# HBV Genotype B Is Associated With Better Response to Interferon Therapy in HBeAg(+) Chronic Hepatitis Than Genotype C

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**Hepatitis B virus (HBV) genotype and precore/core promoter mutations have been implicated in spontaneous and interferon alfa (IFN-α)–related hepatitis B e antigen (HBeAg) seroconversion. We performed a retrospective analysis of a previously reported randomized controlled trial to determine the effects of HBV genotype and precore/core promoter mutations on IFN-α response in patients with HBeAg-positive chronic hepatitis. Clinical data and stored sera from 109 (95%) patients in the original trial were analyzed. Seventy-three patients received IFN-α and 34 received no treatment (controls). Almost all patients had HBV genotypes B (38%) and C (60%). Antiviral response was achieved in 39% and 17% of IFN-α–treated patients ($P = .03$) and in 10% and 8% of untreated controls ($P = .88$) with HBV genotype B and C, respectively. Multivariate analysis identified HBV genotype B, elevated pretreatment alanine aminotransferase (ALT) levels, and low pretreatment HBV-DNA levels but not IFN-α treatment as independent factors associated with antiviral response. Among the 66 patients with elevated pretreatment ALT level, antiviral response was achieved in 57% and 21% of IFN-α–treated patients ($P = .019$), and in 25% and 8% of untreated controls ($P = .45$) with HBV genotype B and C, respectively. Multivariate analysis showed that genotype B and low pretreatment HBV-DNA levels were independent predictors of antiviral response. In conclusion, our data showed that HBV genotype B was associated with a higher rate of IFN-induced HBeAg clearance compared with genotype C. Stratification for HBV genotypes should be considered in future clinical trials of antiviral therapy of chronic hepatitis B.** (HEPATOLOGY 2002;36:1425-1430.)

Interferon alfa (IFN-α) and lamivudine are the 2 currently approved treatments for chronic hepatitis B (CHB) in most countries.[1] Both agents have limited long-term efficacy. IFN-α is associated with significant adverse effects, whereas long-term therapy with lamivudine may result in drug resistance. Thus, optimal patient selection for treatment is important. High pretreatment alanine aminotransferase (ALT) levels have been found to be the most important predictor of response to both IFN-α and lamivudine therapy.[2-4] Low pretreatment serum hepatitis B virus (HBV)-DNA levels also have been shown to be a predictor of response in many studies on IFN-α therapy.[2,3]

Recently, HBV genotypes and precore and core promoter variants have been implicated in spontaneous hepatitis B e antigen (HBeAg) seroconversion as well as response to antiviral treatment. HBV can be classified into 7 genotypes (A to G).[5] Genotype A is more common in North America and northwestern Europe; genotypes B and C are mainly found in Asia; genotype D is predominant in the Mediterranean area, Middle East, and India; whereas the distribution of genotypes E, F, and G is less well studied.[6] Genotype A was found to be associated with a higher rate of IFN-α–induced HBeAg seroconversion than genotype D (37% vs. 6%, $P = .03$) in a study of 64 German patients with HBeAg-positive CHB.[7] Another study of 58 Taiwanese patients who received IFN-α treatment for HBeAg-positive CHB found that patients with

*Abbreviations: IFN-α, inteferon alfa; CHB, chronic hepatitis B; ALT, alanine aminotransferase; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; OR, odds ratio; CI, confidence interval.*

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genotype B had a significantly higher rate of HBeAg loss compared with those with genotype C (41% vs. 15%, $P = .045$).[8] In the German study, a high number of mutations in the core promoter region and pretreatment HBV-DNA level of less than 10 pg/mL also were associated with better response whereas in the Taiwan study, younger age was the only other factor associated with a higher rate of response. Both studies did not include an untreated group. Thus, it is not clear if IFN-$\alpha$ treatment had an incremental effect on HBeAg seroconversion when HBV genotype was controlled for.

The 2 most well-defined, naturally occurring HBV mutations are the point mutation in the precore region ($G_{1896}A$), creating a stop at codon 28, and the dual mutation $A_{1762}T/G_{1764}A$ at the basic core promoter region.[9] Precore and core promoter mutations have been found to precede or emerge at the time of HBeAg seroconversion and to affect response to IFN-$\alpha$ therapy. In previous studies using direct sequencing, we showed that HBeAg-positive patients with detectable precore and core promoter mutations were more likely to undergo spontaneous HBeAg clearance.[10] Presence of precore mutations also was associated with a higher rate of response to IFN-$\alpha$ therapy (55% vs. 17%, $P = .04$) as compared with those without precore mutations.[11] However, other studies involving a smaller number of patients showed that the rate of IFN-$\alpha$–induced HBeAg seroconversion was not related to presence of precore stop codon mutations.[12,13] Two studies, one involving German and another involving Chinese patients, found that presence of core promoter mutations was associated with a higher rate of IFN-$\alpha$–induced HBeAg loss, whereas a third study from Germany failed to confirm this finding.[7,14,15] These conflicting results may be caused by differences in patient characteristics, pretreatment ALT levels, and other virologic factors such as HBV genotypes. Almost all the earlier-mentioned studies included small numbers of patients and examined only a few potential predictors. Thus, further studies involving a larger number of patients are needed to identify independent predictors of response to IFN-$\alpha$ treatment. In addition, a parallel control group should be included to determine if IFN-$\alpha$ has any incremental benefit when baseline factors are controlled.

The effect of HBV genotype on response to nucleos(t)ide analogues is less clear because few studies have been reported to date. Of 43 (33 HBeAg positive and 10 HBeAg negative) CHB patients treated with lamivudine, those with ayw subtype had a trend toward better virologic and biochemical response than those with adw subtype.[16] In another study on 31 HBeAg-positive CHB patients treated with lamivudine, no significant difference in HBeAg seroconversion was seen in patients with HBV genotype B or C.[17] Finally, a recent study of 1,032 CHB (both HBeAg positive and negative) patients treated with adefovir dipivoxil showed no difference in viral load reduction after 48 weeks of treatment.[18]

We performed a retrospective analysis of a previously reported randomized controlled trial to determine the effects of HBV genotype, precore/core promoter mutations, as well as demographic factors and pretreatment ALT and HBV-DNA levels, on IFN-$\alpha$ response in Chinese patients with HBeAg-positive CHB.

## Patients and Methods

***Patients.*** Clinical data and stored sera from a placebo-controlled trial comparing IFN-$\alpha$ with and without prednisone versus placebo were studied.[19] All patients were ethnic Chinese with the presence of hepatitis B surface antigen in serum for more than 6 months, and detectable HBeAg and serum HBV DNA (by direct spot hybridization). They were randomized to receive IFN-$\alpha$ with prednisone priming, IFN-$\alpha$ only, or no treatment (controls). Prednisone priming was given orally in daily doses of 45, 30, and 15 mg each for 2 weeks, followed by a 2-week rest before administration of IFN-$\alpha$. Interferon $\alpha$-2b (Intron A; Schering Plough, Kenilworth, NJ) was administered subcutaneously for 16 weeks in doses of 10 MU 3 times weekly. Liver biopsies were performed within 6 months of entry and again at month 12. Antiviral response was defined as sustained clearance of serum HBV DNA by direct spot hybridization (lower limit of detection of 10 pg/mL) and clearance of HBeAg at month 12.

***Serologic Testing.*** Hepatitis B serologic markers: hepatitis B surface antigen, HBeAg, and hepatitis B e antibody were tested by using commercially available enzyme-linked immunosorbent assay kits from Abbott Laboratories (North Chicago, IL).

***HBV Genotype, Precore, and Core Promoter Mutations.*** Residual sera collected within 6 months before entry, which were stored at −70°C, were retrieved. HBV genotypes, precore ($G_{1896}A$) and core promoter ($A_{1762}T$ and $G_{1764}A$) mutations, were determined by line-probe assay (Inno-Lipa, Innogenetics Inc., Ghent, Belgium) as described previously.[20] Comparison of the results of the line-probe assay and direct sequencing showed a concordance rate of 100% for HBV genotypes and greater than 95% for precore and core promoter mutations.[21,22]

***Quantification of HBV DNA.*** Serum HBV-DNA level was quantified by a polymerase chain reaction assay with a lower limit of detection of 200 copies/mL and a linearity range of $2 \times 10^2$ to $2 \times 10^5$ copies/mL (Cobas Amplicor HBV Monitor, Roche Diagnostic Systems,

**Table 1. Demographic and Clinical Characteristics of Patients With or Without IFN Treatment**

| | Controls (n = 34) | IFN-α + Prednisone Priming (n = 36) | IFN-α No Prednisone Priming (n = 39) | IFN-α Combined (n = 75) |
|---|---|---|---|---|
| Age, yr | 29 ± 1 | 30 ± 1 | 30 ± 1 | 30 ± 1 |
| Sex: Male | 20 (59%) | 24 (67%) | 25 (64%) | 49 (66%) |
| Pretreatment ALT level, U/L | 82 ± 14 | 103 ± 15 | 133 ± 25 | 118 ± 15 |
| No. with elevated pretreatment ALT | 16 (47%) | 25 (69%) | 27 (69%) | 52 (69%)* |
| Pretreatment HBV DNA, $\log_{10}$ copies/mL | 8.96 ± 0.17 | 8.56 ± 0.18 | 8.63 ± 0.20 | 8.59 ± 0.14 |
| Pretreatment histology showing cirrhosis | 4 (12%) | 3 (8%) | 5 (13%) | 8 (11%) |
| Genotype | | | | |
| B | 10 (29%) | 17 (47%) | 14 (36%) | 31 (41%) |
| C | 24 (71%) | 17 (47%) | 25 (64%) | 42 (56%) |
| D | 0 | 2 (6%) | 0 | 2 (3%) |
| Precore mutation | | | | |
| $G_{1896}A$ | 6 (18%) | 16 (44%) | 13 (33%) | 29 (39%)† |
| $G_{1898}A$ | 1 (3%) | 0 | 0 | 0 |
| Core promoter mutation | | | | |
| $A_{1762}T$, $G_{1764}A$ | 12 (35%) | 12 (33%) | 15 (39%) | 27 (36%) |
| Deletion | 2 (6%) | 1 (1%) | 0 | 1 (1%) |
| Single mutation ($A_{1762}T$ or $G_{1764}A$) | 0 | 2 (3%) | 0 | 2 (3%) |
| Antiviral response | 3 (9%) | 11 (31%) | 10 (26%) | 21 (28%)‡ |

Comparisons between IFN-treated patients and controls:
*$P$ = .033.
†$P$ = .038.
‡$P$ = .064.

Inc., Pleasanton, CA). All samples were prediluted up to $10^6$ times. A 100,000-fold dilution was used for the initial testing of all samples as recommended by the manufacturer's manual. Retesting with either a higher or lower dilution was performed when results of the initial testing were out of the range of linearity of the assay.

***Statistical Analysis.*** Results were expressed as mean ± standard error of mean. Data were analyzed by using SPSS version 10.0 software package (SPSS Inc., Chicago, IL). Categoric variables were compared by the $\chi^2$ test. Continuous variables were compared by the Student's $t$ test. Multivariate analysis using stepwise logistic regression was performed to identify independent factors associated with IFN-α response. Results were considered statistically significant at $P < .05$.

## Results

***Patient Characteristics.*** Sera collected within 6 months before entry were successfully retrieved in 109 (95%) of the original 115 patients. Among these 109 patients, 75 (69%) were treated with IFN-α (36 with and 39 without prednisone priming), 12 (11%) had cirrhosis on biopsy at entry, and 68 (62%) had elevated ALT levels at baseline. Twenty-four (22%) patients had an antiviral response. Demographic and clinical characteristics of IFN-α–treated patients and controls are shown in Table 1. Because the rates of antiviral response in the 2 IFN-α treatment arms were similar,[19] these 2 groups were combined in the subsequent analysis.

***HBV Genotype, Precore, and Core Promoter Mutations.*** Forty-one (38%) patients had genotype B, 66 (60%) had genotype C, and 2 (2%) had genotype D. Thirty-five (32%) patients had precore stop codon ($G_{1896}A$) mutation. Of these, 23 had predominant wide-type precore sequence, 6 had an equal mix of wide-type and variant sequence, and 6 had predominant variant sequence. Thirty-nine (36%) patients had dual core promoter ($A_{1762}T$ and $G_{1764}A$) mutations. Of these, 8 had predominant wide-type core promoter sequence, 21 had an equal mix of wide-type and variant sequence, and 10 had predominant variant sequence.

***Comparison Between Genotype B and C Patients.*** At entry, the 2 groups were comparable in age, and pretreatment HBV-DNA and ALT levels, but patients with genotype B had a higher prevalence of precore and a lower prevalence of core promoter mutations (Table 2). The gender distribution in the 2 groups also was different, being equal among patients with genotype B and male predominant among patients with genotype C.

Patients with HBV genotype B had a significantly higher rate of antiviral response to IFN-α, 39% versus 17% among patients with genotype C ($P$ = .03) (Table 2).

***Factors Associated With HBeAg Clearance.*** Factors associated with HBeAg clearance within 12 months of entry into the study among the 107 patients with genotype B and C were analyzed. HBV genotype B, elevated pretreatment ALT level, low pretreatment HBV-DNA level, and treatment with IFN-α were found to be significant

**Table 2. Comparison of Patients With HBV Genotype B and C**

| | Genotype B (n = 41) | Genotype C (n = 66) | P |
|---|---|---|---|
| Age, yr | 30 ± 1 | 29 ± 1 | NS |
| Sex: male | 21 (51%) | 47 (71%) | .042 |
| Pretreatment ALT, U/L | 86 ± 11 | 120 ± 17 | .08 |
| No. with elevated pretreatment ALT level | 25 (61%) | 41 (62%) | NS |
| Pretreatment HBV DNA, $log_{10}$ copies/mL | 8.85 ± 0.16 | 8.60 ± 0.14 | NS |
| Pretreatment histology showing cirrhosis | 4 (10%) | 8 (12%) | NS |
| Precore $G_{1896}A$ mutation | 18 (44%) | 15 (23%) | .041 |
| Core promoter $A_{1762}T$, $G_{1764}A$ mutation | 5 (12%) | 33 (50%) | <.001 |
| Treatment with IFN-α | 31 (76%) | 42 (64%) | NS |
| Antiviral response | 13 (32%) | 9 (14%) | .029 |
| IFN-α treatment | 12/31 (39%) | 7/42 (17%) | .034 |
| No treatment | 1/10 (10%) | 2/24 (8%) | NS |

Abbreviation: NS, not significant.

**Table 4. Univariate Analysis of Factors Associated With Antiviral Response Among Patients Treated With IFN**

| | Responder (n = 19) | Nonresponder (n = 54) | P |
|---|---|---|---|
| Age, yr | 31 ± 1 | 29 ± 1 | .32 |
| Sex: male | 14 (74%) | 34 (63%) | .58 |
| Pretreatment ALT level, U/L | 151 ± 22 | 107 ± 19 | .20 |
| No. with elevated pretreatment ALT level | 18 (95%) | 32 (59%) | .004 |
| Pretreatment HBV DNA, $log_{10}$ copies/mL | 7.86 ± 0.38 | 8.82 ± 0.12 | .002 |
| Pretreatment histology showing cirrhosis | 1 (5%) | 7 (13%) | .67 |
| Genotype | | | |
| B | 12 (63%) | 19 (35%) | .057 |
| C | 7 (37%) | 35 (65%) | |
| Precore $G_{1896}A$ mutation | 10 (53%) | 17 (32%) | .17 |
| Core promoter $A_{1762}T$, $G_{1764}A$ mutation | 7 (37%) | 19 (35%) | .92 |
| Prednisone priming | 9 (48%) | 25 (47%) | 1.00 |

predictors of HBeAg clearance in univariate analysis (Table 3). Multivariate analysis with stepwise logistic regression identified HBV genotype B (odds ratio [OR], 1.28; 95% confidence interval [CI], 1.06-1.42; $P = .006$), low pretreatment HBV-DNA level (OR, 1.10; 95% CI, 1.03-1.17; $P = .007$), and elevated pretreatment ALT level (OR, 1.22; 95% CI, 1.05-1.42; $P = .011$), but not IFN-α treatment as independent factors associated with HBeAg clearance.

Among the 75 patients who were treated with IFN-α, low pretreatment HBV-DNA, and elevated pretreatment ALT levels were significant predictors of antiviral response in univariate analysis whereas HBV genotype B was borderline significant (Table 4). All 3 factors were found to be significant predictors of antiviral response in multivariate analysis.

***Patients With Elevated Pretreatment ALT Levels.*** Of the 66 patients with elevated pretreatment ALT levels, 20 (30%) had HBeAg clearance. Antiviral response was achieved in 57% and 21% of IFN-α–treated patients ($P = .019$), and in 25% and 8% of untreated controls ($P = .45$) with HBV genotype B and C, respectively (Fig. 1). Multivariate analysis showed that genotype B (OR, 1.47; 95% CI, 1.18-1.82; $P = .001$) and low pretreatment HBV-DNA level (OR, 1.10; 95% CI, 1.01-1.21; $P = .029$) were independent predictors of HBeAg clearance.

***Patients With Normal Pretreatment ALT Levels.*** Antiviral response was uniformly low among the 41 patients with normal ALT levels. None of the 16 patients

**Table 3. Univariate Analysis of Factors Associated With HBeAg Clearance Among All Patients**

| | HBeAg Clearance (n = 19) | No HBeAg Clearance (n = 54) | P |
|---|---|---|---|
| Age, yr | 30 ± 1 | 29 ± 1 | .22 |
| Sex: male | 16 (73%) | 52 (61%) | .46 |
| Pretreatment ALT level, U/L | 146 ± 20 | 97 ± 13 | .049 |
| No. with elevated pretreatment ALT level | 20 (91%) | 46 (54%) | .001 |
| Pretreatment HBV DNA, $log_{10}$ copies/mL | 8.04 ± 0.34 | 8.86 ± 0.09 | .030 |
| Pretreatment histology showing cirrhosis | 2 (10%) | 10 (12%) | 1.00 |
| Genotype | | | .029 |
| B | 13 (59%) | 28 (33%) | |
| C | 9 (41%) | 57 (67%) | |
| Precore $G_{1896}A$ mutation | 11 (50%) | 22 (26%) | .059 |
| Core promoter $A_{1762}T$, $G_{1764}A$ mutation | 9 (41%) | 29 (34%) | .73 |
| Treatment with IFN-α | 19 (86%) | 54 (64%) | .044 |

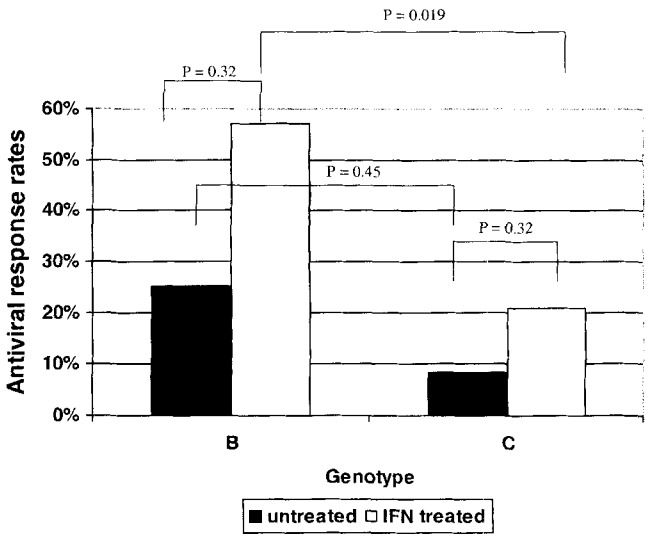


Fig. 1. Antiviral response rates in patients with elevated ALT levels in HBV genotypes B and C. ■, untreated; □, IFN treated.

with genotype B (10 IFN-α treated and 6 controls), and only 2 of the 25 patients with genotype C (1 of 13 IFN-α treated and 1 of 12 controls) had an antiviral response.

## Discussion

Our study confirmed a previous report from Taiwan[8] that HBV genotype B is associated with a higher rate of antiviral response to IFN-α treatment than HBV genotype C among Chinese patients with HBeAg-positive CHB. The absence of a control group in the Taiwan study and the finding of a higher rate of spontaneous HBeAg seroconversion in patients with genotype B,[20] raise questions as to whether the better response in patients with genotype B is attributed to the IFN-α treatment. In this study, IFN-α treatment increased the antiviral response in patients with both genotype B (39% vs. 10%) and C (17% vs. 8%), compared with untreated patients with the same genotype, but these differences did not reach statistical significance. The lack of statistical significance between treated patients and controls may be related to the small sample size. However, multivariate analysis with stepwise logistic regression identified HBV genotype B and not IFN-α treatment as an independent factor predictive of antiviral response, suggesting that the additional benefit of IFN-α treatment is small in patients who are likely to undergo spontaneous HBeAg seroconversion.

We found that the presence of precore stop codon mutation at entry was associated with a higher rate of antiviral response on univariate analysis. This is in accord with our previous analysis using a less sensitive technique—direct sequencing—to detect the precore stop codon mutation.[11] Direct sequencing is unable to identify minor amounts of variant viruses in a background of wild-type sequences.[23] The use of a line-probe assay increases the sensitivity of detection of precore variants, which explains the higher rate of precore stop codon mutation detected in this study (32%) than in our previous study (7%). Precore stop codon mutation usually is selected around the time of HBeAg seroconversion. Thus, HBeAg-positive patients with detectable precore stop codon mutation may be on the verge of spontaneous HBeAg seroconversion. Whether IFN-α treatment hastened this process is unclear. Precore stop codon mutation was not an independent factor predictive of antiviral response on multivariant analysis. This may be related to the association between precore stop codon mutation and HBV genotype B, with the latter being a more important factor. Alternatively, precore stop codon variant, when present as a minor species, is less predictive of imminent HBeAg seroconversion than when it is present as the predominant viral species. In this study, presence of the dual core promoter mutation at entry was not related to antiviral response. Although our study is larger than previous studies, the role of core promoter mutation on response to IFN-α and other antiviral therapy should be further examined.

We confirmed that elevated pretreatment ALT and low pretreatment HBV-DNA levels were independent predictors of antiviral response.[2,3] Elevated pretreatment ALT level also was found to be the most important predictive factor of response to lamivudine treatment among patients with HBeAg-positive CHB.[4] Our results support recommendations from the American Association for the Study of Liver Diseases and the Asian Pacific Association for the Study of the Liver that patients with normal pretreatment ALT levels should not be treated because the response to currently available treatment is poor.[24,25]

In summary, our study showed that in addition to low pretreatment HBV DNA and elevated pretreatment ALT levels, HBV genotype B was associated with a higher rate of antiviral response to IFN-α treatment in Chinese patients with HBeAg-positive CHB than genotype C. Further studies are needed to determine if HBV genotype also plays a role in response to IFN-α treatment in chronic hepatitis B patients from other geographic regions where other HBV genotypes prevail. More importantly, the role of HBV genotypes in response to nucleos(t)ide treatment of HBeAg-positive as well as HBeAg-negative CHB should be examined. Careful analysis of these data may lead to better selection of CHB patients for antiviral treatment and possibly development of therapeutic regimens tailored to viral genotype as in the case of hepatitis C.

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