停藥 3個月
96-10-1公告
97.8.1健保新制
復發
HBsAg (+) >6 個月及HBeAg (+) >3 個月
HBsAg (+) >6 個月及HBeAg (-) >3 個月
ALT ≧5 X
2X ≦ ALT < 5 X
ALT ≧ 2X
(半年內2次，每次間隔3個月)
Liver Biopsy HBcAg(+)
Liver Biopsy HBcAg(+)
HBeAg (+) 健保給付
Pegasys, Interferon 6個月
(無肝功能代償不全)
HBeAg (-) 健保給付
Pegasys, Interferon 12個月
(無肝功能代償不全)

Thanks for your attention

CHINA MEDICAL UNIVERSITY