

## LONG-TERM FOLLOW-UP OF HBeAg-POSITIVE PATIENTS TREATED WITH INTERFERON ALFA FOR CHRONIC HEPATITIS B

CLAUS NIEDERAU, M.D., TOBIAS HEINTGES, M.D., STEFAN LANGE, M.D., GEORG GOLDMANN, M.D., CHRISTOPH M. NIEDERAU, M.D., LEONHARD MOHR, M.D., AND DIETER HÄUSSINGER, M.D.

**Abstract Background.** In patients with chronic hepatitis B, treatment with interferon alfa and the consequent loss of hepatitis B e antigen (HBeAg) from the blood leads to a reduction in inflammatory activity, but the clinical benefits of this treatment have not been established. We evaluated whether HBeAg seroconversion induced by interferon alfa improves clinical outcome.

**Methods.** We studied prospectively a cohort of 103 patients treated with interferon alfa for chronic hepatitis B; the mean ( $\pm$ SD) follow-up was  $50.0 \pm 19.8$  months. Fifty-three untreated patients served as controls.

**Results.** After treatment with interferon alfa, 53 of 103 patients no longer had detectable HBeAg or hepatitis B virus DNA, although only 10 patients became seronegative for hepatitis B surface antigen (HBsAg) (Kaplan–Meier estimates of cumulative clearance rates at five years, 56.0 percent for HBeAg and 11.6 percent for HBsAg). Of the 53 untreated patients, only 7 spontaneously eliminated HBeAg (28.1 percent at five years), and all remained positive for HBsAg ( $P < 0.001$  for the com-

parison with the treated patients, by the proportional-hazards model). During follow-up, 6 of the 103 treated patients died of liver failure, and 2 needed liver transplantation; all 8 were persistently positive for HBeAg. In another eight treated patients, complications of cirrhosis developed; all but one of these patients remained positive for HBeAg. Overall survival and survival without clinical complications were significantly longer in patients who were seronegative for HBeAg after therapy with interferon alfa than in those who remained seropositive ( $P = 0.004$  and  $P = 0.018$ , respectively). In a regression analysis, clearance of HBeAg was the strongest predictor of survival. Of the 53 untreated patients, 13 had severe complications (including 4 deaths and 1 need for liver transplantation); all 13 continued to be HBeAg-positive.

**Conclusions.** In patients with chronic hepatitis B infection, the clearance of HBeAg after treatment with interferon alfa is associated with improved clinical outcomes. (N Engl J Med 1996;334:1422-7.)

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CHRONIC hepatitis B is associated with high morbidity and mortality. Several randomized clinical trials have reported that therapy with recombinant interferon alfa increases the rate of elimination of hepatitis B e antigen (HBeAg), from a low rate of spontaneous clearance of 5 to 10 percent without treatment to between 30 and 50 percent with treatment.<sup>1-7</sup> Seroconversion from HBeAg to anti-HBeAg antibodies is often associated with the disappearance of hepatitis B virus (HBV) DNA, as assessed by dot blot hybridization. Three long-term studies that evaluated serologic and laboratory outcomes in patients with chronic hepatitis B who were treated with interferon reported that there was a low frequency of viral reactivation and that conversion to HBeAg seronegativity was usually followed by the return of serum aminotransferase levels to normal.<sup>8-10</sup> A single report shows that long-term interferon therapy also has a positive effect on histologic findings in the liver.<sup>11</sup> Although the few long-term studies suggest that treatment with interferon alfa reduces inflammatory activity in patients with chronic hepatitis B, antiviral therapy has not been proved to affect the prognosis. We undertook the present study to determine whether HBeAg seroconversion induced by interferon alfa improves the clinical

outcome of patients with chronic hepatitis B (formerly called chronic active hepatitis B).

### METHODS

#### Patients Treated with Interferon Alfa

Between March 1988 and September 1994, 103 patients with chronic hepatitis B were treated with interferon alfa-2b (Intron A, Essex Pharma, Munich, Germany). Forty of these patients had been included in an earlier randomized clinical trial.<sup>12</sup> Although different doses of interferon and slightly different treatment schedules were used, the diagnostic criteria were similar for all patients. Twenty patients had initially been treated with 2 million units of interferon alfa three times per week after a short course of cortisone; the remaining patients were initially treated with 5 million units three times per week. The treatment periods ranged from four to six months. In 63 of the 103 patients, HBeAg was not eliminated during a nine-month period after interferon therapy; 29 of these 63 patients subsequently received a second course of interferon therapy. In patients who had initially received 2 million units three times per week, the dose was increased to 5 million units three times per week, and in patients who had initially received 5 million units, the dose was increased to 10 million units three times per week. One of the 17 patients who did not respond to the second course of therapy had a third course with 5 million units of interferon alfa three times per week for six months.

The inclusion criteria were the same for all patients; the results of tests for hepatitis B surface antigen (HBsAg), HBeAg, and HBV DNA (determined by dot blot hybridization) had to be positive in at least two different samples obtained within six months before therapy. In all patients, HBsAg was present and serum alanine aminotransferase levels had been elevated for at least one year before therapy. Only patients who had at least a twofold increase in the serum alanine aminotransferase level and histologic evidence of active hepatitis were treated. Patients with antibodies against hepatitis D virus (HDV) or human immunodeficiency virus and patients with advanced cirrhosis (Child–Pugh class B or C) were excluded. Patients enrolled in the clinical trial gave consent according to standards of the local ethics committees. The patients were examined every 3 months for the first year after therapy and every 12 months

From the Department of Medicine, Division of Gastroenterology, Hepatology, and Infectious Diseases, Heinrich Heine University Düsseldorf, Düsseldorf (C.N., T.H., G.G., C.M.N., L.M., D.H.), and the Department of Medical Informatics, Biometrics and Epidemiology, Ruhr University Bochum, Bochum (S.L.) — both in Germany. Address reprint requests to Dr. Claus Niederau at the Department of Medicine, Division of Gastroenterology, Hepatology, and Infectious Diseases, Heinrich Heine University Düsseldorf, Moorenstr. 5, 40225 Düsseldorf, Germany.

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thereafter, with a mean ( $\pm$ SD) follow-up of  $50.0 \pm 19.8$  months (range, 12 to 90).

### Control Group of Untreated Patients

A cohort of 53 untreated patients (control group) was followed at yearly intervals for  $38.5 \pm 18.2$  months (range, 12 to 89). Twenty of these patients had served as untreated controls in a previous randomized trial.<sup>12</sup> After the completion of the trial, 18 of these 20 patients were treated with interferon alfa (the other 2 refused treatment for personal reasons); the 18 subjects were included as untreated controls in the present study until they were treated. The other 33 patients, who remained in the control group, were not treated for the following reasons: refusal of treatment (15 patients), a history of psychiatric problems (7), presence of thyroid abnormalities (5), a wish to become pregnant (3), and presence of bleeding disorders (3). Except for these reasons for remaining untreated, all 53 patients in the control group met the same inclusion criteria and had the same follow-up as the interferon-treated patients. Thus, the base-line characteristics were similar in the two groups.

### Total Cohort of Treated and Untreated Patients

Since 18 patients who had served as controls were later transferred to the interferon-treated group, the total cohort consisted of 138 patients — all patients with chronic hepatitis B who had been referred to our study center between March 1988 and September 1994 and who met the inclusion criteria. Testing for serum antibodies to the hepatitis C virus produced negative results in all patients. The follow-up ended with the last recorded visit before August 1995. Between 92 and 100 percent of the patients were seen at our referral center at each of the scheduled follow-up dates; for the remaining patients, relevant data were obtained from the primary care physician. None of the patients were lost to follow-up. The following events were prospectively defined as severe clinical complications: death; need for liver transplantation; development of ascites, jaundice, or hepatic encephalopathy; and occurrence of, or bleeding from, esophageal varices.

### Measurements

We tested for markers of HBV infection (HBsAg, anti-HBsAg antibodies, HBeAg, and anti-HBeAg antibodies) and anti-HDV antibodies with commercial radioimmunoassays (Abbott Laboratories, North Chicago, Ill.). Serum HBV DNA was measured with a standard dot blot hybridization technique.<sup>13</sup> Liver-function tests were performed by standard methods. The nested polymerase chain reaction (PCR) for HBV DNA was performed with standard methods. We used a 24-bp sense primer (nucleotides 1640 through 1663) and a 24-bp antisense primer (2466 through 2489) for the outer PCR. For the second PCR, inner primers (antisense, nucleotides 1940 through 1959, 21 bp; sense, 1747 through 1771, 24 bp) were used.

### Statistical Analysis

Because the loss of HBeAg, HBsAg, and HBV DNA and the normalization of alanine aminotransferase levels could be detected only at the examinations performed at 3-month intervals in the first year and at yearly intervals thereafter, the time at which one of these events occurred was recorded as the midpoint between successive examinations (e.g., if the loss of HBeAg was detected at the 6-month examination, the time until HBeAg loss was recorded as 4.5 months). The Kaplan–Meier method was used to estimate survival; survival without clinical complications; the time to clearance of HBeAg, HBsAg, and HBV DNA; and the time to normalization of alanine aminotransferase levels, with HBeAg seroconversion status (i.e., with or without loss of detectable HBeAg) and treatment (i.e., with or without interferon alfa) as grouping factors. For the calculation of survival times, the need for liver transplantation was combined with death. Patients who became HBeAg-seronegative should have had longer survival times than those who did not, because they lived at least until seroconversion. To avoid this bias, survival time was estimated conservatively as follows. First, the time until HBeAg seroconversion was subtracted from the observation time for patients who had clearance of HBeAg; second, data from all patients were used for the

Kaplan–Meier estimates of persons in whom HBeAg had not yet been eliminated, with elimination as a reason for data censoring. The same procedure was used to estimate the time to clearance with respect to laboratory and serologic markers in treated and untreated patients, since 18 patients were included in both the control group and the interferon-treated group.

Statistical hypothesis testing was performed by Cox regression (with a proportional-hazards model), with conversion to HBeAg seronegativity and treatment as the time-dependent variables. Multivariate analyses were performed with age, sex, base-line HBV DNA and alanine aminotransferase levels, duration of hepatitis, and preexisting cirrhosis as prognostic factors; P values are given for tests that evaluated whether the regression coefficients equaled zero. The influence of seroconversion and treatment on survival and time to clearance of HBsAg was evaluated by a likelihood-ratio test, because no deaths had occurred in patients who lost HBeAg, and all untreated patients remained positive for HBsAg. All analyses were performed with the SAS software package, version 6.08; for the Cox regression, the PHREG procedure was used.

## RESULTS

### Serologic and Laboratory Markers

Of the 103 patients treated with interferon alfa, 40 (39 percent) had clearance of HBeAg during the first nine months after the start of therapy. Of the 63 patients with no response to the first course of interferon (many of whom were treated with a dose of 2 million units three times per week), 29 received a second course of therapy with a higher dose (see the Methods section). Twelve of the 29 retreated patients eventually had clearance of HBeAg and HBV DNA (41 percent). One of the 17 who did not respond to this second course received a third course of therapy and finally lost HBeAg and HBV DNA.

The cumulative rates of clearance of HBeAg, HBV DNA, and HBsAg and the normalization of alanine aminotransferase levels in treated and untreated patients are shown in Figure 1. Fifty-three of the 103 treated patients ultimately had a loss of HBeAg (Kaplan–Meier estimate of cumulative rate of clearance at five years, 56.0 percent); all of these 53 patients also lost HBV DNA and had newly detectable anti-HBeAg antibodies. Clearance of HBeAg and HBV DNA occurred almost simultaneously; only a few patients became HBV DNA-negative (by the dot blot technique) some time before becoming seronegative for HBeAg (median difference, 0 months; range, 0 to 24). None of the patients with responses had a recurrence of either of these markers. Only 10 of the 103 treated patients had clearance of HBsAg (cumulative rate of clearance at 5 years, 11.6 percent), often a considerable time after they had lost HBeAg (median difference, 14.2 months; range, 0 to 60). Thus, only 19 percent of the patients who lost HBeAg (10 of 53) eventually also lost HBsAg. All 10 patients who lost HBsAg also became negative for HBV DNA by PCR analysis. In 51 of the 53 patients who lost HBeAg, the alanine aminotransferase level became normal after a median of 12.0 months (range, 7.5 months before to 60 months after loss of HBeAg).

Only 7 of the 53 untreated patients had spontaneous clearance of HBeAg during follow-up (cumulative rate of clearance at five years, 28.1 percent), and none lost

HBsAg. All untreated patients who remained HBeAg-positive also continued to have elevated HBV DNA and alanine aminotransferase levels. Of the seven patients who lost HBeAg, only five also lost HBV DNA and had normal levels of alanine aminotransferase; in the remaining two patients, an HBeAg-negative mutant HBV was probably responsible for continuing viral replication and inflammation. As compared with the interferon-treated patients, the untreated patients had lower rates of loss of HBeAg ( $P < 0.001$ ), HBsAg ( $P = 0.005$ ), and HBV DNA ( $P < 0.001$ ) and of normalization of alanine aminotransferase levels ( $P < 0.001$ ) (Fig. 1).

**Survival and Clinical Complications**

During follow-up, severe clinical complications developed in 16 of the 103 interferon-treated patients. Six HBsAg- and HBeAg-positive patients died from decompensated cirrhosis. Full clinical reports about the cause of death were available for all six patients, and autopsy data were available for three of them. Two other patients had liver failure necessitating liver transplantation. Jaundice and ascites developed in three patients, hepatic encephalopathy in one patient, and esophageal varices in four patients, in two of whom bleeding occurred during follow-up. All complications occurred in patients who did not clear HBeAg, except for one patient with ascites who became seronegative.

The length of survival (until liver transplantation or death) and survival without clinical complications was significantly longer in patients who had clearance of HBeAg after interferon therapy than in patients who did

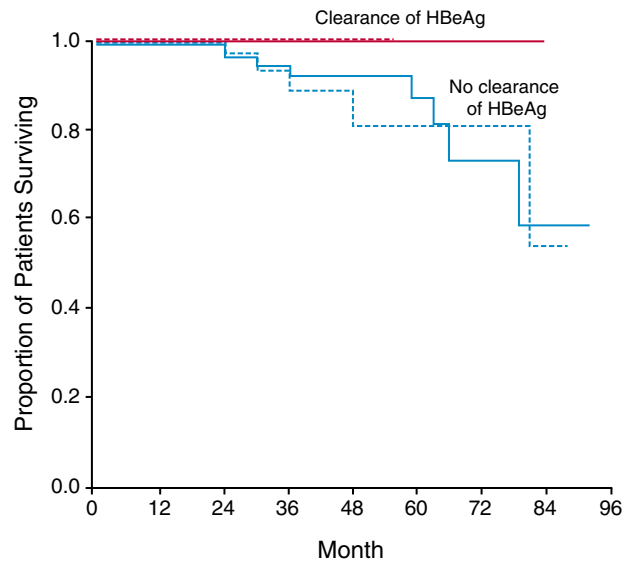
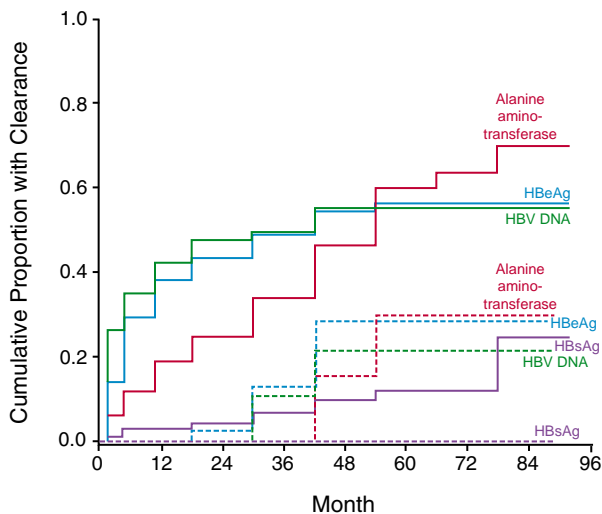


Figure 2. Cumulative Survival (until Liver Transplantation or Death) among Interferon-Treated Patients (Solid Lines) and Untreated Patients (Dashed Lines) Who Were HBeAg-Negative at the End of Follow-up, with the Time to HBeAg Seroconversion Subtracted from the Observation Time, and among Patients Who Had Not Yet Lost HBeAg, with HBeAg Seroconversion as a Reason for Censoring Data.

Survival was significantly longer among the patients in whom HBeAg was eliminated after interferon therapy than among those who did not have clearance ( $P = 0.004$  by the proportional-hazards model). Survival did not differ significantly between the patients who had spontaneous elimination of HBeAg and those who did not ( $P = 0.091$ ).



NO. UNDER OBSERVATION		0	12	24	36	48	60	72	84	96
Treated	103	101	85	74	58	35	17	5	0	0
Untreated	53	52	35	22	15	11	5	2	0	0

Figure 1. Cumulative Clearance of HBeAg, HBV DNA, and HBsAg and Normalization of Alanine Aminotransferase Levels, Calculated by the Kaplan–Meier Method, in 103 Patients with Chronic Hepatitis B Treated with Interferon Alfa (Solid Lines) and 53 Untreated Patients (Dashed Lines).

not ( $P = 0.004$  for survival and  $P = 0.018$  for survival without clinical complications, according to the proportional-hazards model) (Fig. 2 and 3 and Table 1). Multivariate analysis showed that, in addition to HBeAg seroconversion, age and, to a minor degree, preexisting cirrhosis and base-line alanine aminotransferase levels affected the occurrence of clinical complications (Table 1).

Thirteen of the 53 control patients had severe clinical complications; none of these 13 patients had spontaneous elimination of HBeAg. Ascites developed in two patients; jaundice and encephalopathy in one; and jaundice, encephalopathy, and esophageal varices in one. Four patients had only esophageal varices, and bleeding from the varices occurred in three of them during follow-up. Four patients died, and one needed liver transplantation. Three of the four deaths were caused by cirrhosis, and one by suicide. Survival without clinical complications was significantly longer in patients who spontaneously cleared HBeAg than in those who did not ( $P = 0.006$  by the proportional-hazards model) (Fig. 3). Although all deaths and liver transplantations occurred in patients who did not have spontaneous elimination of HBeAg, survival did not differ significantly between the untreated patients in whom spontaneous elimination of HBeAg occurred and those in whom HBeAg remained present, probably because of

**Table 1. Adjusted Relative Risk of Clinical Complications in 103 Patients Treated with Interferon Alfa for Chronic Hepatitis B, According to Demographic and Clinical Characteristics.\***

VARIABLE	ADJUSTED RELATIVE RISK (95% CI)	P VALUE
HBeAg seroconversion	0.06 (0.01–0.61)	0.02
Age (per decade)	1.75 (1.09–2.79)	0.02
Alanine aminotransferase (per 10 U/liter)	0.81 (0.65–1.01)	0.06
Cirrhosis	2.90 (0.96–8.77)	0.06
Duration of hepatitis (per yr)	0.93 (0.76–1.13)	0.44
Male sex	0.59 (0.14–2.46)	0.47
HBV DNA (per 25 pg/ml)	1.00 (0.90–1.10)	0.99

\*Clinical complications included the following events: death; need for liver transplantation; development of ascites, jaundice, or hepatic encephalopathy; and the occurrence of, or bleeding from, esophageal varices. Relative risk is expressed as the risk of complications among the patients with the risk factor in question as compared with those without the risk factor. For age, alanine aminotransferase, duration of hepatitis, and HBV DNA, relative risks are for each increment shown in the variable. CI denotes confidence interval.

the low number of events ( $P=0.091$  by the proportional-hazards model) (Fig. 2).

#### Factors Predicting Seroconversion after Interferon Therapy

Patients in whom HBeAg was eliminated after interferon therapy had significantly lower levels of HBV DNA (by dot blot hybridization) and higher levels of alanine aminotransferase than patients who remained positive for HBeAg, according to the proportional-hazards model (Table 2). In contrast, there were no significant differences between the two groups in the duration of hepatitis, age, sex, or the presence or absence of preexisting cirrhosis (Table 2). In untreated patients, none of the base-line prognostic factors predicted seroconversion, although the level of HBV DNA was higher and the level of alanine aminotransferase was lower in patients who did not spontaneously eliminate HBeAg than in those who did (Table 2).

#### DISCUSSION

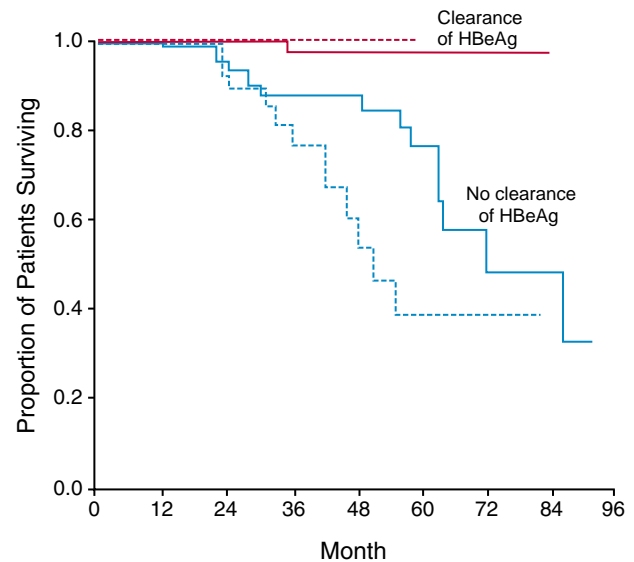
Although controlled clinical trials have proved that therapy with interferon alfa reduces the levels of laboratory markers of viral replication and inflammatory activity in patients with chronic hepatitis B,<sup>1-5</sup> to our knowledge there are only three studies on the long-term outcome in these patients.<sup>8-10</sup> Two of these studies<sup>8,9</sup> did not follow patients with no response to therapy, and none of the studies reported data on the clinical outcome. Our study prospectively evaluated the clinical outcomes of a cohort of patients with chronic hepatitis B who were treated with interferon alfa. A cohort of untreated patients served as controls. We collected complete clinical data on all patients, none of whom were lost to follow-up. Only a few patients underwent liver biopsy during follow-up, because it was considered unethical to perform biopsies in patients who did not have evidence of liver disease according to clinical or laboratory criteria.

Our results show that patients who were successfully

treated with interferon alfa, as indicated by the clearance of HBeAg and HBV DNA (on dot blot hybridization), had a better long-term clinical outcome than those in whom these markers of viral replication persisted. The frequency of death, liver transplantation, and severe clinical complications due to cirrhosis was significantly lower among the patients with elimination of HBeAg than among those with persistence of HBeAg. Our data thus provide further evidence of a benefit of interferon alfa in patients with chronic hepatitis B and may also be used in cost-benefit and cost-effectiveness analyses.

The frequency of pretreatment cirrhosis was similar in patients who had a response to interferon therapy and in those who did not. Thus, the presence or absence of preexisting cirrhosis did not affect the response to interferon.

Seroconversion with respect to HBeAg was the most important prognostic factor. None of the patients with clearance of HBeAg had severe clinical complications, needed liver transplantation, or died during or shortly after interferon therapy. Such complications during interferon treatment have been reported in particular for patients with advanced cirrhosis (Child-Pugh class B or C),<sup>14</sup> who were excluded from our study. Thus, our data strongly suggest that interferon therapy improves



**Figure 3. Cumulative Survival without Complications among Interferon-Treated Patients (Solid Lines) and Untreated Patients (Dashed Lines) Who Were HBeAg-Negative at the End of Follow-up, with the Time until HBeAg Seroconversion Subtracted from the Observation Time, and among Patients Who Had Not Yet Lost HBeAg, with HBeAg Seroconversion as a Reason for Censoring Data.**

Survival was significantly longer among the patients in whom HBeAg was eliminated after interferon therapy than among those who did not have clearance ( $P=0.018$  by the proportional-hazards model). In the control group, survival was significantly longer among the patients who had spontaneous elimination of HBeAg than among those who did not ( $P=0.006$ ).

Table 2. Characteristics of Patients with or without Loss of HBeAg in the Treatment and Control Groups.\*

VARIABLE	INTERFERON-TREATED GROUP (N = 103)			CONTROL GROUP (N = 53)		
	LOSS OF HBeAg	NO LOSS OF HBeAg	P VALUE	LOSS OF HBeAg	NO LOSS OF HBeAg	P VALUE
HBV DNA (pg/ml)	88.2±8.8	280.8±25.2	<0.001	74.9±18.7	151.0±23.3	0.28
Alanine aminotransferase (U/liter)	143.3±13.1	81.3±6.4	<0.001	125.3±27.9	105.1±10.4	0.60
Duration of hepatitis (yr)	4.77±0.37	4.84±0.46	0.68	3.43±0.37	3.83±0.31	0.78
Age (yr)	39.6±1.6	39.9±1.9	0.53	40.0±1.65	42.8±1.94	0.63
Sex (no. of patients)			0.30			0.27
Male	40	40		4	38	
Female	13	10		3	8	
Preexisting cirrhosis (no. of patients)			0.08			0.46
Yes	17	10		1	15	
No	36	40		6	31	

\*Plus-minus values are means ±SE. A proportional-hazards model in which HBeAg seroconversion was the outcome event was used to evaluate the value of these factors in predicting seroconversion.

the clinical outcome of patients with chronic hepatitis B, probably even in the presence of cirrhosis.

Our conclusions about the clinical benefit of the interferon-induced elimination of markers of viral replication are supported by the results of previous studies of the natural history of chronic hepatitis B.<sup>15-18</sup> Both our findings and those results show that the spontaneous clearance of HBeAg is associated with an improvement in the clinical outcome of untreated patients. However, the rate of spontaneous HBeAg seroconversion was rather low in our series, even after several years of follow-up. Our cohort of untreated patients does not represent a randomized control group, and therefore the differences between treated and untreated patients need to be interpreted cautiously. Nevertheless, the rates of elimination of HBeAg, HBsAg, and HBV DNA, as well as of the normalization of alanine aminotransferase levels, were markedly higher among the interferon-treated patients than among the untreated patients. Similar results have been reported in randomized trials,<sup>1-7,12</sup> most of which, however, had a considerably shorter follow-up than our study. In previous studies, continued viral replication (persistent HBeAg) was associated with substantial mortality and morbidity during approximately five years of follow-up, with numbers similar to those reported here.<sup>17,18</sup> The benefit to patients in whom HBeAg was cleared after interferon therapy could be due to a selection bias, however, and not to interferon therapy. There is no experimental or epidemiologic support for this hypothesis, but the issue cannot be definitely settled, because it would be unethical to withhold long-term treatment with interferon alfa from patients with chronic hepatitis B. Thus, for comparisons, we have to rely on data from patients who remained untreated for a variety of reasons and on data about the natural history of chronic hepatitis B before interferon therapy became available.<sup>15-18</sup> Nevertheless, both types of data support the hypothesis that treatment with interferon improves the

clinical outcome, so long as it eliminates HBeAg.

Our study confirmed that patients who had a response to interferon therapy had significantly higher levels of inflammatory activity (determined by alanine aminotransferase level) and lower viral replication (determined by HBV DNA level) before treatment than patients who did not have a response.<sup>7,19,20</sup> The two groups did not differ in other characteristics, including the frequency of preexisting cirrhosis.

In our study, only a small percentage of patients who had clearance of HBeAg also lost HBsAg during follow-up ranging up to more than seven years. Three long-term studies

dealing with this issue have produced controversial results.<sup>8-10</sup> In a U.S. study, 23 percent of all interferon-treated patients and 65 percent of those in whom HBeAg was eliminated had clearance of HBsAg, sometimes years after the elimination of HBeAg.<sup>8</sup> A study from China reported loss of HBsAg in 1.6 percent of all interferon-treated patients and in 6.9 percent of those in whom HBeAg was eliminated.<sup>10</sup> The corresponding rates for a study from Spain were 8.5 and 25.0 percent.<sup>9</sup> Our results are similar to those from Spain. This is somewhat surprising, because interferon treatment is usually more successful in patients who acquire the infection later in life,<sup>7,19,20</sup> and most German patients acquire hepatitis B as adults, whereas in southern Europe, because of the high prevalence of hepatitis B, a considerable number of infections occur perinatally or during childhood. In accordance with previous reports, all our patients who lost HBsAg also lost HBV DNA (as assessed by PCR). One might speculate that during further follow-up, additional patients would clear HBsAg. In any case, the clinical outcome was markedly improved in the patients treated with interferon alfa, even though the majority did not have clearance of HBsAg.

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#### IMAGES IN CLINICAL MEDICINE

Images in Clinical Medicine, a weekly *Journal* feature, presents clinically important visual images, emphasizing those a doctor might encounter in an average day at the office, the emergency department, or the hospital. If you have an original unpublished, high-quality color or black-and-white photograph representing such a typical image that you would like considered for publication, send it with a descriptive legend to Kim Eagle, M.D., University of Michigan Medical Center, Division of Cardiology, 3910 Taubman Center, Box 0366, 1500 East Medical Center Drive, Ann Arbor, MI 48109. For details about the size and labeling of the photographs, the requirements for the legend, and authorship, please contact Dr. Eagle at 313-936-4819 (phone) or 313-936-5256 (fax), or the *New England Journal of Medicine* at [images@edit.nejm.org](mailto:images@edit.nejm.org) (e-mail).