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A pilot study of β-interferon for treatment of patients with chronic hepatitis B who failed to respond to α-interferon ☆

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***Background/Aims*: Alpha-interferon achieves persistent loss of hepatitis B virus (HBV) in about 30–40% of patients with chronic hepatitis B. In non-responder patients, the disease may progress leading to complications such as cirrhosis and hepatocellular carcinoma. The aim of the current study was to evaluate the efficacy of beta-interferon in patients with chronic hepatitis B who did not respond to one course of alpha-interferon.**

***Methods*: Twenty nine alpha-interferon-non-responder patients with chronic hepatitis B (11 hepatitis B e antigen, HBeAg-positive; 18 HBeAg-negative) were treated with 6 million units beta-interferon five times a week for 24 weeks. The post-treatment follow-up lasted for 48 weeks.**

***Results*: At the end of treatment, 38% of patients (18% HBeAg-positive; 50% HBeAg-negative) had normal serum aminotransferase levels and negative serum HBV DNA. At the end of follow-up, HBV DNA was no longer detectable in serum in 21% of patients (18% HBeAg-positive; 22% HBeAg-negative). Beta-interferon was well tolerated and safe.**

***Conclusions*: This pilot study suggests that beta-interferon therapy is effective and safe in the retreatment of patients with chronic hepatitis B who had not responded to a previous alpha-interferon cycle.**

***Keywords*: Chronic hepatitis B; β-Interferon therapy; Safety**

1. Introduction

Chronic hepatitis B is a serious condition that often leads to complications of progressive liver disease including cirrhosis and hepatocellular carcinoma [1,2]. Treatment with alpha-interferon (IFNα) has shown to arrest the progression of this hepatic injury [3,4]. However, IFNα is only effective in 30–40% of patients [5,6]. Liver disease may progress in patients with chronic hepatitis B who fail to respond to this therapy [3,4]. Therefore, other treatments are required for these patients. Lamivudine, an oral nucleoside analog, has been approved for use in chronic hepatitis B virus (HBV) infection and evaluated in long-term clinical trails [7–9]. Although lamivudine therapy has favorable effects on virologic, histologic and biochemical features of disease [7,8], a high rate of viral resistance limits the efficacy of this treatment. Furthermore, combination of IFNα with lamivudine was disappointing for the treatment of IFNα-non-responder chronic hepatitis B patients [10]. Further attempts to suppress viral replication with combination of interferon with acyclovir [11], zidovudine [12] or ribavirin [13] or with repeated courses of IFNα [14] have also proved disappointing. Another alternative might be the administration of beta-interferon (IFNβ).

Production of IFNβ is mainly induced in fibroblasts by viral and other foreign nucleic acids. IFNβ activates target cells by binding to receptors on the cell surface. Although the molecular homology between IFNα and IFNβ is only 30%, both interferons shear the same cellular receptors and intracellular signaling pathways and have many common biological functions [15]. There are two types of IFNβ,

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natural and recombinant (IFNβ-1a and IFNβ-1b). Several studies have demonstrated the efficacy of different forms of IFNβ in the treatment of patients with active multiple sclerosis [16] or chronic hepatitis B [17]. As much as we are aware, only one study has been published, in which IFNβ was used in the retreatment of children with chronic hepatitis B who had not responded to previous therapy with IFNα [18].

We report here the results of a pilot study using IFNβ for retreatment of adult patients with chronic hepatitis B who failed to respond to a previous IFNα cycle.

2. Patients and methods

2.1. Patients

Twenty nine adults patients with chronic hepatitis B who had the following characteristics were eligible for the study: positive test for serum hepatitis B surface antigen (HBsAg) and HBV DNA; serum alanine aminotransferase (ALT) concentration above 65 IU/l (normal values, <45 IU/l) on two or more occasions during the preceding 6 months; findings consistent with chronic hepatitis on liver biopsy performed during the preceding 6 months; and they had undergone a previous course of IFNα therapy (4.5–6 million units (MU)/daily for 24 weeks), and at the end of this cycle (at least 12 months before enrollment in this study) patients remained HBV DNA-positive.

Criteria for exclusion were: decompensated liver cirrhosis; coinfection with hepatitis C; pregnancy or breast-feeding; leukopenia (<3000 per cubic millimeter); neutropenia (<1500 per cubic millimeter); thrombocytopenia (platelet count <100 000 per cubic millimeter); seizure disorders; preexisting psychiatric condition; other relevant disorders including human immunodeficiency virus-I infection, severe cardiac or pulmonary disease, autoimmune disease or renal failure.

All patients included in this study gave informed consent for participation, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Hospital Ethics Committee.

2.2. Methods

Each patient received natural IFNβ (Frone, Serono Laboratories, Rome, Italy) at a dose of 6 MU given intramuscularly five times a week for 24 weeks. The patients were monitorized for serum levels of ALT and aspartate aminotransferase (AST), total protein, albumin, and bilirubin, and erythrocyte, leukocyte and thrombocyte counts before treatment, at least every 4 weeks during treatment and at month 1, 3, 6, 9, and 12 after the end of treatment. Patients were asked about adverse events at each clinic visits following a pre-established questionnaire.

In addition to these determinations, electrocardiogram, chest roentgenogram, and abdominal ultrasound were performed prior to IFNβ therapy. Moreover, serum concentration of iron, ferritin, thyroid hormones, thyroid-stimulating hormone, antinuclear, anti-mitochondrial, anti-smooth muscle, liver and kidney anti-microsomal and antithyroid antibodies, HBsAg, hepatitis B e antigen (HBeAg), hepatitis B e antibody (anti-HBe) and HBV DNA were also determined before treatment, at an interval of 3 months during treatment, and at the end of treatment and follow-up.

The end point of this study was the sustained virologic response, defined as the absence of serum HBeAg and HBV DNA 48 weeks after treatment was completed. A lack of response was defined as the persistence of elevated serum ALT levels more than 1.3 times the upper limit of normal and/or the persistence of HBV DNA after 24 weeks of treatment. Response at the end of treatment was defined as normal serum ALT concentrations and undetectable serum HBV DNA levels at the end of 24 weeks of treatment. Reactivation was defined as the reappearance of HBV DNA during the post-treatment follow-up.

HBsAg, HBeAg, and anti-HBe were tested with commercially available radioimmunoassay (Abbot Laboratories, North Chicago, IL), and HBV DNA was analyzed by a DNA enzyme immunoassay for detecting products of polymerase chain reaction (Sorin Biomedica, Saluggia, Italy) [19]. The sensitivity of this assay was 200 copies/ml. Routine serum biochemical tests were done using automated techniques (Hitachi 747 Roche Diagnostic Corp., Indianapolis, IN). Liver biopsy specimens were graded with respect to the degree of periportal necrosis, portal and lobular inflammation, and fibrosis according to the Scheuer scoring system [20].

2.3. Statistical analysis

For quantitative variables, the normality of distribution was checked statistically. When the distribution was normal, results were expressed as arithmetical mean ± standard deviation (SD). Data that did not conform to a normal distribution were expressed as median and ranges. Qualitative variables were expressed as percentages. Comparison between groups were performed by the Student's *t*-test for parametric data, the Willcoxon's rank sum test for non-parametric samples or the chi-square test for proportions. Data were analyzed with the SPSS for Windows statistical package version 10 (SPSS Inc., Chicago, IL, USA). *P* values less than 0.05 were considered significant.

3. Results

This study was conducted from 1994 to 1999 and included 29 patients (20 men and nine women; mean age 38.3 years; range, 19–62 years). The mean disease duration before treatment was 108.8 months (range, 42–276 months). The most likely source of infection was sexual in two patients and vertical in another two. One patient had been undergone hemodialysis and five had family history of HBV infection. Nineteen patients had no known cause for their HBV infection. The baseline characteristics of the 29 patients included in this study are summarized in Table 1. The ALT and AST values were continuously abnormal before retreatment. In 11 patients, HBeAg was positive, while in the remaining 18 patients HBeAg was negative and anti-HBe were positive. On the admission to the study, liver histology showed chronic hepatitis in 21 patients (72%) and chronic active hepatitis with cirrhosis in the remaining eight patients. In the initial liver biopsy specimens, the mean necroinflammatory activity score was 3.76 ± 1.48 (median, 4; range, 1–8) and the mean fibrosis score was 2.2 ± 1.42 (median, 2; range, 0–4).

Normalization of serum ALT concentrations was observed in 13 patients (45%) after 6 months of treatment. Eleven of these patients became HBV DNA negative after this period of time (Table 2). Thus, a virologic and biochemical response at the end of treatment was observed in 11 patients (38%) (two HBeAg-positive and nine HBeAg-negative patients). During the post-treatment follow-up, ALT levels remained within the normal range and HBV DNA was undetectable in two HBeAg-positive (18%) and four HBeAg-negative (22%) patients. HBV reactivated in the remaining five HBeAg-negative patients, but in none of the responder HBeAg-positive patients. In three of those

Table 1
Base-line characteristics of patients retreated with IFNβ[a]

Characteristics	No (%)
Age, years	38.27 ± 13.5
Sex, M/F	20 (69)/9 (31)
Source of infection	
● Parenteral	1 (3.49)
● Sexual	2 (6.9)
● Familial	5 (17.2)
● Vertical	2 (6.9)
● Unknown	19 (65.5)
Estimated duration of infection, months	108.8 ± 73.2
● >60 months	13 (45)
● <60 months	16 (55)
Liver tests	
● AST (IU/l) (normal values, <45 IU/l)	84.9 ± 53.2
● ALT (IU/l) (normal values, <45 IU/l)	167 ± 113.2
● GGT (IU/l) (normal values, <52 IU/l)	55.5 ± 62.2
● AP (IU/l) (normal values, <295 IU/l)	197.8 ± 84.7
HBeAg-positive	11 (38)
HBeAg-negative and anti-Hbe-positive	18 (62)
Liver biopsy histology	
● Grade of necroinflammatory activity [median (range)]	4 (1–8)
● Stage of fibrosis [median (range)]	2 (0–4)

[a] M, male; F, female; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltranspeptidase; AP, alkaline phosphatase; No, number of patients. Plus-minus values are means ± SD.

five patients, ALT relapsed as well during the follow-up. Two (one HBeAg-positive, one HBeAg-negative) of the eight patients (four HBeAg-positive, four HBeAg-negative) with cirrhosis had sustained virologic response. Seroconversion from HBeAg to anti-HBe was found in the two HBeAg-positive patients who became HBV-DNA negative. No patient lost HBsAg or cleared HBV DNA after the end of treatment.

Table 2
Biochemical and virologic response at the end of treatment and follow-up[a]

	Normal serum ALT No [% (interval)]	Negative HBV-DNA No [% (interval)]
Response at the end of treatment (no, 29)	13 [45 (27–65)]	11 [38 (21–58)]
HBeAg-positive (no, 11)	2 [18 (5–51)]	2 [18 (2–51)]
HBeAg-negative (no, 18)	11 [61 (36–83)]	9 [50 (26–74)]
Sustained virologic response (no, 29)	10 [34 (18–54)]	6 [21 (8–40)]
HBeAg-positive (no, 11)	2 [18 (2–51)]	2 [18 (2–51)]
HBeAg-negative (no, 18)	8 [44 (22–70)]	4 [22 (6–48)]

[a] Interval, 95% confidence intervals.

Control biopsy specimens were obtained from 12 patients, six sustained responders and six non-responders, approximately 48 weeks after the end of treatment. The results of histological scoring are shown in Fig. 1. A decreased in the necroinflammatory score was found in all responder patients at the end of follow-up [median basal score, 4 (range, 4–6); median final score, 2 (range, 1–3)], but only in two non-responders [median basal score, 4 (range, 3–5); median final score, 5 (range, 2–5)]. However, these changes were not significant. Fibrosis stage did not change in five responders and decreased two points in the remaining patient. In five of the six patients who did not respond to therapy, fibrosis stage increased one point, and remained in four points in a cirrhotic patient (Fig. 1).

IFNβ was generally well tolerated and no patient discontinued therapy or reduced the dose because side effects (Table 3).

4. Discussion

Several clinical trials have shown that IFNα is effective in inducing a sustained clearance of HBV DNA and in improving liver histology in about 30–50% of patients with HBeAg-positive chronic hepatitis B [1,5,6]. Fifty to 70% of chronic hepatitis B patients with negative HBeAg clears

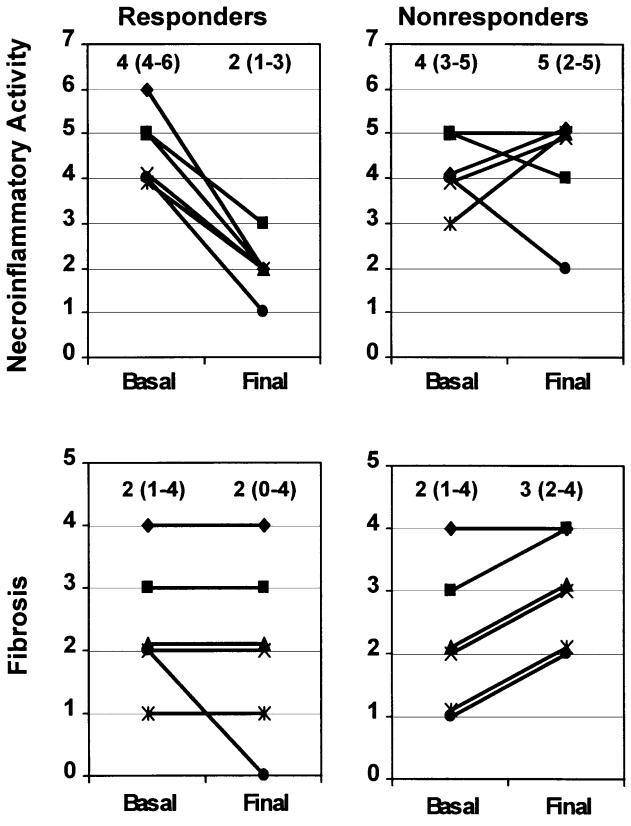

Fig. 1. Histological scoring of serial liver biopsy specimens before treatment and at the end of follow-up. Data are expressed as median and ranges.

Table 3
Side effects during IFNβ therapy compared with those during the previous IFNα course in 29 patients with chronic hepatitis B[a]

Side effect	IFNα No (%)	IFNβ No (%)	*P* values
Flu-like syndrome	26 (89.6)	10 (34.5)	< 0.001
Fatigue	19 (65.5)	3 (10.3)	< 0.001
Weight loss	7 (24.1)	0	< 0.001
Alopecia	7 (24.1)	0	< 0.001
Arthralgia/myalgia	9 (31)	1 (3.4)	< 0.001
Decreased appetite	3 (10.3)	0	< 0.01
Headache	4 (13.8)	0	< 0.001
Nausea	1 (3.4)	0	NS
Depression	1 (3.4)	4 (13.8)	NS
Irritability	2 (6.9)	7 (24.1)	< 0.01
Insomnia	1 (3.4)	0	NS
Erythema*	2 (6.9)	7 (24.1)	< 0.01
Diarrhea	2 (6.9)	0	NS
Hypertriglyceridemia	1 (3.4)	5 (17.2)	NS
Hyperglycemia	1 (3.4)	2 (6.9)	NS
Neutropenia	4 (13.8)	3 (10.3)	NS
Thrombocytopenia	8 (27.6)	2 (6.9)	< 0.001
Positive anti-thyroid antibody	0	2 (6.9)	NS
Positive anti-peroxidase antibody	0	2 (6.9)	NS

[a] (*) Erythema at the site of puncture. NS, not significant.

HBV DNA at the end of treatment with IFNα. However, 60–95% of these responder patients treated for 4–6 months relapses short after IFNα therapy is stopped [21–25]. Nevertheless, in a previous study, we showed that IFNα treatment maintained for 12 months induced a similar response rate and histological improvement in patients with anti-HBe-positive chronic hepatitis B than in patients with classical HBeAg-positive form of chronic hepatitis B [26].

Patients with chronic hepatitis B who do not respond to IFNα therapy had higher rates of live-related complications and mortality [1–4]. These non-responder patients may potentially benefit from another course of IFNα treatment. A sustained clearance of HBV DNA has been reported in around 11–33% of patients with HBeAg-positive chronic hepatitis B who received retreatment with IFNα thrice weekly for 6 months [14,27]. However, the response rate to a new course of IFNα treatment is less than 5% in HBeAg-negative patients. Lamivudine, at a dose of 100 mg/day for 52 weeks, as initial treatment, induced a sustained suppression of HBV-DNA to undetectable levels in 44% of patients and loss of HBeAg in 21–32% of patients [7,28]. However, the efficacy of this treatment is limited by the development of viral resistance associated with mutation at the thyrosine-methionine-aspartate-aspartate (YMDD) locus in the HBV polymerase gene [5,7–9,28]. Retreatment of IFNα-resistant patients with a combination of IFNα and lamivudine was disappointing, as only 5% of HBV-infected patients treated with this combination had a sustained HBV DNA clearance [10].

In this study, we analyzed the efficacy of IFNβ in the treatment of a group of adult patients with chronic hepatitis B who had not responded to a previous IFNα cycle. All patients received IFNβ at a dose of 6 MU given intramuscularly five times a week for 24 weeks. IFNβ has not been used previously for retreatment of adult patients. In a study performed in children with chronic hepatitis B who had not responded to IFNα, retreatment with IFNβ induced sustained clearance of HBV DNA in 45% of children [18]. In our group of adult patients, we found a sustained response rate of 21%, 18% in HBeAg-positive patients and 22% in HBeAg-negative patients. Results in HBeAg-positive patients are not different from those reported by other authors in similar patients treated with a second course of IFNα [14,27]. The 22% of sustained virologic response found in our group of HBeAg-negative patients is comparable to the response rate obtained by other authors in patients treated with IFNα combined with ribavirin [29]. It is unlikely that the benefits observed in HBeAg-negative patients could be a consequence of the natural course of chronic hepatitis B, since analysis of the natural history of this type of patients has shown that spontaneous remissions of the disease are uncommon [22]. Furthermore, all patients showed positive markers of HBV replication for at least 1 year before starting IFNβ therapy. Finally, improvement of the necroinflammatory score was observed in patients with sustained virologic response who underwent repeat liver biopsy at the end of follow-up, but not in non-responders, in whom fibrosis stage increased during IFNβ treatment. However, improvement of the necroinflammatory score was not significant, likely because of the small number of patients biopsied at the end of treatment.

It is not known why non-responders to IFNα therapy do respond to a new course of IFNβ. Both interferons shear the same receptor on the cell surface and both have the same biological functions. Some authors have suggested that IFNβ may facilitate HBV clearance from hepatocytes through recognition by cytotoxic T cells [18], since IFNβ promotes the expression of class I human leukocyte antigen (HLA) molecules on the cell surface [15]. However, as Ruiz-Moreno et al. [18] have pointed out, this mechanism of better response to IFNβ does not seem to be the case, as hepatitis flare-up are uncommon in patients treated with IFNβ [18]. In the present study, only two of 11 patients with undetectable HBV DNA at the end of treatment experienced hepatitis flare-up. On the other hand, absence of response to IFNα can be ascribed to the presence of neutralizing antibodies against IFNα [30]. As these antibodies do not cross-react with IFNβ, patients with anti-IFNα antibodies who do not respond to IFNα therapy may respond to IFNβ retreatment [15].

At the end of follow-up, all patients remained positive for HBsAg. It is well known that clearance of HBsAg usually occurs years after the elimination of HBV DNA in IFNα treated patients [3,4]. Therefore, we cannot exclude that some responder patients would clear HBsAg in the future.

IFNβ therapy was well tolerated, and side effects were mild and infrequent, as has also been reported by other authors [17,18]. Flu-like syndrome, myalgias, arthralgias,

fatigue, hair loss and weight loss were significantly less frequent when patients were receiving IFNβ than when they were treated with IFNα. Thrombocyte count fell below 100 000 per cubic millimeter in 7% of patients during IFNβ course, but occurred in 26% of the patients during the previous cycle of IFNα.

In conclusion, this pilot study suggests that IFNβ therapy is effective and safe in the treatment of patients with chronic hepatitis B who had not responded to IFNα. Retreatment with IFNβ, instead of with IFNα, is particularly advisable in patients with HBeAg-negative/HBV DNA-positive chronic hepatitis B.

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References

[1] Weissberg JI, Ljudevit LA, Coleman IS, Weick S, Nichols JE, Garcia G, et al. Survival in chronic hepatitis B: an analysis of 379 patients. Ann Intern Med 1984;101:613–616.
[2] Beasley R, Lin C, Hwang L, Chein C. Hepatocellular carcinoma and hepatitis B virus. Lancet 1981;2:1129–1133.
[3] Niederau C, Heintges T, Lange S, Goldman G, Niederau GM, Mohr L, et al. Long term follow-up of HBeAg positive patients treated with interferon alfa for chronic hepatitis B. N Engl J Med 1996;334:1422–1427.
[4] Lau DT, Everhart J, Kleiner DE, Park Y, Vergalla J, Schrnid P, et al. Long-term follow-up of patients with chronic hepatitis B treated with interferon alfa. Gastroenterology 1997;113:1660–1667.
[5] Torresi J, Locarnini S. Antiviral chemotherapy for the treatment of hepatitis B virus infection. Gastroenterology 2000;118:83–103.
[6] Perrillo RP, Schitt ER, Davis GL, Bodenheimer Jr HC, Lindsay K, Payne J, et al. A randomized, controlled trial of interferon in patients with chronic hepatitis B. The Hepatitis International Therapy Group. N Engl J Med 1990;323:295–301.
[7] Dienstag JL, Schiff ER, Wright TL, Perrillo RP, Hann HW, Goodman Z, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. N Engl J Med 1999;341:1256–1263.
[8] Tassopoulos NC, Volpes R, Pastore G, Heathcote J, Buti M, Goldin RD, et al. Efficacy of lamivudine in patients with hepatitis B antigen-negative/hepatitis B virus DNA-positive (precore mutant) chronic hepatitis B. Hepatology 1999;29:889–896.
[9] Lau DT, Khokhar MF, Doo E, Ghany MG, Herion D, Park Y, et al. Long-term therapy of chronic hepatitis B with lamivudine. Hepatology 2000;32:828–834.
[10] Mutimer D, Naoumov N, Honkoop P, Marinos G, Ahmed M, De Man R, et al. Combination alpha interferon and lamivudine therapy for alpha interferon resistant chronic hepatitis B infection: results of a pilot study. J Hepatol 1998;28:923–929.
[11] Berk L, Schalm SW, de Man RA, Heytink RA, Berthelot P, Brechot C, et al. Failure of acyclovir to enhance the antiviral effect of alpha lymphoblastoid interferon on HBe-seroconversion in chronic hepatitis B. A multi-centre randomized controlled trial. J Hepatol 1992;14:305–309.
[12] Janssen HLA, Berk L, Heijtink RA, Ten Kate FJW, Schalm SW. Interferon-alpha and zidovudine combination therapy for chronic hepatitis B: results of a randomized, placebo-controlled trial. Hepatology 1993;17:383–388.
[13] Kakumu S, Yoshioka K, Wakita T, Ishikawa T, Takayanagi M, Higashi Y. Pilot study of ribavirin and interferon-beta for chronic hepatitis B. Hepatology 1993;18:258–263.
[14] Janssen HLA, Schalm SW, Berk L, de Man RA, Heijtink RA. Repeated courses of alpha-interferon for treatment of chronic hepatitis type B. J Hepatol 1993;17:47–51.
[15] Weissmann C, Weber M. The interferon genes. Prog Nucleic Acid Res Mol Biol 1986;33:251–300.
[16] Weinstock-Guttman B, Jacobs LD. What is new in the treatment of multiple sclerosis? Drugs 2000;59:401–410.
[17] Kagawa T, Morizane T, Saito H, Tsunematsu S, Tada S, Kumagai N, et al. A pilot study of long-term weekly interferon β administration for chronic hepatitis B. Am J Gastroenterol 1993;88:212–216.
[18] Ruiz M, Fernández P, Leal A, Bartolomé J, Castillo I, Oliva H, et al. Pilot interferon β trial in children with chronic hepatitis B who had previously not responded to interferon α therapy. Pediatrics 1997;99:222–225.
[19] Mantero G, Zonaro A, Albertini A, Bertolo P, Primi D. DNA enzyme immunoassay: general method for detecting products of polymerase chain reaction. Clin Chem 1991;37:422–429.
[20] Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. J Hepatol 1991;13:372–374.
[21] Oliveri F, Santantonio T, Bellati G, Colombatto P, Colloredo G, Carriero L, et al. Long term response to therapy of chronic anti-HBe positive hepatitis B is poor independent of type and schedule of interferon. Am J Gastroenterol 1999;94:1366–1372.
[22] Brunetto MR, Oliveri F, Rocca G, Criscuolo D, Chiaberge E, Capalbo M, et al. Natural course and response to interferon of chronic hepatitis B accompanied by antibody to hepatitis B e antigen. Hepatology 1989;10:198–202.
[23] Hadziyannis S, Bramou T, Makris A, Moussoulis G, Zignego L, Papaioannou C. Interferon α-2b treatment of HBeAg negative/serum HBV-DNA positive chronic hepatitis type B. J Hepatol 1990;11(Suppl. 1):S133–S136.
[24] Fattovich G, Farci P, Rugge M, Brollo L, Mandas A, Pontisso P, et al. A randomized controlled trial of lymphoblastoid IFN alpha in patients with chronic hepatitis B lacking HBeAg. Hepatology 1992;15:584–589.
[25] Pastore G, Santantonio T, Milella M, Monno L, Mariano N, Moschetta R, et al. Anti-HBe positive chronic hepatitis B with HBV-DNA in the serum: response to a 6 month course of lymphoblastoid IFN. J Hepatol 1992;14:221–225.
[26] Fernández I, Castellano G, Manzano ML, Colina F, Canga F, Muñoz R, et al. Twelve months interferon-α therapy induces a similar sustained response in anti-HBe-positive and HBeAg-positive chronic hepatitis B patients. Hepatogastroenterolgy 2000;47:1351–1355.
[27] Carreno V, Marcelin P, Hadziyannis S, Salmeron J, Diago M, Kitis GE, et al. Retreatment of chronic hepatitis B e antigen-positive patients with recombinant interferon alpha-2a. Hepatology 1999;30:277–282.
[28] Lai CL, Chien RN, Leung NW, Chang TT, Guan R, Tai DI, et al. A 1-year trial of lamivudine for chronic hepatitis B. N Engl J Med 1998;339:61–68.
[29] Cotonat T, Quiroga JA, López-Alcorocho JM, Clouet R, Pardo M, Manzabeitia F, et al. Pilot study of combination therapy with ribavirin and interferon alfa for the retreatment of chronic hepatitis B e antibody-positive patients. Hepatology 2000;31:502–506.
[30] Porres JC, Carreño V, Ruiz-Moreno M, Marrón JA, Bartolomé J. Interferon antibodies in patients with recombinant interferon. J Hepatol 1989;8:351–357.