Radiol Oncol 1993; 27: 312-5.

Our experience with alpha 2-b interferon in the treatment of chronic active hepatitis B

Vladimir Brinovec

Clinic for Infectious Diseases and Febrile States, Ljubljana, Slovenia

Clinical investigations of alpha-2 b interferon (Intron A - Schering-Plough) and other interferons have led to the registration of this substances for the treatment of chronic active hepatitis (CAH) B. In the present study patients were administered a dose of 3 million units (or 6 million units) of Intron A three times a week for three months (treatment failure was observed in one woman only; in this patient the dose was increased to 6 million units of Intron A and the treatment continued for another three months). As regards the therapeutical scheme, optimal instructions, as recommended by other European authors, were followed. Before therapy was introduced, all objective factors influencing the outcome of treatment were thoroughly examined. Liver histology, repeated comparative tests of the virus replication markers (HBV-DNA, HBeAg), and biochemical liver examinations (bilirubin, ALT, AST) were good indicators of the efficacy of the therapy. All the above laboratory tests were performed monthly. Therapy was stopped as soon as the laboratory tests and histological liver findings showed satisfying results. A prolongation of therapy was indicated only in one patient (non-responder) in whom therapy was prolonged until an improvement of the laboratory and histological liver test was achieved.

Key words: hepatitis B-drug therapy; hepatitis, chronic active; interferon-alpha-2B

Introduction

Chronic active hepatitis (CAH) B still represents a therapeutic problem. Corticosteroids, which had been widely used for the treatment of CAH B in the past, proved unsuccessful because they were shown to even induce HBV replication without reducing the clinical signs of the disease.[1,2] At present, interferon alpha is considered to be the most promising antiviral agent in the treatment of chronic HBV infection.[3-6] It exerts an additional effect on clearing HBeAg and HBV DNA from serum with or without the disappearance of HBs Ag. By this action interferon alpha is believed to cause an interruption of the viral replication phase (proved by HBeAg seroconversion) resulting in an improvement of the clinical, biochemical and histological changes of the liver.[7] It has been demonstrated that HBeAg seroconversion occurs in about 30–40 % of patients treated with alpha-interferon (IFN).[6-8] In the remaining over 50 % of patients the treatment is unsuccessful

Correspondence to: Asist. Prof. Vladimir Brinovec, MD, DSci, Clinic for Infectious Diseases and Febrile States, Japljeva 2, 61000 Ljubljana, Slovenia.

UDC: 616.36-002.2-085

leading to further development of the inflammatory activity of the HBV infection.

A better therapeutical approach has not been found yet.

Patients and methods

In the period from June 1988 till December 1992 6 patients underwent treatment.

Table 1. Patients characteristics prior to interferon therapy.

Men/women	4/2
Age/women	25 and 61 years
Age/men	18, 20, 26, and 32 years
History of acute hepatitis	M 3/W 1
Duration of infection (months)	beyond 6 moths or up to several years
Time preceding the IFN therapy	6 months up to several years
CPH/CAH	0/6
HBV DNA (pg/ml)	0-210
AST (μkat/L)	0-5.3
anti-HIV	negative

Prior to the initiation of therapy, chronic active hepatitis B following HBV infection was histologically confirmed in all 6 patients under therapy. All patients were HBsAg positive, anti HBs negative, anti HBc positive (IgM negative), and HBeAg positive. Markers of active viral replication (positive HBeAg and HBV DNA) were detected by serum testing. Hepatitis D infection was excluded. All patients had signs of HBV infection (positive HBsAg) for at least 6 months or more. To 3 out of 4 men Intron A was administered at a dose of 6 million units three times a week for three months. Only one male patient received a dose of 3 million units during an equal treatment period.

In 2 women the therapeutic dose was 3 million units of Intron A given three times a week for 3 months. Since the older female patient (61 years) did not respond to the above treatment regimen therapy was prolonged for another 3 months during which time she was given a dose of 6 million units three times a week. During the course of therapy laboratory liver function tests (bilirubin, AST, ALT, prothrombin, proteinogramme) and tests for hepatitis B and HBV DNA serum markers were carried out regularly. Tests were performed every fortnight during the first month of treatment, later monthly, and every 3 months during the follow-up period. After three months of treatment all patients underwent liver biopsy which was used to evaluate the efficacy of interferon therapy. In the older woman (aged 61) biopsy was repeated at the end of the prolonged therapy. Blood count values were expressed in SI units, AST, ALT in μkat/L; HBsAg, and anti HBc were determined according to the RIA method with reagents obtained from Abbott, and were expressed in mmol/L, while anti HBs was determined according to the enzymatic method developed by Berhringwerke and was expressed in IU/L. HBV DNA was expressed in pg/ml and was determined according to the RIA method with reagents obtained from Abbott.

Results

After therapy with Intron A the histologic picture of the liver showed that chronic persistent hepatitis B (CPH) was present in 4 men. In 1 (32 years) of the 2 women, to whom Intron A was administered at a dose of 3 million units three times a week for 3 months, repeated liver biopsy showed chronic CPH B, while in the other patient (61 years) the therapy was ineffective. In this non-responding patient, the dose of Intron A was increased to 6 million units given three times a week and the treatment prolonged for another 3 months. The histological finding obtained after this prolonged administration confirmed the presence of chronic persistent hepatitis (CPH) B.

Four men and one woman (5 patients) remained HBsAg positive throughout the whole treatment and follow-up period. In the 61 year old woman in whom therapy was prolonged for another 3 months, HBsAg disappeared from serum and has remained negative up to the present. In all patients converted to HBeAg

negative, seroconversion of anti HBe was observed after the cessation of therapy.

At the end of therapy HBV DNA was normal in all patients. In one woman (32 years) an increase reappeared after therapy had been stopped, but disappeared spontaneously after some time.

Aminotransferases returned to normal values in all patients at the end of treatment.

As regards the side effects, a flue-like syndrome was noticed which was most frequent after the first application of the drug and disappeared spontaneously in the majority of patients during the continuation of therapy. Only in the 61 year old woman who was under prolonged interferon treatment, an increase in body temperature occurred (lasting for several hours after application) associated with nausea, loss of appetite, and reduced body weight. After repeated application these side effects diminished and totally disappeared by the end of therapy.

In all patients leukopenia associated with a relative lymphocytosis and mild thrombocytopenia occurred after application, so that therapy could be continued and concluded in the whole group of patients.

The patients are followed up every three months.

Discussion

The aim of alpha 2b interferon therapy (Intron A) was to prevent further development of HBV infection. The sole disappearance of HBeAg and HBV DNA from serum cannot be seen as a sign of complete eradication of HBV since many investigators have found that in patients with chronic liver diseases HBV DNA division in liver cells occurs even after complete disappearance of HBeAg and occurrence of anti HBe antibodies.[9,10] In patients under immunosupressive therapy (and also spontaneously) clinical activation of hepatitis and reactivation of HBV replication developed despite the occurrence of anti HBe antibodies.[11,12]

In all 6 patients under trial interferon therapy led to disappearance of HBeAg and HBV DNA from serum. In our patient group the occurrence of anti HBe in serum was, except for one patient, not followed by reappearance of increased HBV DNA values. Later on these values were not detectable. The HBV DNA value before treatment is another important parameter. Some authors have reported that lower serum HBV DNA was associated with a better response to interferon therapy.[13,14]

In our patient group the loss of HBeAg from serum was associated with normalization of aminotransferases and an improvement of the hepatic histology (histologically, in all patients CAH B turned to CPH before the beginning of therapy).

It is known that in about 5-15 % of patients with chronic liver disease seroconversion from HBeAg can occur also spontaneously.[15-17]

Disappearance of HBsAg from serum (lasting up to the present) occurred only in one patient under prolonged therapy. This finding is in accordance with the study results obtained by other authors,[8,18,19] who reported that after therapy with alpha-interferon disappearance of HBsAg from serum occurred in 0–20 % of patients under therapy.

Due to a small number of patients involved in the trial, the evaluation of the obtained results lacks to a certain degree the required objectivity. However, the frequency of the disappearance of HBs from serum will probably increase with prolonged therapy and follow-up period, depending, of course, on the dose of interferon. For that very reason my work has been directed towards further investigation of the efficacy of this treatment regimen already from the beginning.

References

1. European Association for the Study of the Liver (Trial Group): Steroids in chronic B-hepatitis. A randomized double-blind, multinational trial on the effect of low-dose, long-term treatment on survival. *Liver* 1986; **6:** 227–32.

2. Lam KC, Lai CL, Trepo C, Wu PC. Deleterious effect of prednisolone in HBsAg positive chronic active hepatitis. *New Engl J Med* 1981; **304:** 380–6.

3. Alexander GJM, Brahm J, Fagan EA, Smith HM, Daniels HM, Eddleston ALWF, Williams R. Loss of HBsAg with interferon therapy in chronic hepatitis B virus infection. *Lancet* 1987; **2:** 66–9.

4. Scully LJ, Shein R, Karayiannis P, McDonald JA, Thomas HC. Lymphoblastoid interferon therapy of chronic HBV infection: A comparison of 12 vs 24 weeks of thrice weekly treatment. *J Hepatol* 1987; **5:** 51–8.

5. Hoofnagle JH, Peters M, Mullen KD, Jones DB, Rustgi V, DiBisceglie AM, Hallahan C, Park Y, Meschievitz C, Jones EA. Randomized, controlled trial of recombinant human alphainterferon in patients with chronic hepatitis B. *Gastroenterology* 1988; **95:** 1318–25.

6. Brook MG, Chan G, Yap I, Karayiannis P, Lever AML, Jacyna M, Main J, Thomas HC. Randomized controlled trial of lymphoblastoid interferon alpha in Europid men with chronic hepatitis B virus infection. *Br Med J* 1989; **299:** 652–6.

7. Fattovich G, Rugge M, Brollo L, et al. Clinical virologic and histologic outcome following seroconversion from HBeAg to anti HBe in chronic hepatitis type B. *Hepatology* 1986; **6:** 167–72.

8. Perrillo RP, Schiff ER, Davis GL, et al. A randomized controlled trial of interferon alpha-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. *N Engl J Med* 1990; **323:** 295–301.

9. Harrison TJ, Anderson MG, Murray-Leon IM, Zuckerman AJ. Hepatitis B virus DNA in the hepatocyte: A series of 160 biopsies. *J Hepatol* 1986; **2:** 1–10.

10. Brechot C, Degos F, Lugassy C, Thiers V, Zafrani S, Franco D, Bismuth H, Trepo C, Benhamou JP, Wands J, Isselbacher K, Tiollais P, Berthelot P. Hepatitis B virus DNA in patients with chronic liver disease and negative tests for hepatitis B surface antigen. *N Engl J Med* 1985; **312:** 270–6.

11. Lok ASF, Lai CL, Wu PC, Leung EKY, Lam TS. Spontaneous hepatitis B e antigen to antibody seroconversion and reversion in Chinese patients with chronic hepatitis B virus infection. *Gastroenterology* 1987; **92:** 1839–43.

12. Davis GL, Hoofnagle JH, Waggoner JG. Spontaneous reactivation of chronic hepatitis B virus infection. *Gastroenterology* 1984; **86:** 230–5.

13. Lok ASF, Lai CL, Wu PC, Lau JYN, Leung EKY, Wong LSK. Treatment of chronic hepatitis B with interferon: Experience in Asian patients. *Semin Liver Dis* 1989; **4:** 249–53.

14. Yokosuka O, Omata M, Imazeki F, Okuda K, Summers J. Changes of hepatitis B virus DNA in liver and serum caused by recombinant leukocyte interferon treatment: Analysis of intrahepatic replicative hepatitis B virus DNA. *Hepatology* 1985; **5:** 728–34.

15. Craxi AIV, Weller MF, Bassendine, Fowler MJF, Manjardino J, Thomas HC, Sherlock S. Relationship between HBV-specific DNA polymerase and HBe antigen antibody system in chronic HBV infection: Factors determining selection of patients and outcome of antiviral therapy. *Gut* 1985; **24:** 143–7.

16. Liaw YF, Chu ChM, Su IJ, Huang MJ, Lin DY, Chang-Chien ChS. Clinical and histological events preceding hepatitis B antigen seroconversion in chronic type B hepatitis. *Gastroenterology* 1983; **84:** 216–9.

17. Realdi, Alberti GA, Rugge M, Bortolotti F, Rigoli A, Tremolada MF, Ruol A. Seroconversion from hepatitis B e antigen to anti-HBe in chronic hepatitis B virus infection. *Gastroenterology* 1980; **79:** 195–9.

18. Hoofnagle JH, Peters MG, Mullen KD, et al. Randomized, controlled trial of recombinant human alpha-interferon in patients with chronic type B hepatitis. *Gastroenterology* 1988; **95:** 1318–25.

19. Brook MG, McDonald JA, Karayiannis P, et al. Randomized controlled trial of interferon alpha 2a (rbe) (Roferon-A) for the treatment of chronic hepatitis B virus (HBV) infection: Factors that influence response. *Gut* 1989; **30:** 1116–22.