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Interferon re-treatment for resistance to lamivudine plus interferon treatment

Lamivudine interferon kombinasyon tedavisi sonrasi direnç gelişen olgularda tekrar interferon tedavisi

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Background/aims: *The most important problem of the lamivudine therapy is the frequent development of drug resistance. Treatment of chronic hepatitis B patients resistant to lamivudin remains to be established. We investigated in this study the efficacy of interferon therapy for breakthrough infection to combination therapy with interferon and lamivudine.* ***Methods:*** *Interferon therapy was applied to nine patients who experienced HBV DNA breakthrough with ALT elevation for at least three months during the lamivudine treatment, which was given in combination with interferon for the first six months. These patients were compared with 10 patients who developed breakthrough but were not given interferon. All the patients continued to receive lamivudine.* ***Results:*** *Of the nine patients who were given interferon, two lost HBV DNA and had normal ALT after six months of treatment. ALT levels returned to normal in two patients who had no virological response. Of those patients not given interferon, none lost HBV DNA, but three had normal ALT at the end of the same duration of follow-up.* ***Conclusions:*** *The patients with breakthrough infection during lamivudine treatment, which was combined with interferon at the beginning, may benefit from another cycle of interferon treatment.*

Keywords: Interferon, lamivudine, resistance, retreatment

Amaç: *Lamivudin tedavisinde en önemli problem sıklıkla ilaca karşı direnç gelişmesidir. Lamivudine dirençli hepatit B olgularının nasıl tedavi edileceği bilinmemektedir. Bu çalışmada interferon lamivudin kombinasyon tedavisi sırasında breakthrough infeksiyon gelişen olgularda yeniden interferon tedavisinin etkinliği araştırılmıştır.* ***Yöntem:*** *İlk 6 ay interferonla kombine, daha sonra yalnız lamivudine kullanırken en az 3 aydır ALT yüksekliği ve HBV DNA pozitifliği (Breakthrough infeksiyon) gelişen 9 hastaya interferon tedavisi uygulandı. Bu hastaların sonuçları breakthrough infeksiyon gelişen interferon verilmeyen 10 hasta ile karşılaştırıldı. Bütün hastalar lamivudine almaya devam etti.* ***Bulgular:*** *6 ay interferon alan 9 hastanın 2'inde HBV DNA kayboldu, ALT normal değerlerlere düştü. Ayrıca virolojik cevap vermeyen 2 hastada ALT değerleri normal değerlere indi. interferon verilmeyen hastaların hiçbirinde HBV DNA kaybı olmadı, fakat 3'ünde aynı takip süresinde ALT değerleri normal düzeylere düştü.* ***Sonuç:*** *Başlangıçta interferon ile kombine edilen, lamivudin tedavisi sırasında breakthrough infeksiyonlu hastalar tekrar interferon tedavisinden yarar görebilirler.*

Anahtar kelimeler: interferon, lamivudine, direnç, retreatment

INTRODUCTION

More than 350 million people around the world are infected with hepatitis B virus, and 10% of them will die due to HBV infection-related complications (1). Treatment of this infection with either of two approved drugs, interferon alpha and lamivudine, is not satisfactory (2, 3). Therefore, combination of these drugs has been tried in various studies, but thus far no definite advantage has been observed over their single use (4, 5). In our trial we administered lamivudine (150 mg/day) and interferon (9 MU tiw) simultaneously for six months, then lamivudine was continued alone for at least 18 months (6). Drug resistance, which is the major problem of lamivudine treatment, was found to be as high as seen in single lamivudine use. At the end of the two-year treatment, phenotypic breakthrough was encountered in 36.5% of patients who were treated with interferon plus lamivudine, and in 41.9% of those treated with lamivudine alone. There has been no definite data regarding how to manage lamivudine-resistant infection. Treatment with ganciclovir and famciclo-

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vir has proved disappointing, while adefovir and entecavir seem to have some benefit (7-10). The other approved drug, interferon, has limited use in lamivudine-resistant infection (11, 12). It was found to be beneficial in a limited number of patients. Although interferon retreatment in patients who have no sustained response to previous interferon treatment is partially successful (13, 14), considering that lamivudine-resistant mutants are different from wild type HBV with respect to replication capacity and probably virulence, interferon is worth trying in resistant infection that has been treated with interferon plus lamivudine.

In this study interferon alpha was tried in patients who had been treated with interferon plus lamivudine and who developed resistance to therapy.

MATERIALS AND METHODS

Patients

Patients were recruited from two ongoing studies in which lamivudine monotherapy and lamivudine plus interferon (IFN) treatment (primary IFN therapy) were compared (Figure 1). The first study group consisted of 94 patients who were HBeAg (+), and HBV DNA (+); 31 had lamivudine monotherapy (150 mg/d for at least 2 years), and 63 had IFN (9 MU tiw for 6 months) and lamivudine (150 mg/d for at least 2 years) combination therapy.

After two years, the patients were randomized to continue LAM, or to cease use of the drugs if they were HBV DNA (-).

The second study group consisted of 160 patients with chronic hepatitis B, who were HBeAg (-), anti-HBe (+), and HBV DNA (+). They had the same treatment protocol of the first study.

Before the treatment, all of the patients were evaluated extensively for other etiological factors for liver disease, and for histopathology. They had compensated liver disease.

The patients who had breakthrough infection from both study groups, recorded as of December 2000, were included in this study.

Breakthrough was defined as persistent elevation of ALT and reappearance of HBV-DNA in serum samples preceded by at least two consecutive HBV DNA (-) results during lamivudine therapy. Patients with breakthrough infection were followed for at least three months before randomization. The patients were randomized to recive either IFN

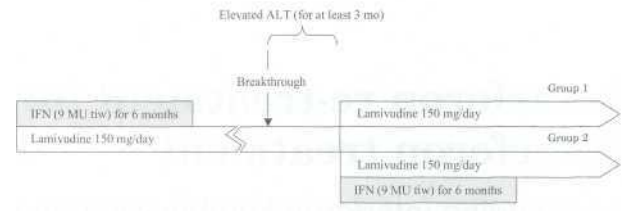

Figure 1. Study design of primary treatment and treatment after breakthrough

alpha-2a(9 million units 3 times a week for 6 months without cessation of lamivudine) (n=9), or continued lamivudine therapy alone (n=10), consecutively. The treatment scheme is depicted in (Figure 1).

The objectives of the study were normalization of ALT, and loss of HBV DNA at the 12th month of the study (at the 6th month after the end of the treatment for patients who were given IFN).

Informed consent was obtained from each patient and the ethical committee approved the stud}'.

Laboratory studies: HBsAg, HBeAg, anti-HBe, anti-HCV, and anti-HDV were assessed by qualitative microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL, USA). Serum HBV DNA was quantified by a hybrid capture assay (Digene; Murex, Gaithersburg, MD, USA) with a lower limit of detection of 1.6 pg/ml of serum. HBV DNA values above 2000 pg/ml were not quantified and were recorded as >2000 pg/ml. All patients were tested for biochemical parameters every four weeks and for HBV DNA every eight weeks.

Interferon-treated and -untreated patients were compared with respect to basal and end of follow-up HBV DNA and ALT values using Mann-Whitney U test.

RESULTS

Demographic and laboratory findings of the total of 19 patients with breakthrough infection, 9 from the HbeAg (+) group, and 10 from the HBeAg (-) group, are summarized in Table 1.

When both treatment groups were compared by means of HBV DNA and ALT levels, at the onset and at the 3rd, 6th, 9th, and 12th months after the start of the study, there was no significant difference between them (Table 1). There was also no statistically significant difference in each group in serum ALT and HBV DNA levels from the onset of the therapy and at controls at the 3rd, 6th, 9th, and 12th months.

Table 1. Demographic, serological, biochemical and virological profile of patients who continued lamivudine alone or who received interferon in addition to lamivudine following the development of breakthrough during the lamivudine plus interferon combination treatment

		Interferon receiving patients	Controls
n		9	10
Age		33 (16-60)	38 (22-52)
Sex M/F		6/3	6/4
HBeAg(+)/anti HBeAg (+)		6/3	3/7
Breakthrough time* (month)		22 (8-28)	18 (11-26)
HBV-DNA (pg/ml)	Basal	246 (6-2000)	392 (12-2000)
	3 months	240 (0-2000)	329 (124-2000)
	6 months	110(0-2000)	541(88-1760)
	9 months	110 (0-2000)	522 (112-2000)
	12 months	87 (0-2000)	684.5 (38-2000)
ALT (U/L)	Basal	88 (48-242)	73 (48-132)
	3 months	76 (28-118)	79 (46-112)
	6 months	78 (32-146)	72 (44-118)
	9 months	56 (16-98)	53 (38-96
	12 months	55 (14-135)	68.5 (24-120)

*from the beginning of the combination treatment from which studied patients were recruited.
Numbers represent the median and (the range).
No difference was found in the comparison of the HBV DNA and ALT values between the groups at the study entry or during the follow-up

In two of nine patients who had combination therapy (22%), HBV DNA disappeared and transaminase levels returned to normal (Table 2). One of these patients had HBeAg seroconversion at the 6th month of IFN retreatment. The course of HBV DNA and ALT levels of this patient is illustrated in Figure 2. Of seven patients who remained HBV DNA positive, two had normal ALT at the 12th month of the study. None of the patients from group 2 lost HBV DNA; however, ALT levels returned to normal in three of them (30%). None of the patients in either group lost HBsAg (8).

Interferon therapy was associated with its typical side effects (pyrexia, rigors, myalgia, fatigue) in seven (64%) patients, but no reduction in the IFN dose was required.

Table 2. Demographic features, HBeAg status, breakthrough time during the primary therapy, and ALT and HBV-DNA changes during secondary treatment for each patient

Age	Sex	HBeAg	Breakthrough time* (month)	HBV DNA at the beginning (pg/ml)	ALT at the beginning (U/L)	HBV DNA at 12th month	ALT at 12th month (U/L)
Interferon-combined patients[0]							
33	M	+	24	1728	50	227	89
41	M	-	27	>2000	48	148	14
60	F	-	22	206	70	13	135
21	F	+	8	1455	201	>2000	28
29	M	+	28	>2000	88	0	36
42	M		24	246	82	56	64
37	M	+	22	41	121	87	100
23	F	+	21	124	242	0	19
16	M	+	12	6	98	>2000	55
Lamivudine-continued patients[b]							
38	F	-	18	1428	48	>2000	28
42	M	+	21	260	56	786	24
52	F		18	>2000	82	1300	112
29	M	-	16	1286	112	68	78
46	M		16	78	52	242	64
38	F	-	22	48	56	118	72
45	M		21	786	78	645	86
32	M	+	18	46	132	724	120
28	F	+	26	524	116	942	38
22	M		11	12	68	86	65

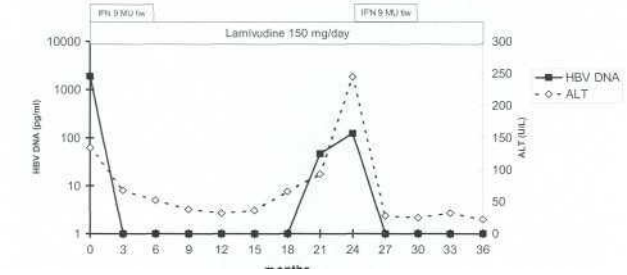

Figure 2. Biochemical and virological course of Patient 8 who responded to second interferon course

DISCUSSION

Breakthrough hepatitis B infection during lamivudine therapy is usually associated with the development of mutations in the YMDD motif of the polymerase gene, but their long-term clinical significance is not known. Serum HBV DNA and ALT levels usually remain lower than pre-treatment levels, suggesting that there may be a continued suppressive effect of lamivudine on the wild type virus and a lower virulence and replicative capacity of the mutant (11). HBeAg seroconversion has been reported in some patients after the development of lamivudine-resistant mutations (11, 15). In contrast, marked flares of serum ALT elevation after emergence of the YMDD mutant were reported in Asian patients (16). Flares in hepatitis, resulting in hepatic decompensation, have also been reported, indicating that these mutants can cause significant liver damage (11). Lamivudine-resistant HBV has been found to be susceptible to adefovir, lobucavir (8, 9) and entecavir (10). Because of the unavailability of these drugs on the market, interferon is worth trying in lamivudine-resistant infection.

We investigated in this study the efficacy of the interferon therapy for breakthrough infection in nine patients who had been receiving lamivudine after an initial combination therapy with interferon. Two patients lost HBV DNA and their ALT levels returned to normal. Six months after discontinuation of interferon, they remained HBV DNA negative and ALT normal. In contrast, none of the patients with breakthrough infection who were not treated with interferon became HBV DNA negative.

Interferon has been used in breakthrough infection in a limited number of patients. Someya et al. tried interferon in a patient with breakthrough during lamivudine therapy, which was not initiated with a combination therapy. Treatment with interferon alpha resulted in a rapid loss of hepatitis B virus DNA, resolution of hepatitis and clinical recovery (17). Seehofer et al. used combination therapy with interferon and lamivudine for re-infection with lamivudine-resistant hepatitis B after liver transplantation. All patients had reinfection of the graft and breakthrough of HBV during consecutive famciclovir and lamivudine monotherapy. Subsequently a combination therapy of lamivudine and interferon alpha 2a (3 MU/TIW, n=4) was initiated. Addition of interferon reduced viral replication rate in all patients. Three patients became HBV DNA negative, but only two had a sustained response. No patient became HBsAg negative or lost HbeAg, but all patients showed normalization of transaminases (18).

To our knowledge, there are no reports about the repeated usage of interferon after an initial combination therapy with interferon and lamivudine. Interferon retreatment in patients who had been previously treated with interferon has been shown to have a considerable success. In an international study, a sustained clearance of HBV DNA and HBeAg was observed in nine of the 27 (33.3%) patients who had received retreatment with interferon alpha compared with 3/30 (10%) patients who spontaneously cleared these markers in the untreated control group (14). But this result cannot be extrapolated to our patients. Although they were treated previously with interferon, they had breakthrough infection under lamivudine treatment. Lamivudine- resistant mutants have been shown to have a lower replication capacity and probably less virulence compared with the wild type virus. Therefore their interferon response might differ from those of the wild type virus. However, interferon response of two patients among nine with breakthrough infection indicates that interferon retreatment of interferon plus lamivudine combination therapy may have benefits.

In conclusion, the patients with breakthrough infection during lamivudine treatment, which was combined with interferon alpha for the first six months, may benefit from another cycle of interferon treatment. Thus, retreatment with interferon alpha may be considered a therapeutic option.

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