HEPATITIS

Response to interferon alfa is hepatitis B virus genotype dependent: genotype A is more sensitive to interferon than genotype D

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Gut 2005;54:1009–1013. doi: 10.1136/gut.2004.060327

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Revised version received 20 February 2005
Accepted for publication 9 March 2005

Background and aims: Current interferon alfa (IFN) treatment of chronic hepatitis B has limited efficacy. The role of hepatitis B virus (HBV) genotypes for response to IFN was investigated.

Patients and methods: HBV genotype was determined by direct sequencing of the HBV X gene in 165 consecutive patients with chronic replicative hepatitis B treated with standard IFN. HBV genotype A or D was found in 144 cases.

Results: Sustained response (six months after treatment) to standard IFN therapy was higher in HBV genotype A compared with HBV genotype D infected patients (49% v 26%; $p < 0.005$). Sustained response to IFN was 46% versus 24% ($p < 0.03$) in hepatitis B e antigen (HBeAg) positive hepatitis (n = 99) and 59% versus 29% ($p < 0.05$) in HBeAg negative hepatitis (n = 45) for HBV genotype A compared with HBV genotype D. HBeAg status had no negative impact on IFN response. Multivariate logistic regression identified HBV genotype A and high pretreatment alanine aminotransferase levels ($> 2 \times$ upper limit of normal) as independent positive predictive parameters of IFN response.

Conclusions: The present study indicates that HBV genotypes A and D are important and independent predictors of IFN responsiveness in chronic hepatitis B. HBV genotype adapted treatment regimens may further improve treatment efficacy in chronic hepatitis B.

Chronic hepatitis B affects approximately 360 million persons worldwide.^{1–2} Interferon alfa (IFN) and nucleos(t)ide analogues are the currently approved treatments for chronic hepatitis B.³ Hepatitis B e antigen (HBeAg) seroconversion is associated with increased survival in patients with chronic hepatitis B.⁴ However, HBeAg seroconversion is only achieved in 30–40% of HBeAg positive patients using standard interferon therapy. Treatment of HBeAg negative hepatitis B apparently gives even poorer sustained responses.⁵ Treatment regimens with nucleos(t)ide analogues have not proved superior to IFN treatment.

Alanine aminotransferase (ALT) levels, HBV-DNA titres, and degree of liver inflammation have been associated with prediction of IFN response in chronic HBV infection.^{4–6} However, the immunological disposition of the host and genetic factors of the virus itself may be major determinants of IFN response.^{7–8} Virus genotypes are strongly related to IFN response in chronic hepatitis C.^{9–10} Unlike the role of hepatitis C virus genotypes, the role of HBV genotypes on the response to IFN treatment is not as clear.

To date, eight HBV genotypes (A–H) have been identified.^{11–13} HBV genotypes are classified by more than 8% divergence of the full nucleotide sequence.¹⁴ Determination of amino acid variability at amino acids 122 and 160 of the HBV surface protein allows subtyping of HBV. Several mutations in the nucleotide sequence of HBV are associated with specific HBV genotypes such as the precore stop codon mutation (G1896A).^{15–16} The precore mutation that prevents translation of the precore polypeptide and thereby eliminates HBeAg production is particularly found in HBV genotypes B, C, and D.¹⁷

The geographic distribution of HBV genotypes varies significantly.¹³ HBV genotype A is common in Northern Europe and North America whereas HBV genotype D is found mainly in the Mediterranean area, Middle East, and India. HBV genotypes B and C are frequent in Asia. HBV genotype E

has mainly been found in West Africa and South Africa and HBV genotype F in South America and Central America. Geographic distribution of HBV genotypes G and H is less well studied; both HBV genotypes seem to be rare in Europe.

The aim of the present study was to investigate the role of HBV genotypes in a large cohort of patients with chronic hepatitis B for response to standard IFN treatment.

PATIENTS AND METHODS

A total of 165 consecutive patients seen between 1988 and 2002 with chronic hepatitis B were investigated. Among these, 119 patients (72%) had HBeAg positive and 46 (28%) HBeAg negative hepatitis B infection. None of the patients had markers of hepatitis D virus (HDV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) infection. Markers of HBV, HCV, and HIV (hepatitis B surface antigen, antibody to hepatitis B surface antigen, antibody to hepatitis B core antigen, HBeAg, antibody to hepatitis B e antigen, anti-HDV, anti-HCV, and anti-HIV) were tested by commercial immunoassays. All patients were HBV DNA positive. HBV DNA was measured by a commercial hybridisation assay (Digene 2.0; Murex Diagnostika, Burgwedel, Germany). The detection limit of the quantitative HBV DNA assay was 2.5 pg/ml. Ninety six per cent of patients (159/166) had elevated ALT levels.

Patients had received 3×4.5 –10 million units (MU) or 7×4.5 MU of IFN- $\alpha 2b$ or IFN- $\alpha 2a$ weekly for at least four months (range 4–15 months). The vast majority of patients (92.5%) had received 3×4.5 –6 MU IFN- α weekly. A daily

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; IFN- α , interferon alfa; ETR, end of treatment response; SR-6, sustained response six months post treatment; SR-12, sustained response 12 months post treatment; HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase; ULN, upper limit of normal

Table 1 Hepatitis B virus (HBV) genotype distribution according to hepatitis B e antigen (HBeAg) status

HBV genotype	HBeAg positive (%) (n = 119)	HBeAg negative (%) (n = 46)	All (%) (n = 165)
A	51.4 (61)	37.0 (17)	47.3 (78)
B	5.0 (6)	—	3.6 (6)
C	8.4 (10)	2.2 (1)	6.7 (11)
D	31.9 (38)*	60.8 (28)*	40.0 (66)
E	2.5 (3)	—	1.8 (3)
G	0.8 (1)	—	0.6 (1)

*HBV genotype D distribution between HBeAg negative and HBeAg positive patients was significantly different ($p < 0.01$).

IFN- α schedule was given to 5% of patients and 3×9 –10 MU IFN- α were administered to 2.5% of patients. Distribution of treatment schedules did not differ between HBV genotypes A and D.

For HBeAg positive patients, sustained response was defined as negative HBV-DNA in the hybridisation assay, normalisation of ALT levels, and seroconversion from HBeAg to anti-HBeAg at six months after stopping IFN treatment (SR-6). For HBeAg negative patients, sustained response was defined as persistent loss of HBV-DNA in the hybridisation assay and normalisation of ALT levels at six months after stopping IFN treatment (SR-6). In addition to SR-6, sustained response 12 months after stopping treatment (SR-12) was also determined for HBeAg negative and HBeAg positive patients. Data for the 12 month follow up were available in 142 patients; two patients were lost to follow up. Liver biopsy at the time of IFN treatment was available for 100 of 165 patients (61%). Histological scoring was performed according to Desmet and colleagues.¹⁸ The diagnosis of liver cirrhosis was based on pretreatment liver histology. Data on disease duration were obtained by medical history (date of blood transfusion, needle stick injury, appearance of clinical signs and symptoms such as jaundice, etc).

HBV genotype was determined by direct sequencing of the HBV X gene in all patients, as described previously.⁸ The HBV X gene sequences of patients were compared with HBV databank entries of known HBV genotypes A–H with the following GenBank accession numbers: AB048704, AF160510, AF160501, D00329, D00330, D00331, D00630; D12980, D23677, D23678, D23679, D23684, LAS2523, L08805, L27106, M12906, M32138, M38454, M38605, M54923, M57663, V00866, V00867, V01460, X01587, X02496, X02763, X04615, X52939, X59795, X69798, X75656, X75657, X75658, X75663, X75664, X75665, X97848, Z35716, Z35717. Alignments of DNA sequences were performed with Lasergene Megalign software (DNASTar Inc., Madison, Wisconsin, USA).

Statistical analysis was done using SPSS software (SPSS Inc., Munich, Germany). The Student's t test was used for analysis of continuous variables, the Mann-Whitney test for non-continuous variables, and the χ^2 test for analysis of categorical variables. Logistic regression models were used to examine the association between HBV genotype and IFN response. A p value < 0.05 was considered significant.

RESULTS

Of 165 patients investigated, 47.3% were infected with HBV genotype A, 40.0% with HBV genotype D, 6.7% with HBV genotype C, 3.6% with HBV genotype B, 1.8% with genotype E, and 0.6% with genotype G. HBV genotypes H and F were not encountered. HBV genotype D was found significantly more often in HBeAg negative hepatitis B than in HBeAg positive hepatitis B ($p < 0.01$) (table 1). HBV genotype A was the predominant HBV genotype in HBeAg positive hepatitis B (table 1). Due to insufficient power, HBV genotypes B, C, E, and G were not included in further statistical analysis.

Baseline HBV-DNA, cumulative IFN dose, and cirrhosis prevalence did not differ significantly between HBV genotypes (table 2). Infection with HBV genotype B or C was characterised by a longer disease duration and a higher rate of females compared with other HBV genotypes. ALT levels

Table 2 Characteristics of patients with chronic hepatitis B according to hepatitis B virus (HBV) genotype*

	Genotype A (n = 78)	Genotype B (n = 6)	Genotype C (n = 11)	Genotype D (n = 66)	Genotype E (n = 3)	All (n = 165)
Origin (%)						
Germany	76	—	9	23	—	46
Mediterranean	6	—	—	63	—	28
Eastern Europe	14	—	—	11	—	11
Asia	—	100	91	3	—	11
Africa	4	—	—	—	100	4
Sex (%)						
Female	13	50	36	26	—	21
Male	87‡	50‡	64	74	100	79
HBeAg positive (%)	78	100	91	58	100	72
Age (y)	47 (7)‡	27 (2)‡	40 (4)	39 (14)‡	27 (2)	47 (7)
Mode of acquisition (%)						
Perinatal	20§	67§	55§	45§	—	34
Sexual	15	16	—	8	100	13
Transfusion	31	—	—	20	—	22
Health care	4	—	9	6	—	5
Other/unknown	30	17	36	21	—	26
Cirrhosis† (%)	27	ND	20	26	ND	25
ALT (U/l)	96 (8)‡	33 (11)‡	104 (33)	82 (10)‡	55 (22)	86 (6)
DNA (pg/ml)	590 (317)	442 (874)	1078 (2072)	459 (135)	507 (597)	580 (212)
Cumulative IFN dose (MU)	418 (21)	552 (118)	574 (100)	447 (20)	596 (144)	450 (15)

*The patient with HBV genotype G was not included in the analysis.

†Diagnosis of liver cirrhosis was made on liver histology. Liver histology was available in 100 patients.

‡Sex distribution, age, and ALT levels were significantly different in HBV genotype B patients compared with HBV genotype A or D (all $p < 0.05$).

§Perinatal infection rate was higher among patients with HBV genotypes B, C, and D compared with HBV genotype A ($p < 0.03$).

HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase; ND, not determined.

Table 3 Response rates (SR-6) to interferon alfa (IFN) therapy in patients with chronic hepatitis B according to hepatitis B virus (HBV) genotype

	Genotype A	Genotype D	p Value
All patients			
n	78	66	
Cumulative IFN dose (MU)	418 (21)	447 (20)	NS
Treatment duration (months)	6.7	6.2	NS
ETR (%)	59	46	NS
Relapse (% of ETR)	17	43	0.02
SR-6 (%)	49	26	0.005
HBeAg positive			
n	61	38	
Cumulative IFN dose (MU)	395 (21)	442 (29)	NS
Treatment duration (months)	5.8 (0.2)	6.7 (0.4)	0.05
ETR (%)	53	29	0.02
Relapse (% of ETR)	13	18	NS
SR-6 (%)	46	24	0.03
HBeAg negative			
n	17	28	
Cumulative IFN dose (MU)	502 (54)	455 (27)	NS
Treatment duration (months)	7.6 (0.8)	6.7 (0.4)	NS
ETR (%)	82	68	NS
Relapse (% of ETR)	29	58	NS
SR-6 (%)	59	29	0.05

SR-6, sustained response six months post treatment; ETR, end of treatment response; HBeAg, hepatitis B e antigen.

were significantly lower in patients with HBV genotype B compared with HBV genotype A, C, or D. Disease duration was not different between patients with HBV genotype A compared with HBV genotype D (78 (10) v 74 (15) months) despite a higher frequency of perinatal infections in genotype D. Disease duration was determined in 74% of patients. Neither frequency of liver cirrhosis (table 2) nor mean stage of liver fibrosis (2.2 v 2.1) or mean grade of inflammatory activity (2.3 v 2.0) differed significantly between HBV genotypes A and D.

Mean treatment duration and cumulative IFN dose were not different between patients with HBV genotype A and HBV genotype D (table 3). Treatment duration and cumulative IFN dose were slightly higher among patients with HBeAg negative hepatitis compared with HBeAg positive hepatitis (7.0 v 6.1 months ($p<0.03$); 473 v 413 MU IFN ($p<0.06$)). In HBeAg positive hepatitis, 16.9% of patients compared with 37% of HBeAg negative patients were treated for longer than six months. For HBeAg positive hepatitis B, treatment duration and cumulative IFN dose were slightly in favour of HBV genotype D whereas in HBeAg negative hepatitis B, treatment duration and cumulative IFN dose were slightly in favour of HBV genotype A (table 3).

Overall sustained response to IFN six months post treatment (SR-6) was 35%. SR-6 rates to IFN therapy varied greatly between the different HBV genotypes (table 3). Despite administration of slightly lower cumulative IFN

doses compared with other HBV genotypes, patients with HBV genotype A showed the best end of treatment response (ETR) and SR-6 rates. Among patients with HBV genotype B ($n=6$), HBV genotype C ($n=11$), and HBV genotype E ($n=3$), SR was 0%, 18% and 0%, respectively. ETR was 50%, 46%, and 0% among patients with HBV genotypes B, C, and E. The only patient with HBV genotype G achieved a sustained IFN response.

A significantly better SR-6 rate was observed in patients with HBV genotype A (49%) compared with patients with HBV genotype D (26%; $p<0.005$). This was also the case for the subgroups of HBeAg positive (46 v 24%; $p<0.03$) and negative (59 v 29%; $p<0.05$) patients with HBV genotype A or D. The higher SR-6 in patients with HBV genotype A compared with HBV genotype D was the result of both a higher primary IFN response rate and a lower relapse rate in HBV genotype A hepatitis patients. In HBeAg positive hepatitis, relapse rates were comparably low in both HBV genotypes (13% for HBV genotype A v 18% for HBV genotype D; NS) but ETR differed significantly (53% for HBV genotype A v 29% for HBV genotype D; $p<0.02$). HBeAg negative hepatitis was characterised by higher and more divergent relapse rates between HBV genotype A and D (29% v 58%; $p<0.09$) and by higher but less different ETR (82% v 68%; NS) compared with HBeAg positive hepatitis B.

Data on sustained response 12 months post treatment (SR-12) were available in 142 patients with HBV genotype A or D.

Table 4 Univariate logistic regression analysis of factors associated with sustained response (SR-6) among patients with hepatitis B virus (HBV) genotype A and D

	Responders (n = 55)	Non-responders (n = 89)	p Value	OR	95% CI
Genotype A (%)	69	45	0.005	2.7	1.3–5.5
Genotype D (%)	31	55			
ALT (U/l)	107 (12)	79 (6)	0.008	3.2	1.4–7.7
HBV-DNA (pg/ml)	1317 (349)	1391 (194)	0.14	1.7	0.8–3.4
HBeAg positive (%)	67	70	0.57	0.9	0.5–3.1
Sex, male (%)	84	80	0.18	1.3	0.7–4.9
Cirrhosis (%)	33	21	0.76	1.9	0.4–1.8

SR-6, sustained response six months post treatment; HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase; ULN, upper limit of normal; OR, odds ratio; 95% CI, 95% confidence interval. Parameters were categorised for univariate analysis. ALT, $\leq 2 \times \text{ULN}$ versus $> 2 \times \text{ULN}$; HBV-DNA level, ≤ 200 versus > 200 pg/ml.

SR-12 was 47% for HBV genotype A compared with 23% in HBV genotype D ($p<0.002$). Among HBeAg positive patients, SR-12 was 44% compared with 24% ($p<0.04$) and among HBeAg negative patients SR-12 was 59% versus 21% ($p<0.01$) for HBV genotype A and HBV genotype D, respectively.

Univariate regression analysis revealed no effect of sex, cirrhosis, HBeAg status, or HBV-DNA titre on response rate to IFN (table 4). HBV genotype A and ALT levels were relevant predictive parameters of IFN response and were further included in the multivariate analysis. SR-6 was 45% among patients with ALT levels $>2\times$ upper limit of normal (ULN) but only 20% in patients with ALT levels $\leq 2\times$ ULN ($p<0.001$). SR-6 for patients with HBV genotype A and ALT >2 ULN was 56% compared with 26% for ALT $\leq 2\times$ ULN ($p<0.03$), and 31% and 14%, respectively, in patients with HBV genotype D.

Multivariate logistic regression analysis identified HBV genotype A (odds ratio (OR) 2.7 (95% confidence interval (CI) 1.3–5.8); $p<0.009$) and elevated pretreatment ALT level ($\leq 2\times$ ULN $v >2\times$ ULN; OR 3.0 (95% CI 1.2–7.5); $p<0.02$) as independent parameters for sustained response. Low pre-treatment HBV-DNA level (≤ 200 pg/ml $v >200$ pg/ml), sex, or cirrhosis were not found to be independent factors associated with sustained response (table 4).

DISCUSSION

In the present study, we demonstrated that in chronic hepatitis B, response to standard IFN was HBV genotype dependent. HBV genotype A was associated with a significantly higher SR to IFN than HBV genotype D and showed better SR rates than HBV genotype C, B, or E. Furthermore, our findings indicate that HBeAg negativity per se is not a negative predictor of IFN response. The reported low SR rates in HBeAg negative patients compared with HBeAg positive patients seem to be the result of a higher prevalence of low IFN responding HBV genotype D patients in HBeAg negative hepatitis B. We focused on IFN treatment as IFN is still recommended as the firstline treatment for chronic hepatitis B in most cases.⁵

In chronic hepatitis C, viral genotypes have been identified as major determinants of IFN or IFN/ribavirin responsiveness, and treatment regimens are adapted to HCV genotype.¹⁰ Unlike HCV genotypes, the role of HBV genotypes on the response to IFN treatment is not as clear. In a study from China involving 73 HBeAg positive patients, HBV genotype B was associated with a better SR to IFN or a combination of IFN with prednisone priming than HBV genotype C (39% v 17%; $p<0.03$).¹⁹ A study from Taiwan comprising 58 HBeAg positive patients also demonstrated a better SR rate in HBV genotype B compared with HBV genotype C infection (41% v 15%; $p<0.05$).²⁰ A small study, with only HBeAg negative patients treated with highly variable IFN doses of 3×1 MU to 3×8 MU weekly, suggested a better SR rate for HBV infections with HBV genotype A compared with HBV genotype D or E.²¹ In the present study we investigated IFN response in 144 patients with HBV genotype A or D, among them 99 HBeAg positive and 45 HBeAg negative patients.

Twenty one patients with HBV genotype C, B, E, or G were not included in the analysis of IFN response due to insufficient statistical power. The overall IFN response rate of 35% in the present study was in line with that of a larger meta-analysis.²² The study demonstrates that IFN response in chronic hepatitis B is HBV genotype dependent. HBV genotype A was found to be an independent positive predictor whereas HBV genotype D was an independent negative predictor of IFN response. Although HBV genotypes correlated with viral dynamics and mutational patterns during treatment with nucleoside analogues,²³ differences

in response rates have not been observed to date.^{24–25} One limitation of the present study, related to its retrospective character, was that patients did not receive a standardised IFN dose. However, cumulative IFN dose and treatment duration did not differ significantly among patients with HBV genotypes A and D. Prospective studies will have to further address the role of HBV genotypes for IFN response.

The genotype dependent response to IFN may explain the highly divergent sustained response rates to IFN therapy among different geographic regions as a result of the geographic variability in HBV genotype prevalence. This holds true for HBeAg negative hepatitis B in particular. In the present study, 89% of patients of Mediterranean origin carried HBV genotype D and 61% of HBeAg negative patients were infected with HBV genotype D. In contrast, HBV genotype A was the predominant genotype (78%) in patients of German origin and only 37% of HBeAg negative patients were carriers of HBV genotype A. Low sustained response rates of even less than 10% have been reported for HBeAg negative patients; most of the studies in these patients were performed in the Mediterranean area.^{26–29} In contrast, we did not find a significant difference in SR between HBeAg positive and HBeAg negative patients (37% v 40%; NS). Higher relapse rates were observed in HBeAg negative hepatitis B confirming the results of previous studies. Even after stratification for HBV genotype A or D, no differences in SR were found between HBeAg negative and HBeAg positive patients (table 3). Thus in view of the present data, the low response rate for HBeAg negative patients observed so far in some geographic areas appears to be the result of a high prevalence of a low IFN responder HBV genotype (for example, D and E) than that of HBeAg status itself.

Because of the small patient numbers it is difficult to draw conclusions regarding IFN response for HBV genotypes B, C, E, and G. The response rate for HBV genotype C reported in the present investigation is consistent with that reported in studies from Taiwan and China.^{19–20} The unresponsiveness of HBV genotype B patients may be due to a high proportion of patients with normal ALT levels, as reflected by the low mean ALT values (table 2). The primary non-response of patients carrying HBV genotype E (all from Africa) should give rise to further investigations. It has recently been demonstrated in hepatitis C that Black Americans have a significantly lower HCV genotype independent response to IFN/ribavirin combination treatment, indicating that ethnic factors may play a role in IFN responsiveness.³⁰

Current interferon treatment of chronic hepatitis B has limited efficacy. Treatment regimens with nucleos(t)ide analogues have not proved superior to IFN treatment although nucleos(t)ide analogue therapy has negligible side effects.^{31–34} Based on the present data it would be useful to evaluate HBV genotype adapted IFN treatment regimens as they may provide clues to further improve IFN response rates in chronic hepatitis B.

ACKNOWLEDGEMENTS

The study was supported by a grant from the Forschungskommission der Heinrich-Heine-Universität Düsseldorf

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Conflict of interest: None declared.

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EDITOR'S QUIZ: GI SNAPSHOT

Answer

From question on page 1002

The clue to the diagnosis in this case is the inverted orientation between the superior mesenteric artery (SMA) and the superior mesenteric vein (SMV). Due to the normal 270° counter clockwise rotation of the midgut during embryological development, the SMA is normally positioned left of the SMV. Here the ultrasound scan demonstrated the SMA to the right of the SMV. In addition, a dilated small bowel was present. These features are characteristic of an intestinal malrotation (non-rotation) of the midgut. Endoscopy followed by upper gastrointestinal contrast series revealed duodenal obstruction. A contrast enhanced computed tomography scan showed complete malrotation with an obstruction in the distal duodenum. This was confirmed at laparotomy and a gastrojejunostomy and resolving of adhesions were performed. A gastrointestinal contrast series four days postoperatively demonstrated correct contrast passage into the jejunum. After oral refeeding, the patient's postprandial complaints were improved.

Intestinal malrotation occurs in approximately 1 in 1000 live births. Symptomatic malrotation is estimated to occur in 1/6000 live births, with an increased risk for volvulus, twisting, small bowel obstruction, or other anomalies. Approximately 90% of patients present within the first months of life. It has to be considered an uncommon diagnosis in adult patients presenting with signs and symptoms of acute or chronic small bowel obstruction.

doi: 10.1136/gut.2004.060053