영남의대학술지 제15권 제2호
The Yeungnam Univ. Med. J.
Vol. 15. No. 2. December 1998.

Effect of α-Interferon 2b on Chronic Hepatitis B Patients with High Serum ALT

Heon Ju Lee, Young Doo Song

Department of Internal Medicine
Yeungnam University, Medical School
Taegu, Korea

Introduction

Whether interferon (IFN) reduces the risk of cirrhosis and hepatocellular carcinoma in patients with chronic hepatitis B (CHB) is still under investigation, but α-interferon 2b (IFN 2b) can terminate viral replication and eradicate the carrier state in patients with chronic hepatitis B virus (HBV) infection who are HBeAg positive (Wong et al., 1993). Indeed, IFN is the only drug accepted as a fundamentally acting therapeutic agent against HBV. Seroconversion from HBeAg positive to anti-HBe positive occurrs at rates of 8% to 62% soon after recombinant IFN therapy(Davis and Hoffnagle, 1986; Coppens et al., 1990; Lok et al., 1992; Kayrakta et al., 1993; Mauracher, 1993; Zuckerman and Thomas, 1993). However, comparison of the results of many studies of the efficacy of recombinant IFN is difficult because each study has a different type of patients and therapy protocol, and both the dosage and the duration of IFN therapy(Davis and Hoffnagle, 1986) and the pretreatment characteristics of the patients(Brook et al., 1989) appear to influence the response to IFN.

Among the factors that might predict seroconversion(Brook et al., 1989; Zuckerman and Thomas, 1993), customized dosage and duration of IFN therapy and one marker of disease intensity - abrupt marked elevation of alanine aminotransferase (ALT) - were examined in this prospective study as predictors of a higher HBeAg/anti-HBe seroconversion rate in response to α-IFN 2b.

Materials and Methods

Patients

All 95 Korean patients were (82 men and 12 women) enrolled in the study met the following critera: documented HBsAg in the serum has for several years, positive tests for HBeAg and

serum HBV DNA, fluctuating serum aminotransferase levels above the normal value, biopsy-proved CHB, and negative tests for serum anti-HCV. The 40 IFN-treated patients (group A) and the 45 control patients (group C) had had fluctuating high levels of or abrupt severe increases in the level of serum ALT over 3 months. Ten patients with stable elevations of ALT (group B) less than three times the upper normal value also were treated with IFN. The infection had been vertically transmitted in 43% of the patients in group A, 50% of those in group B, and 47% of those in group C. The characteristics of these groups are summarized in Table 1. No patient had a history of travel out of Korea, transfusion, drug abuse or homosexual behavior.

Biochemical and Serological Methods

Liver function was evaluated using a Hitachi 747 autoanalyzer. The mean aminotransferase levels shown are from the tests carried out at the start of therapy in group A and the highest values from the beginning of the exacerbation period in group C. Serum HBsAg, HBeAg, anti-HBe, and IgM anti-HBe were tested with radioimmunoassay kits from Abbott Laboratories (N. Chicago, IL). Serum HBV DNA was measured semiquantitatively by the dot-blot hybridization method.

Follow-up was done every 1 to 2 months for 0.5 to 2 years after the end of αIFN 2b therapy in group A and group B but irregularly in group C, in which the patients were evaluated one or more times in a year.

Treatment Protocol

Fifty patients received recombinant IFN 2b for average of 5.1 (range 3-12) months empirically until seroconversion developed unless adverse reactions or economic difficulty blocked

Table 1. Pretreatment characteristics of patients by group

	A	B	C
Sex (M:F)	34 : 6	10 : 0	38 : 7
Age (Yr)[a]	34.4 (14 – 59)	30.6 (21 – 42)	33.2 (19 – 59)
HBsAg-positive mother and/or siblings (%)	16 (43.2)	5 (50.0)	20 (46.7)
AST (IU/L)[b]	319.3 ± 275.1	62.3 ± 18.0	456.1 ± 323.4
ALT (IU/L)[b]	498.7 ± 394.2	91.9 ± 25.1	640.0 ± 458.1
IgM anti-HBc (%)	8/16 (50.0)	–	4/17 (23.5)
Histology[c]			
CPH	1	1	0
CAH	32	9	37
CAH+C	7	0	8

a: Median (range)

b: Mean ± S.D

c: CPH=chronic persistent hepatitis; CAH=chronic active hepatitis; C=cirrhosis

Table 2. Characteristics of patients according HBeAg/anti-HBe seroconversion after interferon therapy and natural course

	Interferon		Control			
	A (n=40)		B (n=10)		C (n=45)	
Seroconversion	+	-	+	-	+	-
Sex(M:F)	26 : 2	8 : 4	2 : 0	8 : 0	16 : 2	22 : 5
Age(Yr)[a]	35.3 (14-59)	36.9 (21-50)	21	31.1 (21-42)	34.8 (19-54)	31.5 (21-51)
HBsAg-positive mother and/or siblings (%)	8 (32)	8 (66)	2 (100)	5 (63)	6 (33)	14 (52)
DNA(%)						
+	8 (16)	2 (17)	2 (100)	1 (11)	-	-
+	1 (4)	1 (8)	0	0	-	-
+++	4 (16)	1 (8)	0	3 (33)	-	-
++++	15 (60)	8 (67)	0	5 (56)	-	-
AST(IU/L)[b]	402.8 ± 343.6	226.8 ± 119.5	57.3	65.9 ± 19.9	475.3 ± 333.5	358.6 ± 251.8
ALT(IU/L)[b]	580.6 ± 504.0	404.5 ± 212.6	66.5	102.8 ± 32.2	834.6 ± 595.2	545.5 ± 372.0
IgM anti-HBc(%)	5/8 (62.5)	3/8 (37.5)	-	-	0/13	4/4 (100)
DNA(-), HBeAg/anti-HBe seroconversion(%)	28 (70.0)		2 (20.0)		18 (40.0)	
(follow-up period : yr)	1.1 ± 0.5 (0.5-2)				2.9 ± 3.1 (0.2-10)	
Disappearancee rate of HBeAg(%)	33 (83)		5 (50)		20 (44)	
Seroconversion with DNA (+)(%)	5		1		-	
Time to seroconversion(M)[c,d]	4.1 ± 2.5 (2-10)		4.5 (4-5)		8.1 ± 12.8 (2-120)	
Reappearance of HBeAg(%)	10 (32)		0		2 (11)	
Time to reappearance of HBeAg(M)[c]	6.9 (2-15)		-		2.5 (2-3)	
Seroconversion with DNA(-)(%/yr)	67.5*		20.0		12.8	
IFN therapy or spontaneously(%/yr)						
Reappearance HBeAg (%/1st year)	29		0		11	

a: Median(range)
b: Mean ± S.D
c: Mean ± SD(range)
d: month
* P<0.025

further therapy. Every patient received 3 million units (MU) αIFN 2b every day for 2 weeks followed by 3 MU every other day. Interferon was started after confirmation of the presence of serum HBeAg and HBV DNA when the serum aminotransferase levels were declining from peak levels at the start of therapy. Follow-up tests were conducted every week at first and then every 2 to 3 weeks until seroconversion (in responders) or the termination of therapy (in non-responders).

Results

The differences in the characteristics of the patients who revealed HBeAg/anti-HBe

Table 3. Duration of α IFN 2b therapy according to HBeAg/antiHBe seroconversion status

Seroconversion	+		−		Total
	A	B	A	B	
Duration(%)					
3 Mos	9(32)	1(50)	1(8)	2(25)	13
< 6 Mos	9(32)	1(50)	5(42)	4(50)	19
< 12 Mos	10(38)	0	6(50)	2(25)	18

Mos, Months

Table 4. Time to reappearance of serum HBeAg after cessation of αIFN 2b therapy

Time after therapy(Mos)	No. of Patient
< 3	4
< 6	3
< 12	2
> 12	1
Total	10

Mos, Months

seroconversion after αIFN 2b therapy and those with spontaneous seroconversion are described in Table 2. In both group A and group C, the percentage of patients with HBsAg-positive family members was lower among patients with spontaneous seroconversion (32% and 33%, respectively) than in those without seroconversion (67% and 52%, respectively). In group B, the responders showed lower serum viral DNA levels than did the non-responders. The serum AST and ALT levels were higher in responders than in non-responders in groups A and C but not in group B. In group A, IgM anti-HBc was positive in 63% of the responders but in 38% of the non-responders. The HBeAg/anti-HBe seroconversion rate was 70%, 20%, and 44% in groups A, B, and C, respectively. The HBeAg clearance rates were 82% and 50% in groups A and B, respectively. HBV DNA was still positive in the serum in 6 of 38

Table 5. Short time effect of α IFN 2b retreatment in patients relapsing with seroconversion or HBeAg seronegative after first IFN therapy

Patients[a]	Age	Sex	Duration of IFN (M)		Time to Seroconversion (SC) or Seronegative (SN) (M)		Time to Relapse after 1st Tx(M)
			1st	2nd	1st	2nd	
1	14	M	3	6	3 (SC)	2.5 (SC)	12
2	17	M	4	6	2 (SC)	1.5 (SC)	7
3	39	M	3	12	3 (SN)	10 (SC)	4
4	33	M	3	12	3 (SC)	2 (SC)	1
5	43	M	4	0.5	4 (SN)	3 (SC)	6
6	32	M	9.5	6	9 (SN)	2 (SC)	1
7	38	F	6	6	2 (SC)	3 (SC)[b]	3

a: ALT levels were elevated over 4 to 10 folds of the upper normal limit with reappearance of serum HBeAg and/or positive DNA probe in all patients.

b: Breakthrough with reappearance of HBeAg and positive DNA by PCR at 6th month of 2nd therapy was followed by seroconversion with negative DNA 1 month later.

seronegative patients in groups A and B. Four of them showed seroconversion with positive DNA probe tests and the reamining two showed positive PCR test for HBV DNA. The average time to seroconversion after αIFN 2b therapy or flare-up was 4.1, 4.5, and 8.1 months in groups A, B, and C, respectively.

HBeAg reappeared in 32% of group A vs. none of group B after a follow-up period of 1.1 years after the end of αIFN 2b therapy and 11% of group C after follow-up period of 2.9 years. Thus, seroconversion rate in a year was 68% in group A, 20% in group B, and 13% in group C. The reappearance rate of HBeAg in a year was 29% and 11% in group A and C, respectively.

The dosage and duration of αIFN 2b therapy according to seroconversion status is shown in Table 3. The time to the relapse and the number of HBeAg relapse are described in Table 4.

Seven patients who showed reappearance of HBeAg and ALT elevation were treated again with αIFN 2b (Table 5). All patients showed seroconversion during or shortly after IFN therapy, with one case of breakthrough.

Discussion

High serum aminotransferase concentrations, marked hepatic inflammatory activity, the presence of serum IgM anti-HBc, and low serum HBV DNA are known predictors of a good response to IFN(Zuckerman and Thomas, 1993). In our series, the rate of seroconversion was markedly higher in group A (high ALT) than in group B (modest ALT elevation). The true annual seroconversion rate, excluding relapses and spontaneous seroconversions, was also higher in group A than in groups B and C. There were no differences in sex, age or the quantity of serum HBV DNA between responders and non-responders. The frequency of vertical transmission was significantly higher in non-responder of group A but not in group C ($P<0.05$). IgM anti-HBc could be checked in only 33 of 95 patients, but the positive rate was higher in responders.

After IFN therapy, clearance of HBeAg has been reported in 21.5% to 88% of patients (Barbara et al., 1986; Hoofnagle et al., 1988; Brook et al., 1989; Saracco et al., 1989; Peririllo et al., 1990; Lok et al., 1992), and the published HBeAg/anti-HBe seroconversion rate is between 24% and 55%(Coppens et al., 1990; Lee et al., 1990; Janssen et al., 1992). The results of the many studies of HBeAg-negative and seroconversion rates cannot easily be compared, however, because of differences in HBV status among patients, the dosage and duration of IFN therapy, the length of follow-up, and the time of evaluation. Our HBeAg elimination and HBeAg/anti-HBe seroconversion rates are higher than those by others(Coppens et al., 1990; Lee et al., 1990; Janssen et al., 1992), which might be attributable to the selection of patients who had elevated serum aminotransferase levels at the start of αIFN 2b therapy. No correlation was found between quantity of HBV DNA in the serum or IgM anti-HBc positivity and seroconversion.

The HBeAg relapse rate among patients undergoing HBeAg/anti-HBe seroconversion after IFN therapy has been reported as 5% to 10% of responders(Realdi et al., 1980; Viola et al., 1981; Takeda et al., 1990). HBV DNA-positive relapse rate among patients who show HBV DNA clearance after IFN therapy is reported as 47% to 87%. However, in our study, HBeAg relapsed in 32% of responders in the year after αIFN 2b therapy. Among patients with a rise in serum ALT and reappearance of HBeAg or DNA after the stoppage of IFN therapy, a second cycle of the agent was given to seven and was effective in all of them.

The spontaneous annual seroconversion rate has been reported as 2.7% to 30%(Realdi et al., 1980; Hoofnagle et al., 1981; Viola et al., 1981), and 13% found in our study was compatible with these reports. More than half of such spontaneous seroconversion are preceded by an abrupt increase in serum aminotransferase levels (Liaw et al., 1984), and seroconversion occurs concurrently with or several months before the fall in aminotransferase levels. No difference was reported in the aminotransferase levels between patients who have seroconversion and those who do not(Hoofnagle et al., 1981). Approximately one fourth of exacerbation episodes were reported to be followed by HBeAg clearance within 3 months(Liaw et al., 1984).

The patients in our control group visited the out patient clinic irregularly. Therefore, the number of disease flare-ups and the time of seroconversion could not be evaluated exactly. However, it is clear that, in some patients, at least one flare-up had preceded persistent seroconversion. Even after HBeAg/anti-HBe seroconversion, whether spontaneous or induced αIFN 2b therapy, HBV DNA reappeared in the serum within 1 month after the end of therapy. This event was followed by ALT elevation to 400 IU/L, which then returned to the nearly normal in 3 months with positive serum HBeAg and DNA. Most of the patients with rising values of serum enzymes showed improvement to normal or nearly normal liver function, either spontaneously or with αIFN 2b therapy, but demonstrated persistence of HBV replication activity. One patient in group C, who had abrupt exacerbation of liver function abnormalities, revealed transient HBeAg/anti-HBe seroconversion and a negative HBV DNA test but positive serum PCR during his illness. The HBeAg reappeared with nearly normal ALT levels during convalescence 3 months after the onset of the exacerbation. A second exacerbation followed the reappearance of HBeAg in 1 month. An HBeAg/anti-HBe seroconversion with sustained HBV DNA is more likely to be the result of infection with precore HBV mutants (Takeda et al., 1990). HBeAg-negative hepatitis responds in much the same way as HBeAg-positive disease(Liaw et al., 1984). In this study, four patients in group A and one in group B revealed seroconversion with positive serum HBV DNA after αIFN 2b therapy. Precore mutants were not checked for, but three patients revealed fluctuating high ALT levels. The effects of IFN on patients with mutant HBV and on the development of precore mutants are

unclear(Brunetto et al., 1989; Hadziyannis et al., 1990).

Interferon therapy for chronic HBV liver disease produced HBeAg/anti-HBe seroconversion or an HBeAg seronegative state more frequently and more rapidly than in control patients, even considering relapses. Earlier seroconversion might be helpful in preventing progress to cirrhosis in patients who would demonstrate seroconversion after future exacerbations of the disease or who are absolutely unable to obtain seroconversion. To obtain better results from IFN therapy and to decrease the likelihood of reactivation after therapy is stopped a variable therapeutic protocol and more accurate tests for the evaluation of successful and complete treatment in individual patients are needed. One of the most important factors that affect the result of IFN therapy might be the time and the situation resulting from the interaction between HBV and the immune system. At a minimum, the condition of each patient, as well as serum aminotransferase levels, should be considered in comparing the results of IFN therapy in different studies.

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- 초 록 -

급상승된 혈청 ALT치를 나타낸 만성 B형 간염 환자에 대한 α-Interferon 2b의 치료 효과

영남대학교 의과대학 내과학교실

이헌주 · 송영두

만성 B형 간염 환자에서 Interferon (IFN) 치료 후 혈청 HBeAg 소실 및 anti-HBe의 양전율을 높이고 효율적인 치료의 근거를 알기 위하여 치료 전 간기능검사상 갑자기 상승한 혈청 ALT치를 나타낸 환자군과 그렇지 않은 대조군을 대상으로 하여 IFN을 투여한 군과 IFN 치료없이 정상 HBeAg의 자연 소실을 보인 환자군을 임상적으로 장기간 관찰하고 조사하였다.

ALT치가 정상 상한치의 4배 이상 높이 증가되어 3개월 이상 왕복을 보인 40명의 환자(A군)와 ALT치가 정상 상한치의 3배 이하로 증가된 10명(B군)에게 α-IFN 2b를 매일 300만 단위 피하주사로 3~12개월 주사하였다. 대조군으로는 ALT치가 A군처럼 상승한 45명(C군)이었으며, IFN 치료없이 평균 2.9년을 관찰하였다.

HBeAg/anti-HBe 혈청 양전율은 A군 68%, B군 20%, C군 13%이었으며 IFN 치료 중단 후 1년까지의 HBeAg 재양성율은 A군에서 29%였고 HBeAg이 소실된 A와 B군의 38명중에서 6명에서 HBV DNA가 양성이었다. 6명중 4명은 HBeAg/anti-HBe 양전을 보였으나 HBV DNA 양성이었고 나머지 2명은 HBeAg, anti-HBe 및 HBV DNA (hybridization) 모두 음성이었으나 중합효소연쇄반응검사상 HBV DNA 양성이었다.

이상의 결과를 보면 비록 IFN 치료 후에 HBeAg이 소실되었다가 다시 양성화되더라도 IFN은 단기간내에 혈중 HBeAg이나 DNA가 자연적으로 감소가 될 환자나 그렇지 않은 환자에게도 HBV의 비증식화를 유발하여 도움이 될 것으로 사료된다. 그러나 IFN 투여 후에도 혈중 HBeAg과 DNA 소실에 전혀 도움이 되지 않을 환자 및 HBV 증식 억제효과가 기대되는 HBV 간질환 환자의 조건, IFN 투여량, 기간 등에 대한 계획적이고 체계적인 연구로 더 나은 치료효과를 기대할 수 있으리라 생각된다.

핵심용어: 인터페론 알파, B형 간염, 만성질환, ALT