

Treatment of chronic hepatitis B with interferon: Long term follow-up

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J-P VILLENEUVE, B WILLEMS. Treatment of chronic hepatitis B with interferon: A long term follow-up. Can J Gastroenterol 1996;10(1):21-25. The aim of treatment of chronic hepatitis B with interferon is to induce a transition from the replicative phase of the disease to a nonreplicative state, with loss of hepatitis B virus (HBV)-DNA, seroconversion from hepatitis B e antigen (HBeAg)-positive to anti-HBe antibody-positive, and normalization of liver enzymes. The authors' experience in 22 patients with chronic hepatitis B treated with recombinant human interferon alpha-2b (5 MU/m² subcutaneously three times/week for 16 weeks) is reported. Before treatment all patients had been positive for hepatitis B surface antigen (HBsAg) and HBeAg for at least six months, had abnormal serum aminotransferases, had no evidence of hepatitis D or human immunodeficiency virus (HIV) infection and had compensated liver disease. Eleven of 22 patients (50%) responded to treatment with loss of HBeAg and appearance of anti-HBe antibodies, and normalization of serum aminotransferases within six months of interferon cessation. Patients were followed for 3.4±1.2 years after treatment. Ten of 11 responders remained negative for HBeAg and HBV-DNA; one patient relapsed and responded to a second course of interferon with loss of HBeAg and HBV-DNA. Seven of the 11 nonresponders underwent spontaneous (n=5) or retreatment-induced (n=2) seroconversion from HBeAg to anti-HBe and loss of HBV-DNA during follow-up. The other four nonresponders remained positive for HBeAg and HBV-DNA; three of the four progressed to decompensated liver disease. It is concluded that interferon is an effective treatment of chronic hepatitis B in 50% of patients with features similar to those used as selection criteria in the present study. These criteria probably also identify patients who have a high likelihood of spontaneous HBeAg to anti-HBe seroconversion, and it is possible that the benefit of interferon is its acceleration of this seroconversion.

Key Words: Chronic hepatitis B, Interferon, Treatment

Traitement de l'hépatite chronique B par l'interféron: suivi a long terme

RÉSUMÉ : L'objectif du traitement de l'hépatite chronique B par l'interféron est d'induire une transition de la phase répliquative de la maladie à la phase non-répliquative. Cette transition se manifeste par une disparition de l'ADN sérique du virus de l'hépatite B (ADN-VHB) et de l'antigène e du VHB (HBeAg) avec apparition d'anticorps anti-HBe, et une normalisation des aminotransférases. Nous rapportons ici notre expérience chez 22 patients avec hépatite chronique B traités par l'interféron à une dose de 5 millions d'unités/m² par voie sous-cutanée trois fois par semaines pendant 16 semaines. Avant le traitement, tous les patients étaient positifs pour l'antigène de surface du VHB (HBsAg) et l'HBeAg depuis au moins 6 mois, avaient des aminotransférases anormales, n'avaient pas d'infection concomitante par les virus de l'hépatite D et le virus de l'immunodéficience humaine (VIH) et avaient une maladie hépatique bien compensée. Onze des 22 patients (50%) ont présenté une réponse favorable au traitement avec disparition de l'HBeAg, apparition d'anticorps anti-HBe, et normalisation des aminotransférases 6 mois après l'arrêt de l'interféron. Après l'arrêt du traitement, les patients ont été suivis pendant une période moyenne de 3.4±1.2 ans. Chez 10 des 11 répondeurs, l'HBeAg et l'ADN-VHB sont demeurés négatifs alors qu'un des onze répondeurs a présenté une rechute et a répondu à un second traitement à l'interféron. Durant le suivi à long terme des 11 non-répondeurs, 7 ont éventuellement fait une séroconversion de HBeAg à anti-HBe avec disparition de l'ADN-VHB, soit de façon spontanée (n=5) ou suite à un retraitement (n=2), alors que 4 non-répondeurs sont demeurés positifs pour l'HBeAg et l'ADN-VHB. Trois de ces quatre patients ont développé une maladie hépatique sévère décompensée. Ces résultats indiquent que l'interféron est un traitement efficace de l'hépatite chronique B chez 50% des patients présentant les critères de sélection utilisés dans cette étude. Ces critères de sélection identifient probablement aussi les patients ayant une probabilité élevée de faire une séroconversion spontanée, et il est possible que l'intérêt de l'interféron soit d'accélérer la survenue de cette séroconversion.

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The natural history of chronic hepatitis B can be divided into two phases: an initial replicative phase and a later nonreplicative phase (1). During the initial phase, there is ongoing viral replication, hepatic inflammation and liver cell necrosis. Hepatitis B e antigen (HBeAg) and hepatitis B virus (HBV)-DNA are present in the blood, and serum aminotransferases are usually elevated. This initial phase may last only a few months or years in some subjects, but may persist for decades in others. Some authors have further subdivided the replicative phase into an immune tolerance phase followed by an immune clearance phase to account for the observation that serum transaminases can be initially normal, particularly in carriers of Asian origin (2). At some stage in the natural history of the disease, viral replication stops or decreases, with the disappearance of HBeAg, appearance of anti-HBe antibodies and normalization of liver enzymes. Seroconversion from HBeAg to anti-HBe is usually followed by an improvement in symptoms and a reduction in hepatic inflammation and liver damage. HBV-DNA is no longer measurable by conventional hybridization assays, but can be detected in serum by sensitive molecular amplification techniques. It may therefore be more appropriate to describe this phase as low replicative or latent hepatitis B infection. Carriers usually remain hepatitis B surface antigen (HBsAg)-positive. The mechanisms responsible for spontaneous HBeAg to anti-HBe seroconversion are still poorly understood (3). According to the length and severity of the initial replicative phase, HBsAg carriers may have histological lesions ranging from near-normal liver to severe cirrhosis with hepatic failure. The aim of chronic hepatitis B treatment is to induce an early transition from the replicative to the nonreplicative phase and stop the progression of the disease.

Several clinical trials have shown that interferon treatment induces HBeAg to anti-HBe seroconversion in 30 to 40% of treated patients, and a loss of HBsAg in 5 to 10% (4-6). In a recent meta-analysis (7), the difference in the percentage of treated and control patients losing HBeAg was 21%. Other antiviral agents (adenine arabinoside, acyclovir, ganciclovir, foscarnet) are less effective, and some new drugs (famciclovir, lamivudine) are being evaluated. We report our experience in the treatment of chronic hepatitis B with interferon in a usual clinical setting (ie, outside of controlled clinical trials).

PATIENTS AND METHODS

Patients: From 1988-92, 22 patients with chronic hepatitis B were treated with interferon in a prospective uncontrolled fashion. The selection criteria used were as follows: positive HBsAg and HBeAg in serum for at least six months before treatment; abnormal aminotransferases (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT] greater than 40 IU/L); compensated liver disease (absence of ascites, hepatic encephalopathy and variceal bleeding, and serum bilirubin less than 50 μ m/L and serum albumin greater than 28 g/L); absence of antibodies against human immunodeficiency virus (HIV) (anti-HIV) and against

TABLE 1
Clinical and biological features in 22 patients with chronic hepatitis B who were treated with interferon

Feature	Value*
Age (years)	40 \pm 9
Sex	
Male	18 (82%)
Female	4 (18%)
Ethnic origin	
French Canadian	20 (91%)
Other	2 (9%)
Risk factors for hepatitis B	
Homosexuality	8 (36%)
Hospital work	7 (32%)
Immigrant from areas with high endemicity	2 (9%)
Transfusion	1 (4.5%)
Intravenous drug abuse	1 (4.5%)
Unknown	3 (14%)
Number of years known as HBsAg carrier	3.3 \pm 2.5
Aspartate aminotransferase (IU/L)	180 \pm 167
Alanine aminotransferase (IU/L)	254 \pm 243
Bilirubin (μ mol/L)	15 \pm 9
Albumin (g/L)	39 \pm 5
Prothrombin time (seconds above control)	1.0 \pm 0.8
Hepatitis B virus-DNA (ng/L)	199 \pm 307
Liver biopsy	
Chronic hepatitis	5 (23%)
Chronic hepatitis with cirrhosis	17 (77%)

*Expressed as mean \pm SD or number (%). HBsAg Hepatitis B surface antigen

hepatitis D virus (HDV) (anti-HDV); and liver biopsy confirming a diagnosis of chronic hepatitis B and excluding other causes of liver disease.

Treatment: Patients were treated with 5 MU/m² recombinant human interferon alpha-2b administered subcutaneously three times a week for 12 to 20 weeks. The first three doses were administered at the out-patient clinic for the teaching of drug auto-administration. Patients were seen at the out-patient clinic at one, two and four weeks after the beginning of treatment and every four weeks thereafter, then at one and six months after the end of treatment and every six to 12 months thereafter. At each visit, patients were questioned and examined; blood was drawn for complete blood count, liver enzymes determination and hepatitis B serology, and urine was obtained for routine analysis. During the treatment and follow-up period, patients received only interferon as an antiviral agent.

Definition of response to treatment: A favourable response to treatment was defined as the loss of HBeAg and the appearance of anti-HBe occurring within six months of treatment completion.

Laboratory methods: Serum AST and ALT, albumin, bilirubin and complete blood counts were measured by standard laboratory procedures. HBsAg and anti-HBs, HBeAg and anti-HBe, anti-HDV and anti-HIV were measured by immunoenzymatic assays (ELISA, Abbott Laboratories, Illinois). Antibodies to hepatitis C virus (HCV) (anti-HCV) were measured with a second-generation ELISA test (HCV-ELISA; Ortho Diagnostic Systems, New Jersey). HBV-DNA

TABLE 2
Effects of treatment with interferon in 22 patients with chronic hepatitis B

	Responders (n=11)			Nonresponders (n=11)		
	Before treatment	After treatment		Before treatment	After treatment	
		One month	Six months		One month	Six months
HBeAg-positive (# of cases)	11	2	0	11	11	11
Anti-HBe-positive (# of cases)	0	9	11	0	0	0
HBsAg-negative (# of cases)	0	3	3	0	0	0
Aspartate aminotransferase (IU/L)*	232±192	49±29	33±11	129±118	71±31	185±213
Alanine aminotransferase (IU/L)*	337±299	61±51	35±9	172±124	91±31	225±204
Hepatitis B virus-DNA (ng/L)*	220±400	8±19	0±0	178±164	156±142	183±228

*Results expressed as mean ± SD. HBeAg Hepatitis B e antigen; HBsAg Hepatitis B surface antigen

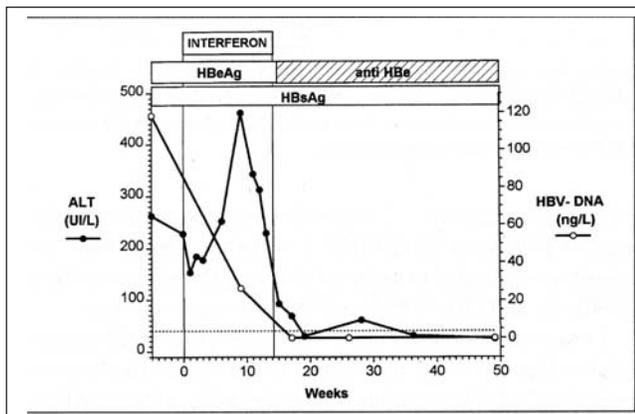


Figure 1) Representative example of a favourable response to interferon alpha 2b treatment with seroconversion from hepatitis B e antigen (HBeAg) to anti-HBe, loss of hepatitis B virus (HBV)-DNA and normalization of liver enzymes. Hepatitis B surface antigen (HBsAg) remained positive. The dashed line is the upper normal limit of serum alanine aminotransferase (ALT)

was measured in serum by a solution hybridization assay using an ^{125}I -labelled probe (Genostics, Abbott Laboratories) (8). Slides of liver biopsies were assessed by standard histological criteria (9), and HBsAg and hepatitis B core antigen (HBcAg) in paraffin sections were demonstrated by an immunoperoxidase method (10).

Statistics: Data were analyzed according to an intention-to-treat strategy, and no patient was excluded from analysis even if treatment was incomplete. Results are expressed as mean ± SD. Differences between responders and nonresponders were assessed by Fisher exact test, χ^2 test and Student's *t* test.

RESULTS

Patients: The clinical and biological features of the study group are presented in Table 1. Twenty patients were of French-Canadian origin and two came from countries with high hepatitis B endemicity (Greece and Haiti). The major risk factors for the acquisition of hepatitis B were homosexuality (36% of cases) and hospital work with frequent exposition to blood (32%). All patients were positive for HBsAg and HBeAg for at least six months, had abnormal liver enzymes and were negative for anti-HDV and anti-HIV. One patient was positive for anti-HCV. Liver histology showed

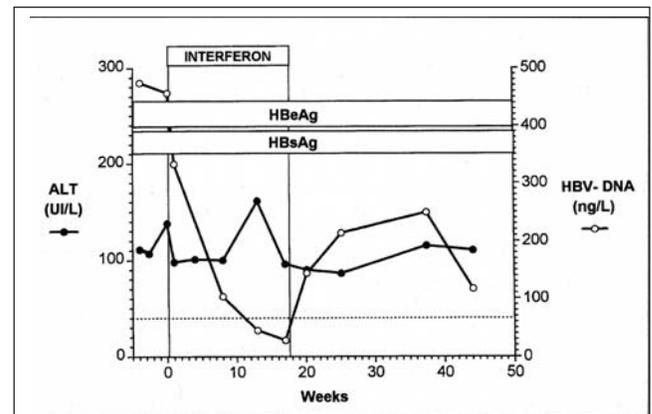


Figure 2) Representative example of interferon alpha 2b treatment failure, with persistence of hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg). Hepatitis B virus (HBV)-DNA level decreased during treatment but increased following cessation of treatment. The dashed line is the upper normal limit of serum alanine aminotransferase (ALT)

cirrhosis in a majority of cases, with positive staining for HBcAg in all cases.

Response to treatment: Eleven of 22 patients responded to treatment, with loss of HBeAg and appearance of anti-HBe at six months after discontinuing interferon. In three of 11 responders, there was also a loss of HBsAg with appearance of anti-HBs. Biological data before and after treatment in responders and nonresponders are compared in Table 2.

A representative example of treatment success is shown in Figure 1. In the majority of responders, HBV-DNA became undetectable between eight and 16 weeks after treatment initiation, followed shortly by the seroconversion from HBeAg to anti-HBe. HBeAg to anti-HBe seroconversion was preceded by a transient and significant rise (at least twice the basal value) of AST and ALT aminotransferases in only four of 11 responders.

A representative example of treatment failure is shown in Figure 2. HBV-DNA levels decreased during treatment in nonresponders, but rose to initial values following the end of treatment. In three nonresponders, a rise of aminotransferases to at least twice the basal value was observed after eight to 12 weeks of treatment, but was not followed by HBeAg to anti-HBe seroconversion.

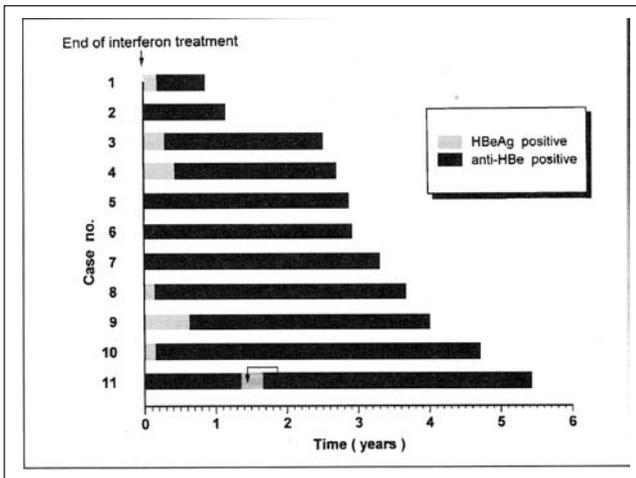


Figure 3) Long term follow-up in 11 patients with chronic hepatitis B who responded to interferon treatment. The short arrows indicate retreatment with interferon. HBeAg Hepatitis B e antigen

Prediction of treatment response: Comparison of baseline clinical and laboratory data reported in Table 2 did not show significant differences between responders and nonresponders. Baseline AST and ALT levels were slightly higher in responders than in nonresponders (AST: 232 ± 192 versus 129 ± 118 IU/L; ALT: 337 ± 299 versus 172 ± 124 IU/L), but the difference between the two groups was not significant. Baseline HBV-DNA levels were also comparable in responders and nonresponders (220 ± 400 versus 178 ± 164 ng/L). The proportion of patients with cirrhosis was similar (nine of 11 responders versus eight of 11 nonresponders) as was the known duration of disease before treatment (2.9 ± 2.5 versus 3.6 ± 2.8 years).

Side effects and toxicity of treatment: The usual side effects of interferon were seen in the majority of cases: fever, myalgia and headache after the initial doses, which decreased in intensity with further dosing; and fatigue, anorexia, irritability, leukopenia (neutropenia) and thrombocytopenia lasting the entire treatment period. In three cases, the dose of interferon was decreased because of significant neutropenia (neutrophil count less than 750×10^9 cells/L) but treatment was maintained. In three other cases, treatment was discontinued prematurely. One patient presented severe allergic reactions at the site of interferon injection and treatment was discontinued after five weeks; he remained HBeAg-positive. A second patient developed jaundice (serum bilirubin 97 μ mol/L) and marked elevation of liver enzymes (ALT 1908 IU/L) eight weeks after starting interferon and treatment was stopped. In this patient, liver enzymes decreased progressively over the following months, with loss of HBeAg and appearance of anti-HBe six months after stopping interferon. A third patient decided to use natural products and discontinued interferon after 10 weeks; he did not respond to treatment.

Long term follow-up: Following the end of treatment, patients were followed for an average of 3.4 ± 1.2 years. All but one responder remained HBeAg-negative and anti-HBe positive with normal liver enzymes (Figure 3). One responder

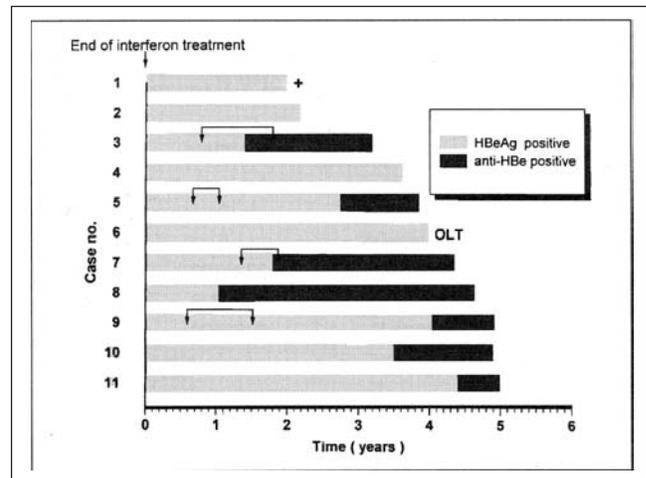


Figure 4) Long term follow-up in 11 patients with chronic hepatitis B who did not respond to interferon treatment. The short arrows indicate retreatment with interferon. + Deceased; HBeAg Hepatitis B e antigen; OLT Orthotopic liver transplantation

relapsed 46 weeks after the end of treatment, with reappearance of HBeAg and HBV-DNA and elevation of liver enzymes; he responded to a second course of interferon with loss of HBeAg and HBV-DNA and has not relapsed since.

Long term follow-up in the 11 nonresponders is summarized in Figure 4. Four patients have remained HBeAg-positive: one died of liver failure, one underwent orthotopic liver transplantation, one has decompensated liver disease (Child-Pugh class C) and one remains asymptomatic. Four nonresponders were retreated with a second course of interferon: two seroconverted from HBeAg to anti-HBe during retreatment, and the other two did not respond but eventually underwent spontaneous seroconversion during follow-up. The remaining three nonresponders also underwent spontaneous seroconversion during follow-up.

DISCUSSION

In this study, we examined the efficacy of interferon to treat chronic hepatitis B in a usual clinical setting, ie, outside the context of randomized controlled trials. Interferon induced seroconversion from HBeAg to anti-HBe in 50% of patients. These results are better than those generally reported in the literature (35% rate of seroconversion) and are probably due to the absence of factors predictive of a poor response to treatment in our study group. It has been shown that the response to interferon is lower in patients who are anti-HIV positive, who have a co-infection with HDV and who are positive for HBeAg but have normal liver enzymes (5). We chose not to treat such patients. In addition, none of our patients was of Asian origin, an ethnic group in whom the response to interferon seems less favourable (11).

In patients who responded to treatment, interferon induced a progressive decrease of HBV-DNA blood levels, which became nondetectable after eight to 16 weeks of treatment (Figure 1). In nonresponders, there was a similar decrease of HBV-DNA levels but without complete disappearance, and levels rose to initial values when treat-

ment was stopped (Figure 2). This profile suggested that a treatment duration of more than 16 weeks could have been beneficial in some nonresponders; thus, four nonresponders were retreated with interferon for periods ranging from 20 to 32 weeks. Two nonresponders responded with a loss of HBeAg at the end of retreatment; the other two lost HBeAg 1.5 and 2.5 years after retreatment and were considered to have had spontaneous seroconversion. Controlled trials are underway to evaluate the effect of prolonged treatment or retreatment in patients who failed a conventional 16-week treatment with interferon.

Patients included in this study all had compensated liver disease, even though 77% of them had cirrhosis. The proportion of patients with cirrhosis was comparable in responders and nonresponders. Thus the presence or absence of cirrhosis did not seem to modify the treatment response. Perillo et al (6) also reported that the response to interferon was comparable in patients with and without cirrhosis. These observations differ from those made in patients with chronic hepatitis C, where the efficacy of interferon is better in patients without cirrhosis.

Interferon treatment was associated with side effects in a majority of patients and required close observation. Asthenia, neutropenia and thrombocytopenia were the most common side effects, but they did not require interruption of treatment. Treatment was discontinued prematurely in two of 22 patients (9%) because of side effects. In one of these patients, treatment was stopped after eight weeks because of jaundice and a marked elevation of liver enzymes. This type of reaction is thought to be related to the sudden destruction of HBV-infected hepatocytes by an immune reaction triggered by interferon, and it underlines the risk of using interferon in patients with severe liver disease. Flares in the underlying hepatitis during interferon treatment can lead to severe and occasionally fatal hepatic failure (12). Auto-immune hyperthyroidism and hypothyroidism are known to occur in 10 to 15% of patients during therapy or even after interferon has been stopped (13), but no case of clinical thyroid dysfunction was seen in the present study.

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CONCLUSIONS

Alpha-interferon for the treatment of chronic hepatitis B was effective in 50% of the patients when used in selected subjects and in a standard clinical setting. Although a significant proportion of nonresponders will eventually undergo spontaneous seroconversion, new treatment strategies are needed for those who remain HBeAg-positive because they have a high risk of developing liver failure.



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