Efficacy of High Dose Interferon – Alpha Treatment of Chronic Hepatitis B†

SATIEN TECHAPAITOON, M.D.*

Abstract

Fifteen consecutive Hepatitis B virus chronic hepatitis patients were treated with interferon alfa-2B 10 mu tiw for 5-6 months. All patients could tolerate the side effects without serious complications throughout the treatment period. Overall, 12 cases had normalization of ALT (80%), 7 cases had loss of HbeAg with appearance of anti-Hbe (58.33%) and 2 cases had loss of HbsAg with the presence of antiHBs (13.33%). The response usually associated with improvement in histology and decrease in viral load. These results seemed to be better than other studies with a lower dose. Further study with more patients should be done in the future.

Key word : Chronic Hepatitis B, Interferon-Alpha, Treatment

Hepatitis B caused by a double strand DNA virus, is a major medical problem in Thailand. There are approximately 4 million Hepatitis B carriers in Thailand[1]. Approximately 10 per cent of acute hepatitis patients are chronic carriers of the disease[1], and 16-59 per cent of carriers have hepatic inflammation and viral replication[2]. The annual probability of developing cirrhosis of the liver was 1 per cent for anti-Hbe positive patients and 12 per cent for HbeAg positive patients older than 30 years of age[3]. It is probably the etiologic agent for the vast majority of hepatocellular carcinoma (HCC) in Asia and Africa[4] and world wide[5]. People who acquired infection at birth or early childhood reported an annual probability of developing HCC in chronic Hepatitis B virus carriers of 0.49 per cent per year in Taiwanese men[6].

There is no completely satisfactory therapy for Hepatitis B. Most extensively evaluated has been interferon alfa (IFN-alfa), which has been reported to induce remission of disease in 25 per cent to 40 per cent of patients[7-10]. The recommended regimen of interferon alfa is either 5 mil-

* Department of Medicine, Rajavithi Hospital, Bangkok 10400, Thailand.

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lion units daily or 10 million units thrice weekly, given subcutaneously for four months[7,11] and up to 6 months[12]. The side effects of interferon typically involve an influenza-like reaction with fever, chills, weakness, myalgia and headaches which begin 6 to 8 hours after the first injection and last for up to 12 hours. Chronic side effects may appear, including a variable degree of fatigue, depression and bone marrow suppression. Approximately 2 per cent of patients have a severe adverse reaction[7]. However, many patients in Thailand have been treated by using a much lower dose of interferon with different results. The aim of this study was to evaluate the efficacy and tolerability of the standard high dose of interferon-alfa in a selected group of patients. Many parameters, such as biochemical changes, virologic markers, viral load and pathological changes were measured before, during and after treatment for a period of time.

MATERIAL AND METHOD

Patients. 15 consecutive patients (10 male, 5 female) in the Gastroenterology Unit, Department of Medicine, Rajavithi Hospital who were at least 18 years old, HbsAg positive for at least 6 months, serum ALT at least twice the upper normal limit for at least 6 months, no decompensated liver disease and anti-HCV and anti-HIV negative were selected.

Drug regimen : Interferon alfa-2B 5 mu. was administered daily, subcutaneously for 7 days. Then 10 mu. subcutaneously 3 times weekly for 5-6 months.

Monitoring. At the pre-treatment and post-treatment period, every patient was examined for CBC and platelet count, liver function test, HbsAg, anti-Hbs, HbeAg, antiHBe, HBV-DNA by Chiron – Branch – DNA Method (PCR method in some cases) and liver needle biopsy with pathological examination.

During treatment, the patients were followed-up every 2 – 4 weeks and blood examination for CBC and platelet count and liver function test were done.

After treatment, the patients were followed-up every 3-6 months and blood examination for CBC and platelet count, HBV-DNA, liver function test, HbsAg, anti-HBs, HbeAg and antiHBe was done. The results at 6 months after interferon treatment were compared to the pre-treatment ones.

Other adverse reactions and side effects of interferon were notified and recorded at every patient visit.

Statistical analysis.

Chi-square test (X^2 – Test) was employed for analysis and a P value <0.05 was considered significant.

Table 1. Results of interferon treatment in patients with chronic hepatitis B.

	Mean	Range
No. of cases	15	
Male : Female	10 : 5	
Induction day	5.4	(5 – 7)
Dose of IFN	10 mu.	tiw
Duration of treatment (m.)	5.066	(5 – 6)
Duration of follow-up (m.)	15	(6 – 48)
Normalization of ALT	12 case	(80%)
Loss of HbeAg	7 case	(58.33%)
Loss of HbsAg	2 case	(13.33%)
Lowest PMN (per mm^3)	812	(812 – 1500)
Lowest Platelet (per mm^3)	76×10^3	(76×10^3 -211×10^3)
DNA count (per ml)		
Pre-Rx	862.34×10^6	($<0.7 \times 10^6$ – 5483×10^6)
Post-Rx	148.54×10^6	(891×1 – 1030×10^6)
Histologic Improvement	5 in 7 cases	(71.42%)
Drop Out	0 / 15	
Serious side effects	0 / 15	

M = month; IFN = interferon; tiw = three times in a week

Table 2. Patients profile and ALT levels every 6 months.

No.	Age (y)	Sex	Induction time (D)	Treatment time (M)	ALT (u/l) normal 8-40 u/l in 6 m interval								
					0	6	12	18	24	30	36	42	48
1	28	M	5	5.5	82	46	42	30	28	-	40	-	35
2	32	F	5	5	93	41	34	26	40	30			
3	21	F	5	6	148	70	68	75					
4	26	F	5	5	134	-	45	55					
5	40	F	5	5.5	162	45	31	43	44				
6	49	M	5	6	179	27	33	33					
7	56	F	5	6	87	23	33	30					
8	27	M	5	6	93	29	293	224					
9	47	M	5	6	210	37	51						
10	36	M	5	6	300	45	24	26	33				
11	40	M	5	5	141	38	32	25					
12	33	M	5	5	98	40	38	-	46				
13	35	M	7	5	229	41	27						
14	48	M	7	5	92	65	74						
15	28	M	7	5	251	44	35						

(Y) = Year, (D) = Day, (M) = Month

RESULTS

As in Table 1, the induction period was 5 – 7 days (mean 5.4 days), duration of treatment was 4 – 6 months (mean 5.066 months). Six months after treatment, 12 cases had normal ALT (80%), 7 out of 12 HbeAg positive cases became HbeAg negative and anti-Hbe positive (58.33%), 5 of these 7 patients had histological improvement (71.42%).

Concerning the bone marrow suppression, the lowest PMN was 812 per mm^3 and lowest platelet count was 76 x 10^3 per mm^3, so no interferon adjustment was needed throughout the treatment period.

Except for flu – like symptoms, weight loss, loss of hair, anorexia and nausea, no other serious side effects were detected. Many patients used acetaminophen to relieve this flu-like symptom. So all patients tolerated this therapeutic regimen and there were no drop out cases.

Serum HBV-DNA was done by using the b-DNA method (PCR method in some cases) before and after interferon treatment and the results are shown in Table 1, 4. The mean HBV-DNA count before treatment was 862.34 x 10^6 copies per ml, and 148.54 x 10^6 copies per ml. After completion of treatment, HBV-DNA <0.7 x 10^6 copies / per ml were found in most cases who were seroconverted from HbeAg positive to HbeAg negative with anti-Hbe (case no 5, 6, 10, 13).

Concerning the histological changes, 7 chronic active hepatitis cases before interferon treatment had improvement in histology i.e. 2 cases of normal liver and 3 cases of chronic persistent hepatitis (case no 2, 5, 6, 9 and 13).

In comparison to other studies done in Thailand (Table 5) and in Table 6, only the HbeAg positive patients were shown for comparison[13,

Table 3. Patients' HBsAg, Ab and HBeAg, Ab every 6 months.

No.	Age	Sex	HBsAg/Ab in 6 m interval									HBeAg/Ab in 6 m interval								
			0	6	12	18	24	30	36	42	48	0	6	12	18	24	30	36	42	48
1	28	M	+/-	+/-	+/-	-	-	-	+/-	-	+/-	+/-	+/-	+/-	-	-	-	-	-	+/-
2	32	F	+/-	+/-	+/-	+/-	+/-	+/-				+/-	-	+/-	-	+/-	+/-			
3	21	F	+/-	+/-	+/-	+/-	+/-					+/-	-	+/-	-	+/-				
4	26	F	+/-	+/-	+/-	+/-						-/-	-/-	-/-	-/-					
5	40	F	+/-	+/-	+/-	-/+	-/+					+/-	-/+	-/+	-/-	-/+				
6	49	M	+/-	-/+	-/+	-/+						+/-	-/+	-/+	-/+					
7	56	F	+/-	+/-	+/-	+/-						-/-	-/-	-/-	-/-					
8	27	M	+/-	+/-	+/-	+/-						+/-	+/-	+/-	+/-					
9	47	M	+/-	+/-	+/-							+/-	-/+	-/+	-/+					
10	36	M	+/-	-	+/-	+/-	+/-					+/+	+/+	+/+	-/+	-/+				
11	40	M	+/-	-	+/-	+/-						+/-	+/-	-/+	-/+					
12	33	M	+/-	-	+/-	+/-						+/-	-/+	-/+	-/+	-/+				
13	35	M	+/-	-	+/-							+/-	-/+	-/+						
14	48	M	+/-	-	+/-							-/-	-/-	-/-						
15	28	M	+/-	+/-	+/-							+/-	+/-	+/-						

14). The percentage of normalization of ALT, loss of HbeAg and loss of HbsAg were better in this study than others to a different extent but most of these results had no statistical significance by Chi-Square analysis. These results are also shown in Fig. 1, 2.

DISCUSSION

This study prospectively evaluated the clinical outcome of a group of patients with chronic Hepatitis B who were treated with a standard dose of 10 mu. Tiw of interferon for up to 6 months.

Every patient tolerated the interferon's clinical and bone marrow side effects without reduction or discontinuation of the interferon throughout the treatment course.

Biochemical response rate was about 80 per cent (normaliztion of ALT). Seroconversion of HbeAg positive to HbeAg negative with anti-Hbe was 58.33 per cent in which 4 cases had HBV-DNA less than 0.7×10^6 copies per ml. These cases could probably have had a better long term clinical outcome[7,15]. Two cases could eliminate HbsAg with the appearance of antibody, both of these were

Table 4. Patients' HBV - DNA every 6 month, liver histology, lowest PMN and lowest platelet count.

No.	Age	Sex	HBV-DNA (x 10^6/ml) in 6 m interval						Liver Histology		Lowest PMN (per mm^3)	Lowest Platelet x $10^3/mm^3$
			0	6	12	18	24	30	Pre-Rx	Post-Rx		
1	28	M	1739	1030					-	-	1300	182
2	32	F	2544	690	-	777			CAH	Normal	960	145
3	21	F	578	1.36	8.9				CAH	-	1200	120
4	26	F	216	303					-	-	1500	150
5	40	F	<0.7	<0.7	-	-	<0.7		CAH	Normal	812	150
6	49	M	100	<0.7	1.88	<0.7			CAH	CPH	884	76
7	56	F	39	898*					CAH	CAH	1170	145
8	27	M	5483	5.6					CAH	CAH	840	211
9	47	M	506	22					CAH	CPH	868	164
10	36	M	6	<0.7	-	-	<0.7		-	-	1200	170
11	40	M	-	-					-	-	1100	165
12	33	M	-	-					CH	-	980	180
13	35	M	6.7	<0.7					CAH	CPH	1000	100
14	48	M	14	36					CPH	-	1050	100
15	28	M	40	13					CPH	-	1100	150

CH = Chronic Hepatitis CPH = Chronic Persistent Hepatitis

CAH = Chronic Active Hepatitis

* 898 copies/ml

the HbeAg seroconversion patients and HBV-DNA less than 0.7 x 10^6 copies per ml ones. The results of this study seem to be better than other studies in Thailand that used a lower dose of IFN (13,14). But statistically, only the normalization of ALT had a significant difference. A larger cohort of patients could be included in these studies to clarify these controversies in the future.

Patients with HBeAg positive had a more favorable result than those who were HbeAg negative (pre core mutant)(7,16). So patients with mutant type HBV-chronic hepatitis should be treated with a different regimen or different agents to yield a better response rate.

Most patients who respond well and become HbeAg seroconversion have HBV DNA levels below the detection limit of 0.7 mega-equivalence per ml after treatment. The pretreatment DNA vary from low to high. So there was no level above which patients could not respond(16).

In conclusion, in this study, patients tolerated the side effects of this standard dosage of interferon alfa 2B without serious complications. The results of treatment seem to be better clinically than the lower dose regimen but not statistically. Further study with more patients should be carried out in the future to clarify these results.

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Table 5. Comparison of four studies in Thailand.

	S. Techapaitoon	B. Ovartlarnporn[13]		K. Klanklin[13]		M. Hongsirinirachon[14]	
Study Type	Prospective	Prospective		Prospective		Retrospective	
Induction Day	5.4 (5-7)	With and Without		14		-	
Dose of IFN	10 mu. tiw	3 mu. tiw		3 mu. tiw		3-10 mu. tiw	
Prednisolone priming	-	8/15		Yes		-	
Duration of R_X	5.066 (5.3 m)	29.6±19 (12-72 w)		16 w		6 m	
Duration of F/U	15 (6-48 m)	35 (6-66 m)		12 m		NA	
No. of cases	15	15		12		36	
HBeAg + : -	12:3	9:6		12:0		27:9	
Normal ALT	12/15 (80%)	6/15 (40%)	P>0.05	4/12 (33%)	P<0.05	14/29 (48%)	P>0.05
Loss of HBeAg	7/12 (58%)	NA	P -	5/12 (42%)	P >0.05	10/21 (47%)	P>0.05
Loss of HBsAg	2/5 (13%)	1/15 (6%)	P>0.05	1/12 (0.83%)	P>0.05	NA	P -
DNA counts/ml							
Pre - R_X	862.34 x 10^6 (<0.7 x 10^6 - 5,483 x 10^6)	NA		NA		NA	
Post - R_X	148.54 x 10^6 (891 x 1 - 1,030 x 10^6)	NA		NA		NA	
Histologic improvement	5/7 (71%)	NA		3/9 (33%) P>0.05		NA	
Lowest PMN/mm^3	812	NA		NA		NA	
Lowest platelet/mm^3	76 x 10^3	NA		NA		NA	

m = month NA = not available

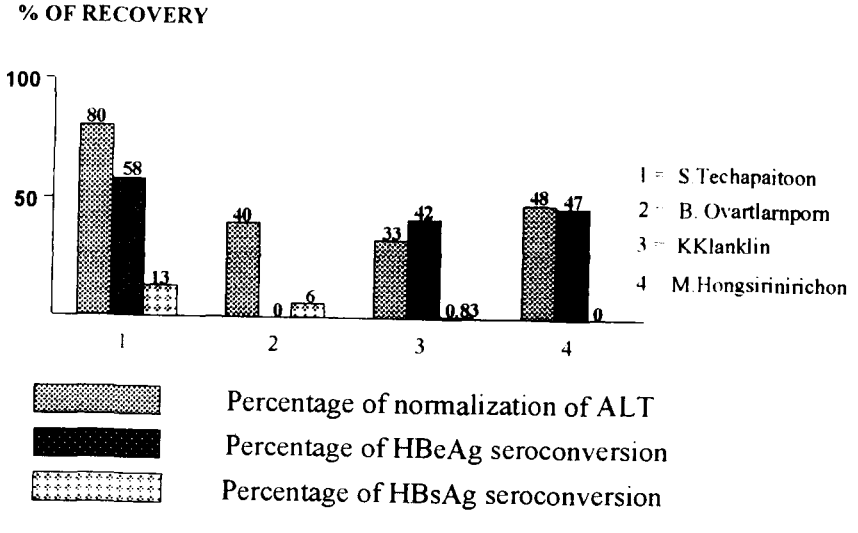

Fig. 1. Comparison of the results from Table 5.

Table 6. Comparison of only HBeAg positive patients.

	S. Techapaitoon	B. Ovartlarnporn[13]		K. Klanklin[13]		M. Hongsirinirachon[14]	
Study Type	Prospective	Prospective		Prospective		Retrospective	
Induction Day	5.4 (5.7)	With and Without		14		-	
Dose of IFN	10 mu. tiw	3 mu. tiw		3 mu. tiw		3-10 mu. tiw	
Prednisolone priming	-	With and Without		Yes		-	
Duration of R_X	5.066 (5.6 m)	29.6 ± 19 (19-72 m)		16 w		6 m	
Duration of F/U	15 (6-48 m)	35 (6-66 m)		12 m		NA	
No. of cases	12	9		12		27	
HBeAg + : -	12:0	9:6		12:0		27:0	
Normal ALT	12/15 (83%)	5/9 (55%)	P>0.05	4/12 (33%)	P<0.05	10/21 (47%)	P>0.05
Loss of HBeAg	7/12 (58%)	NA	P -	5/12 (42%)	P>0.05	10/21 (47%)	P>0.05
Loss of HBsAg	2/12 (16%)	1/9 (11%)	P>0.05	1/12 (0.88%)	P>0.05	NA	P -
Histologic improvement	5/7 (71%)	NA		3/9 (33%)	P> 0.05	NA	

w = week m = month NA = not available

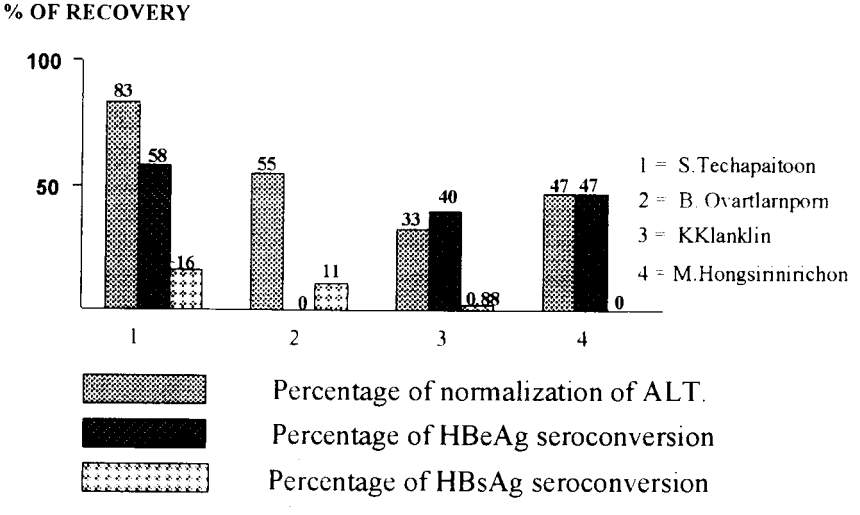

Fig. 2. Comparison of the results from Table 6.

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ผลของยาอินเตอเฟอรอน-แอลฟ่า ปริมาณสูง ต่อผู้ป่วยตับอักเสบเรื้อรังจากไวรัสตับอักเสบบี

*เสถียร เตชะไพฑูรย์, วท.บ., พ.บ., ว.ว., อ.ว.**

ได้ทดลองใช้ยาอินเตอเฟอรอน-แอลฟ่า ขนาดสูง (10 ล้านหน่วย สัปดาห์ละ 3 ครั้ง เป็นเวลา 5-6 เดือน) ในผู้ป่วยตับอักเสบเรื้อรังจากไวรัสตับอักเสบบี จำนวน 15 คน และติดตามเป็นเวลา 6 - 48 เดือน (เฉลี่ย 15 เดือน) หลังการรักษา ผลปรากฏว่าหลังการรักษา 6 เดือน 12 ราย มีค่า ALT ปกติ (80%), 7 ราย HBeAg หายไปและมี Anti-HBe (58.33%) และ 2 ราย HBsAg หายไปและมี Anti-HBs (13.33%) ผู้ป่วยที่ดีขึ้นมักจะมีผลชิ้นเนื้อตับซึ่งตรวจทางพยาธิวิทยาดีขึ้น และจำนวนไวรัสในกระแสโลหิตลดลงเช่นกัน. ผู้ป่วยทั้งหมดสามารถรับการรักษาจนครบกำหนดและทนต่อผลข้างเคียงของยาได้ดี ไม่มีผู้ใดหยุดยาก่อนกำหนด ผลที่ได้รับเมื่อเปรียบเทียบกับอีก 3 รายงาน ปรากฏว่าได้ผลที่ดีกว่า อย่างไรก็ตามคงจะต้องมีการศึกษาเพิ่มขึ้นอีกด้วยตัวอย่างผู้ป่วยที่มากกว่านี้

คำสำคัญ : ตับอักเสบเรื้อรังจากไวรัสตับอักเสบบี, อินเตอเฟอรอน-แอลฟ่า, การรักษา

* กลุ่มงานอายุรกรรม, โรงพยาบาลราชวิถี, กรมการแพทย์, กระทรวงสาธารณสุข, กรุงเทพ ฯ 10400