

## ALFA-INTERFERON THERAPY FOR CHRONIC HEPATITIS B VIRUS INFECTION IN KUWAITI PATIENTS

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Alfa-interferon is the standard treatment of chronic hepatitis B. However, the response rate varies widely in patients from different parts of the world, reflecting differences in the natural history of the disease and the immune reactivity of the population studied. The aim of this study is to assess the efficacy of alfa-interferon in the treatment of Kuwaiti patients with chronic replicative hepatitis B infection. Twenty-two adult Kuwaiti patients with biopsy-proven chronic hepatitis B were treated with alfa-interferon after an observation period of six months. All patients had abnormal transaminase levels and were HBeAg and HBV-DNA positive. Alfa-interferon-2b, 5 million units, was administered five days a week for 16 weeks. Patients were followed for at least 12 months after completing therapy. One of the 22 patients dropped out of the study after a single dose of interferon, because of side effects. Of the remaining 21 patients, three (14%) had a sustained loss of HBV-DNA and HBeAg. None of the patients lost HBsAg. There were no episodes of hepatic decompensation or deaths during the study. One patient developed hepatocellular carcinoma 28 months after completing treatment with interferon. Overall, Kuwaiti patients with chronic replicative hepatitis B responded poorly to interferon therapy. *Ann Saudi Med 1997;17(3):279-282.*

The World Health Organization estimates that 300 million people are chronically infected by the hepatitis B virus (HBV). Many infected patients are at considerable risk of developing cirrhosis and hepatocellular carcinoma. The majority of infected individuals reside in Southeast Asia and Africa, where prevalence rates of 10%-20% have been reported.<sup>1</sup> The Middle East and Gulf countries have intermediate endemicity rate of 1%-5%. In Kuwait, the carrier rate of HBV in blood donors is 2.9%.<sup>2</sup> Recombinant alfa-interferon has become the standard therapy for chronic replicative HBV infection. However, there is considerable variance in the response rate between the different trials from various parts of the world, reflecting the heterogenous nature of trial participants.<sup>3</sup> The efficacy of alfa-interferon in treating chronic hepatitis B has not been examined in the Arab population residing in the Middle East. In this study we report the results of interferon therapy in 22 adult Kuwaiti patients suffering from chronic replicative hepatitis B.

### Materials and Methods

Between June 1992 and June 1995, 165 HBsAg-positive, anti-HBc-IgM-negative patients were referred to the hepatology clinics of Thunayan Al Ghanim Gastroenterology Center and Mubarak Al Kabir Hospital. Twenty-three patients satisfied the following criteria: age of 16 or older, abnormal ALT documented for at least three months, HBeAg and HBV-DNA positive, anti-HCV, anti-Delta negative, normal serum bilirubin and albumen, WBC equal or greater than  $3 \times 10^9/L$ , platelet count equal or greater than  $100 \times 10^9/L$ , prothrombin time less than three seconds above control, no ascites, variceal hemorrhage or encephalopathy. None of the patients had received immunosuppressive or antiviral therapy previously. There was no past history of hepatitis or jaundice in any of the patients. HBV infection was discovered in the following settings: abnormal liver function tests on routine screening (11 patients), family screening of HBsAg-positive individuals (seven patients), blood donation (four patients), cirrhosis discovered incidentally during laparoscopic cholecystectomy (one patient). All patients were Kuwaiti nationals. We did not include a parallel control group because interferon was already known to be more effective than placebo.

Patients were managed according to a pre-established, three-phase protocol. During the first phase, patients were observed for six months. The following tests were carried

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out on two occasions at least two months apart: hepatitis B surface antigen (HBsAg), hepatitis B e-antigen (HBeAg), antibody to HBsAg (anti-HBs), antibody to HBeAg (anti-HBe), and HBV-DNA. Moreover, serum alanine aminotransferase (ALT), total serum bilirubin, and serum albumen were determined on at least three occasions. All patients underwent percutaneous liver biopsy during phase I.

Patients who remained HBeAg and HBV-DNA positive during phase I were treated with interferon (phase II). The treatment schedule was as follows: recombinant alpha-interferon-2b (Intron A, Schering-Plough, USA), 5 million units administered subcutaneously five days a week for 16 weeks. To ascertain compliance, injections were given by the nursing staff in the outpatient clinic. Patients were evaluated two, four, eight, 12 and 16 weeks after starting interferon. Evaluations consisted of clinical assessment, complete blood count, and liver function tests. Serologic tests for HBeAg and HBV-DNA were obtained on the 16th week of treatment.

Phase III consisted of 12 months of follow-up during which monthly clinical evaluation and liver function tests were carried out. HBsAg, HBeAg, anti-HBe and HBV-DNA were repeated at 6 months and 12 months after the end of interferon therapy.

HBsAg, HBeAg, anti-HBe, anti-HBc IgM, anti-HDV and anti-HCV were determined by commercial immunoassays (Abbott Laboratories, North Chicago, IL). HBV-DNA was tested by a hybridization assay (Abbott). The lower limit of sensitivity was 1.5 pg/mL. Liver histological findings were interpreted using conventional criteria. Patients were considered to have responded to therapy if they had cleared HBeAg and HBV-DNA at the end of the study.

Pathologic changes in liver biopsy specimens were analyzed by conventional criteria and were graded by Knodell's Histologic Activity Index (HAI) according to the degree of periportal necrosis, portal and lobular inflammation, and fibrosis.<sup>4</sup>

## Results

Of 23 patients who satisfied the criteria, one patient seroconverted spontaneously and cleared HBV-DNA during phase I. Thus 22 patients entered phase II. The demographic, biochemical, serologic and liver histology profiles of these patients are summarized in Table 1. Three of the 22 patients (13.6%) seroconverted to anti-HBe and cleared HBV-DNA. All three patients (two males and one female) had pretreatment ALT levels exceeding 150 IU/L (range 174-224 IU/L), and HBV-DNA levels less than 200 pg/mL (range 56-88 pg/mL). Two of the responders had chronic active hepatitis (CAH) and one had active

TABLE 1. Characteristics of 22 patients enrolled in the study.

Age (years)	
Range	16-49
Mean±SD*	31.6±10.4
Median	31
Sex (M/F)	14/8
Patients with a HBsAg + sibling or parent**	15/18 (83%)
ALT (IU/L) <sup>†</sup>	
Range	68-224
Mean±SD	102±43
Median	86
≥150 IU/L (n)	4
HBV-DNA (pg/mL)	
Range	25-516
Mean±SD*	193±134
Median	188
≥200 pg/mL (n)	9
Liver histology	
CPH/CAH/Cirrhosis	12/7/3
Mean HAI <sup>‡</sup>	2.9/7.1/7.3

\*SD=standard deviation; \*\*family screening was possible in only 18 patients; <sup>†</sup>reference range for ALT=10-60 IU/L; <sup>‡</sup>HAI=hepatitis activity index.

cirrhosis. ALT flares, up to three times the basal level, occurred in all responders and four non-responders. Seroconversion and loss of HBV-DNA were maintained during phase III. None of the responders lost HBsAg.

Eighteen patients (86%) were non-responders, i.e., they remained HBeAg and HBV-DNA positive during phase II and phase III of the study. Nevertheless, these patients had a 32% reduction in their mean HBV-DNA levels at the end of interferon therapy.

Side effects were common. All patients experienced flu-like symptoms, which subsided in 86% of patients within two weeks. Other adverse reactions included fatigue (76%), anorexia (67%), depression (52%), and stomatitis (5%). One patient withdrew after receiving treatment for one week because of severe flu-like symptoms. The dose of interferon was reduced in another patient to 3 million units thrice weekly because of severe thrombocytopenia (platelet count less than 40,000). This patient received 67% of the total scheduled dose. He did not respond to therapy. The remaining 20 patients received the entire scheduled dose (400 million units). There were no deaths during the study. One patient (a non-responder) developed unresectable hepatocellular carcinoma 28 months after completing the course of interferon. He is currently receiving chemotherapy. None of the patients had hepatic decompensation.

## Discussion

Several trials of interferon therapy have been conducted in the United States and Europe.<sup>4-7</sup> The average rate of HBeAg seroconversion and HBV-DNA loss was around 25%-40%. Approximately 10% lost HBsAg. A number of

pretreatment factors predicted the outcome of interferon therapy. High transaminase levels ( $>2 \times$  normal) and low HBV-DNA levels ( $<200$  g/mL) were associated with the highest response rates. Other patient characteristics predictive of a favorable response include a history of acute hepatitis B, short duration of infection, HBeAg seropositivity, the presence of severe necroinflammation on liver biopsy, and the absence of conditions associated with immunosuppression, such as HIV infection. Finally, important differences exist between Oriental patients and Caucasians in their response to interferon therapy. The overall response rate in Orientals is around 15%<sup>8</sup> which is much lower than in Caucasians. However, Orientals with raised ALT and active liver histology have response rates comparable to those observed in Caucasians.<sup>3,8</sup> Therefore, the difference in response rate between Orientals and Caucasians cannot be attributed to genetic differences alone. An alternative explanation for the low seroconversion rates in Orientals is that most of these patients acquire HBV infection in the neonatal period or during early childhood when the immune system is immature. A state of immunotolerance to the virus develops leading to: 1) poor response to interferon therapy; 2) high level of viremia; 3) mild hepatic necroinflammation; and 4) normal or near normal serum transaminase levels.

In the present study, the response rate to interferon therapy was similar to that of Orientals. This is not surprising since our patients had several characteristics in common with Oriental patients. For instance, the high prevalence of chronic HBV infection among the parents and/or siblings of Kuwaiti patients suggests that the infection was acquired at an early age. Moreover, most of our patients had slightly raised transaminase levels, relatively high circulating HBV-DNA and mild hepatitis on biopsy specimens. These characteristics are consistent with being in an immunotolerance phase of HBV infection, hence, the poor response to interferon. Another conceivable explanation for the poor response is the emergence of neutralizing antibodies to interferon.<sup>9</sup> We did not test patients for such antibodies. However, alfa-interferon-2b is known for its low incidence of neutralizing antibodies.<sup>10</sup> Even when these antibodies emerge during interferon therapy their titers are low and the anti-viral activity is not usually compromised. Non-compliance is another potential cause of poor response to therapy. In our study, compliance was excellent because patients were highly motivated by thorough counselling regarding the consequences of untreated chronic hepatitis B and about the side effects of interferon therapy. Finally, the optimal dose of interferon for the treatment of chronic hepatitis B is not known. Generally, the highest response rates were achieved by cumulative doses of 360 to 480 million units administered over a 3-6-month period.<sup>12</sup> The cumulative

dose of interferon in this was 400 million units, which is a moderately high dose. We do not think a higher dose would have made a significant impact on the response rate.

Early pilot trials suggested that the anti-viral efficacy of interferon may be enhanced by prednisolone priming.<sup>11,12</sup> However, this was not confirmed by large-scale randomized controlled trials.<sup>6,13</sup> Therefore, we did not pre-treat our patients with prednisolone.

In summary, Kuwaiti patients with chronic replicative hepatitis B infection respond poorly to interferon therapy. The most likely reason for the poor response is immune tolerance to HBV. Alternative approaches to the treatment of hepatitis B are badly needed. A number of drugs such as thymosin, famciclovir, and lamivudine are currently under investigation. However, the control of hepatitis B in endemic areas such as the Middle East rests largely on public health programs of universal vaccination.

## References

1. WHO. Global health situation and projections and estimates. Geneva: World Health Organization, 1992.
2. Al-Nakib W, Bashir AA. Prevalence of hepatitis B surface antigen among healthy blood donors in Kuwait. *J Kwt Med Assoc* 1977;11:137-44.
3. Wong DKH, Cheung AM, O'Rourke K, Naylor CD, Detsky AS, Heathcote J. Effect of alpha-interferon treatment in patients with HBeAg-positive chronic hepatitis B: a meta-analysis. *Ann Intern Med* 1993;119:312-23.
4. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology* 1981;1:431-5.
5. Hoofnagle JG, Peters M, Mullen KD, Jones DB, Rustgi V, Di Bisceglie A, et al. Randomized, controlled trial of recombinant human interferon in patients with chronic hepatitis B. *Gastroenterology* 1988;95:1318-25.
6. Brook MG, Chan G, Yap I, Karayiannis P, Lever AM, Jacyna M, et al. Randomized controlled trial of lymphoblastoid interferon-alfa in Euroid men with chronic hepatitis B virus infection. *Br Med J* 1989;299:652-6.
7. Perrillo RP, Schiff ER, Davis GL, Bodenheimer HC, Lindsay K, Payne J, et al. A randomized controlled trial of interferon alfa-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. *N Engl J Med* 1990;323:295-301.
8. Di Bisceglie AM, Fong T-L, Fried MW, Swain MG, Baker B, Korenmann J, et al. A randomized controlled trial of recombinant  $\alpha$ -interferon therapy for chronic hepatitis B. *Am J Gastroenterol* 1993;88:1887-92.
9. Lok ASF. Alpha-interferon therapy for chronic hepatitis B virus infection in children and Oriental patients. *J Gastroenterol and Hepatol* 1991;Suppl.1:15-17.
10. Lik ASF, Lai CL, Leung EKY. Interferon antibodies may negate the antiviral effects of recombinant  $\alpha$ -interferon treatment in patients with chronic hepatitis B virus infection. *Hepatology* 1990;12:66-70.
11. Antonelli G, Currenti M, Turriziani O, Dianzani F. Neutralizing antibodies to interferon- $\alpha$ : relative frequency in patients treated with different interferon preparations. *J Infect Dis* 1991;163:882-5.
12. Tine F, Liberati A, Craxi A, Almasio P, Pagliaro L. Interferon treatment in patients with chronic hepatitis B: a meta-analysis of the published literature. *J Hepatol* 1993;18:154-62.
13. Omata M, Imazeki F, Yokosuka O, et al. Recombinant leukocyte A interferon treatment in patients with chronic hepatitis B virus infection:

- pharmacokinetics, tolerance, and biologic effects. *Gastroenterology* 1985;88:870-80.
14. Perillo RP, Regenstein FG, Peters MG, DeSchyver-Kecskemeti K, Bodicky CJ, Campbell CR, et al. Prednisone withdrawal followed by recombinant alpha interferon in the treatment of chronic type B hepatitis: a randomized, controlled trial. *Ann Intern Med* 1988;109:95-100.
  15. Reichen J, Bianchi L, Frei PC, Male PJ, Lavanchy D, Schmidt M. Efficacy of steroid withdrawal and low dose interferon treatment in chronic active hepatitis B. Results of a randomized multicenter trial. *J Hepatol* 1994;20:175-80.